SOUTH AFRICAN PRIMARY HEALTHCARE ESSENTIAL MEDICINES LIST
PRIMARY HEALTH CARE CHAPTER 11: HIV AND AIDS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2020 -24 REVIEW CYCLE)

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG).

All reviews and costing reports may be accessed at: https://www.health.gov.za/nhi-edp-stgs-eml/

Note that the associated EML chapter has been subjected to subsequent clinical editing. These editorial amendments may not be reflected in the report below.

MEDICINE AMENDMENTS:

SECTION	MEDICINE	ADDED/DELETED/AMENDED/NOT ADDED/RETAINED
	Reference to national ART guidelines	Cross reference to national ART guidelines aligned to Paediatric EML
A: HIV INFECTION IN ADULTS		
11.1 Antiretroviral therapy, adults and adolescents		
- TB co-infection	ART	Directions amended
- TB meningitis co-infection	ART	Directions amended
- Asymptomatic cryptococcal infection	ART	Directions amended
11.1 Antiretroviral therapy, adults and adolescents *- Treatment-naïve patients without TB*	TDF +EFV+FTC	Retained
	TDF +3TC + DTG	Indication expanded from ≥6 weeks gestation to ALL women
	TAF	Added for patients with chronic hepatitis B coinfection and RF
11.1 Antiretroviral therapy, adults and adolescents *- Treatment-naïve patients with TB*	TDF + EFV + FTC (TEE)	Retained
	Double-dosed DTG	Indication expanded to DTG-naïve patients initiating ART with concomitant rifampicin-containing TB therapy
11.1 Antiretroviral therapy, adults and adolescents *- Contraindication to TDF*	TAF as (TAF+FTC+DTG):	Added for select cohort of patients
	ABC + 3TC+DTG	Amended as preferred treatment
11.1 Antiretroviral therapy, adults and adolescents *- Contraindication to TDF/TAF and ABC intolerance*	AZT+3TC with DTG	Amended as preferred treatment
	Aminoglycoside nephrotoxicity caution	Deleted
11.1 Antiretroviral therapy, adults and adolescents *- Recycling TDF in virological failure*	AZT	Deleted
	TDF	Added
11.1 Antiretroviral therapy, adults and adolescents *DTG contra-indicated/not tolerated/failing*	LPV/r	Retained
	ATV/r	Expanded to include all patients - preferred 2nd line PI
	DRV/r	Not added to the STG, but proposed for inclusion in therapeutic interchange database for patients not on TB-rifampicin therapy
11.1 Antiretroviral therapy, adults and adolescents – ART Regimens *- DTG resistance*	Resistance testing	Retained, and emphasised
11.1 Antiretroviral therapy, adults and adolescents *- Rifampicin-based TB treatment (already on DTG-regimen)*	DTG	Added
11.1 Antiretroviral therapy, adults and adolescents *- Currently available ARV FDC preparations on contract*	ATV/r	Added
	ABC + 3TC + DTG	Added
Re-initiating ART in patients who have interrupted treatment	Guidance	Amended
Monitoring on ART *- Baseline evaluation*	CrAg screening	Amended
	Sputum screen for TB	Amended
	HIV viral load monitoring schedule	Amended
ART: Dosing and important adverse effects	3TC	Amended
	FTC	Amended

	TDF, ABC, 3TC, FTC	Amended - very low risk, "Hyperlactataemia/ steatohepatitis" was deleted
	Dolutegravir, oral – weight gain	Deleted
	Dolutegravir, oral – serum creatinine	Guidance clarified
	Nevirapine, oral	Adverse effects and dosing information deleted
	Raltegravir, oral	Adverse effects and dosing information deleted
	TAF, oral	Added
ART interactions with rifampicin and recommendations for administration	Rifabutin, oral	Not added
Drug interactions with boosted PIs	Rifampicin	Guidance amended
Referral	Criteria	Amended
11.2 Opportunistic Infections, Prophylaxis in adults		
11.2.1 Cotrimoxazole prophylaxis	WHO clinical stage II	Deleted
11.2.2 Tuberculosis preventive therapy (TPT)	TPT	Added as a therapeutic group
-Adult PLHIV initiated on ARVs	Isoniazid (12H)	Retained as an example of class in the STG
	Rifapentine + isoniazid (3HP)	Added as a therapeutic alternative in the therapeutic interchange database
	Pregnant women	Guidance amended
11.3.3 Candidiasis, oesophageal	Fluconazole	Guidance amended
11.3.4 Cryptococcosis	CrAg screening	Guidance clarified
	CrAg screening – CD4 threshold	Amended
	Fluconazole, oral	Dose for children added
	Fluconazole, oral	Caution updated
	Flucytosine, oral	Not added
-Asymptomatic cryptococcosis	ART initiation	Amended
-Referral	Criteria	Amended
11.3.5 Diarrhoea, HIV associated	Cotrimoxazole dosing	Guidance clarified
11.3.11 Herpes Zoster (shingles)	Paracetamol	Amended
11.4 HIV and kidney disease	Routine screening for renal disease	Retained
B: HIV INFECTION IN CHILDREN (<10 YEARS OLD)		
Diagnosis in children	Testing in children	Amended
Clinical staging of HIV and AIDS	WHO clinical staging	Editorial update
11.5 The HIV exposed infant	Description	Amended
	Feeding advice	Aligned to Paediatric EML
	Terminology - PMTCT	Amended
	Medicine treatment	Aligned to Paediatric EML
	NVP & AZT – infants on VTP	Dosing guidance amended
	Cotrimoxazole, oral	Prophylaxis in high risk infants - amended
	HIV prophylaxis in high risk infants	Flow diagram - amended
11.6 Management of HIV-infected children (<10 years)	Viral load monitoring	Amended
	Cotrimoxazole prophylaxis	Amended to include WHO clinical stages
	BCG immunisation	Amended
	Social issues for successful treatment	Amended
	Counselling guidance	Editorial amendments
	Side effects of ARVs	Amended
	ART regimens - DTG	Added
	Guidance on ART regimens	Amended
-Transition from ABC/3TC/LPV/r to DTG based regimens	Guidance	Added
-Treatment failure	Guidance	Amended
-Confirmed virological failure in adolescents on TLD	Guidance	Added
-Viral load monitoring for clients on TLD	Guidance	Added
-ART dosing	Dosing tables	Added
11.7 Opportunistic infections, prophylaxis in children	Cotrimoxazole, oral	Directions for use amended
	Cotrimoxazole, oral- WHO clinical staging	Added

	Immunisation	Aligned with Section 11.6
11.8.7 Tuberculosis (TB)	Description	Amended
C: HIV PREVENTION		
11.11 Pre-exposure prophylaxis (PrEP)		
-Contraindications to PrEP	eGFR	Guidance clarified
- Oral PrEP regimen	TDF + FTC	Duration of therapy amended
-Screening investigations before starting PrEP	HBsAg screening	Guidance clarified
-PrEP Initiation	Algorithm	Guidance clarified
- Oral PrEP follow up and monitoring	Estimated creatinine clearance	Monitoring updated
-Medicine interaction information	MDR-TB guidance	Deleted
- Stopping oral PrEP	TDF + FTC	Duration of therapy amended
- Other PrEP agents	Dapivirine vaginal ring	Not added
	Cabotegravir	Not added
D: SIDE EFFECTS AND COMPLICATIONS OF ART		
11.14 Lactic acidosis	STG	Deleted

ABC= Abacavir, ATV/r=Atazanavir/ritonavir, AZT=Zidovudine, 3TC= Lamivudine, DRV/r=Darunavir/ritonavir, DTG= Dolutegravir, EFV= Efavirenz FTC = Emtricitabine, LPV/r=Lopinavir/ritonavir, PrEP=Pre-exposure prophylaxis; TAF=tenofovir alafenamide, TDF = Tenofovir disoproxil fumarate

SUBSEQUENT UPDATES TO THE 2020-4 EDITION

Version no.	Section	Amendments
2.1	11.1 Drug interactions with dolutegravir	**Metformin** Guidance amended

The cross reference to the national ART guidelines 20231 has been amended and aligned to the Paediatric EML as tabulated below:

Amended from:
Consult the most recent HIV Guidelines from the National Department of Health. https://www.knowledgehub.org.za/elibrary/national-consolidated-guidelines-management-hiv-adults-adolescents-children-and-infants
Amended to:
Comprehensive guidelines are available for ART and the care of adults and children with HIV infection in the 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates.

[1] South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023.

A. HIV INFECTION IN ADULTS & ADOLESCENTS (10-19 YEARS OLD)

11.1 ANTIRETROVIRAL THERAPY, ADULTS & ADOLESCENTS (10-19 YEARS OLD)

TB co-infection

STG text was aligned to the Adult Hospital Level STG.

» In TB co-infection, start with TB treatment first, followed by ART initiation according to CD4 count (except TB meningitis – see below):

- CD4 counts < 50 cells/mm^3: start ART within 2 weeks of starting TB treatment.
- CD4 count ≥ 50 cells/mm^3: defer ART until 8 weeks after starting TB treatment, which does not increase the risk of mortality and reduces the risk of deterioration due to the immune reconstitution inflammatory syndrome (IRIS).

TB meningitis co-infection

STG text was aligned to the Adult Hospital Level STG.

- In patients with TB meningitis (irrespective of CD4 count), defer ART until 8 weeks after starting TB treatment.

Positive cryptococcal antigen and no evidence for meningitis on LP:

STG text was aligned to the National ART guideline as tabulated below:

Positive cryptococcal antigen and no evidence for meningitis on LP:

Amended from:

- Defer ART until 2 weeks after initiating fluconazole

Amended to:

- No need to delay ART. ART can be started immediately.

Treatment-naïve patients without TB

TDF +EFV+FTC: *Retained*

Tenofovir + lamivudine + dolutegravir, oral: *amended indication to include all women*

Indication expanded from "≥6 weeks gestation" to "ALL women," see NEMLC recommendation as tabulated below. A copy of the full review[2] may be found at the end of this document or alternatively accessed on the NHI webpage.

PHC/ADULT HOSPITAL LEVEL COMMITTEE AND NEMLC RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
					X

Recommendation: The PHC/Adult Hospital Level Committee recommends that dolutegravir should be part of the preferred first line ART regimen for all adults and adolescents living with HIV, including pregnant women and women of child-bearing potential. The existing contra-indication in pregnancy should be removed from the STG.

Rationale: The estimated risk of neural tube defects in infants exposed to dolutegravir in early pregnancy that was first identified in the Tsepamo observational study in Botswana has diminished over time, with the accumulation of further data. The risk difference between dolutegravir and efavirenz is no longer significant.
Dolutegravir (especially when combined with tenofovir alafenamide) is associated with more weight gain during pregnancy than efavirenz, but the difference is of uncertain clinical relevance.
Randomised controlled trials have shown non-inferiority in terms of maternal viral suppression rates at 48 weeks. Dolutegravir causes more rapid viral suppression than efavirenz, resulting in increased viral suppression rates by time of delivery in randomised controlled trials of ART initiation in the second and third trimester of pregnancy. This has not yet translated into a demonstrable difference in mother-to-child transmission risk, but event rates are very low with both regimens.
A standardised regimen for all adults and adolescents living with HIV is likely to be easier to provide.
Based on those findings and observations, the PHC/Adult Hospital Level Committee feel that the potential long-term benefits to pregnant women and WOCP, as well as potential short-term benefits to their infants, outweigh the risks.
Level of Evidence: Moderate certainty of evidence
Review indicator: New evidence of harms
(Refer to appendix 2 for the evidence to decision framework)

NEMLC MEETING OF 24 JUNE 2021:
NEMLC Recommendation: The NEMLC accepted the recommendation as proposed by the PHC/Adult Hospital Level Committee, which would support the universal test-and-treat (UTT) strategy of the National HIV Programme.
It was also duly noted that the South African Health Products Regulatory Authority were currently reviewing the label of dolutegravir products registered on the South African market.

[2] NDoH Evidence Review. DTG in pregnancy. PHC-Adults Medicine review_17June2021_v2

Tenofovir alafenamide (TAF): *Added (for a select cohort)*

An update to the TAF review was conducted in March 2024 for PLHIV with chronic Hepatitis B co-infection and renal impairment.[3] TAF has been added to the EML as part of a fixed dose combination for PLHIV with chronic hepatitis B co-infection and renal impairment (eGFR 30-50mL/min). The updated recommendation is tabulated below. *(A subsequent update was made to the review in June 2024 to include an Addendum which details an evidence summary on the use of TAF for Hepatitis B in non-HIV co-infection*). A copy of the complete review may be found at the end of this report or alternatively accessible on the NHI webpage.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
			X		

Recommendation: The Committee suggests that TAF be considered, if affordable, in patients with chronic hepatitis B co-infection and renal impairment with eGFR 30-50 ml/min/1.73m^2.

TAF could also be considered as an alternative to TDF or ABC in other ART regimens, if cost saving. (TAF- and abacavir-containing regimens were not directly compared in this review however).

Rationale:

Based on the best available evidence, TAF has similar efficacy to TDF. TAF has probable safety benefits vs TDF (renal and bone), but a slightly worse lipid profile and is associated with weight gain (though this may be mostly due to TDF's weight suppressive effects). Because TAF, when combined with emtricitabine or lamivudine, can be safely used in patients with an estimated glomerular filtration rate of >= 30 ml/min/1.73m^2, it may be considered for patients with contraindications to TDF, i.e. renal disease, especially if there are cost savings. Patients with an eGFR 30-50 ml/min/1.73m^2 and chronic hepatitis B coinfection potentially constitute the strongest use case, since a form of long-term tenofovir is required for this group of patients and TDF is contraindicated below an eGFR of 50 ml/min/1.73m^2.

Level of Evidence: Systematic Reviews and Meta-Analysis of Randomized Clinical Trials
Review indicator: New high quality evidence of a clinically relevant benefit. Significant cost savings over alternative regimens.

NEMLC MEETING OF 19 MARCH 2019:
NEMLC accepted this evidence review and the proposal as recommended by the Adult Hospital Level Expert Review Committee, above. NEMLC also acknowledged that TAF-containing fixed-dose combination formulations are currently not SAHPRA registered and thus not currently available on the South African market. The current antiretroviral recommendations, as recommended in the Standard Treatment Guidelines (Adult Hospital Level, 2019 edition) and National HIV Guidelines, 2019 edition are sufficient.

NEMLC MEETING OF 23 JUNE 2022:
NEMLC Discussion

- *Renal impairment:* It was noted that patients with renal impairment are generally referred to the tertiary level of care and TAF may be potentially advantageous for this cohort so there may be some consideration to limit access to tertiary centres
- *SAHPRA registration:* TAF is currently not registered locally.

NEMLC Recommendation
The NEMLC upheld the previous decision from 2019 which was not to recommend TAF for the inclusion on the national EML. **However, TAF could be accessed by Provinces for individual patients on a named-patient basis**. NEMLC also acknowledged that TAF-containing fixed-dose combination formulations are currently not SAHPRA registered.

NEMLC MEETING OF 14 MARCH 2024: The Committee supported that a TAF-containing fixed dose combination (either emtricitabine 200mg or lamivudine 300mg together with tenofovir alafenamide 25mg and dolutegravir 50mg) be added to the EML as an alternative to the current standard of care for PLHIV with hepatitis B coinfection and renal impairment (eGFR 30-50 ml/min/1.73m^2).

Monitoring and evaluation considerations

Research priorities
Long-term weight gain data comparing TAF, TDF and ABC-based regimens in LMIC.

ART-treatment naïve patients with TB

Tenofovir + Efavirenz + Emtricitabine (TEE): *retained*

Double-dosed dolutegravir (TLD + DTG 50 mg): *indication expanded to DTG-naïve patients initiating ART with concomitant rifampicin-containing TB therapy*

Refer to the updated DTG in HIV-infected patients review with addendum, 21 July 2021 (second update of initial 26 January 2017 review). The NEMLC recommendation is tabulated below, a copy of the complete review[4] may be

[3] Tenofovir alafenamide for HIV Adult Review Update_ 27 June 2024_v5_final

[4] NDoH Evidence Review. NationalDeptOfHealth_EDP_Dolutegravir_HIV-Adults_Review Update_27 July 2021 with updated Addendum: DTG initiation_WithRifampicin_INSPIRINGstudy_PHC-Adults_Summary_27July2021

accessed at the end of this report or alternatively on the NHI webpage.

RECOMMENDATION
Based on this evidence summary, the PHC/Adult Hospital Level Committee recommends that dolutegravir 50mg 12 hourly be included as an option in the standard treatment guidelines for adult patients initiating antiretroviral therapy while taking rifampicin-containing TB treatment, as an alternative to using efavirenz for the duration of TB treatment..
Rationale: Randomised open-label INSPIRING study showed that initiation of DTG-containing ART with DTG double dosing is well tolerated; and that virological suppression for efavirenz-containing ART regimen and double-dosed DTG-containing ART regimen were similar amongst ART-naive adults initiating ART, whilst on rifampicin-based tuberculosis treatment.
Level of evidence: Low certainty evidence

NEMLC MEETING 29 JULY 2021:
The NEMLC accepted the proposed recommendation made by the PHC/Adult Hospital Level Committee above and recommended that the report and review be circulated for external comment.

Contraindication to TDF

Tenofovir alafenamide + emtricitabine + dolutegravir (TAF+FTC+DTG): *added (select cohort)*
TAF has been added to the EML for patients with chronic hepatitis B co-infection and eGFR 30-50ml/min. Refer to the TAF review conducted in March 2024 for PLHIV with chronic Hepatitis B co-infection and renal impairment,[5] which may be found at the end of this report or alternatively accessed on the NHI webpage.

Abacavir + lamivudine + dolutegravir (ABC+3TC+DTG), oral: *amended*
(ABC+3TC+DTG)amended as the preferred treatment for patients other than those with, chronic hepatitis B coinfection and renal impairment (as for TAF+FTC+DTG above).

Contraindication to TDF/TAF and ABC intolerance

Zidovudine + lamivudine with dolutegravir (AZT+3TC with DTG), oral: *amended as preferred treatment*

Aminoglycoside nephrotoxicity caution: *deleted*
The following STG text was deleted:

~~Use of additional nephrotoxic drug e.g., aminoglycoside.~~

Aminoglycosides are no longer recommended for management of drug-resistant TB. However, available evidence did not show a significant increased risk of nephrotoxicity with TDF in DR-TB patients on kanamycin.[6] [7]

The STG has been amended in line with the above recommendations and aligned to the National ART Guidelines as tabulated below. Reference to 1st, 2nd and 3rd line regimens have been removed from the EML in alignment with the National ART Guidelines.

	AMENDED FROM:	**AMENDED TO:**
	1ST LINE ART	**INITIATING ART**
Treatment-naïve patients	» Men ≥35kg and ≥10 years of age » WOCP not actively wishing to conceive » Pregnant women ≥6 weeks gestation, and those who make an informed choice to use DTG • TDF + 3TC + DTG Patients with TB: • TDF + FTC + EFV Pregnant women <6 weeks gestation or actively wanting to conceive: • TDF + FTC + EFV *(Also see section 6.7: HIV in pregnancy)*	Individuals ≥30kg and ≥10 years TDF + 3TC + DTG ("TLD") **Note***:* DTG-based regimens are now recommended as first line ART in all women of childbearing potential. Patients on rifampicin-based TB treatment: TDF + FTC + EFV **OR** TDF + 3TC + DTG *plus* additional dose of DTG 50mg 12 hours later.

[5] Tenofovir alafenamide for HIV Adult Review Update_ 27 June 2024_v5_final
[6] Perumal R, Abdelghani N, Naidu N, Yende-Zuma N, Dawood H, Naidoo K, et al. Risk of nephrotoxicity in patients with drug-resistant tuberculosis treated With kanamycin/capreomycin with or without concomitant use of tenofovir-containing antiretroviral therapy. J Acquir Immune Defic Syndr. 2018;78: 536–542. https://pubmed.ncbi.nlm.nih.gov/29683992/
[7] Sagwa EL, Ruswa N, Mavhunga F, Rennie T, Mengistu A, Mekonen TT, et al.. Renal function of MDR-TB patients treated with kanamycin regimens or concomitantly with antiretroviral agents. Int J Tuberc Lung Dis. 2017;21: 1245–1250. https://pubmed.ncbi.nlm.nih.gov/29297444/

		The extra DTG dose can be stopped two weeks after completion of TB therapy. (Also see section PHC STG 6.8: HIV in pregnancy)
Contraindications/ intolerance to DTG		TDF + 3TC/FTC + EFV
Contraindications and intolerance to EFV	• TDF + 3TC + DTG » WOCP actively wanting to conceive and pregnant women <6 weeks gestation require adequate counselling to make an informed choice to use DTG.	
Contraindications to EFV and DTG	Start protease inhibitor-based regimen: • TDF + 3TC/FTC + LPV/r	<u>Start protease inhibitor-based regimen:</u> TDF + 3TC/FTC + ATV/r **Note:** if patient requires rifampicin-based TB treatment, substitute ATV/r with LPV/r 800/200 mg 12-hourly. **Note:** There is an increased risk of ALT/AST elevations and gastrointestinal disorders. LPV/r dose should be gradually titrated upward over 1-2 weeks (e.g. 600/150 and then 800/200mg). The LPV/r can be switched back to ATV two weeks after completion of TB therapy.
Contraindications to EFV and DTG	Start protease inhibitor-based regimen: • TDF + 3TC/FTC + LPV/r	
Contraindication to TDF » eGFR <50 mL/minute.	Replace TDF + 3TC/FTC with either • ABC+ 3TC or • AZT + 3TC	<u>If chronic hepatitis B coinfection and eGFR 30-50 ml/min:</u> TAF + FTC + DTG. <u>Other scenarios:</u> ABC + 3TC + DTG
Contraindication to TDF and ABC intolerance	• AZT+ 3TC with DTG or EFV	
Contraindication to TDF/TAF and ABC intolerance/hypersensitivity		AZT + 3TC with DTG
NOTE:	**Note:** In the unlikely scenario where there is intolerance/contraindication to all currently available NRTIs, an alternative dual-therapy regimen may be used, e.g. DTG + 3TC (if no resistance/intolerance to 3TC and VL <500 000 copies/mL) **or** EFV + LPV/r **or** DTG + LPV/r may be used. Consult a specialist.	**Note:** In the unlikely scenario where there is intolerance/contraindication to all currently available NRTIs, the following alternative dual-therapy regimens may be used **after** consulting a specialist: • DTG + 3TC (if no resistance/intolerance to 3TC and VL <500 000 copies/mL) • EFV + LPV/r • DTG + LPV/r

Recycling TDF in virological failure

<u>Zidovudine:</u> *deleted*

<u>Tenofovir disoproxil fumarate (TDF):</u> *added*

As the 96-weeks follow up data of the NADIA RCT[8] has been published in peer-review format, an update to the original

[8] Paton NI, Musaazi J, Kityo C, Walimbwa S, Hoppe A, Balyegisawa A, et al. Efficacy and safety of dolutegravir or darunavir in combination with lamivudine plus either zidovudine or tenofovir for second-line treatment of HIV infection (NADIA): week 96 results from a prospective, multicentre, open-label, factorial, randomised, non-inferiority trial. Lancet HIV. 2022. https://pubmed.ncbi.nlm.nih.gov/35460601/

evidence summary[9] was undertaken in May 2022, with the NEMLC recommendation tabulated below. A copy of the complete review[10] may be accessed at the end of this document or alternatively on the NHI webpage.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	
Recommendation: Based on this evidence review, the PHC/Adult Hospital Level Committee suggest that tenofovir should be recycled in 2nd line dolutegravir-based antiretroviral therapy. *Rationale:* For patients in whom neither agent is contraindicated, recycled TDF is non-inferior to AZT in 2nd line therapy (assuming TDF use in 1st line), and adverse events rates are similar. In addition, compared to AZT, it is cheaper, can be given once daily, is available as a single fixed dose combination tablet (TLD), and requires less intense initial monitoring. **Level of Evidence: RCTs of moderate certainty evidence** **Review indicator: Evidence of harm of inferior viral suppression rates**					
NEMLC RECOMMENDATION (MEETING OF 23 JUNE 2022): **NEMLC accepted the proposed recommendation, as mentioned above.**					
Monitoring and evaluation considerations					
Research priorities					

The STG has been amended in line with the above recommendations and aligned to the National ART Guidelines as tabulated below:

	AMENDED FROM:	**AMENDED TO:**
	2ND LINE ART	
Management of viraemia on 1st line ART	If plasma VL between 50–999 copies/mL: » Address adherence, tolerability, medicine interactions & psychosocial factors. » Repeat VL test 3 months later. If plasma VL > 1000 copies/mL: » Assess adherence, tolerability, medicine interactions & psychosocial factors. Repeat VL test 3 months later If plasma VL 50-999 copies/mL: » Continue enhanced adherence support. » Repeat VL test 6 months later. If plasma VL remains at 50-999 copies/mL i.e. persistent low grade viraemia: » Manage as virological failure below.	
Management of virological failure on 1st line ART	If plasma VL confirmed ≥1000 copies/mL (on 2 tests), and adherence issues addressed: » Change regimen to 2nd line therapy. **Note:** Always check hepatitis B surface antigen (HBsAg) before stopping TDF*:* » If patient has chronic hepatitis B, stopping TDF may lead to a fatal hepatitis flare. » If hepatitis B positive, TDF should be continued in the 2ndline regimen.	
		VIROLOGICAL FAILURE
Management of viraemia on TLD		If plasma VL >50 copies/mL: » Address adherence, tolerability, medicine interactions & psychosocial factors. » Repeat VL test 3 months later. If plasma VL remains > 50: » Assess adherence, tolerability, medicine interactions & psychosocial factors again. » If on TLD <2 years, or persistent low-level viraemia (50-999 copies/mL), or adherence suboptimal, repeat VL at next scheduled visit (i.e. in 6 months' time).

[9] NDoH Evidence Summary. NDoH_EML_HIV_NADIA&ARTIST summary_30November2021_v1.0
[10] NDoH Evidence Summary. TDF-backbone as 2nd line in HIV_Adults_Evidence summary_19May2022_ v3.0

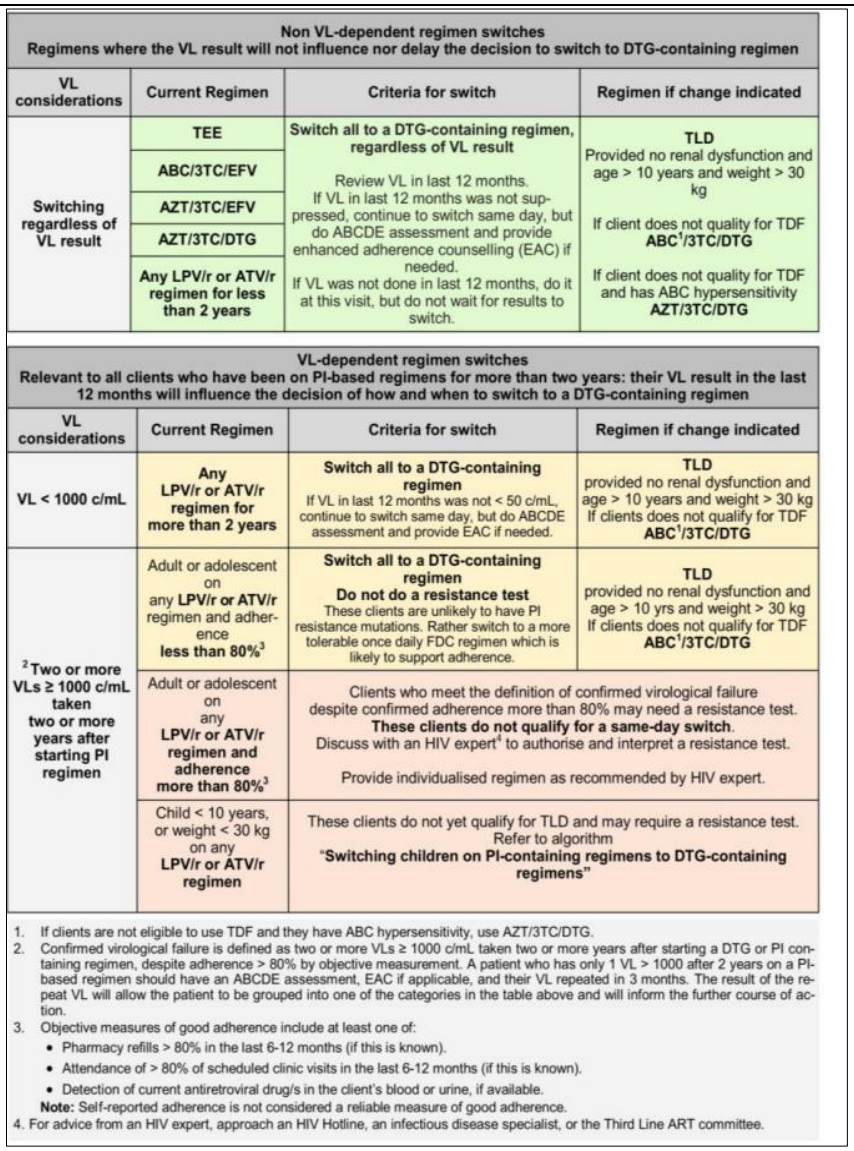
		» If on TLD >2 years and ≥2 consecutive VL ≥1000 copies/mL (or 1 VL ≥1000 copies/mL plus CD4 <200 or opportunistic infection), discuss with an HIV expert* whether a resistance test is indicated (as a rule it is not, and efforts to resolve adherence issues should be intensified instead).
Failing a NNRTI-based 1st line regimen *(TDF+3TC/FTC+EFV/NVP)*	AZT + 3TC + DTG. If HBsAg positive: TDF + 3TC + DTG If DTG contraindicated/ not tolerated: AZT + 3TC +LPV/r (**PLUS** TDF, if HBsAg positive). If AZT and TDF contraindicated/ not tolerated (e.g. anaemia and renal impairment): ABC + 3TC + LPV/r	
Failing a DTG- based 1st line regimen for >2 years *(TDF+3TC+DTG)* » Resistance testing for adults and adolescents failing a DTG-based regimen and who meet the definition of confirmed virological failure may be authorized by an expert on a case-by-case basis.	AZT + 3TC +LPV/r If HBsAg positive: TDF + 3TC/FTC +LPV/r	
		CLIENTS WITH DTG RESISTANCE
Any DTG resistance shown on genotype authorised by HIV expert		Discuss case with an HIV expert*. The regimen will be determined by an Expert Committee based on the pattern of resistant mutations and the prior history of antiretroviral exposure. Application for 3rd line using the standard motivation form may be required (available from TLART@health.gov.za or from https://www.righttocare.org/)
Dyslipidaemia requiring lipid-lowering therapy or diarrhoea associated with LPV/r	Switch LPV/r to ATV/r	
3RD LINE ART		
Failing any 2nd line regimen	Refer to a specialist. Resistance to LPV/r or ATV/r and/or DTG must be shown on genotype antiretroviral resistance test in order to qualify for 3rd line – this test is expensive and should only be done in patients with at least 2 years exposure to a PI and objective evidence of good adherence. Application for 3rd line using the standard motivation form is required (available from TLART@health.gov.za) –the regimen will be determined by an Expert Committee based on the pattern of resistant mutations and the prior history of antiretroviral exposure.	

Switching existing clients to DTG-containing regimens

The STG has been amended to include guidance on switching existing clients to DTG-containing regimens as tabulated below:

SWITCHING EXISTING CLIENTS TO DTG-CONTAINING REGIMENS	
Patient on: » **TDF/FTC/EFV** » **ABC/3TC/EFV (or NVP)** » **AZT/3TC/EFV (or NVP)** » **AZT/3TC/DTG** » **Any LPV/r- or ATV/r-containing regimen for <2 years** » **Any LPV/r- or ARV/r-containing regimen with latest VL <1000 copies/mL**	Switch to DTG-containing regimen regardless of VL result: TDF + 3TC + DTG ("TLD") (*Refer to Figure 11.1 below*). If contraindications to DTG or TDF, use alternative regimen as in "Initiating ART" section above.
Patient on: » **ATV/r or LPV/r regimen for >2 years and ≥2 consecutive VL ≥1000 copies/mL**	If adherence >80%, discuss with an HIV expert to authorise and interpret a resistance test before switching.* Provide individualised regimen as recommended by HIV expert. If adherence < 80%. switch to DTG-containing regimen: TDF + 3TC + DTG ("TLD") If contraindications to DTG or TDF, use alternative regimen as per "Initiating ART" section above.

The treatment pathway for switching existing clients to DTG-containing regimens as illustrated below, has been adopted from the NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates.



Non VL-dependent regimen switches
Regimens where the VL result will not influence nor delay the decision to switch to DTG-containing regimen

VL considerations	Current Regimen	Criteria for switch	Regimen if change indicated
Switching regardless of VL result	TEE	Switch all to a DTG-containing regimen, regardless of VL result Review VL in last 12 months. If VL in last 12 months was not suppressed, continue to switch same day, but do ABCDE assessment and provide enhanced adherence counselling (EAC) if needed. If VL was not done in last 12 months, do it at this visit, but do not wait for results to switch.	**TLD** Provided no renal dysfunction and age > 10 years and weight > 30 kg If client does not quality for TDF **ABC[1]/3TC/DTG** If client does not quality for TDF and has ABC hypersensitivity **AZT/3TC/DTG**
	ABC/3TC/EFV		
	AZT/3TC/EFV		
	AZT/3TC/DTG		
	Any LPV/r or ATV/r regimen for less than 2 years		

VL-dependent regimen switches
Relevant to all clients who have been on PI-based regimens for more than two years: their VL result in the last 12 months will influence the decision of how and when to switch to a DTG-containing regimen

VL considerations	Current Regimen	Criteria for switch	Regimen if change indicated
VL < 1000 c/mL	Any LPV/r or ATV/r regimen for more than 2 years	Switch all to a DTG-containing regimen If VL in last 12 months was not < 50 c/mL, continue to switch same day, but do ABCDE assessment and provide EAC if needed.	**TLD** provided no renal dysfunction and age > 10 years and weight > 30 kg If clients does not qualify for TDF **ABC[1]/3TC/DTG**
[2]Two or more VLs ≥ 1000 c/mL taken two or more years after starting PI regimen	Adult or adolescent on any LPV/r or ATV/r regimen and adherence less than 80%[3]	Switch all to a DTG-containing regimen Do not do a resistance test These clients are unlikely to have PI resistance mutations. Rather switch to a more tolerable once daily FDC regimen which is likely to support adherence.	**TLD** provided no renal dysfunction and age > 10 yrs and weight > 30 kg If clients does not qualify for TDF **ABC[1]/3TC/DTG**
	Adult or adolescent on any LPV/r or ATV/r regimen and adherence more than 80%[3]	Clients who meet the definition of confirmed virological failure despite confirmed adherence more than 80% may need a resistance test. **These clients do not qualify for a same-day switch.** Discuss with an HIV expert[4] to authorise and interpret a resistance test. Provide individualised regimen as recommended by HIV expert.	
	Child < 10 years, or weight < 30 kg on any LPV/r or ATV/r regimen	These clients do not yet qualify for TLD and may require a resistance test. Refer to algorithm **"Switching children on PI-containing regimens to DTG-containing regimens"**	

1. If clients are not eligible to use TDF and they have ABC hypersensitivity, use AZT/3TC/DTG.
2. Confirmed virological failure is defined as two or more VLs ≥ 1000 c/mL taken two or more years after starting a DTG or PI containing regimen, despite adherence > 80% by objective measurement. A patient who has only 1 VL > 1000 after 2 years on a PI-based regimen should have an ABCDE assessment, EAC if applicable, and their VL repeated in 3 months. The result of the repeat VL will allow the patient to be grouped into one of the categories in the table above and will inform the further course of action.
3. Objective measures of good adherence include at least one of:
   - Pharmacy refills > 80% in the last 6-12 months (if this is known).
   - Attendance of > 80% of scheduled clinic visits in the last 6-12 months (if this is known).
   - Detection of current antiretroviral drug/s in the client's blood or urine, if available.

   Note: Self-reported adherence is not considered a reliable measure of good adherence.
4. For advice from an HIV expert, approach an HIV Hotline, an infectious disease specialist, or the Third Line ART committee.

DTG CONTRAINDICATED/ NOT TOLERATED/FAILING

Lopinavir/ritonavir: *retained*

Atazanavir/ritonavir: *expanded to include all patients - preferred 2nd line PI*

A summary of the recommendation from the evidence review is included below. The complete evidence summary[11] may be found at the end of this document or alternatively accessed on the NHI webpage.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative (strong)	We suggest not to use the option (conditional)	We suggest using either the option or the alternative (conditional)	We suggest using the option (conditional)	We recommend the option (strong)
				X	
Recommendation: The PHC/Adult Hospital Level Committee suggests that ritonavir-boosted atazanavir be the preferred protease inhibitor for second-line therapy in all adult patients without concomitant TB. Ritonavir-boosted lopinavir must still be available for use with rifampicin-containing TB therapy. *Rationale:* Ritonavir-boosted atazanavir is at least non-inferior to ritonavir-boosted lopinavir in terms of viral suppression, is associated with fewer gastrointestinal side-effects and lipid profile abnormalities than ritonavir-boosted lopinavir, and is dosed once-daily. **Level of Evidence: Low to moderate certainty evidence**					
NEMLC MEETING 9 DECEMBER 2021: **NEMLC Recommendation:** The NEMLC accepted the proposed recommendation. It was furthermore noted that the global market is shifting from LPV/r to other protease inhibitors (i.e. DRV/r and ATV/r) and competition will likely push down the price of other protease inhibitors.					
Monitoring and evaluation considerations					

[11] NDoH evidence summary. ATV/r vs LPV/r_2 nd line adult HIV therapy_ AdultReview_18 November 2021

Darunavir/ritonavir: *not added to the STG, but proposed for inclusion in therapeutic interchange database for patients not on TB-rifampicin therapy*

A summary of the recommendation from the evidence review is included below. The complete evidence summary[12] may be found at the end of this document or alternatively accessed on the NHI webpage.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			
Recommendation: The Committee suggests that DRV/r not be used in preference to LPV/r. *Rationale:* Despite DRV/r-containing ART regimens being associated with higher viral suppression rates and being better tolerated than LPV/r, at the current cost it is considered unaffordable, and there are concerns regarding the supply. It would also not be suitable for the minority of patients on a PI-based regimen who require rifampicin-based tuberculosis treatment. DRV/r is recommended for inclusion on the therapeutic interchange database as an alternative to LPV/r and ATV/r, for patients not on TB-rifampicin therapy. **Level of Evidence:** Moderate certainty of evidence **Review indicators:** Reduction in DRV/r price					
NEMLC MEETING 29 JULY 2021: The NEMLC accepted the proposed recommendation made by the PHC/Adult Hospital Level Committee above.					
Monitoring and evaluation considerations					
Research priorities					

The STG has been aligned to the national HIV program guideline as tabulated below:

CLIENTS WITH DTG RESISTANCE	
Any DTG resistance shown on genotype authorised by HIV expert	Discuss case with an HIV expert*. The regimen will be determined by an Expert Committee based on the pattern of resistant mutations and the prior history of antiretroviral exposure. Application for 3rd line using the standard motivation form may be required (available from TLART@health.gov.za or from https://www.righttocare.org/)

Resistance testing: *emphasised*

The PHC/Adult Hospital Level Committee raised concerns regarding the emergence of DTG resistance in 4 NADIA participants, especially as DTG is used in second-line antiretroviral therapy in South Africa. Therefore, the statement in the STG, prompting consideration of resistance testing for patients failing DTG-containing antiretroviral therapy, was emphasised.

The therapeutic interchange database update as follows:

Indication	Medicine (INN)	Daily dosing	Therapeutic class	Therapeutic ATC
Adult 2nd line HIV management (patients not on rifampicin TB therapy)	Darunavir and ritonavir	800/100 mg	Protease inhibitors for HIV (combinations)	J05AR
	Lopinavir and ritonavir	800/200 mg	Protease inhibitors for HIV (combinations)	J05AR

Rifampicin-based TB treatment (on DTG-regimen)

DTG: *added*

STG text was amended to align with the previously reviewed addendum to the DTG review (see details above):

If on DTG: DTG needs to be given at a dose of 50 mg 12-hourly (add DTG 50mg)

The STG has been aligned to the national HIV program guideline as tabulated below:

RIFAMPICIN-BASED TB TREATMENT	
Rifampicin-based TB treatment	If on DTG: Add DTG 50 mg 12 hours after TLD dose. If on ATV/r: Switch ATV/r to LPV/r 800/200 mg 12 hourly (i.e. double dose). **Note:** There is an increased risk of ALT/AST elevations and gastrointestinal disorders. LPV/r dose should be gradually titrated upward over 1-2 weeks. The LPV/r can be switched back to ATV/r two weeks after completion of TB therapy.

[12] NDoH evidence summary. DRV/r vs LPV/r as 2nd line adult HIV therapy_PHC-AdultsMedicineReview_27 July 2021.

Currently available FDC preparations on contract

ATV/r: *added*

ABC + 3TC + DTG: *added*

STG text was updated to reflect currently available fixed-dose combination ARVs that are accessible on the current public sector tender.[13]

Re-Initiating ART in patients who have interrupted treatment

Previous EML guidance as tabulated below has been removed and replaced with Figure 11.1 Algorithm of a patient who returns to care after interrupting treatment, as adapted from the NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates.

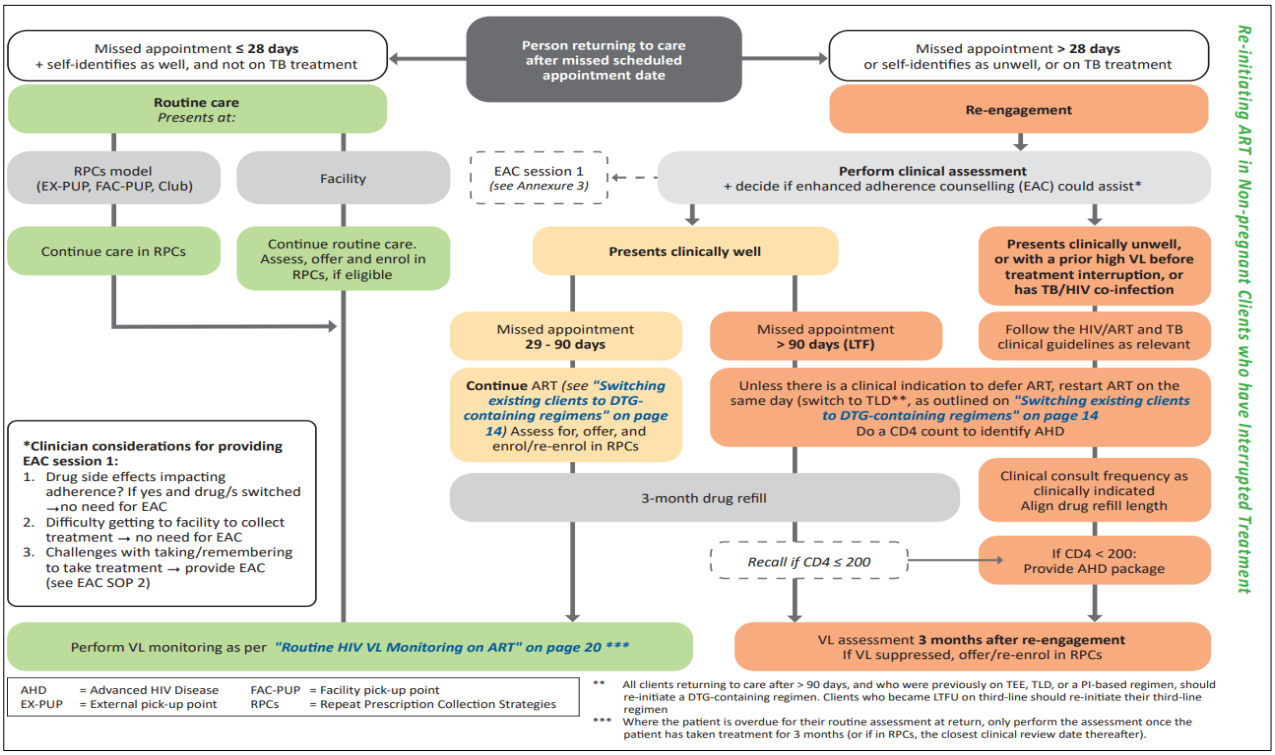
AMENDED FROM:

» Do VL, recommence ART regimen unless there is a clinical indication to defer ART, repeat VL at 3 months. . Recommence previous regimen (unless patient would qualify for a switch to TLD anyway as per above, in which case start dolutegravir-based regimen, e.g. TLD).

» If VL does not to decrease to <1000 copies/mL at 3 months, manage as per virological failure above.

AMENDED TO:

Management algorithm of a patient who returns to care after interrupting treatment. Incorporated from the NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. (*Refer to the EML Section 11.1 Antiretroviral therapy, adults and adolescents (10-19 years old*).



MONITORING ON ART

CrAg Screening

CrAg screening - threshold*: Amended*

The CD4 threshold for screening for Cryptococcal Antigen (CrAg) in PLHIV was amended to CD4<200 cells/mm^3. Current WHO guidelines states: "Screening for cryptococcal antigen followed by pre-emptive antifungal therapy among cryptococcal antigen–positive people to prevent the development of invasive cryptococcal disease are recommended before initiating or reinitiating ART for PLHIV who have a CD4 count <100 cells/mm^3 (*strong recommendation, moderate certainty evidence*).[14] This may be considered at a higher CD4 threshold of <200 cells/mm^3 (conditional recommendation,

[13] Contract circular HP13-2022ARV http://www.health.gov.za/

[14] WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021.

moderate certainty evidence)." The cost per disability-adjusted life year saved was estimated as $21 (95% CI, $15-$32) for CrAg screening of PLHIV at CD4<100 cells/mm^3 with pre-emptive fluconazole treatment.[15] Ford et al.'s systematic review showed that Africa had the highest prevalence of CD4<100 cells/mm^3 and the authors suggest that "consideration should be given to screening at a higher CD4 count of ≤200 cells/mm^3 in settings where there are sufficient resources to implement such an approach, or where a simplified package of care for advanced disease is required based on a unified CD4 threshold."[16] The South African HIV Clinician Society Guideline[17] recommends reflex monitoring of CrAg at a CD4 ≤200 cells/mm^3. A NHLS technical report based on a period where the CD4 threshold for CrAg testing was temporarily increased from 100 to 200 cells/mm^3 found that there was an increase of 36% in detected cryptococcal antigenaemia, with a prevalence of 2.6% in the 100-200 cell/mm^3 range which exceeded the previously-determined 0.6% threshold cut-off for cost-effectiveness. Following engagement with both the NHLS and the National HIV program guideline team, the NEMLC recommends that a threshold of CD4 ≤200 cells/mm^3 be applied, in view of the clinical value, and given that state facilities currently offer reflex CrAg testing at less than 100 cells/mm^3. The STG has been amended as tabulated below:

MONITORING ON ART

Baseline evaluation

» WHO staging.

» Check CD4 count.

» CD4 <200 cells/mm^3:
Check cryptococcal antigen (If positive, perform LP regardless of whether symptoms are present or not). Reflex CrAg testing is done on the CD4 sample if CD4 <100 cells/mm^3. If patient's CD4 is 100-199, a serum CrAg test must be ordered separately.

Sputum screening

Sputum screen for TB: *amended*

As part of the baseline evaluation of all patients on ART, the EML has been amended to include sputum TB-NAAT screening in all patients who can produce sputum. The terminology has also been updated to the general term "TB-NAAT" to reflect a broadening of the diagnostic assays beyond the GeneXpert platform. The amendments have been aligned to the updated National ART guidelines[18] and are as tabulated below:

Amended from:

» Screen for TB using the WHO screening questionnaire (any one of cough, fever, night sweats, or weight loss). If positive, investigate for TB with a sputum Xpert MTB/RIF Ultra ®. Also do urine LAM if severely ill or CD4 ≤100 cells/mm^3

» In pregnancy do sputum XpertMTB/RIF Ultra® in all.

Amended to:

» Sputum TB-NAAT* in all who can produce sputum, regardless of symptoms.
*TB-NAAT: TB Nucleic Acid Amplification Tests (e.g. GeneXpert Ultra MTB/RIF)

Viral load monitoring

HIV viral load monitoring schedule: *amended*

The HIV viral load monitoring schedule as illustrated in the national ART guideline has also been incorporated in the EML as tabulated below:

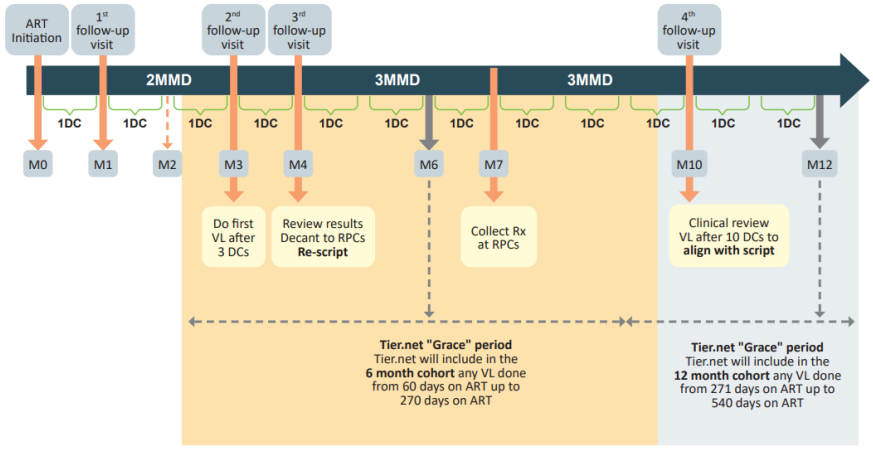
[15] Meya DB, Manabe YC, Castelnuovo B, Cook BA, Elbireer AM, Kambugu A, Kamya MR, Bohjanen PR, Boulware DR. Cost-effectiveness of serum cryptococcal antigen screening to prevent deaths among HIV-infected persons with a CD4+ cell count < or = 100 cells/microL who start HIV therapy in resource-limited settings. Clin Infect Dis. 2010 Aug 15;51(4):448-55.

[16] Ford N, Shubber Z, Jarvis JN, Chiller T, Greene G, Migone C, Vitoria M, Doherty M, Meintjes G. CD4 Cell Count Threshold for Cryptococcal Antigen Screening of HIV-Infected Individuals: A Systematic Review and Meta-analysis. Clin Infect Dis. 2018 Mar 4;66(suppl_2):S152-S159.

[17] Nel J, Meintjies G, Osih R et al. Southern African HIV Clinicians Society guidelines for antiretroviral therapy in adults: 2023 update. https://sahivsoc.org/Files/crypto%20guidelines.pdf

[18] NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates.

Routine VL monitoring	Intervention	Comments
First VL after ART initiation	Do 1st VL after **3 dispensing cycles**	• Allows for earlier detection of factors influencing viral suppression • Allows for earlier decanting for suppressed clients to minimise visits and promote continued engagement in care • This VL will form part of the **6 month VL completion cohort** in Tier.net
Second routine VL after ART initiation (in clients who remain virally suppressed)	This VL can be done from **10 dispensing cycles** but should be aligned with the clients scripting cycle	• This VL will form part of the **12 month VL completion cohort** in Tier.net
Third routine VL after ART initiation (in clients who remain virally suppressed)	This VL can be done **from 22 dispensing cycles**, but should be aligned with the clients scripting cycle	• This VL will form part of the 24 month **VL completion cohort** in Tier.net
Fourth and all subsequent VLs	VLs will be taken at intervals of 12 dispensing cycles for all clients who remain virally suppressed	
The timing of dispensing cycles, follow-up visits, and VL monitoring is illustrated in the diagram below		



- For the 1st VL taken after 3 dispensing cycles, clients should be requested to return to the facility one DC later to review results and so that the client can be assessed for RPCs eligibility.
- For all subsequent VL monitoring (and other routine monitoring investigation) in clinically well clients: Clients should be rescripted at the same visit that their VL is taken. Clients should not be required to come back to the facility the following month for VL result review prior to rescript. Rather, recall to the facility only those clients with an elevated VL or other abnormal result.
- Facilities should ensure that results management processes are in place to ensure that results are reviewed by a clinician, that abnormal results are identified, and the client is appropriately actioned. The NHLS Results for Action (RfA) reports are a useful tool to facilitate the review of results.

! Breastfeeding women should have their VL monitored every 6 months starting from the time of delivery

ART: DOSING AND IMPORTANT ADVERSE EFFECTS

Lamivudine (3TC) – renal adjusted dose : *Amended*

The eGFR range was amended from 10-50mL/min to eGFR 10-30mL/min for which a dose of lamivudine 150mg daily is recommended. No changes were made for eGFR <10mL/min for which a dose of 50mg daily is recommended.

AMENDED FROM:

CrCl 10-50 mL/min:
150 mg daily
CrCl <10 mL/min:
50 mg daily

AMENDED TO:

eGFR 10-30 mL/min:
150 mg daily
eGFR <10 mL/min:
50 mg daily

Emtricitabine (FTC) – renal adjusted dose: *Amended*

As emtricitabine is only available in a fixed dose combination with TDF or TAF, dose adjustments in renal impairment would need to be guided by all components of the FDC formulation. TDF is contraindicated in patients with eGFR<50mL/min so these patients should be managed with a TAF-containing FDC. Amendments to the dosing guidance below is informed by the expert opinion based on pragmatic considerations of formulations available locally.

AMENDED FROM:	AMENDED TO:
eGFR 30-50 mL/min: 200 mg every 2 days eGFR 15-29 mL/min: 200 mg every 3 days eGFR <15 mL/min: 200 mg every 4 days	eGFR 15-29 mL/min: 200 mg every 3 days eGFR <15 mL/min: 200 mg every 4 days Note: FTC is not available as a single-ingredient formulation.

Tenofovir, abacavir, lamivudine, emtricitabine, oral: *amended - very low risk, "Hyperlactataemia/ steatohepatitis" deleted*
Dolutegravir, oral: *amended - weight-gain deleted*
Dolutegravir, oral – serum creatinine: *Guidance clarified*
Nevirapine, oral: *adverse effects and dosing information deleted*
Raltegravir, oral: *adverse effects and dosing information deleted*
Tenofovir alafenamide (TAF), oral: *added*

Dolutegravir (weight gain):
Refer to the NEMLC recommendation below for the use of dolutegravir (DTG) in pregnancy. *"Dolutegravir (especially when combined with tenofovir alafenamide) is associated with more weight gain during pregnancy than efavirenz, but the difference is unlikely to be clinically relevant".* A copy of the complete review on the use of DTG in pregnancy[19], may be found at the end of this report, or alternatively on the NHI webpage.

PHC/ADULT HOSPITAL LEVEL COMMITTEE AND NEMLC RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
					X
Recommendation: The PHC/Adult Hospital Level Committee recommends that dolutegravir should be part of the preferred first line ART regimen for all adults and adolescents living with HIV, including pregnant women and women of child-bearing potential. The existing contra-indication in pregnancy should be removed from the STG.					
Rationale: The estimated risk of neural tube defects in infants exposed to dolutegravir in early pregnancy that was first identified in the Tsepamo observational study in Botswana has diminished over time, with the accumulation of further data. The risk difference between dolutegravir and efavirenz is no longer significant. Dolutegravir (especially when combined with tenofovir alafenamide) is associated with more weight gain during pregnancy than efavirenz, but the difference is of uncertain clinical relevance. Randomised controlled trials have shown non-inferiority in terms of maternal viral suppression rates at 48 weeks. Dolutegravir causes more rapid viral suppression than efavirenz, resulting in increased viral suppression rates by time of delivery in randomised controlled trials of ART initiation in the second and third trimester of pregnancy. This has not yet translated into a demonstrable difference in mother-to-child transmission risk, but event rates are very low with both regimens. A standardised regimen for all adults and adolescents living with HIV is likely to be easier to provide. Based on those findings and observations, the PHC/Adult Hospital Level Committee feel that the potential long-term benefits to pregnant women and WOCP, as well as potential short-term benefits to their infants, outweigh the risks. **Level of Evidence: Moderate certainty of evidence** **Review indicator: New evidence of harms** *(Refer to appendix 2 for the evidence to decision framework)*					
NEMLC MEETING OF 24 JUNE 2021: **NEMLC Recommendation:** The NEMLC accepted the recommendation as proposed by the PHC/Adult Hospital Level Committee, which would support the universal test-and-treat (UTT) strategy of the National HIV Programme. It was also duly noted that the South African Health Products Regulatory Authority were currently reviewing the label of dolutegravir products registered on the South African market.					
Monitoring and evaluation considerations					
Research priorities					

Dolutegravir (serum creatinine):
An increase in serum creatinine is noted as an important adverse effect. The STG guidance has been clarified to indicate that an increase in serum creatinine of less than 30mmol/L is clinically insignificant[20]. Serum creatinine increases greater than 30mmol/L may warrant further workup.

Nevirapine, oral: The Information on the dosing and adverse effects of nevirapine was removed as long-term use of nevirapine has been removed from the national ART Guideline.

[19] NDoH evidence summary. DTG in pregnancy_PHC-Adults Medicine review_17June2021_v2
[20] Mpofu R, Kawuma AN, Wasmann RE, et al. Determinants of early change in serum creatinine after initiation of dolutegravir-based antiretroviral therapy in South Africa. *Br J Clin Pharmacol*. 2024; 90(5): 1247-1257. doi:10.1111/bcp.16009

Raltegravir, oral: Dosing and adverse effects information was deleted, as raltegravir has been removed from the 3rd line National ARV protocols.

Tenofovir alafenamide (TAF), oral: Adverse effects including acute kidney injury, Fanconi syndrome, reduced bone mineral density added.

ART INTERACTIONS

Drug interactions with rifampicin and recommendations for administration

Rifabutin, oral: *not added*

Rifabutin, oral was not added as an essential medicine for primary level of care, as the medicine which has a sole supplier with intermittent supply constraints, and is already included on the Adult Hospital Level EML. However, a cross-reference to the respective Adult Hospital STG was added, as follows:

Patients on atazanavir or darunavir, or if double dose LPV/r is not tolerated, replace rifampicin with rifabutin (doctor prescribed) – see Adult Hospital Level STGs and EML. section 10.1: Antiretroviral therapy.

Drug Interactions with dolutegravir

Metformin: *Guidance amended*

Updates to the interaction between metformin and DTG were made in the STG (*Version 2.1*) in response to communication received by NELMC, from investigators who conducted a local South African cross-sectional study in 15 obese diabetic patients taking DTG 50mg daily and metformin 1000mg daily.[21] Findings from this pharmacokinetic study identified that metformin concentrations were half those seen in the healthy volunteer study by Song et al[22]. This raised concern that limiting metformin daily dosing to 1000 mg may result in sub-therapeutic concentrations and ineffective treatment in obese patients living with HIV and on concomitant DTG.

A brief literature search was undertaken to identify if there were any recent safety concerns with metformin - a summary of the findings is tabulated below:

Metformin safety Metformin is an old medicine for which we have extensive clinical and published outcome experience. Metformin is generally well-tolerated, and the dose can be titrated to a maximum of 2 550 mg daily[23] with the standard release formulation. It is worth noting that while metformin is a well-established therapy, a clear definition of its 'therapeutic concentration is lacking. In fact, a systematic review of therapeutic monitoring of metformin reported 65 different recommendations for therapeutic plasma concentrations or ranges with little consensus. Therapeutic monitoring of metformin concentrations was not included in the large longitudinal studies of metformin efficacy, and incidence of adverse events, and of lactic acidosis in particular, was not specified as an endpoint.[24,25] Lactic acidosis While lactic acidosis is noted as a caution in the product information[26], it has not translated into a significant concern in clinical practice. A Cochrane review, which pooled data from 347 comparative studies involving 96 295 participants followed for 125 941 patient years,[27] did not identify a single case of lactic acidosis in 70 490 metformin patient-years or among 55 451 non-metformin patient-years. The upper limit of the 95% confidence interval (95% CI) for their estimate of incidence of lactic acidosis per 100 000 patient-years was 4.3 cases in the metformin group and 5.4 cases in the non-metformin group. The Cochrane reviewers thus concluded that there is no evidence that metformin is associated with an increased risk of lactic acidosis compared with other anti-hyperglycaemic therapies.

[21] Roland van Rensburg,1 Tracy Kellermann,1 Veshni Pillay-Fuentes Lorente,1 Christiena du Plessis,1 Catherine Orrell,2 Innocent Maposa,3 Gert van Zyl,4 Giovanni Schifitto,5 Eric Decloedt1. Reduced Metformin Concentrations in Obese Women with HIV Treated with Dolutegravir (pre-publication article shared with NEMLC)

[22] Song IH, Zong J, Borland J, Jerva F, Wynne B, Zamek-Gliszczynski MJ, Humphreys JE, Bowers GD, Choukour M. The Effect of Dolutegravir on the Pharmacokinetics of Metformin in Healthy Subjects. J Acquir Immune Defic Syndr. 2016 Aug 1;72(4):400-7. doi: 10.1097/QAI.0000000000000983. PMID: 26974526; PMCID: PMC4935531.

[23] Product Information. Glucophage. Merck (Pty) Ltd. Last renewed 4 Nov 2021. Accessed online https://pi-pil-repository.sahpra.org.za/wp-content/uploads/2023/08/Glucophage-PI-approved-04.11.2021.pdf 14 Nov 2024

[24] Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):854-65. Erratum in: Lancet 1998 Nov 7;352(9139):1558. PMID: 9742977.

[25] Ekström N, Schiöler L, Svensson AM, Eeg-Olofsson K, Miao Jonasson J, Zethelius B, Cederholm J, Eliasson B, Gudbjörnsdottir S. Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. BMJ Open. 2012 Jul 13;2(4):e001076. doi: 10.1136/bmjopen-2012-001076. PMID: 22798258; PMCID: PMC3400073.

[26] Package Insert. Glucophage. Merck (Pty) Ltd. Date of first authorisation: 4 Nov 2021. Accessed online https://pi-pil-repository.sahpra.org.za/wp-content/uploads/2023/08/Glucophage-PI-approved-04.11.2021.pdf

[27] Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev 2010; 4: CD002967.

Cases of lactic acidosis in patients on metformin reported to the French pharmacovigilance centre were described in a case series. The metformin daily dose in these patients was high (mean daily dose >2.5 g), and more than 97% of patients in whom creatinine was reported, had renal impairment.")[28].

In view of the limited data on the clinical implications of the interaction between DTG and metformin and the high local prevalence of PLHIV with comorbid diabetes, many of whom are overweight or obese, a pragmatic approach to managing the potential interaction between metformin and DTG is warranted and the updated STG guidance is as tabulated below:

AMENDED FROM *(Version 2.0)*

DRUG INTERACTIONS WITH DOLUTEGRAVIR

Interacting medicine	Effect of co-administration	Recommendation
Metformin	Significant increase in metformin levels	Administer metformin to a maximum of 500 mg 12 hourly.
Rifampicin	Significant reduction in concentration of DTG	Double DTG dose to 50 mg 12 hourly.

AMENDED TO *(Version 2.1)*

DRUG INTERACTIONS WITH DOLUTEGRAVIR

Interacting medicine	Effect of co-administration	Recommendation
Metformin	May increase metformin concentration	*Metformin initiation:* Initiate metformin at a low dose (500-1000mg total daily dose), titrating up as needed. Do not exceed 2 g daily *DTG initiation:* If patient stabilised on metformin dose ≤ 2g daily, retain metformin dose and monitor for side effects. If patient stabilised on >2g daily, reduce dose of metformin to ≤2g daily and monitor. *Patients with renal impairment:* Close monitoring of renal function required. Do not co-prescribe if eGFR <30mL/min.
Rifampicin	Significant reduction in concentration of DTG	Double DTG dose to 50 mg 12 hourly.

Drug Interactions with boosted PIs

Rifampicin: *Guidance amended*

Dosing guidance for the use of double dose LPV/r added to the STG as tabulated below:

DRUG INTERACTIONS WITH BOOSTED PIs:

Interacting medicine	Effect of co-administration	Recommendation
Rifampicin	Significant reduction in PI concentration	Double LPV/r dose. **Note:** There is an increased risk of ALT/AST elevations and gastrointestinal disorders. LPV/r dose should be gradually titrated upward over 1-2 weeks (e.g. 600/150 mg and then 800/200 mg). Adjusted dose of LPV/r should be continued for 2 weeks after rifampicin is stopped. The LPV/r can be switched back to ATV/r two weeks after completion of TB therapy. If ATV/r or DVR/r is required, rifampicin must be replaced with dose-adjusted rifabutin (doctor prescribed) - see AH STG Section 10.1: Antiretroviral therapy.

REFERRAL

Reference to second line ART regimens has been removed from the STG.

Amended from:

Referral

Second-line ART regimen failures

Amended to:

Referral

Dolutegravir resistance demonstrated on resistance testing.

[28] Boucaud-Maitre D, Ropers J, Porokhov B, Altman JJ, Bouhanick B, Doucet J, Girardin E, Kaloustian E, Lassmann Vague V, Emmerich J. Lactic acidosis: relationship between metformin levels, lactate concentration and mortality. Diabet Med. 2016 Nov;33(11):1536-1543. doi: 10.1111/dme.13098. Epub 2016 Mar 6. PMID: 26882092.

11.2 OPPORTUNISTIC INFECTIONS, PROPHYLAXIS IN ADULTS

11.2.1 COTRIMOXAZOLE PROPHYLAXIS

Indications for primary prophylaxis: *WHO clinical stage II deleted*

The indications for primary prophylaxis against opportunistic infections with cotrimoxazole was amended to include WHO clinical stage III or IV i.e. WHO clinical stage II was removed from the STG. The STG has been aligned with the most recent WHO guidance[29] which has been amended from WHO stage II, III or IV in 2000[30] to stage III or IV only. Furthermore, as South Africa's CD4 threshold to stop cotrimoxazole prophylaxis has historically been lower than WHO's threshold (200 vs 350 cells/mm^3), the clinical stage thresholds are now better aligned with the CD4 count thresholds (a CD4 threshold of <200 cells/mm^3 correlates better with a clinical stage III or IV than with stage II).

11.2.2 TUBERCULOSIS PREVENTIVE THERAPY (TPT)

Adult PLHIV initiated on ARVs

TB preventive therapy: *added as a therapeutic group*

Isoniazid (12H): *retained as an example of class in the STG*

Rifapentine + isoniazid (3HP): *added as a therapeutic alternative in the therapeutic interchange database*

During the previous review cycles, the NEMLC approved 12 months of daily isoniazid (12H) for PLHIV and not 3HP. Non-inferiority trials suggested that 3HP prophylaxis was not inferior to 12H in PLHIV. However, 3HP is more expensive than 12H. Refer to the previous NEMLC-approved reviews for rifapentine in PLHIV (14 November 2019)[31] and rifapentine in PLHIV on DTG-containing antiretroviral therapy (11 November 2019)[32] which is accessible on the NHI webpage. However, as there is currently no available RCT evidence for concomitant use of rifapentine with viraemic patients on DTG, the following text was added to the STG:

Adults and adolescents initiating a DTG-containing ART regimen:

- Isoniazid daily for 12 months is the preferred regimen.

For patients who are already virally suppressed on a DTG-based regimen:

- A weekly combination of isoniazid (900mg if weight >30 kg) plus rifapentine (900mg if weight >30 kg) for three months may be used.
  - Do not use rifapentine-containing TPT in patients on protease inhibitor-based ART, or in women on hormonal contraceptives. [*See the therapeutic interchange database for details regarding the rifapentine-containing TPT regimen*].
  - Educate patients on the symptoms of hepatotoxicity (nausea, vomiting, yellow eyes, brown urine, and pain in right upper quadrant) associated with TPT.

ADD

- Pyridoxine, oral, 25 mg once daily for the full duration of the TPT regimen.
  - Instruct patient to present early if any of these symptoms arise.
  - Follow patients up monthly for the first 3 months.

[29] https://www.ncbi.nlm.nih.gov/books/NBK298965/#:~:text=Co%2Dtrimoxazole%20prophylaxis%20is%20recommended,≤350%20cells%2Fmm3.]

[30] Provisional WHO/UNAIDS secretariat recommendations on the use of cotrimoxazole prophylaxis in adults and children living with HIV/AIDS in Africa. Report 29/03/2000. Geneva: World Health Organization, 2000]

[31] NDoH Evidence Summary. NDoH_EDP_Rifapentine_Adults Review Update_14November2019_v1.0

[32] NDoH Evidence Summary. NDoH_EML_Rifapentine_&_Dolutegravir_ TPT_AdultsReview_v1

Rifapentine (3HP) as TPT in PLHIV 14 Nov 2019

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	[X]	[ ]	[ ]	[ ]	[ ]

Recommendation: Based on this evidence review, The Adult Hospital Level Committee recommended that a rifapentine-isoniazid regimen probably has similar efficacy and safety to the current INH recommendation and could be considered as an alternative TLTBI option in PLHIV on an efavirenz or raltegravir based ART regimen. Given the non-inferiority in efficacy and slightly improved safety profile, cost would need to be comparable to the current recommendation of 12H.

Rationale: Current evidence does not show superior efficacy of short course HP to 6-12H.
HP showed decreased adverse events when compared to 6-9H, the adverse event rates reported for INH in these populations are not consistent with the adverse event rates reported from other South African studies. The improved completion rates are already factored into the efficacy results for HP owing to MITT analysis, the improved rates shown did not translate into superior efficacy of HP over 6-9H.

Level of Evidence: I RCTs (moderate quality).

Review indicator: *Reduction in price*

Evidence of efficacy	Evidence of harm	Price reduction
x	x	X

VEN status:

Vital	Essential	Necessary

NEMLC MEETING OF 5 DECEMBER 2019

NEMLC accepted the proposal as reccomended by the Adult Hospital Level Committee, above. Until there is a reduction in price of rifapentine resulted in price parity between treatment regimens 12H and 3HP, rifapentine is considered unaffordable to include on the EML.

Monitoring and evaluation considerations:

- Completion rate in programmatic setting as a process indicator.
- Drug-drug interactions.
- TB incidence in PLHIV

Research priorities

- Results of ongoing trial looking at safety with dolutegravir.
- Durability of protective effect in high tuberculosis areas.
- Efficacy in persons on ART testing negative for LTBI.

Rifapentine in PLHIV on DTG-containing antiretroviral therapy

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	[X]	[ ]	[ ]	[ ]	[ ]

Recommendation: Based on this evidence review, the Adult Hospital Level Committee concludes that in patients with suppressed viral load on DTG, 3HP could be considered as an alternative TLTBI option in PLHIV that are virally suppressed on a DTG-containing regimen. Given the non-inferiority in efficacy and slightly improved safety profile, cost would need to be comparable to the current recommendation of 12H.

Rationale: Preliminary data, suggests that rifapentine has no impact on patients who are already virally suppressed. Co-administration of DTG and HP was well tolerated with no HP-related adverse effects of ≥ grade 3. Although HP decreased DTG bioavailability, which was associated with a modest decrease in trough levels, all trough levels but one were above the DTG IC90. All viral loads were suppressed and DTG can be co-administered with HP without dose-adjustment.

Level of Evidence: III Phase I/II study

Review indicator: *Reduction in price; evidence of efficacy and safety*

Evidence of efficacy	Evidence of harm	Price reduction
x	x	X

VEN status:

Vital	Essential	Necessary

NEMLC MEETING OF 5 DECEMBER 2019

NEMLC accepted the proposal as reccomended by the Adult Hospital Level Committee, above. Until there is a reduction in price of rifapentine resulted in price parity between treatment regimens 12H and 3HP, rifapentine is considered unaffordable to include on the EML.

Monitoring and evaluation considerations:

Therapeutic Interchange

3HP was recommended for inclusion to the therapeutic interchange database:

- 12H: Isoniazid, oral, 300 mg daily for 12 months
- 3HP: Isoniazid, oral 900 mg + Rifapentine, oral 900 mg weekly for 3 months (preferably as a FDC).

NEMLC MEETING OF 23 JUNE 2022:

NEMLC recommended that 3HP be included as a therapeutic alternative to 12H in PLHIV initiated on ART – however, for DTG-containing regimens patients to be virally suppressed (this would promote competitive pricing).

The therapeutic interchange database update as follows:

Indication	Criteria	Medicine (INN)	Treatment course	Therapeutic class	Therapeutic ATC
TPT for ART-naïve HIV adult patients	n/a	Isoniazid	300 mg daily x 12 months	TPT	J04A
	• Initiated on TEE • Initiated on TLD BUT virally suppressed • NOT on a PI • Not on oral hormonal contraceptives	Isoniazid and rifapentine (FDC)	900/900 mg weekly x 3 months	TPT	J04A

FDC=fixed dose combination; TEE= TDF+EFV+FTC; TLD= TDF+3TC+DTG; TPT=TB preventive therapy; PI=protease inhibitor

In pregnant women, starting ART:

TPT in pregnant women: *Guidance amended*

The STG guidance on the use of TPT in pregnant women has been amended as tabulated below:

AMENDED FROM:

➢ In pregnant women, starting ART:

If CD4 >350 cells/mm³.	If CD4 ≤350 cells/mm³.
Defer TPT until after delivery.	Exclude active TB with symptom screen and TB-NAAT, then give TPT.

AMENDED TO:

NOTE: For pregnant women::

➢ Defer TPT until after delivery

➢ Ensure that routine screening against TB is conducted at each antenatal visit.

Refer to the NDoH evidence summary Isoniazid Preventive Therapy in Pregnancy[33] for further details. A copy of the full review may be found at the end of this report or alternatively, accessed on the NHI webpage.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

ERC Recommendation 9 November 2023: We recommend that pregnant women living with HIV, with:

- CD_4 counts ≤ 350 cells/mm^3 and starting ART, receive 12 months of IPT after exclusion of active tuberculosis disease.
- CD_4 counts > 350 cells/mm^3 and starting ART, IPT should be deferred to the post-partum period.

Rationale: The benefit of IPT in preventing tuberculosis disease at CD4 counts ≤ 350 cells/m^3(low certainty evidence) outweighs the increased risk of adverse pregnancy outcomes. However, in pregnant women with higher CD_4 counts, the increased risk of miscarriage after first trimester IPT exposure (low certainty evidence) and increased risk of low birth weight and underweight for age after second trimester IPT exposure (moderate certainty evidence) outweighs any potential benefit (moderate certainty evidence).

Level of Evidence:
Risk of adverse pregnancy outcomes after first trimester exposure (low certainty evidence from observational studies and cohort studies nested in randomised controlled trials)
Risk of adverse pregnancy outcomes after second trimester exposure (moderate certainty evidence from a randomized controlled trial)
Evidence of benefit at CD_4 ≤ 350 cells/mm^3 (low certainty evidence from an observational study)
Review indicator: New high quality evidence of benefit or harm.

Multi stakeholder engagement meeting recommendation- 7 March 2024:
The consensus recommendation from a multi stakeholder engagement meeting, which included representatives from the NEMLC, NDOH TB and maternal healthcare programs and South African Medical Research Council (SAMRC) with reference to local feasibility considerations, is as follows:

- Initiation of IPT should be deferred in all pregnant patients until after delivery
- In the absence of IPT initiation, the importance of ART and continued active screening for TB throughout pregnancy must be emphasized.

Rationale: While the evidence in support of the ERC recommendation dated 9 November 2023 above was not in dispute, concern was expressed with the complexity of multiple guidance for pregnant women at various CD4 counts initiating ART and for pregnant women already established on ART. The consensus recommendation from the multi stakeholder group was therefore for a less complex recommendation to avoid IPT in pregnancy in all pregnant women, regardless of HIV status or CD4 count. It was noted at the meeting that screening for TB as part of routine antenatal care is already included in programmatic guidance, to identify pregnant women with tuberculosis disease timeously and initiate appropriate antituberculosis treatment.

NEMLC RECOMMENDATION (MEETING OF 14 March 2024): NEMLC supported the multi stakeholder recommendation that IPT be avoided during pregnancy.

Monitoring and evaluation considerations, and research priorities:
Pregnant women should be routinely screened for TB at every antenatal visit.
Strenthening of pharmacovigilance systems, with implementaiton of measures for identifying signals of drug-related harm in pregnant women.

11.3.3 CANDIASIS, OESOPHAGEAL

Medicine treatment - fluconazole*: guidance amended*

Guidance on the initiation of ART has been removed to align with amendments in Section 11.1 above.

MEDICINE TREATMENT

- Fluconazole, oral, 200 mg daily for 14 days.

~~Commence ART within 7 days (unless patient has cryptococcal or TB meningitis). See section: 11.1 Antiretroviral therapy, adults~~

11.3.4 CRYPTOCOCCOSIS

CrAg screening*: amended to clarify that guidance applicable to adults and adolescents*

CrAg screening*: CD4 threshold amended*

[33] NdoH Evidence Summary. Evidence review: IPT in pregnancy_v1.2_15 April 2024_final approved

Fluconazole oral: *dose for children added*

The following statements as tabulated below were amended to clarify that the STG guidance is applicable to both adults and adolescents. Dosing guidance for the use of fluconazole in children has been added. Updates to the CD4 threshold for CrAg screening have been included in line with Section 11.1 above. The guidance not to delay the initiation of ART in asymptomatic cryptococcosis has also been aligned to Section 11.1 as detailed above.

INVESTIGATIONS

All ART-naïve adults and adolescents with CD4 < 200 cells/mm^3 should have a serum cryptococcal antigen (CrAg) test done (unless confirmed diagnosis of cryptococcal infection). This is performed as a reflex test on the patient's CD4 sample if it is <100 cells/mm^3. If the CD4 cell count is between 100 and 199, a separate sample should be sent for CrAg testing.

MEDICINE TREATMENT

If CSF CrAg positive:

Refer for liposomal amphotericin B, IV (induction phase) and monitoring of intracranial pressure symptoms - See Adult Hospital STGs and EML, Section 10.2.4: Cryptococcosis.

Patients may be down referred for ~~secondary prophylaxis~~ consolidation and maintenance phase therapy; see below.

If there is any delay in performing LP, start oral fluconazole therapy:

- Adults: Fluconazole, oral, 1200 mg immediately.
- Children: 12mg/kg to a maximum dose of 800mg immediately

Commence ART: See section 10.1: Antiretroviral therapy.

Cryptococcal meningitis: 4–6 weeks after starting antifungal therapy.

Asymptomatic cryptococcosis: ~~After completion of the induction phase i.e. at 2 weeks after starting antifungal therapy~~. No need to delay ART. ART can be started immediately.

Fluconazole, oral: *caution updated*

The fluconazole caution box was updated to align with the amended Adult Hospital Level STG and EML, with the inclusion of the following text:

» Fluconazole is potentially teratogenic when used during the 1st trimester, but pregnant women should be counselled that the benefits of fluconazole likely outweigh the risks in the management of cryptococcosis.

CSF CrAg positive

Flucytosine, oral: *not added*

External comment received regarding flucytosine, oral as induction therapy in this clinical setting was noted. Though, flucytosine, oral is included in the respective Adult Hospital Level STG.

Asymptomatic cryptococcosis

ART initiation: *Amended*

The STG has been amended to align with the national ART guideline as tabulated below:

Amended from:

Asymptomatic cryptococcosis: After completion of the induction phase i.e. at 2 weeks after starting antifungal therapy

Amended to:

Asymptomatic cryptococcosis: No need to delay ART. ART can be started immediately.

Referral

Criteria: *Amended*

The following statement has been amended to clarify that patients should be referred to facilities where there is access to lumbar puncture: *'If LP unavailable: Refer all serum CrAg positive patients ~~for~~ to a facility where LP is available.'*

11.3.5 DIARRHOEA, HIV-ASSOCIATED

Medicine treatment – cotrimoxazole dosing: *Guidance clarified*

Dosing guidance for the management of *Isospora belli* infection has been amended as tabulated below, to clarify that the recommended dose of cotrimoxazole 320/1600mg is equivalent to 4 single strength tablets of the 80/400mg adult tablet formulation and is currently available on tender. This clarification is to avoid any potential confusion with the double strength formulation, cotrimoxazole 160/800mg tablets which is also available locally although not on tender.

AMENDED FROM:

If stool shows *Isospora belli*:

- Cotrimoxazole, oral, 320/1600 mg (4 tablets) 12 hourly for 10 days.
  - Followed by 160/800 mg (2 tablets) daily until CD4 > 200 cells/mm3 on ART.
- Commence ART.

AMENDED TO:

If stool shows *Isospora belli*:

- Cotrimoxazole, oral, 320/1600 mg (4 single strength (80/400 mg) tablets) 12 hourly for 10 days.
  - Followed by 160/800 mg (2 single strength (80/400 mg) tablets) daily until CD4 > 200 cells/mm^3 on ART.
- Commence ART.

11.3.11 HERPES ZOSTER (SHINGLES)

Paracetamol: *dose amended*

The dose of paracetamol has been amended to align with updated guidance in the AH Chp 26 Pain chapter as tabulated below:

Pain:

- Paracetamol, oral, ~~1 g 4–6 hourly when required~~ 500mg-1 g, 4–6 hourly as required (maximum of 4g in 24 hours)
  - Maximum dose: 15 mg/kg/dose.

11.4 HIV AND KIDNEY DISEASE

Routine screening for renal disease: *retained*

An external comment was received regarding annual screening for renal disease, despite use of ARVs that did not include tenofovir. However, HIV was considered a risk factor for chronic kidney disease.[34]

[34] Wyatt CM. Kidney Disease and HIV Infection. Top Antivir Med. 2017 Feb/Mar;25(1):13-16. https://pubmed.ncbi.nlm.nih.gov/28402929/

B. HIV INFECTION IN CHILDREN (<10 YEARS OLD)

Diagnosis in children: *guidance amended*

STG guidance amended to align with the national HIV program guideline as tabulated below:

AMENDED FROM:

WHEN AND HOW TO TEST IN CHILDREN

Which test

Child <18 months of age

HIV PCR test: Always confirm with 2nd HIV PCR test if the first test is positive. Do not delay ART initiation; start ART with the first positive result.

Child ≥ 18 months of age

HIV rapid or ELISA test: If 1st rapid test is positive, confirm the result with:

A HIV PCR test if infant between 18-24 months

A second rapid test using a kit of a different manufacturer, and preferably on a different blood specimen if infant is > 24 months.

HIV rapid tests may be less reliable in children with advanced disease. If clinical findings suggest HIV infection but the rapid test is negative, send a further specimen of blood to the laboratory for HIV ELISA testing. If HIV status is still unclear, do an HIV PCR test.

When to test HIV-exposed children (See section: 11.5 The HIV-exposed infant).

Birth (HIV PCR).

Repeat at 10-week visit (HIV PCR).

Repeat at 6-month visit (HIV PCR)

At any time when clinical signs indicate possible HIV infection.

6 weeks after breastfeeding has stopped.

Do Universal HIV rapid/ELISA test at 18 months (HIV rapid test for ALL children regardless of HIV exposure, except in those who previously tested HIV positive and are on ART).

LoE:IIIb

Also perform PCR testing AT BIRTH on:

Infants born to mothers who were on TB treatment for active TB during their pregnancy.

Infants with congenital pneumonia.

Infants with clinical features suggestive of HIV infection.

High risk infants requiring urgent HIV diagnosis.

If the HIV PCR result is not available at discharge, the mother must return within 1 week for the result.

If the HIV PCR result is negative, repeat at 10 weeks:

- If HIV PCR result at 10–18 weeks, or an age-appropriate test 6 weeks after breastfeeding has stopped, is still negative, perform HIV rapid test at 18 months of age.
- If positive at any time, start infant ART.

Note:

Negative tests do not exclude HIV infection until 10-18 weeks after birth and 6 weeks after exposure to other risk of HIV infection (including breastfeeding).

Discuss children with discordant HIV test results with an expert.

Do not repeat HIV rapid/ELISA tests in children on established ART.

Also perform age-appropriate testing at any time:

Parental request to test the child.

HIV-infected father or sibling.

Death of mother, father or sibling.

Mother's HIV status and her whereabouts are unknown.

Clinical features suggest HIV infection.

Infant has acute severe illness.

Breastfed infant of newly diagnosed HIV-infected breastfeeding mother.

IMCI classification of SUSPECTED SYMPTOMATIC HIV INFECTION or POSSIBLE HIV INFECTION (see below).

TB diagnosis, history of TB treatment or new TB exposure.

Suspicion of sexual assault.

Wet-nursed/breastfed infant fed by a woman of unknown or HIV-infected status (and repeat age-appropriate test 6 weeks later).

Children considered for adoption or fostering.

Newborn child whose mother is of unknown HIV status, has died or is not available due to abandonment or other reasons:

Perform both infant HIV PCR and HIV rapid tests. Initiate PMTCT as for high risk exposure.

Perform age-appropriate HIV testing in an HIV-uninfected child at any other time if clinical symptoms suggest HIV infection.

Clinical indications that HIV infection should be considered in a child are:

If the mother is HIV-infected or if the mother's HIV status is not known.

If the child was HIV PCR-negative but was subsequently breastfed.

If a child has any of the following features:

- Rapid breathing or chest indrawing now ("Pneumonia").
- Persistent diarrhoea now or in the past.

- Ear discharge now or in the past.
- Low weight for age/height or unsatisfactory weight gain.
- ≥ 2 enlarged glands of: neck, axilla or groin.
- Oral thrush.
- Parotid enlargement.

All infants/children accessing care should have their HIV exposure status (recent maternal HIV status) and/or HIV status determined.
Women who previously tested HIV-positive should not be retested.
Where mothers tested negative in pregnancy, maternal HIV status should be determined 3-monthly whilst breastfeeding.

AMENDED TO:

HIV TESTING IN CHILDREN

Age	Test	Note
HIV-exposed		
Birth	HIV PCR	If the HIV PCR is positive at any time, confirm with a second HIV PCR
10 weeks	HIV PCR	
6 months	HIV PCR	
6 weeks post-cessation of breastfeeding	Age appropriate testing: <18 months: HIV PCR ≥18 months: HIV rapid/ELISA	
Universal screening		
18 months	HIV rapid/ELISA	Perform on all children, unless known to be HIV infected
HIV infected confirmatory test (any child with positive HIV test)		
<24 months	HIV PCR	Between 18 and 24 months, the initial test will be HIV rapid/ELISA, but is confirmed with an HIV PCR
≥24 month	HIV rapid/ELISA	Perform the second test on a different blood specimen with a test kit from a different manufacturer
Possible/suspected symptomatic HIV infection		
Any age if IMCI classification of: Pneumonia Ear discharge (ever) Persistent diarrhoea in past 3 months Not growing well, moderate acute malnutrition (MAM) or severe acute malnutrition (SAM). ≥ 2 enlarged glands of: neck, axilla or groin. Oral thrush. Parotid enlargement	Age appropriate testing: <18 months: HIV PCR ≥18 months: HIV rapid/ELISA	
Other situations		
Parents request testing Breastfed infant of a newly diagnosed HIV infected mother Suspicion of sexual assault Wet-nursed/breastfed infant fed by a woman of unknown or HIV-infected status (and repeat age-appropriate test 6 weeks later). Children considered for adoption or fostering	Age appropriate testing: <18 months: HIV PCR ≥18 months: HIV rapid/ELISA	

If an HIV PCR test is indeterminate or discordant, refer to the National Department of Health Guideline for Vertical Transmission Prevention of Communicable Infections, 2023[35].

[35] NDoH. Vertical Transmission Prevention Guideline 2023. Accessible : https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-09/2023%20Vertical%20Transmission%20Prevention%20Guideline%2004092023%20signed%20WEB_1.pdf

Clinical staging of HIV and AIDs for infants and children

WHO clinical staging guidance: *Editorial update*

The hyperlink to the interim *WHO clinical staging of HIV/AIDS case definitions for surveillance (Africa Region)*[36] has been added to the EML. The Committee acknowledged that the WHO clinical staging of HIV and AIDs for infants and children has become less relevant as CD4 counts are readily available. The WHO clinical staging is however still a consideration for cotrimoxazole prophylaxis and has been retained in the EML. Consideration will be given to removing the WHO clinical staging table from the EML in the next review cycle.

11.5 THE HIV-EXPOSED INFANT

Description: *amended editorially*

The description has been amended editorially for improved clarity as tabulated below:

AMENDED FROM:

DESCRIPTION

An infant whose mother is HIV-infected, or in whom HIV infection has not been confirmed or excluded.
Transmission of HIV infection from mother to child may occur during pregnancy, during delivery or via breastfeeding. Transmission of infection from mother to child can be effectively prevented with a very high success rate by means of suppressing the mother's VL and giving ARVs to the infant.
If the mother's VL is not suppressed the risk of breast milk transmission remains significant.

AMENDED TO:

DESCRIPTION

An HIV-exposed infant or child is one born to a mother living with HIV, until HIV infection in the infant or child is reliably excluded and the infant or child is no longer exposed through breastfeeding.

Transmission of HIV infection from mother to child may occur during pregnancy, during delivery or via breastfeeding. Transmission of infection from mother to child can be effectively prevented with a very high success rate by means of suppressing the mother's VL and giving post-exposure prophylaxis to the infant, a strategy now known as Vertical Transmission Prevention (VTP; formerly termed Prevention of Mother to Child Transmission).

The risk of transmission from breast milk is low when the mother is virally suppressed. Ensure maternal VL monitoring is done every 6 months while breastfeeding and offer enhanced adherence counselling to ensure viral suppression is achieved and maintained.

Feeding advice: *aligned to Paediatric EML*

Feeding advice has been aligned to the Paediatric EML as tabulated below:

AMENDED FROM:

Feeding advice

- Exclusive breastfeeding is strongly recommended for the 1st first 6 months, after which the nutritional needs of the child will require the introduction of complementary foods, while breastfeeding continues
- Mothers whose 2nd or 3rd line regimens are failing TLD2 should not breastfeed. However, a sustainable supply of formula must be provided.
- If women are switched from 1st to 2nd line therapy during pregnancy or breastfeeding, consult with a practitioner experienced and knowledgeable of the factors informing the feeding option decision.
- Mothers on effective ART should be encouraged to breastfeed as the advantages of breastfeeding exceed the risks of HIV transmission.
- Use of flash pasteurisation or Pretoria pasteurisation to reduce HIV transmission is supported but may pose significant barriers to successful breast milk feeding due to the effort involved.

AMENDED TO:

Feeding advice

- It is strongly recommended that exclusive breastfeeding be initiated within 1 hour of birth and continued for the first 6 months of life, after which the child's nutritional requirements will require the introduction of complementary foods in addition to breastfeeding.
- Women living with HIV should be fully supported for ART adherence during the breastfeeding period and thereafter.
- Women with a VL > 50 copies/mL on TLD1 should continue breastfeeding while every effort is made to regain viral suppression. Their infants should receive high-risk prophylaxis during breastfeeding.
- The following may be indications to discontinue breastfeeding:
  > Infants of mothers who are failing TLD2.
  > Infants of mothers who are failing third-line PI-based treatment.

[36] https://iris.who.int/bitstream/handle/10665/69058/WHO_HIV_2005.02.pdf

- Discuss appropriate feeding practices with the mother regarding the risks and benefits of continuing breastfeeding vs replacement feeding.
- The use of flash pasteurisation or 'Pretoria' pasteurisation to reduce HIV transmission is supported but may pose significant barriers to successful breast milk feeding due to the effort involved. For instance, it can be used as an interim measure during maternal mastitis.

NOTE: For the above,
- » TLD1 = TLD as a first line ART regimen.
- » TLD2 = TLD in patient who has failed a previous ART regimen.

Terminology – PMTCT: *Amended*

Historical reference to PMTCT (prevention of mother to child transmission), has been replaced throughout the chapter with VTP (vertical transmission prevention) in line with the national clinical guideline[37].

Medicine treatment: *aligned to Paediatric EML*

Guidance on medicine treatment has been aligned to the Paediatric EML as tabulated below:

AMENDED FROM:

Situation	Comment
Low Risk (at birth) • **NVP** at birth and then daily for 6 weeks.	
Mother is on lifelong ART, and VL <1000 copies/ml (most recent VL taken during the last 12 weeks, *prior to delivery*) **or** Maternal VL <1000 copies/ml *at delivery*	» HIV testing* – Do HIV PCR at birth. – Do HIV PCR at 10 weeks. – Do HIV PCR at 6 months. – Do infant HIV testing 6 weeks' post-cessation of breastfeeding (either HIV PCR or ELISA depending on age). » Encourage maternal ART adherence.
High Risk (at birth) • **NVP daily for at least 12 weeks (until maternal VL< 1000 copies/mL) and AZT 12 hourly for 6 weeks.**** ○ (initiate as soon as possible) *LoE:IIIa*	
Mother is on lifelong ART, and VL >1000 copies/ml (most recent VL taken during the last 12 weeks, *prior to delivery*) **or** Maternal VL >1000 copies/ml at delivery. **or** Mother with no VL result in the last 12 weeks. **or** Mother not on ART.	» If new maternal HIV diagnosis, initiate ART (see Section 6.8: HIV in pregnancy). » If mother on ART with elevated VL, encourage ART adherence, and/or switch to second line to suppress maternal VL as a matter of urgency (see Section 6.8: HIV in pregnancy). » HIV testing* – Do infant HIV PCR at birth/ immediately, if infant tests HIV PCR+, do repeat HIV PCR test and initiate ART immediately. – Do HIV PCR at 10 weeks. – Do HIV PCR at 6 months. – Do infant HIV testing 6 weeks post-cessation of breastfeeding (either HIV PCR or rapid test depending on age). » Encourage maternal ART adherence. » If maternal VL ≥ 1000 copies/ml continue infant NVP prophylaxis.
High Risk (during breastfeeding) **NVP daily for at least 12 weeks (until maternal VL<1000 copies/mL) and AZT 12 hourly for 6 weeks.** ○ Initiate as soon as possible.	
Breastfeeding mother newly diagnosed HIV positive > 72 hours after delivery. Mother on ART with latest VL > 1000 copies/ml during breastfeeding.	» If new maternal HIV diagnosis, initiate ART (see Section 6.8: HIV in pregnancy). » If mother on ART with elevated VL, encourage ART adherence, and/or switch to second line to re-suppress maternal VL as a matter of urgency (see Section 6.8: HIV in pregnancy). » Do immediate infant HIV PCR*. » If infant currently breastfeeding, or has breastfed in the last week: provide high-risk infant prophylaxis. » If breastfeeding never started or stopped > 1 week ago: no prophylaxis needed. » Repeat HIV PCR 6 weeks after stopping NVP » Do all other routine HIV tests according to the age and schedule for HIV exposed infants*. » See algorithm below: Management of high maternal VL after delivery.
UNKNOWN RISK (abandoned/orphaned infant) • **NVP daily for 6 weeks and AZT 12 hourly for 6 weeks.** ○ Initiate as soon as possible. *LoE:IIa*	
Unknown maternal status because orphaned or abandoned. (Treat all as high-risk HIV-exposed infants)	» Do an HIV PCR* and HIV rapid test » Start high risk infant prophylaxis for 6 weeks. » Repeat HIV PCR at 10 weeks of age, or 4 weeks after stopping NVP* » Do all other routine HIV tests according to the age and schedule for HIV-exposed infants*. » See algorithm below: Management of infant of unknown risk (abandoned infant).

[37] NDoH. Vertical Transmission Prevention Guideline 2023. Accessible : https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-09/2023%20Vertical%20Transmission%20Prevention%20Guideline%2004092023%20signed%20WEB_1.pdf

Note:
* If infant tests HIV-positive at any stage, confirm positive result, stop any ART prophylaxis, and initiate ART. See Section 11.6: Management of HIV-infected children.
**High-risk infants who are exclusively formula fed from birth: give NVP daily for 6 weeks and AZT 12 hourly for 6 weeks.

LoE:IIIb

Table 11.8: Infant prophylaxis for HIV

AMENDED TO:

Maternal VL	Risk profile	Prophylaxis	Comment
Maternal delivery VL as yet unknown at discharge from labour ward (results pending).	High-risk (until maternal delivery VL results become available)	Provide dual prophylaxis: AZT at birth and then twice daily for 6 weeks. NVP at birth and then daily for a minimum of 12 weeks.	All HIV-exposed infants will be considered high-risk until the final risk profile can be determined by the maternal delivery VL. If the maternal delivery VL result is not available at discharge from labour ward, review result at the 3– 6 day postnatal visit and reclassify the infant accordingly. Dispense a full 6 weeks supply of dual prophylaxis. Ask the mother to return with all medication at the 3–6 day postnatal visit
Maternal delivery VL ≥ 50 copies/mL in a breastfeeding mother	High-risk	Provide dual prophylaxis: AZT at birth and then twice daily for 6 weeks. NVP at birth and then daily for a minimum of 12 weeks.	Do an ABCDE assessment and get the mother's VL resuppressed as a matter of urgency. Stop infant NVP only after confirmation of maternal VL being < 50 copies/mL, or until 4 weeks after cessation of all breastfeeding
Maternal delivery VL ≥ 50 copies/mL in a mother who is exclusively formula feeding her infant from birth.*	High-risk	Provide dual prophylaxis: AZT at birth and then twice daily for 6 weeks. NVP at birth and then daily for 6 weeks.	Do an ABCDE assessment and get the mother's VL resuppressed as a matter of urgency
Maternal delivery VL < 50 copies/mL regardless of feeding choice.	Re-classify as low risk.	Change to low risk prophylaxis: NVP at birth and then daily for 6 weeks	Affirm and encourage good adherence. Repeat maternal VL 6- monthly during breastfeeding.

*Non-breastfeeding mother diagnosed HIV-positive > 72 hours after delivery: Do not start the infant on prophylaxis. Start maternal ART. Perform an HIV PCR test on the infant and, if positive, initiate ART, if negative, continue to monitor HIV risk and perform HIV testing as above.

Nevirapine (NVP) and Zidovudine (AZT) doses for infant on VTP

Dosing guidance: *Amended*

The table detailing dosing guidance for NVP and AZT in children from birth to 24 months of age has been amended to accommodate for infants weighing less than 2kg that may be managed at the PHC level of care. Dosing guidance for children up to the age of 24 months has been included in the dosing table. Amendments to the terminology PMTCT (Prevention of mother to Child Transmission) to the alternative, VTP (Vertical Transmission Prevention)[38] have also been made in line with changes to national guidance. Amendments are as tabulated below.

AMENDED FROM:

Nevirapine (NVP) dose for infant on PMTCT:

Newborns ≥ 2 kg and infants:

- Nevirapine, oral, 4 mg/kg daily.

Weight kg	Dose mg	Syrup 10 mg/mL	Age Months
2–2.5 kg	10 mg	1 mL	Birth–6 weeks
> 2.5 kg	15 mg	1.5 mL	
> 2.5–7 kg	20 mg	2 mL	> 6 weeks–6 months

Children >6 months of age requiring prophylaxis should use treatment doses. See the Paediatric Hospital STGs and EML, section 9.1.3 The HIV Infected Infant/Child.

Zidovudine (AZT) dose for infant on PMTCT:

Newborns ≥ 2 kg and infants:

- Zidovudine, oral, 4mg/kg/dose 12 hourly.

Weight kg	Dose mg	Syrup 10 mg/mL	Age Months

[38] NDoH Guideline. Guideline for the Prevention of Vertical Transmission of Communicable Infections 2023

2–2.499kg	10mg	1 mL	Birth–6 weeks
≥ 2.5 kg	15 mg	1.5 mL	
≥ 2.5–7 kg	60 mg	6 mL	> 6 weeks–6 months

AMENDED TO:

Nevirapine (NVP) and Zidovudine (AZT) doses for infant on VTP:

Newborns and infants:

- Nevirapine, oral, 4 mg/kg daily.
- Zidovudine, oral, 4mg/kg/dose 12 hourly.

	Birth–6 weeks			6 weeks – 6 months	6 – 9 months	9 – 24 months
	1.5-1.9 kg	2.0– 2.49 kg	≥ 2.5 kg			
NVP (Daily)	0.35 mL (0.35 mg) for 2 weeks THEN 0.6 mL (0.6 mg)	1 mL (10 mg) daily	1.5 mL (15 mg) daily	2 mL (20 mg) daily	3 mL (30 mg) daily	4 mL (40 mg) daily
AZT (Twice daily)	2mg/kg for 2 weeks THEN 3mg/kg for 2 weeks THEN 4mg/kg	1 mL (10 mg) twice daily	1.5 mL (15 mg) twice daily	6 mL (60 mg) twice daily	Children > 6 months of age requiring AZT prophylaxis should use treatment doses.	

Cotrimoxazole prophylaxis in high risk infants: *Amended*

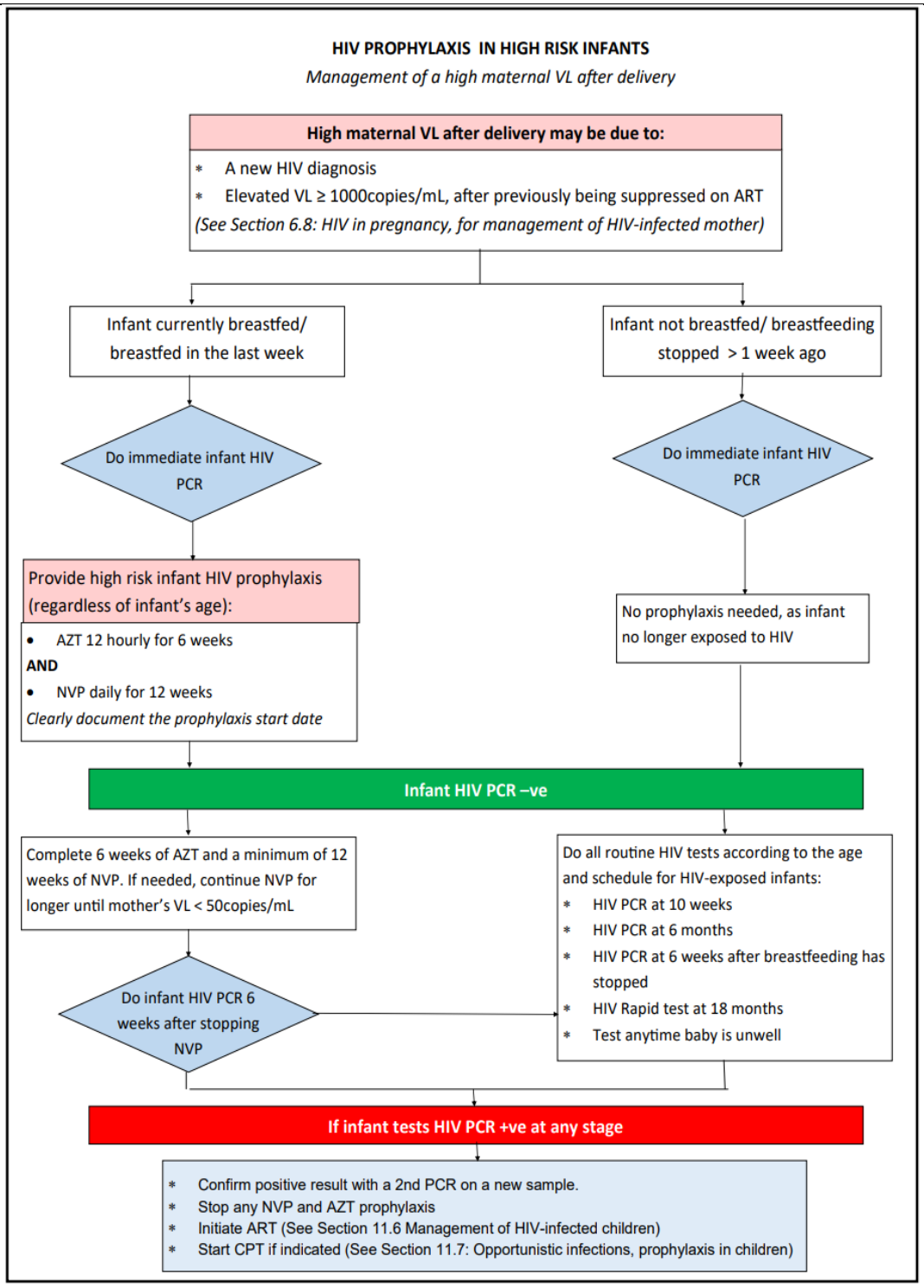
Cotrimoxazole prophylaxis is no longer recommended for high-risk infants older than 6 weeks of age, and this has been removed from the EML, in line with the national ART guideline[39] recommendations. Cotrimoxazole prophylaxis is now only recommended for children confirmed to be HIV positive.

HIV Prophylaxis in high-risk infants: *flow diagram updated*

The flow diagram detailing HIV prophylaxis in high-risk infants has been updated to reflect a lower threshold of VL<50 copies/cell as a measure of viral suppression. Recommendation on cotrimoxazole prophylaxis has been aligned as detailed above (i.e. high-risk infants > 6 weeks of age no longer require cotrimoxazole prophylaxis). This guidance has been aligned to the National ART guideline.[40] The updated flow diagram is as tabulated below:

[39] NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates.

[40] NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates.



11.6 MANAGEMENT OF HIV-INFECTED CHILDREN (<10 YEARS)

Monitoring for infants and children with HIV

Viral load: amended

Guidance for viral load monitoring in children on ART aligned to the national ART guideline as tabulated below:

Viral load: At month 3 on ART, after 12 months on ART, then every 12 months if virologically suppressed. More frequent monitoring (3–6 monthly) recommended in patients with treatment failure. ~~At month 6 on ART, after 12 months on ART, then every 12 months~~.

Eligibility for cotrimoxazole prophylaxis (CPT) – WHO staging: *amended*
Amended in line with Section 11.7 below.

Medicine treatment

Immunisation, deworming and vitamin A programme

BCG immunization: *guidance amended*

The STG has been amended for clarification as tabulated below:

Amended from:

Immunisation, deworming and vitamin A programme

- Continue deworming and vitamin A programme as in the HIV-uninfected child.
- Continue immunisation as in the HIV-uninfected child (See Section 13.3: Vaccines for routine administration), except do not give birth BCG vaccine.

Amended to:

Immunisation, deworming and vitamin A programme

- Continue deworming and vitamin A programme as in the HIV-uninfected child.
- Continue immunisation as per the SA-EPI (See section 13.3). If signs of HIV infection present, defer the BCG vaccination.

Social issues that must be addressed to ensure successful treatment

Adherence**:** *aligned to Paediatric Hospital EML*

The STG has been amended editorially as tabulated below in alignment with the Paediatric Hospital EML and national ART guideline.

AMENDED FROM:

Social issues that must be addressed to ensure successful treatment

These are extremely important for success and impact on adherence. Social challenges should be overcome and not be barriers to care. Adherence to treatment must at least be considered probable. Disclosure to another adult living in the same house is encouraged so that there is someone else who can assist with the child's treatment. However, absence of disclosure should not preclude ART initiation.

Mandatory component: At least one identifiable caregiver able to supervise the child and/or administer medication. All efforts should be made to ensure that the social circumstances of vulnerable children (e.g. orphans) be addressed to facilitate treatment.

AMENDED TO:

Social issues that must be addressed to ensure successful treatment

These are extremely important for success and impact on adherence. Social challenges should be overcome and not be barriers to care. Disclosure to another adult living in the same house is encouraged so that there is someone else who can assist with the child's treatment. However, absence of disclosure should not preclude ART initiation.

Mandatory component: At least one identifiable caregiver able to supervise the child and/or administer medication. All efforts should be made to ensure that the social circumstances of vulnerable children (e.g. orphans) be addressed to facilitate treatment.

Counselling before ART is initiated

Counselling guidance: *Editorial amendments*

Guidance for counselling caregivers before ART is initiated in children has been amended as tabulated below:

AMENDED FROM:

Requirements before ART is initiated:

The child's family (parents, caregivers) should understand:

» ART is life-long.
» The prognosis of the condition (treated and untreated).
» Medicines' adverse effects and modes of action, and the risk and implications of developing resistance, if incorrectly used.
» That all medicines should be given - if two ARVs are missing from the medicine regimen, stop treatment until they are all available again.

AMENDED TO:

Counselling before ART is initiated:

The health care worker should ensure the caregiver/s understanding of HIV, ART and the importance of virological suppression and should train caregivers on practical skills to adhere to ART.

ART Regimens

Dolutegravir: *added*

ARV regimen aligned to the Paediatric EML and national ART guideline recommendations.

Guidance on ART regimens for infants and children: *Amended*

The STG guidance on ART regimens for infants and children has been amended to align with the updated National ARV guidelines. Amendments are as tabulated below:

AMENDED FROM

ART regimens

Are chosen according to age, weight, expected adverse effects, efficacy and prior antiretroviral exposure.

Adjust the dosage of ART according to weight, during follow up visits.

Do not change regimens or move to 2nd line therapy without clear guidance from a paediatric expert, as unnecessary loss of effective regimens can shorten life expectancy. Adherence problems need to be addressed thoroughly before switching to a 2nd or 3rd line regimen.

Single medicine substitutions may only be made when medicine-specific adverse effects are encountered, on condition that virological suppression is documented and the matter is discussed with a practitioner experienced in child ARV medicine.

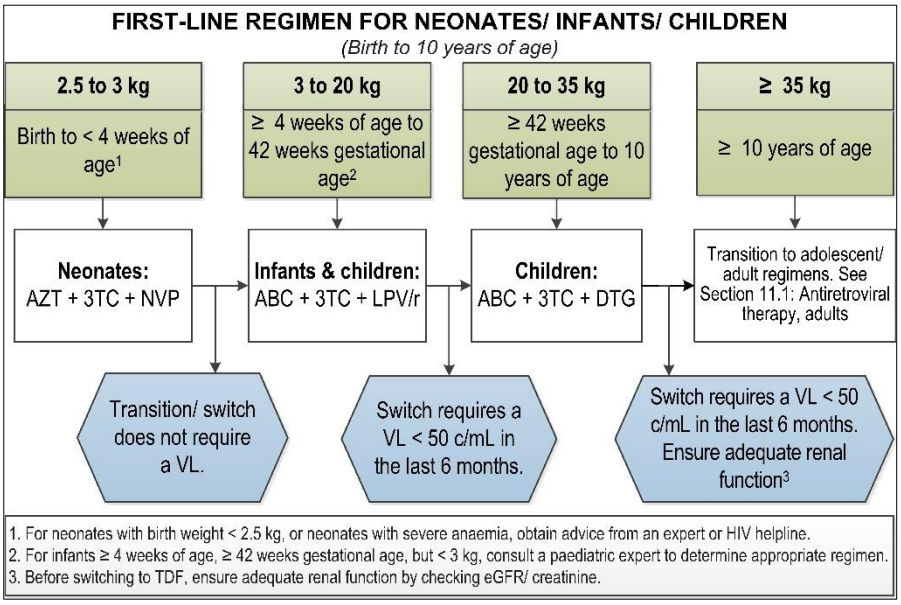
FIRST-LINE REGIMEN	
Infants < 4 weeks or < 3 kg: Consult paediatric expert on treatment regimen and dosage, or refer.	
If weight 3–19.9 kg, and child ≥ 4 weeks of age and ≥ 42 weeks gestational age:	ABC + 3TC + LPV/r.
If weight ≥ 20 to < 35 kg or < 10 years of age:	ABC + 3TC + DTG.
If weight ≥ 35 kg AND ≥10 years of age	TDF + 3TC + DTG

General ART comments

Switch to tablets or capsules from pellets, syrups or solutions as soon as possible.

Fixed-dose combinations are preferred to single agents.

If available, use daily dose regimens.



Initiating ART in children (the 6 steps/IMCI child NIMART)

(These steps that were taken from the IMCI nursing protocol were removed from the EML as no longer relevant)

Side effects:

(The table detailing side effects of ARVs was removed as no longer relevant to the updated ARV treatment guidance.)

AMENDED TO:

ART regimens

- Treatment regimens are chosen according to age, weight, expected adverse effects, efficacy and prior antiretroviral exposure.
- Adjust the dosage of ART according to weight during follow up visits. Assess weight gain and need for adjustment at each visit.
- Do not change regimens or move to an alternative regimen, without clear guidance from a paediatric expert, as unnecessary loss of effective regimens can shorten life expectancy. Address adherence problems thoroughly before switching to an alternative regimen.

- Single medicine substitutions may only be made when medicine-specific adverse effects are encountered, on condition that virological suppression is documented and the matter is discussed with a practitioner experienced in child ART.

First-line ART regimens for infants and children:
ALD1: Clients on a DTG-containing regimen, having never failed a previous regimen (old 'first-line' terminology).
ALD2: Clients on a DTG-containing regimen, who have failed a previous regimen (old 'second- line' terminology).

ALD: abacavir, lamivudine, dolutegravir.

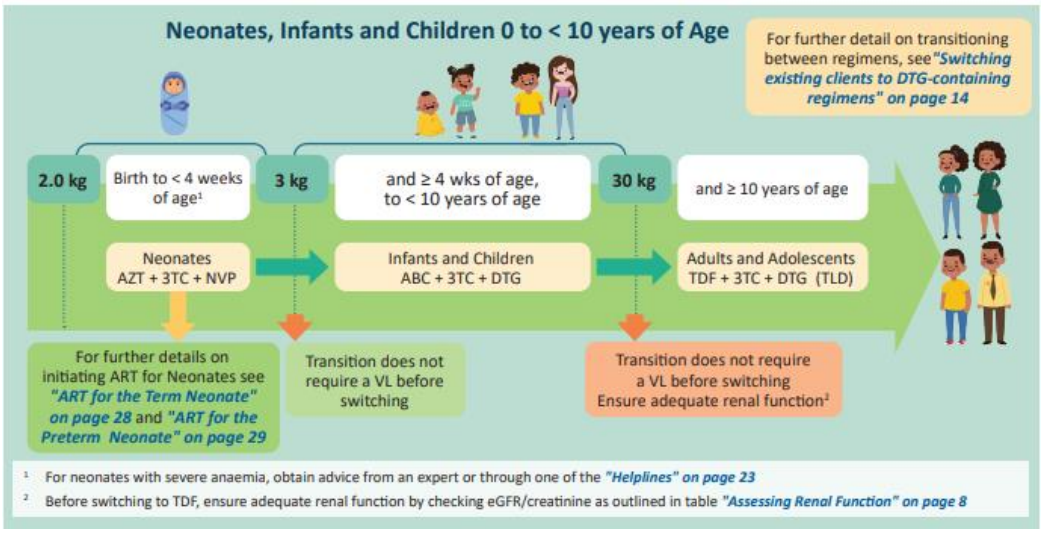
General ART comments

- Switch to tablets or capsules from pellets, syrups or solutions as soon as possible.
- Fixed-dose combinations are preferred to single agents.
- If available, use once daily dose regimens.

Side effects:

In patients being considered for an AZT-containing regimen, monitor for anaemia prior to initiation of ART.

A small proportion of patients initiated on ABC are at risk of abacavir hypersensitivity reaction, which presents with fever, rash and gastrointestinal disturbances. If this reaction is suspected, consult an expert.



Transition from ABC/3TC/LPV/r to DTG based regimens

Guidance to transition from ABC/3TC/LPV/r to DTG based regimens**:** *Added*

New STG guidance on transitioning to DTG based ART regimens for infants and children has been added to align with the updated National ARV guidelines with adoption of the flow diagram. Guidance for patients not eligible to transition to a DTG based regimen is also included. Additions to the STG are as tabulated below:

Transition from ABC/3TC/LPV/r to DTG based regimens

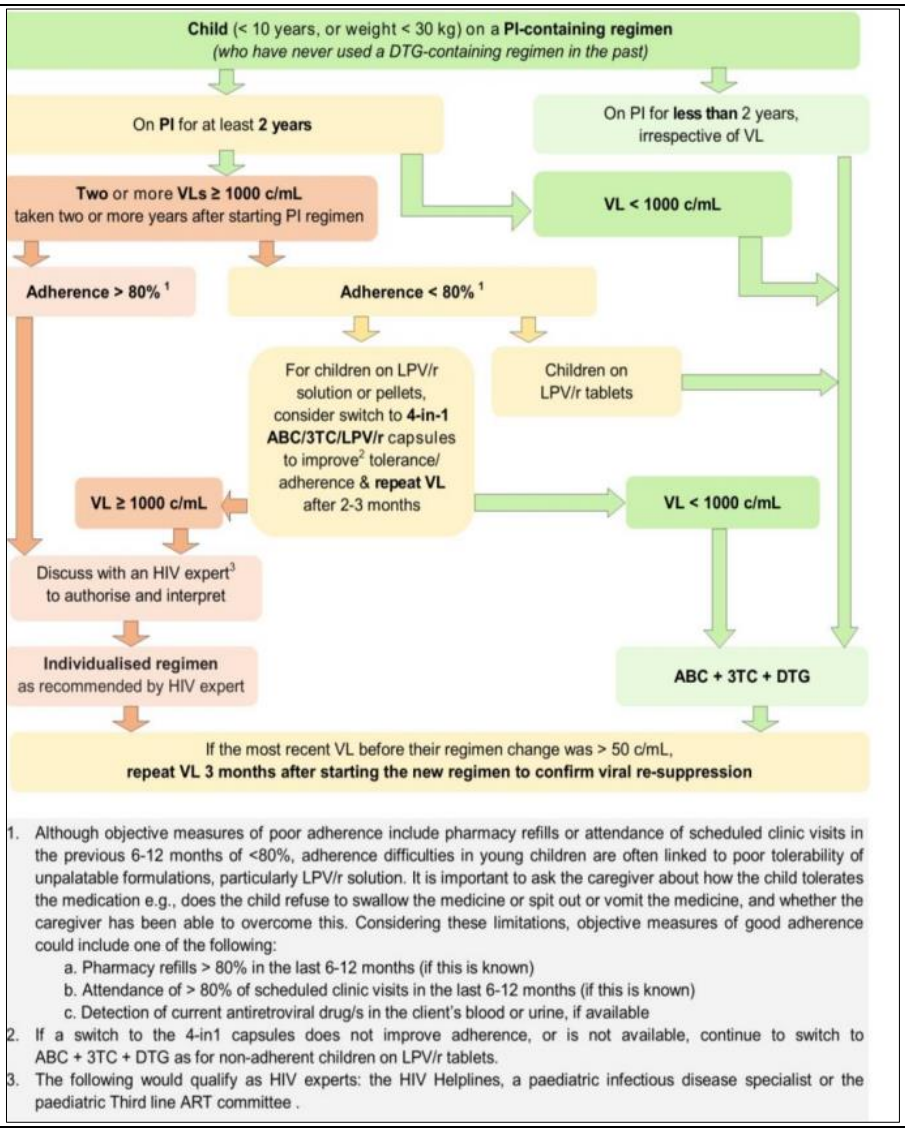
Children < 10 years or weight < 30 kg

- On PI based regimen for < 2 years: switch to DTG based regimen (no VL required)
- On PI based regimen for ≥ 2 years: review VL results, manage as per algorithm in figure 11.6

For patients not eligible for transition to DTG based regimen

- Consider switching to ABC/3TC/LPV/r 4-in-1 formulation and repeating HIV VL in 3 months. If HIV VL < 1000 copies/mL, change to ABC/3TC/DTG and if > 1000 copies/mL, perform an HIV drug resistance test (DR).
- Perform an HIV DR if 4-in-1 formulation not available.
- If NRTI mutations on the HIV DR show:
  - No mutations or only M184V – switch to ABC/3TC/DTG.
  - M184V + other mutations – discuss with an experienced practitioner in child ARV medicine.

Switching children on PI-containing regimens to DTG regimens



Treatment failure

Guidance on managing treatment failure: *Amended*

STG guidance on managing treatment failure in infants and children has been amended to align with the updated National ARV guidelines. Amendments are as tabulated below:

AMENDED FROM:

Treatment failure

- » VL is the most sensitive method to detect failure of response to ART.
- » Virological failure can be defined as a measurable viral load, despite optimal adherence and optimal dosing over a 4-month period. Clinical and immunological deterioration are late features of ART failure.
- » The most common cause of treatment failure is poor adherence. Adherence has to be addressed, before switching to 2nd-line therapy.

AMENDED TO:

Treatment failure

The HIV viral load is the most sensitive method to detect failure of response to ART.

Virological failure can be defined as a measurable viral load despite optimal adherence and dosage over 4 months. Treatment failure is primarily defined by viral loads, as waiting for clinical or immunological failure increases the chances of increasing viral resistance to other available antiretroviral agents.

Poor adherence is the most common cause of treatment failure. Adherence issues should be assessed and then implement strategies to improve adherence.

*For guidance on the step-up adherence package, refer to the National adherence guidelines. https://www.nacosa.org.za/wp-content/uploads/2016/11/Integrated-Adherence-Guidelines-NDOH.pdf

Third-line (patients failing ALD2)

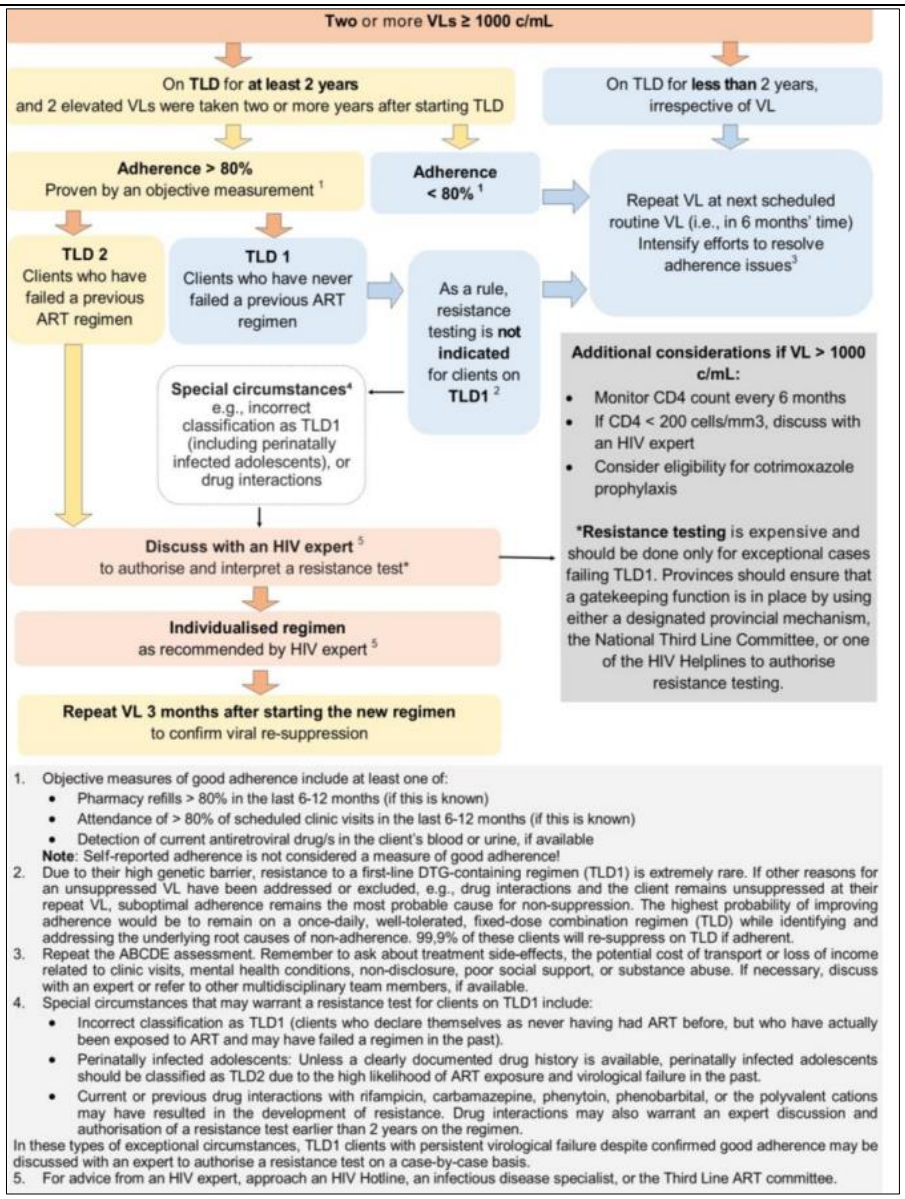
Discuss with expert

» Application forms for third-line antiretroviral therapy (patients failing ALD2) can be accessed at the following link: http://www.sahivsoc.org/Files/Application%20for%20Third%20Line%20Antiretrovirals_2017.pdf
» Important information to assist in applying for third-line antiretrovirals can be found at www.righttocare.org/what-we-do/third-line-art/
Applications can be emailed to TLART@health.gov.za

Management of confirmed virological failure in adolescents on TLD

Guidance on virological failure in adolescents on TLD: *Added*

The flow diagram on the management of confirmed virological failure in adolescents on TLD has been adopted from the National ARV guidelines as tabulated below:

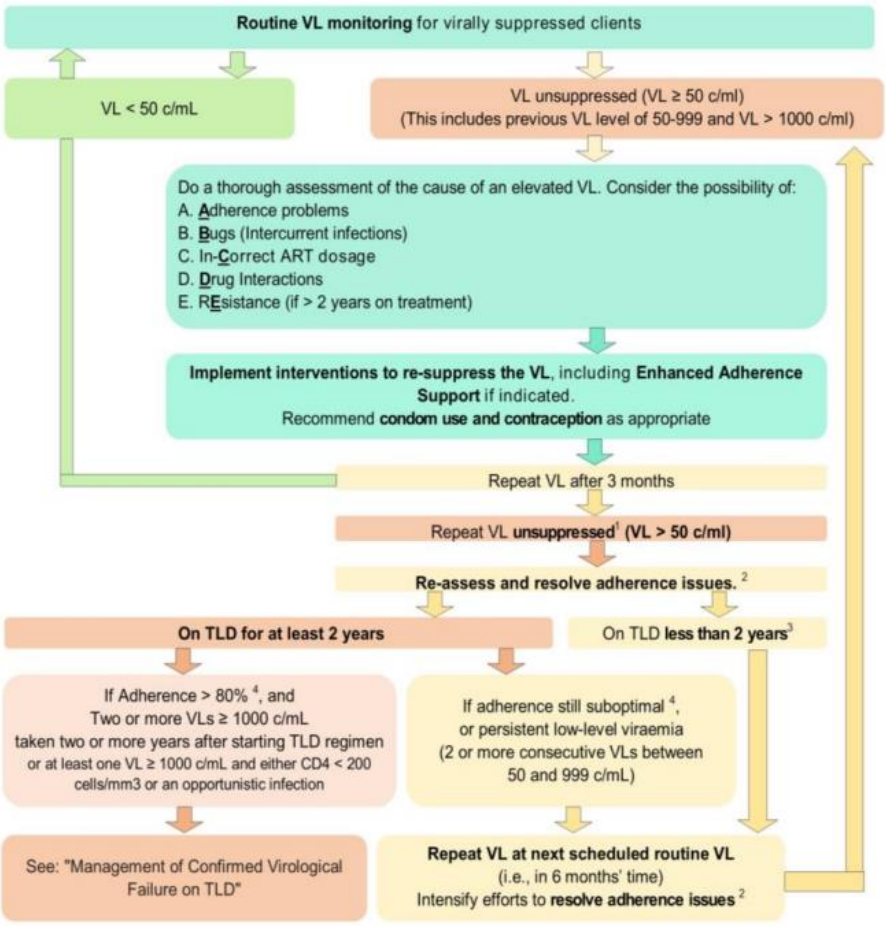


NOTE:
TLD1 = TLD as a first line ART regimen.
TLD2 = TLD in patient who has failed a previous ART regimen.

Viral Load Monitoring for clients on TLD

Guidance on viral load monitoring while on TLD: *Added*

The flow diagram guiding on viral load monitoring while on TLD therapy, has been adopted from the National ARV guidelines as tabulated below:



1. Due to their high genetic barrier, resistance to a first-line DTG-containing (TLD1) regimen is extremely rare. If other reasons for an unsuppressed VL have been addressed or excluded, e.g., drug interactions, and the client remains unsuppressed at their repeat VL, suboptimal adherence remains the most probable cause for non-suppression. The highest probability of improving adherence would be to remain on a once-daily, well-tolerated, fixed-dose combination regimen (TLD) while identifying and addressing the underlying root causes of non-adherence. 99,9% of these clients will re-suppress on TLD if adherent!
2. Repeat ABCDE assessment as outlined on "ABCDE assessment of an Elevated Viral Load" on page 20. Remember to ask about treatment side-effects, the potential cost of transport or loss of income related to clinic visits, non-disclosure, gender-based violence (GBV), and current or prior drug interactions. Current or previous drug interactions with rifampicin, carbamazepine, phenytoin, phenobarbital, or the polyvalent cations may have resulted in the development of resistance.
3. Drug interactions may also warrant an expert discussion and authorisation of a resistance test earlier than 2 years on the regimen. If necessary, discuss with an expert
4. Objective measures of good adherence include at least one of:
   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

Note: Self-reported adherence is not considered a measure of good adherence.

ART dosing tables for infants and children

Dosing tables: *aligned to the national ART guideline*

The ARV dosing tables from the national ART guideline have replaced previous ARV dosing tables (refer to tables 11.12 included in the EML).

11.7 OPPORTUNISTIC INFECTIONS, PROPHYLAXIS IN CHILDREN

Cotrimoxazole prophylaxis (CPT), oral: *directions for use amended*

Aligned with the Paediatric Hospital Level HIV chapter (2021) based on the benefit:risk assessment of CPT in HIV exposed, uninfected (HEU) infants at low- and high-risk of HIV infection through vertical mother-to-child transmission (MTCT).

Evidence: There is strong evidence that CPT significantly reduces mortality and infectious morbidity amongst HIV-infected adults and children; and CPT has been shown to be beneficial in HEU infants living in malaria endemic areas. However, a recent appraisal of the evidence by the World Health Organization included two Sub-Saharan studies (n= 2848 and n=1219, respectively), which showed that CPT did not improve survival amongst HEUs with low risk for MTCT,

in areas unaffected by malaria. CPT also was shown not to have an effect on hospitalisation, or the incidence of grade 3 or 4 common childhood illnesses (pneumonia or diarrhoea) compared to no CPT. However, harms such as more grade 3/4 neutropaenia as well as cotrimoxazole resistance was more prominent amongst HEUs on CPT.
Broad-spectrum CPT has also been shown to select for antimicrobial resistance of other non-sulfonamide antimicrobials, by decreasing gut microbiome diversity and increasing antibiotic resistance. Powis et al. showed that HEUs on CPT had commensal gastrointestinal bacteria that were more resistant to cotrimoxazole and amoxicillin compared to the placebo group.[9]
Therefore, targeted CPT rather than global CPT for HEU infants has been proposed in order to minimise unnecessary selection of antimicrobial resistance and unnecessary adverse effects, especially amongst HEUs who are at low risk of MTCT of HIV.

Cotrimoxazole prophylaxis (CPT) – WHO clinical staging : *Added*
The WHO clinical stage 3 and 4 has been added as criteria for consideration for the initiation of cotrimoxazole prophylaxis in children over the age of 1 year[41]. Amendments to the STG are detailed below:

AMENDED FROM:

Cotrimoxazole prophylaxis

Initiation

- All HIV-infected infants (< 1 year), starting from 6 weeks of age.
- Any child 1–5 years of age with CD4% < 25%.
- Any child > 5 years of age with CD4 count < 200 cells/mm3.
- Cotrimoxazole, oral, once daily (everyday). See dosing table, pg 23.4.

Discontinuation

- HIV-infected child > 1 year of age whose immune system is fully reconstituted on ART (i.e. 1–5 year: CD4% > 25% or > 5 years: CD4 count > 200 cells/mm^3 on two tests at least 3–6 months apart).
- Child is HIV-infected with PJP infection: after treatment, continue cotrimoxazole prophylaxis until 5 years of age.

AMENDED TO

Cotrimoxazole prophylaxis

Initiation

- All HIV-infected infants (< 1 year), starting from 6 weeks of age.
- Any child 1–5 years of age with CD4 < 25%, or WHO stage 3 and 4
- Any child > 5 years of age with CD4 count < 200 cells/mm^3, or WHO stage 3 and 4.

• Cotrimoxazole (sulfamethoxazole/trimethoprim), oral, once daily.

Recommended daily dosage by weight band	Dose of sulfamethoxazole/ trimethoprim	Suspension (200/40 mg per 5 mL)	Single strength tablet (400/80 mg)	Double strength tablet (800/160 mg)
3 to 5.9 kg	100/20 mg	2.5 mL	¼ tablet	-
6 to 13.9 kg	200/40 mg	5 mL	½ tablet	-
14 to 24.9 kg	400/80 mg	10 mL	1 tablet	½ tablet
25 kg	800/160 mg	-	2 tablets	1 tablet

Discontinuation
Prophylaxis may be discontinued if the immune system is fully reconstituted on ART i.e.
Child > 1 year of age, *AND* immune system shows signs of full reconstitution on two CD4 tests at least 3-6 months apart (regardless of clinical stage), i.e.:
Child 1-5 years of age: CD4 > 25%
Child > 5 years of age: CD4 > 200 cells/mm^3

Immunisation
Amended to align with Section 11.6 above as follows: *'Continue immunisation as per the SA-EPI (See section 13.3). If signs of HIV infection present, defer the BCG vaccination.'*

[41] Temporal Trends in Co-trimoxazole Use Among Children on Antiretroviral Therapy and the Impact of Co-trimoxazole on Mortality Rates in Children Without Severe Immunodeficiency | Journal of the Pediatric Infectious Diseases Society | Oxford Academic (oup.com)

11.8.7 TUBERCULOSIS (TB)

Description: *amended for improved clarity*

The STG has been amended as tabulated below for improved clarity:

AMENDED FROM:

DESCRIPTION

TB and HIV are often comorbid conditions. Exclude TB in all patients before starting ART. See Section 17.4.2: Pulmonary tuberculosis, in children.
Re-evaluate the risk for TB and TB contact at each visit on history (including contact history) and clinical examination.
TB should be considered early in non-resolving pneumonias.
Tuberculin tests are often not reliable and a negative test does not exclude TB.
If TB is suspected but cannot be proven, refer early for diagnostic evaluation

TB prophylaxis Z29.2 + (B24)

Give TB prophylaxis to all HIV-infected children in whom no evidence of TB disease is present and who are:

- » Exposed to a close contact with infectious pulmonary TB or
- » TST-positive (only the 1st time a positive TST is shown).
  - Isoniazid, oral, 10 mg/kg/dose once daily for 6 months.
    - Maximum dose 300 mg daily.
    - See Section 17.4.2.1: TB chemoprophylaxis/Isoniazid preventive therapy (IPT) in children.

Repeat course if an HIV-infected patient, irrespective of age, is re-exposed to a TB contact at any point after completing TB treatment or prophylaxis.

If patient has been exposed to a known MDR or XDR-TB source case or the contact case has failed standard TB treatment, refer.

TB treatment

If the child is not yet on ART:
Commence TB treatment first. Follow with ART, usually after 2–8 weeks:

- 2 weeks if CD4 < 50 cells/mm3
- 8 weeks if CD4 > 50 cells/mm3
- » Check ALT before commencing ART. If the ALT is raised, discuss this with an expert as it may not be an absolute contra-indication to treatment.
- » Be aware of the possibility of Immune Reconstitution Inflammatory Syndrome (IRIS).

If the child is already on ART:

- » Commence TB treatment taking into consideration possible medicine interactions.

If the child needs to take concomitant ART and rifampicin:

- » Dolutegravir: use DTG 12 hourly.
- » Efavirenz: use the normal recommended dosage as per dosing table on pg 23.4.
- » Abacavir and lamivudine: no dose adjustment required.
- » Lopinavir/ritonavir: Add additional ritonavir to ensure an equal dose in mg of lopinavir and ritonavir while on rifampicin. For example, for each mL of LPV/r solution (80/20 mg/mL), add 0.75 mL of ritonavir solution (80 mg/mL). See dosing table, pg 23.9.
- » Give pyridoxine (vitamin B6) to all children on TB and ART, to avoid development of peripheral neuropathy.

AMENDED TO:

DESCRIPTION

TB and HIV are often comorbid conditions. Exclude TB in all patients before starting ART. See Section 17.4.2: Pulmonary tuberculosis, in children.
Re-evaluate the risk for TB and TB contact at each visit on history (including contact history) and clinical examination.
TB should be considered early in non-resolving pneumonias. At every follow up visit, ask about symptoms of cough, night sweats, fever, TB contacts and check for failure to thrive.

Refer early for diagnostic evaluation. If TB is suspected:

- Chest radiograph (CXR)
- GeneXpert on any relevant specimen including stool
- Culture on respiratory or appropriate specimen
- Urine-LAM. If no sample obtained, continue evaluation

TB prophylaxis Z29.2 + (B24)
Give TB prophylaxis to all HIV-infected children in whom no evidence of TB disease is present and who are:

- Exposed to a close contact with infectious pulmonary TB or
- TST-positive (this test is only reliable the first time TPT is given).
- Isoniazid, oral, 10 mg/kg/dose once daily for 6 months.
  Maximum dose: 300 mg daily.
  See Section 17.4.2.1: TB chemoprophylaxis/Isoniazid preventive therapy (IPT) in children.

Repeat course if an HIV-infected patient, irrespective of age, is re-exposed to a TB contact at any point after completing TB treatment or prophylaxis.
Refer if patient has been exposed to a known MDR or XDR-TB source case or the contact case has failed standard TB treatment.

TB treatment
If the child is not yet on ART:
- » TB treatment and ART can be started at the same time, with the exception of children with TB meningitis – start ART at 4 weeks regardless of CD4 count to avoid IRIS.
- » Assess the child for possible disseminated TB disease.
- » Be aware of the possibility of Immune Reconstitution Inflammatory Syndrome (IRIS).

If the child is already on ART:
- » Commence TB treatment, considering possible drug interactions and the need for ART dosage adaptations.

If the child needs to take concomitant ART and rifampicin-containing treatment:
- Dolutegravir: use dolutegravir twice daily.
- Efavirenz: use the normal recommended dosage as per the dosing table.
- Abacavir and lamivudine: no adjustment of dosages.
- Lopinavir/ritonavir: refer to the dosage table for the ritonavir boosting doses.
  - Avoid using double-dose lopinavir/ritonavir solution in young children. If ritonavir powder is not available, consult an expert.
- Give pyridoxine (vitamin B6) to all children on TB treatment and ART, to avoid development of peripheral neuropathy.

C. HIV PREVENTION

11.11 PRE-EXPOSURE PROPHYLAXIS (PREP)

Note: Oral PrEP is now available at all primary level facilities in the public sector.

Contraindications to PrEP

The following was amended for clarity purposes:

» Estimated creatinine clearance or eGFR < 60 mL/min.

Oral PrEP Regimen

Tenofovir + emtricitabine: *duration of therapy amended*

To reach adequate protective levels in tissue, guidance is provided to continue oral PrEP for 7 days for all sexual practices, aligned with the 2021 updated National Department of Health PrEP guidelines[42]. Additional guidance to use barrier protection until therapeutic drug concentrations are attained also added.

STG text was amended as follows:

Note: To reach adequate protective levels in tissues, 7 days of daily dosing are required ~~for anal sex and 20 days for vaginal sex.~~ Individuals should be counselled that additional barrier protection should be used until therapeutic levels achieved.

Level of Evidence: III Guidelines[43]

Screening investigations before starting PrEP

Hepatitis B surface antigen (HBsAg) screening: *Guidance clarified*

STG guidance for hepatitis B vaccination has been clarified to ensure that patients are assessed for eligibility in line with the eligibility criteria included in table 11.14: PrEP eligibility determined by hepatitis B immune status.

PrEP Initiation

PrEP Initiation algorithm: *Guidance clarified*

Prep is contraindicated in patients with chronic kidney disease (CKD) and a eGFR <60mL/min. This caution has been added as a footnote to the algorithm on PrEP initiation as tabulated below:

NOTE: In patients with Chronic Kidney Disease (CKD) with eGFR < 60mL/min, PrEP is contraindicated.

Oral PrEP follow up and monitoring

Estimated creatinine clearance: *monitoring updated*

Aligned with 2021 updated National Department of Health PrEP guidelines,[44] and STG text was updated as follows:

Activity	Frequency		
Estimated creatinine clearance	**Frequency dependant on pregnancy status, age and co-morbidity:**		
	Age/ pregnant	**Co-morbidity**	**Creatinine**
	< 30 years	None	n/a
	30–49 years	None	Baseline
	< 49 years	Diabetes/ hypertension	Baseline, annually
	≥ 50 years	None	Baseline
	≥ 50 years	Diabetes/ hypertension	Baseline, annually
	Pregnant	n/a	Baseline, 3 & 6 months

Relevant medicine interaction information

MDR-TB Guidance: *Deleted*

Interactions with MDR-TB medicines have been removed from table 11.16: Oral PrEP drug interactions, as this is no longer relevant with the newly introduced BPaL regimen for the management of MDR-TB.

[42] National Department of Health. 2021 Updated guidelines for the provision of oral pre-exposure prophylaxis (prep) to persons at substantial risk of HIV infection.
[43] National Department of Health. 2021 Updated guidelines for the provision of oral pre-exposure prophylaxis (prep) to persons at substantial risk of HIV infection.
[44] National Department of Health. 2021 Updated guidelines for the provision of oral pre-exposure prophylaxis (prep) to persons at substantial risk of HIV infection.

Stopping oral PrEP

Tenofovir + emtricitabine**:** *duration of therapy amended*

The following was amended, aligned with 2021 updated National Department of Health PrEP guidelines.[45]

Continue oral PrEP for ~~28~~ 7 days after the last potential HIV exposure.

Other PrEP agents:

Dapivirine vaginal ring: *not added*

A summary of the NEMLC recommendation is included below. A copy of the medicine review[46] and economic analysis[47] may be included at the end of this report or alternatively, accessible on the NHI webpage.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			
Recommendation: Based on this evidence review, the PHC/Adult hospital level committee suggests not to use the dapivirine ring as an additional option for prevention of HIV acquisition in women. *Rationale:* Available evidence for the dapivirine ring is restricted to placebo-controlled data, with no studies comparing dapivirine to oral tenofovir plus emtricitabine, the current standard of care in South Africa. There is currently no data for efficacy in adolescents. The dapivirine ring cannot be used in pregnancy. There is sub-group of women who cannot use tenofovir plus emtricitabine for whom the dapivirine ring may be an option. However, at the current proposed price, dapivirine is unaffordable. The estimated threshold price for reviewing this recommendation is R52.00 per ring. **Level of Evidence:** Moderate quality of evidence **Review indicator: Reduction in price**					
NEMLC RECOMMENDATION (23 JUNE 2022): The NEMLC accepted the proposed PHC/Adult Hospital Level ERC recommendation with amendments to the review indicator (added, uptake and social harms), as follows: **Review indicator: Reduction in price; Uptake of all PrEP; Social harms of all PrEP**					
Monitoring and evaluation considerations: see review indicators above					
Research priorities: see review indicators above					

Cabotegravir: *Not added*

A summary of the NEMLC recommendation is included below. A copy of the medicine review[48] and economic analysis[49] may be included at the end of this report or alternatively, accessible on the NHI webpage. NEMLC has also engaged with representatives from the NDoH and the program regarding receipt of donated stock of injectable cabotegravir - refer to the evidence review document for a summary of the NEMLC's deliberations regarding this donated stock.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		x			
Recommendation: Although the efficacy of CAB is high, and the safety profile acceptable, the PHC/Adult Hospital Level Committee suggests not to use CAB as PrEP for HIV, until such time as the price becomes known, and the evidence of efficacy for regimens that do not include an oral lead-in phase are available. *Rationale:* Two phase 3 RCTs both found that PrEP with long-acting injectable CAB had greater efficacy than oral tenofovir plus emtricitabine. A model to assess budgetary impact and cost-effectiveness analysis has been developed, however until a price is confirmed, a final recommendation cannot be made. **Level of Evidence: High certainty evidence** **Review indicator:** Evidence of efficacy in regimens that do not require oral lead-in doses, information on cost.					
NEMLC RECOMMENDATION (MEETING OF 23 JUNE 2022): Accepted **UPDATED NEMLC RECOMMENDATION (e-ratified, 30 MARCH 2023):** Updated recommendation following completion of the budget impact analysis (March 2023) ratified by NEMLC, as above.					
Monitoring and evaluation considerations					
Research priorities					

[45] National Department of Health. 2021 Updated guidelines for the provision of oral pre-exposure prophylaxis (prep) to persons at substantial risk of HIV infection.
[46] NDoH evidence summary. DapivirineRingForPrEP_PHC-Review_9June2022_v5
[47] NDoH Cost effectiveness Analysis Report. DapvirineRingForPrEP_CEA and costing report_23May2022_v2
[48] NDoH evidence summary. CABForPrEP_PHC-Review_13 Sep 2024_v5.1
[49] NDoH Cost effectiveness Analysis and BIA Report. Cabotegravir (CAB-LA) cost effectiveness and budget impact analysis_Final_23 February 2023

D: SIDE EFFECTS AND COMPLICATIONS OF ART

11.14 LACTIC ACIDOSIS

Lactic acidosis STG: *deleted*

An external comment was received querying why guidance was provided for lactic acidosis only and why not other adverse effects. Therefore, section 11.14: Lactic acidosis was deleted and a cross-reference was made to the Adult Hospital Level STGs and EML for detailed information on adverse effects associated with ARVs.

The following was added to the STG text:

Refer to the Adult Hospital Level STGs and EML: Section 10.1.1Management of selected antiretroviral adverse drug reactions, and consult with an infectious disease specialist as required.

And the following was deleted:

~~**11.14 LACTIC ACIDOSIS**~~

~~E87.2 + (Y41.5 + B24)~~

~~**Description**~~

~~All nucleoside analogues have been associated with lactic acidosis, which is rare but life-threatening. Initial symptoms vary and occur between 1-20 months (median 4 months) after starting therapy. The risk is highest with stavudine, followed by didanosine and then zidovudine.~~

~~**Diagnostic criteria**~~

~~*Clinical*~~

~~Clinical prodromal syndrome:~~

~~» Generalised fatigue~~

~~» Weakness and myalgia~~

~~» Gastrointestinal symptoms:~~

~~- nausea - vague abdominal pain~~

~~- vomiting - hepatomegaly~~

~~- diarrhoea - anorexia~~

~~- unexplained weight loss~~

~~» Respiratory symptoms: tachypnoea and dyspnoea.~~

~~» Neurologic symptoms, including motor weakness.~~

~~*Investigations*~~

~~» Laboratory abnormalities:~~

~~- Hyperlactataemia~~

~~Raised: 2.1–5 mmol/L~~

~~Severely raised : > 5 mmol/L~~

~~- Lactic acidosis, defined by:~~

~~Lactate: > 5 mmol/L~~

~~Bicarbonate: < 20 mmol/L~~

~~Severe acidosis i.e. pH < 7.3~~

~~Increased anion gap i.e. > 15 mEq/L~~

~~**Referral**~~

~~All urgently.~~