SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
ADULT HOSPITAL CHAPTER 10: HIV AND AIDS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2020-4 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
10 Antiretroviral therapy, adults and adolescents	Reference to national ART guidelines	Cross reference to national ART guidelines aligned to Paediatric EML
10.1 Antiretroviral therapy, adults - *Clinical indications for deferring ART initiation* *- Asymptomatic cryptococcal infection*	ART	Directions amended
10.1 Antiretroviral therapy, adults *- Treatment-naïve patients without TB*	TDF+3TC+DTG	Amended indication - expanded to ALL women
10.1 Antiretroviral therapy, adults *- Treatment-naïve patients with TB*	TDF +EFV+FTC	Retained
	Double-dosed DTG (TLD + DTG 50 mg)	Indication expanded to DTG-naïve patients initiating ART with concomitant rifampicin-containing TB therapy
10.1 Antiretroviral therapy, adults *- Contraindication to TDF*	ABC + 3TC+DTG	Amended as preferred treatment
	TAF+FTC+DTG	Added for PLHIV with chronic Hep B & RF
10.1 Antiretroviral therapy, adults *- Contraindication to TDF and ABC intolerance*	AZT+3TC with DTG	Amended as preferred treatment
10.1 Antiretroviral therapy, adults *- Recycling TDF in virological failure*	AZT	Deleted
	TDF	Added
10.1 Antiretroviral therapy, adults *- Switching existing clients to DTG-containing regimens*	DTG	New guidance added
	Clients with DTG resistance	Guidance added
10.1 Antiretroviral therapy, adults *- Rifampicin-based TB treatment (on DTG-regimen)*	DTG	Added
10.1 Antiretroviral therapy, adults *- Protease inhibitors (PI)*	LPV/r	Retained
	ATV/r	Indication expanded to preferred 2nd line PI
	DRV/r	Not added to the STG, but included in therapeutic interchange database (patients not on TB-rifampicin therapy)
10.1 Antiretroviral therapy, adults	Resistance testing	Retained, and emphasised
10.1 Antiretroviral therapy, adults *- Currently available ARV FDC preparations on contract*	ATV/r	Added
	ABC + 3TC + DTG	Added
10.1 Antiretroviral therapy, adults *-Re-initiating ART in patients who have interrupted treatment*	Re-initiating ART	New guidance added
ART: Dosing and important adverse effects	3TC – renal adjusted dose	Amended
	FTC – renal adjusted dose	Amended
	TDF, ABC, 3TC, FTC, oral	Amended - very low risk, "Hyperlactataemia/ steatohepatitis" was deleted
	DTG	Amended - weight-gain deleted
	DTG – serum creatinine	Guidance clarified
	Nevirapine, oral	Adverse effects and dosing information deleted
	Raltegravir, oral	Adverse effects and dosing information deleted
	TAF, oral – adverse effects	Added
Monitoring on ART *- At HIV diagnosis: CrAg screening*	CrAg screening	Amended
	Sputum screen for TB	Amended
	HIV viral load monitoring	Amended

	schedule	
10.1.1 Management of selected antiretroviral adverse drug reactions	Algorithm to manage drug-induced liver injury (DILI)	Amended
	Hypersensitivity	Guidance clarified
	Hyperlactataemia:	Guidance clarified
	Hepatitis in patients on ART and anti-tuberculosis therapy:	Guidance clarified
10.1.2 Immune reconstitution inflammatory syndrome (IRIS)	Paracetamol	Amended
10.2 Opportunistic Diseases		
10.2.1 Tuberculosis preventive therapy (TPT) *-Adult PLHIV initiated on ARVs*	TPT	Added as a therapeutic group
	Isoniazid (12H)	Retained as an example of class in the STG
	Rifapentine + isoniazid (3HP)	Guidance for EFV-based ART replaced with DTG-containing ART
	Rifapentine + isoniazid (3HP)	Added as a therapeutic alternative in the therapeutic interchange database
	Pregnant women	Guidance amended
10.2.2 Opportunistic infection prophylaxis, with cotrimoxazole	WHO clinical stage II	Deleted
10.2.3 Candidiasis of oesophagus/trachea/bronchi	Fluconazole, oral	Directions for use amended
10.2.4 Cryptococcosis	Algorithm for the prevention, diagnosis and management of cryptococcosis among PLHIV	Amended
10.2.4.1 Cryptococcosis, CSF CrAg negative	CrAg screening: CD4 threshold	Amended
	ART	Directions amended
10.2.4.2 Cryptococcal meningitis	Flucytosine, oral	Added
	Liposomal amphotericin B	Added
	Amphotericin B	Retained
	Fluconazole, oral	Retained
10.2.4.2 Symptomatic, non-meningeal cryptococcosis *(STG deleted)*	Fluconazole, oral	Deleted
	Amphotericin B	Deleted
	ART	Deleted
10.2.6 Cytomegalovirus (CMV) **-** *maintenance treatment*	Ganciclovir, parenteral	Deleted
	Valganciclovir, oral	Retained
10.2.9 Pneumocystis pneumonia	Primaquine, oral	Directions for access, added
10.5.1 Post-exposure prophylaxis, occupational	LPV/r	Retained
	ATV/r	Expanded to include all patients - preferred 2nd line PI
	DRV/r	Not added to the STG, but included in therapeutic interchange database (not on TB-rifampicin therapy)
- PEP regimens	TDF	Editorial amendments
	TDF-contraindicated	Guidance clarified
- *PEP for healthcare workers following hepatitis B exposure*	Hepatitis B Immunoglobulin	Amended
- Delay in obtaining HBsAb results	Time period of delay	Amended
10.5.2 Non occupational post exposure prophylaxis, sexual assault	LPV/r	Retained
	ATV/r	Expanded to include all patients - preferred 2nd line PI
	DRV/r	Not added to the STG, but included in therapeutic interchange database (not on TB-rifampicin therapy)
	HIV PrEP	Added as a cross reference to the PHC STGs and EML (PrEP section)
- Emergency contraception after pregnancy is excluded	Copper IUCD	Added (as first line option)
	Levonorgestrel, oral	Retained (as 2nd line option)
- *Obese women*	Levonorgestrel, oral	Dose not amended
10.5.3 Non occupational post exposure prophylaxis, inadvertent non-occupational	LPV/r	Retained
	ATV/r	Expanded to include all patients - preferred 2nd line PI
	DRV/r	Not added to the STG, but included in therapeutic interchange database (not on TB-rifampicin therapy)
- Emergency contraception after pregnancy is excluded	Copper IUCD	Added (as first line option)
	Levonorgestrel, oral	Retained (as 2nd line option)

- *Obese women*	Levonorgestrel, oral	Dose not amended
	Description	Editorial amendment

ABC= Abacavir, ART=antiretroviral therapy, ATV/r=Atazanavir/ritonavir, AZT=Zidovudine, 3TC= Lamivudine, CSF=cerebrospinal fluid; CrAg=cryptococcal antigen, DRV/r=Darunavir/ritonavir, DTG= Dolutegravir, EFV= Efavirenz FTC = Emtricitabine, IUCD=intrauterine copper device, 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	10.1 Drug interactions with dolutegravir	**Metformin** Guidance amended
2.1	10.2.4 Cryptococcus	**Erratum** Algorithm corrected

CROSS REFERENCE TO NATIONAL GUIDELINES

The cross reference to the National ART Guidelines 2023[1] has been amended and aligned to the PHC 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.

10.1 ANTIRETROVIRAL THERAPY

ASYMPTOMATIC CRYPTOCOCCAL INFECTION

ART: *Directions amended*

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

Positive cryptococcal antigen and no evidence for meningitis on LP:

AMENDED FROM:

» In patients with positive cryptococcal antigen and no evidence for meningitis on LP, defer ART until 2 weeks after initiating fluconazole.

AMENDED TO:

» In patients with positive cryptococcal antigen and no evidence for meningitis on LP, there is no need to delay. ART can be started immediately.

ART REGIMENS

Treatment-naïve patients without TB

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.

[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.

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

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

ART- TREATMENT-NAÏVE PATIENTS WITH TB

Tenofovir (TDF) + Efavirenz (EFV) + Emtricitabine (FTC) = (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[3] may be 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

Abacavir + lamivudine + dolutegravir (ABC+3TC+DTG), oral: *Amended as preferred treatment*

Abacavir is preferred over zidovudine, as kidney disease is often progressive, resulting in anaemia.

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

TAF+FTC+DTG, oral: *Added (for a select cohort)*

Tenofovir alafenamide (TAF):

An update to the TAF review was conducted in March 2024 for PLHIV with chronic Hepatitis B co-infection and renal impairment.[4] 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.

CONTRAINDICATION TO TDF/TAF AND ABC INTOLERANCE/HYPERSENSITIVITY

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

The following STG text was deleted:

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

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

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.[5] [6]

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 <u>Patients with TB:</u> TDF + FTC + EFV <u>Pregnant women <6 weeks gestation or actively wanting to conceive:</u> TDF + FTC + EFV *(Also see section 6.7: HIV in pregnancy)*	<u>Individuals ≥30kg:</u> TDF + 3TC + DTG ("TLD") **Note***:* DTG-based regimens are now recommended as first line ART in all women of childbearing potential. <u>Patients on rifampicin-based TB treatment:</u> TDF + FTC + EFV **OR** TDF + 3TC + DTG *plus* additional dose of DTG 50mg 12 hours later. The extra DTG dose can be stopped two weeks after completion of TB therapy. (Also see AH STG section 6.6: 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 mg and then 800/200 mg). 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. » Use of additional nephrotoxic drug	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>

[5] 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/

[6] 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/

e.g. aminoglycoside.		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
2ND LINE ART		
Management of viraemia on 1st line ART	<u>If plasma VL between 50–999 copies/mL:</u> » Address adherence, tolerability, medicine interactions & psychosocial factors. » Repeat VL test 3 months later. <u>If plasma VL > 1000 copies/mL:</u> » Assess adherence, tolerability, medicine interactions & psychosocial factors. Repeat VL test 3 months later <u>If plasma VL 50-999 copies/mL:</u> » Continue enhanced adherence support. » Repeat VL test 6 months later. <u>If plasma VL remains at 50-999 copies/mL i.e. persistent low grade viraemia:</u> » Manage as virological failure below.	
Management of virological failure on 1st line ART	<u>If plasma VL confirmed ≥1000 copies/mL (on 2 tests), and adherence issues addressed:</u> » 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		<u>If plasma VL >50 copies/mL:</u> » Address adherence, tolerability, medicine interactions & psychosocial factors. » Repeat VL test 3 months later. <u>If plasma VL remains > 50:</u> » 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). » 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	AZT + 3TC + DTG. <u>If HBsAg positive:</u> TDF + 3TC + DTG	

(TDF+3TC/FTC+EFV/ NVP)	<u>If DTG contraindicated/ not tolerated:</u> AZT + 3TC +LPV/r (**PLUS** TDF, if HBsAg positive). <u>If AZT and TDF contraindicated/ not tolerated (e.g. anaemia and renal impairment):</u> 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 <u>If HBsAg positive:</u> 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.	

RECYCLING TDF IN VIROLOGICAL FAILURE

<u>Zidovudine (AZT):</u> *deleted*

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

As the 96-weeks follow up data of the NADIA RCT[7] has been published in peer-review format, an update to the original evidence summary[8] was undertaken in May 2022, with the NEMLC recommendation tabulated below. A copy of the complete review[9] may be accessed at the end of this document or alternatively on the NHI webpage.

[7] 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/

[8] NDoH Evidence Summary. NDoH_EML_HIV_NADIA&ARTIST summary_30November2021_v1.0

[9] NDoH Evidence Summary. TDF-backbone as 2nd line in HIV_Adults_Evidence summary_19May2022_ v3.0

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:

STG AMENDED TO:

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). » 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).

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: » **TEE** » **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 ATV/r-containing regimen with latest VL <1000 copies/mL**	Switch to DTG-containing regimen regardless of VL result: TDF + 3TC + DTG ("TLD") If contraindications to DTG or TDF, use alternative regimen as for first line 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. If adherence < 80%, switch to DTG-containing regimen: TDF + 3TC + DTG ("TLD") If contraindications to DTG or TDF, use alternative regimen as for first line above.

CLIENTS WITH DTG RESISTANCE
STG ADDITION:

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/)

RIFAMPICIN-BASED TB TREATMENT (on DTG-regimen)
DTG: *added*
STG text was amended to align to the DTG evidence 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:
Amended to:

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.

PROTEASE INHIBITORS
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[10] may be found at the end of this document or alternatively accessed on the NHI webpage. The STG has been aligned to the National ART Guidelines.

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					

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[11] may be found at the end of this document or alternatively accessed on the NHI webpage.

[10] NDoH evidence summary. ATV/r vs LPV/r_2 nd line adult HIV therapy_ AdultReview_18 November 2021
[11] NDoH evidence summary. DRV/r vs LPV/r as 2nd line adult HIV therapy_PHC-AdultsMedicineReview_27 July 2021.

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 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

RESISTANCE TESTING

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.

CURRENTLY AVAILABLE ARV FDC PREPARATIONS ON CONTRACT

ATV/r: *Added*

ABC + 3TC + DTG: *Added*

STG text was updated to reflect currently available fixed-dose combination antiretrovirals that are accessible on the current public sector tender.[12]

RE_INITIATING ART

Re-initiating ART in patients who have interrupted treatment: *New guidance added*

The STG was amended as tabulated below:

AMENDED FROM:

RE-INITIATING ART IN PATIENTS WHO HAVE INTERRUPTED TREATMENT

» Recommence previous regimen.

» Do VL, recommence ART regimen, repeat at 3-6 months.

» If VL does not to decrease to <1000 copies per mL at 6 months, manage virological failure according to the specific regiment (refer to ART regimens table).

AMENDED TO:

RE-INITIATING ART IN PATIENTS WHO HAVE INTERRUPTED TREATMENT

» 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.

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

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:	**AMENDED TO:**
CrCl 10-50 mL/min: 150 mg daily CrCl <10 mL/min: 50 mg daily	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: A*dded*

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[13], 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.					

[13] NDoH evidence summary. DTG in pregnancy_PHC-Adults Medicine review_17June2021_v2

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[14]. 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 Guidelines.

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: DRUG-DRUG INTERACTIONS
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.[15] Findings from this pharmacokinetic study identified that metformin concentrations were half those seen in the healthy volunteer study by Song et al[16]. 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[17] with the standard release formulation. It is worth noting that while metformin

[14] 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
[15] 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)
[16] 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.
[17] 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

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.[18,19]

Lactic acidosis

While lactic acidosis is noted as a caution in the product information[20], 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,[21] 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.

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.")[22].

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. See Appendix II for further guidance on patients with renal impairment.
Rifampicin	Significant reduction in concentration of DTG	Double DTG dose to 50 mg 12 hourly.

[18] 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.

[19] 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.

[20] 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

[21] 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.

[22] 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.

MONITORING ON ART

CrAg screening

CrAg screening - threshold*: Amended*

Reflex screening of 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*). This may be considered at a higher CD4 threshold of <200 cells/mm^3 (conditional recommendation, moderate certainty evidence)."[23] 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.[24] 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."[25] The South African HIV Clinician Society Guideline[26] 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 testing at less than 100 cells/mm^3. The STG has been amended as tabulated below:

MONITORING ON ART

Baseline evaluation

- Confirm HIV positive result with second test.
- WHO staging.
- Check CD4 count.
- If CD4 <200 cells/mm^3:
  - Check cryptococcal antigen (if positive, perform LP regardless of whether symptoms are present or not).
  - Initiate cotrimoxazole prophylaxis (See Section 10.2.2: Cotrimoxazole prophylaxis).
  - 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 [27] 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*

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

[24] 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.

[25] 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.

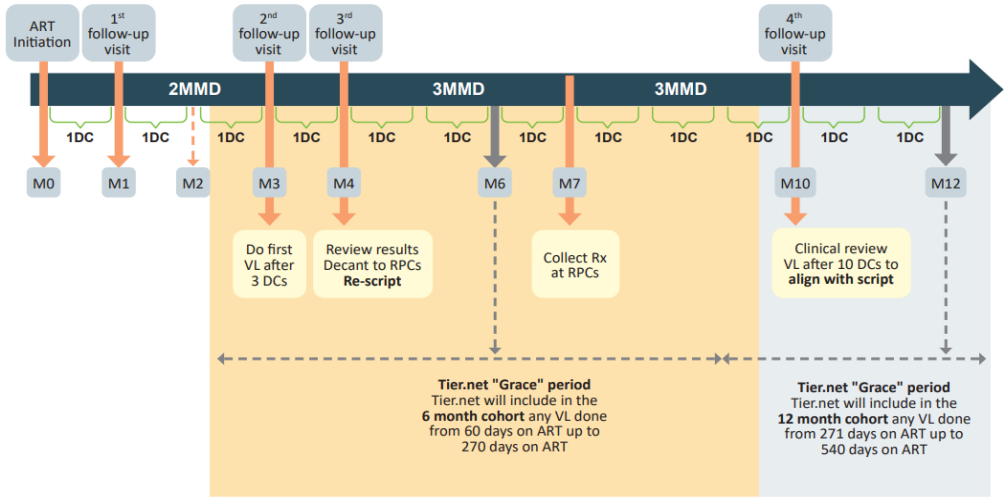
[26] Nel J, Meintjies G, Osih R et al. Southern African HIV Clinicians Society guidelines for antiretroviral therapy in adults: 2023 update. https://sahivsoc.org/Files/crypto%20guidelines.pdf

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

The HIV viral load monitoring schedule as illustrated in the national National ART Guideline has also been incorporated in the STG (figure 10.1).

HIV VIRAL LOAD MONITORING SCHEDULE

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		



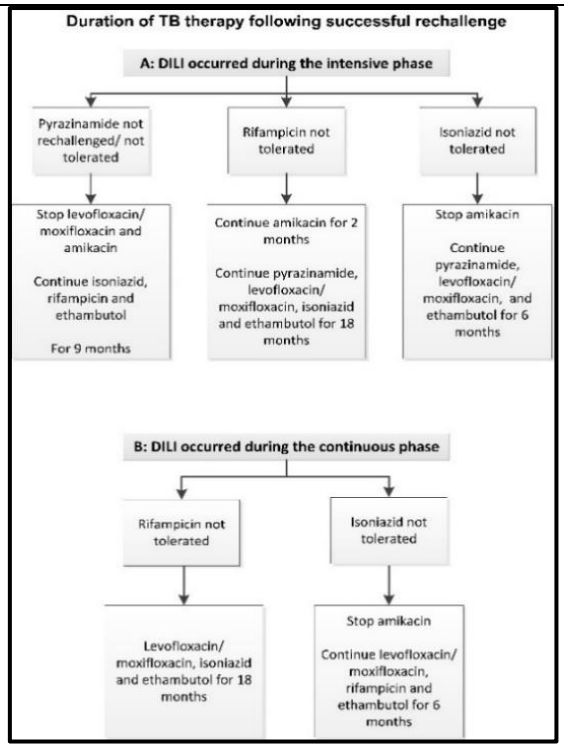
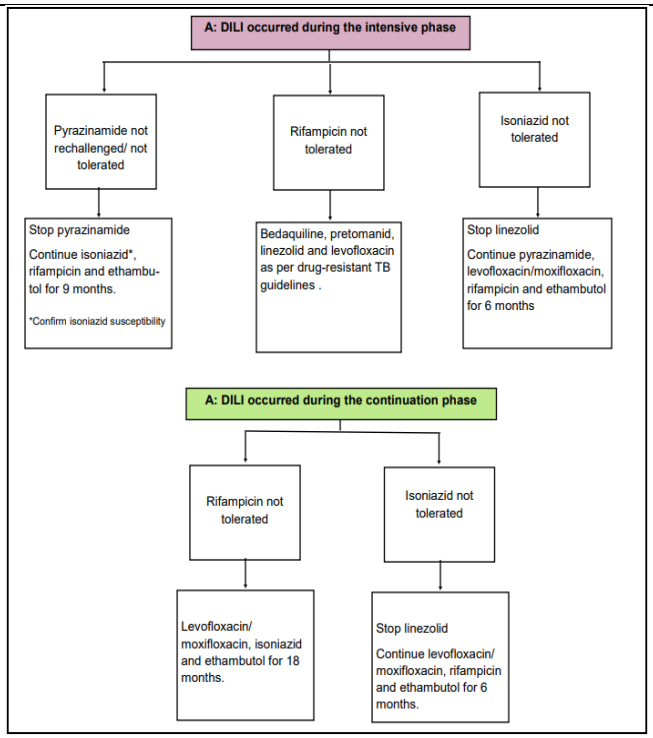
- For the 1st VL taken after 3 dispensing cycles, clients should be requested to return to the facility one DC later to review results and so that the client can be assessed for RPCs eligibility.
- For all subsequent VL monitoring (and other routine monitoring investigation) in clinically well clients: 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

10.1.1 MANAGEMENT OF SELECTED ANTIRETROVIRAL ADVERSE DRUG REACTIONS

Hepatotoxicity: *Amended*

Isolated hyperbilirubinaemia as a criterion for management of hepatotoxicity was removed, as this pattern is rare, and mostly of relevance to patients on ATV/r. ATV/r should only be stopped/switched if hyperbilirubinaemia was cosmetically unacceptable to the person. Treatment algorithm was amended:

AMENDED FROM:	AMENDED TO:
	

Hypersensitivity: *Guidance clarified*

The following editorial amendments were made to clarify that the features as detailed below are relevant specifically for EFV and not generally for all ARVs:

If any of the following features occur when a patient is on EFV, then EFV must be permanently discontinued:
- » Blistering
- » Lesions affecting mucous membranes (mouth, eyes, or genitals)
- » Fever.

Patients with lesions affecting the mucous membranes, or with significant blistering, likely have Stevens Johnson syndrome or toxic epidermal necrolysis, and will require admission.

With mild rashes EFV can be continued with careful observation and the rash will often subside.
If rash worsens or does not improve within a week discontinue EFV.

Hyperlactataemia**:** *Guidance clarified*

Editorial amendments as tabulated below were made for improved clarity. The Committee, however acknowledged that this guidance can be phased out of the STG in the next review cycle, given that treatment with AZT has been phased out.

AMENDED FROM:

A high index of suspicion is necessary. Send blood for lactate levels (check with your local laboratory for specimen requirements for lactate). Alternatively, point of care finger prick lactate monitoring can be done. Check the serum bicarbonate level if lactate is elevated.

Patients with mild hyperlactataemia (lactate 2.5–5 mmol/L):
Therapy should be altered by selecting NRTIs that are less associated with hyperlactataemia.
Note: The resolution of hyperlactataemia may take a few months.

Patients with lactate levels > 5 mmol/L:
Stop the NRTIs.
If the patient is on a 1st line regimen, continue the EFV or DTG and add LPV/r.
If the patient is on the 2nd line regimen, consult with an HIV specialist.
If there is acidosis, then admission to a high care unit is recommended.

Lactic acidosis carries a poor prognosis. Treatment is largely supportive. It is essential to exclude other causes of lactic acidosis, especially sepsis. High dose vitamin B, especially riboflavin and thiamine, may have a role in therapy.

AMENDED TO:
A high index of suspicion is necessary. Send blood for lactate levels (check with your local laboratory for specimen requirements for lactate). Alternatively, point of care finger prick lactate monitoring can be done. Check the serum bicarbonate level if lactate is elevated to confirm metabolic acidosis.

Patients with mild hyperlactataemia (lactate 2.5–5 mmol/L):
Alter therapy, selecting NRTIs that are less associated with hyperlactataemia.
Note: The resolution of hyperlactataemia may take a few months.

Patients with lactate levels > 5 mmol/L:
Stop the ART temporarily.
Consult with an HIV specialist regarding the: future ART plan.
Admission to a high care unit is recommended in patients with acidosis.

Lactic acidosis carries a poor prognosis. Treatment is largely supportive. It is essential to exclude other causes of lactic acidosis, especially sepsis. High dose vitamin B, especially riboflavin and thiamine, may have a role in therapy.

Hepatitis in patients on ART and anti-tuberculosis therapy: *Guidance clarified*

The management of patients on co-treatment with ARVs and TB therapy and who present with hepatitis has been amended as tabulated below. Amikacin should be considered as an alternative to linezolid if patients present with a Hb<8g/dL[28].

AMENDED FROM:
Management:
» Stop TB therapy and initiate background TB therapy and continue throughout rechallenge:
- Linezolid, oral 600 mg daily (amikacin, IV/IM, 15 mg/kg daily is an alternative, but only for short term use).
- Moxifloxacin, oral, 400 mg daily or levofloxacin 750–1000 mg daily.
- Ethambutol, oral, 800–1200 mg daily.

» Stop cotrimoxazole prophylaxis.
» Stop ART as described above.
» Repeat ALT and bilirubin in 2 days (inpatient) or 7 days (outpatient).
» When ALT is <100 IU/L and total bilirubin is less than twice the upper limit of normal, start TB medicine rechallenge as follows:

AMENDED TO:
Management:
» Stop TB therapy, initiate background TB therapy and continue throughout rechallenge:
- Linezolid, oral 600 mg daily (amikacin, IV/IM, 15 mg/kg daily is an alternative if Hb <8g/dL, but only for short term use).
- Levofloxacin, oral, 750–1000 mg daily or Moxifloxacin, oral, 400 mg daily.
- Ethambutol, oral, 800–1200 mg daily.

» Stop cotrimoxazole prophylaxis.
» Stop ART as described above.
» Repeat ALT and bilirubin in 2 days (inpatient) or 7 days (outpatient).
» When ALT is <100 IU/L and total bilirubin is less than twice the upper limit of normal, start TB medicine rechallenge as follows:

10.1.2 IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

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 (to a maximum of 4g in 24 hours)
  - Maximum dose: 15 mg/kg/dose.

[28] Boyles T, Berhanu RH, Gogela N, Gunter H, Lovelock T, Mphothulo N, Parker A, Rabie H, Richards L, Sinxadi P, Wattrus C, Moosa MY. Management of drug-induced liver injury in people with HIV treated for tuberculosis: 2024 update. South Afr J HIV Med. 2024 Mar 30;25(1):1558. doi: 10.4102/sajhivmed.v25i1.1558. PMID: 38628909; PMCID: PMC11019071.

10.2 OPPORTUNISTIC DISEASES

10.2.1 TUBERCULOSIS PREVENTIVE THERAPY (TPT)

ADULT PLHIV INITIATED IN 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)[29] and rifapentine in PLHIV on DTG-containing antiretroviral therapy (11 November 2019)[30] which is accessible on the NHI webpage.

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.

[29] NDoH Evidence Summary. NDoH_EDP_Rifapentine_Adults Review Update_14November2019_v1.0
[30] NDoH Evidence Summary. NDoH_EML_Rifapentine_&_Dolutegravir_ TPT_AdultsReview_v1

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).

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:

Note: For 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 preferred. 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].*

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/mm^3.	If CD4 ≤350 cells/mm^3.
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[31] 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.

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

10.2.2 OPPORTUNISTIC INFECTION PROPHYLAXIS, WITH COTRIMOXAZOLE

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[32] which has been amended from WHO stage II, III or IV in 2000[33] 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).

10.2.3 CANDIDIASIS OF OESOPHAGUS/TRACHEA/BRONCHI

Fluconazole, oral: *directions for use amended*

The STG was editorially amended as follows:

- Fluconazole, IV/oral, 200 mg daily for 14 days.
  - The usual route is oral but give IV if patient unable to swallow or is vomiting.
  - An early relapse should be treated with a 4-week course of fluconazole, using a similar dose as above.
  - If no response to fluconazole, collect sample to confirm diagnosis of candidiasis (perform fungal MC&S).

10.2.4 CRYPTOCOCCOSIS

Algorithm for the prevention, diagnosis and management of cryptococcosis among PLHIV: *Amended*

ART (if CSF CrAg negative): *Directions for use amended (timing of initiation)*

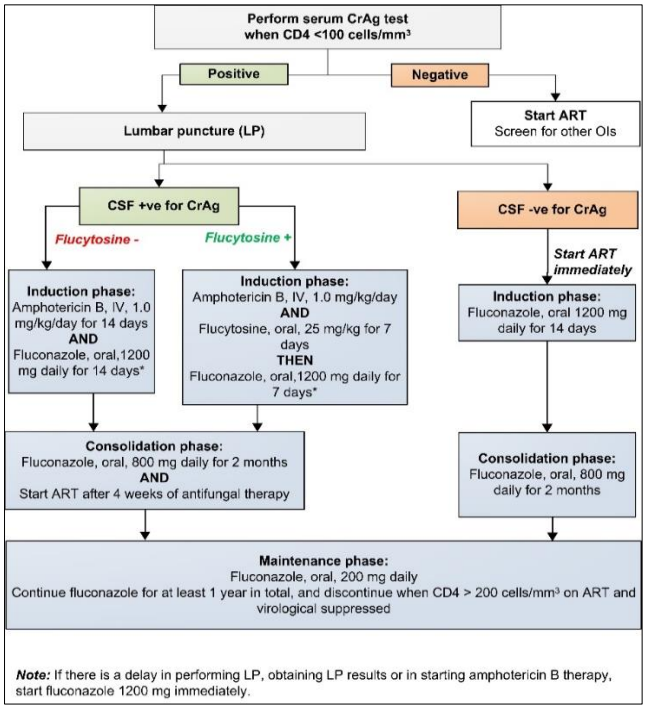
Treatment algorithm was amended for clarity purposes and correctness. It was noted that NEMLC had previously recommended that the SA HIV Clinicians Society algorithm be adapted, and the option to refuse a lumbar puncture be removed from the algorithm. Therefore, this section was delineated into management for i) CSF CrAg negative and ii) Cryptococcal meningitis, aligned with the most recent SA HIV Clinician Society algorithm[34], and section 10.2.4.2: Cryptococcal meningitis, below. Additionally, the algorithm also includes guidance for the use of a liposomal amphotericin regimen in combination with flucytosine. See Section 10.2.4.2 below for further details.

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

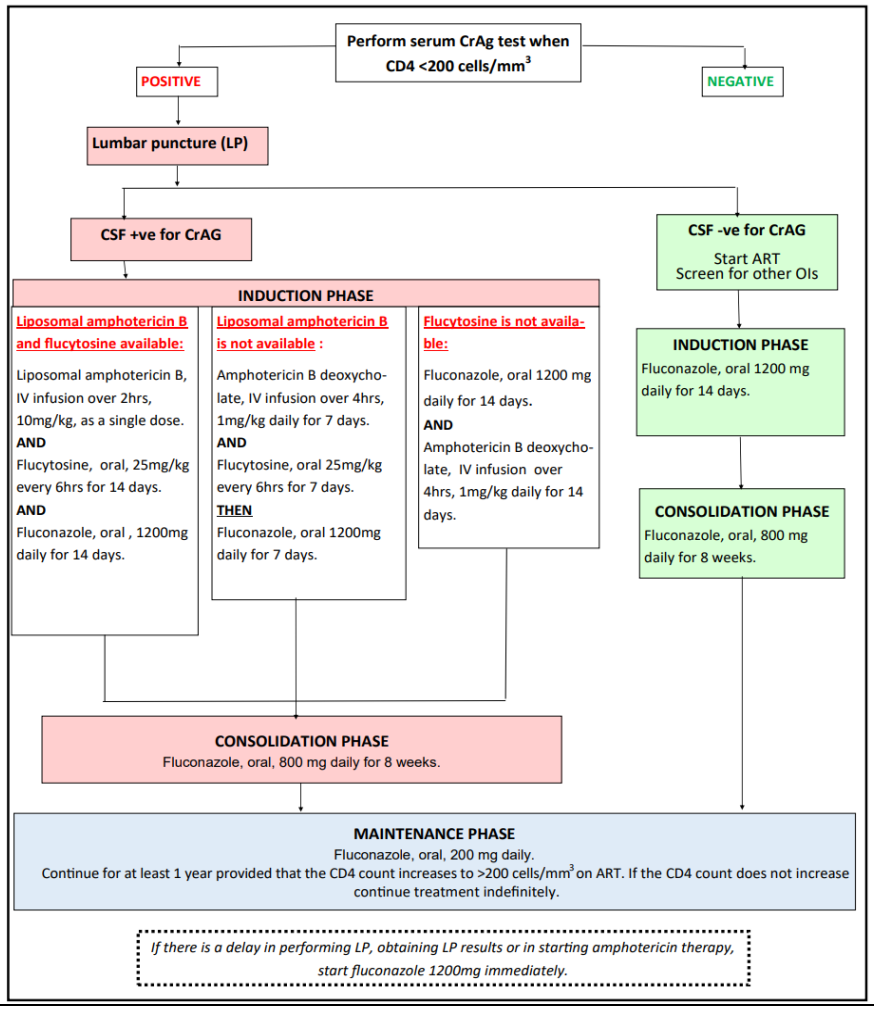
[33] Provisional WHO/UNAIDS secretariat recommendations on the use of cotrimoxazole prophylaxis in adults and children living with HIV/AIDS in Africa. Report 29/03/2000. Geneva: World Health Organization, 2000]

[34] Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. https://doi.org/10.4102/sajhivmed.v20i1.1030

AMENDED FROM:



AMENDED TO: *(V2.1 Erratum approved 28 Nov 2024)*



10.2.4.1 CRYPTOCOCCOSIS, CSF CRAG NEGATIVE

CrAg screening*: CD4 threshold amended*

Refer to discussion above – '*Monitoring on ART: CrAg screening at HIV diagnosis.'*

The description in the STG has been amended as tabulated below:

AMENDED FROM:

DESCRIPTION

All ART-naïve patients with CD4 <100 cells/mm^3 should have cryptococcal antigen (CrAg) test done on serum, plasma or whole blood (unless they had a diagnosis of cryptococcal infection). If positive, all patients should have a lumbar puncture, regardless of whether symptoms of meningitis are present, since asymptomatic cryptococcal meningitis may be present. The CSF should be tested for cryptococcal meningitis by CSF CrAg.

AMENDED TO:

DESCRIPTION

All ART-naïve patients with CD4 <200 cells/mm^3 should have cryptococcal antigen (CrAg) test done on serum, plasma or whole blood (unless they had a 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 count is between 100 and 199, a separate sample should be sent for CrAg testing. If the CrAg test is positive, all patients should have a lumbar puncture, regardless of whether symptoms of meningitis are present, since asymptomatic cryptococcal meningitis may be present. The CSF should be tested for cryptococcal meningitis by CSF CrAg.

ART: *directions for use amended*

Aligned with section 10.1 Antiretroviral therapy, adults - Clinical indications for deferring ART initiation: Asymptomatic cryptococcal infection (refer to discussion above).

10.2.4.2 CRYPTOCOCCAL MENINGITIS

Flucytosine, oral: *Added*

Liposomal Amphotericin B*: Added*

Amphotericin B, IV*: Retained*

Fluconazole, oral: *Retained*

Flucytosine

NEMLC had previously recommended that flucytosine be considered for inclusion in the EML, once SAHPRA registered and if the price for the oral regimen was reduced by 42% (R2195 per pack of 500mg, 100 tablets). Refer to the medicine review (November 2018)[35], economic analysis (June 2019)[36] accessible on the NHI webpage for further details. Flucytosine was registered by SAHPRA in December 2021 and the STG has been updated as tabulated below.

[35] NDoH Evidence Summary. NDoH_EDP_Flucytosine_Adults Review_15Nov2018_v3.0

[36] Flucytosine Health Economic and Budget Impact Analysis – EML June 2019

Flucytosine for treatment of cryptococcal meningitis

Recommendation:

Based on the evidence review, the Adult Hospital Level Committee recommends the following, **pending SAHPRA registration:**

- One-week combination of Amphotericin B deoxycholate and Flucytosine be the preferred regimen for treatment of CM in the induction phase.
- As an alternative, where Amphotericin B is not available or intravenous therapy cannot be administered, two-week oral course of Flucytosine and Fluconazole should be the alternative regimen.

However, cost-effectiveness analysis and budget impact analysis need to be investigated to determine affordability.

Rationale: Meta-analysis evidence shows that 1-week Amphotericin B + Flucytosine is not inferior to 2 weeks Amphotericin B + Fluconazole. When flucytosine was added to amphotericin B in a large multicentre trial conducted in several African countries, flucytosine was associated with a 38% lower risk of death compared to fluconazole (4)

Level of Evidence: I Systematic Review

Review indicators: SAHPRA registration; Price

NEMLC Minutes of 11 July 2019:

Following the review of the health economics and budget impact analyses (accessible at: http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/411-hospital-level-adults-costings) , NEMLC recommended the following:

NEMLC Recommendation: Flucytosine be considered for inclusion to the EML, pending SAHPRA registration with a reduction in price.

Rationale: Simulation confirms that flucytosine is cost-effective as induction therapy for treatment of cryptococcal meningitis amongst HIV-infected. Incremental budget impact of flucytosine compared to current standard of care is an estimated R8 million per annum, but savings could be achieved with early discharge of patients (i.e. LOS 10 days or less).

A 60% reduction in price would result in a cost-neutral budget impact (R1500.00 per 100 flucytosine tablets) for the 1 week AmBd/5FC course and cost neutrality would be achieved at a price of R2195 per pack (42% price reduction) for the oral regimen. However, this is subject to uncertainty in the model, including the impact of reduction in LOS, uptake of flucytosine and use of different regimens and so a price reduction of around 40% is likely to be reasonable.

Level of Evidence: I RCT, Costing analyses, Expert opinion

Liposomal Amphotericin B

Following a reduction in the price of liposomal amphotericin B, the evidence summary and associated cost analysis for the use of liposomal amphotericin B was updated – NEMLC recommendation tabulated below. For a copy of the complete evidence review[37], refer to the end of this report or alternatively to the NHI webpage.

[37] Liposomal Amphotericin B_ cryptococcal meningitis_Adults Review_Update_23 January 2024_final approved

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)**
	☐	☐	☐	☒	☐

Recommendation: Based on the updated evidence review, the PHC/Adult Hospital Level Committee suggests the use of liposomal amphotericin B for treating patients with cryptococcal meningitis.
Liposomal amphotericin B is non-inferior to current standard of care in terms of efficacy and is safer. Liposomal amphotericin B has a similar or lower cost compared to current standard of care, at the latest price of R600 per 50mg vial taking length of hospital stay into account in the costing.
Rationale: The current evidence of moderate risk of bias, shows that liposomal amphoteracin B is as efficacious as amphoteracin B deoxycholate in the management of cryptococcal meningitis. Safety outcomes reflect the superiority of liposomal amphotericin B regarding infusion related reactions, nephrotoxicity, hypokalaemia, and anaemia versus amphoteracin B deoxycholate.
Level of Evidence: Low to moderate certainty evidence
Review indicator: Price reduction

Evidence of efficacy	Evidence of harm	Price reduction
☐	☐	☒

VEN status: n/a

Vital	Essential	Necessary
☐	☐	☐

NEMLC MEETING OF 21 FEBRUARY 2019:
NEMLC ratified the medicine review and accepted the recommendation not to include liposomal amphotericin B in the Adult Hospital Level EML as although small and of moderate risk of bias, it shows that liposomal amphoteracin B is as efficacious as amphoteracin B deoxycholate in the management of cryptococcal meningitis, however it is currently not affordable.

NEMLC MEETING OF 23 JUNE 2022:
NEMLC upheld the previous recommendation not to include liposomal amphotericin B on the national EML, but amended the strength of recommendation from "strong" to "conditional", with a review indicator of "price reduction". The NEMLC further recommended that the proposed Gilead price of $16.25 per 50 mg vial be added as a threshold price.

NEMLC MEETING OF 30 NOVEMBER 2023: NEMLC supports the ERC's recommendation to include the use of liposomal amphotericin B on the EML for the management of cryptococcal meningitis in line with the treatment regimen included in the cost analysis (Addendum A). The Committee supported this recommendation on the basis of the better safety profile of liposomal amphotericin B compared to amphotericin B deoxycholate as well as the potentially lower overall cost with liposomal amphotericin B. The committee however, acknowledged the limitations of modelling the benefits of the better safety profile of liposomal amphotericin B in the cost analysis.

In line with the updated NEMLC recommendations as detailed above for liposomal amphotericin B, the STG has been updated as tabulated below:

AMENDED FROM:

10.2.4.2. CRYPTOCOCCAL MENINGITIS

B20.5 + (B45.1 + G02.1*)

DESCRIPTION

Cryptococcal meningitis is the commonest manifestation of disseminated cryptococcosis in patients with advanced HIV. Severe headache is common due to raised intracranial pressure.

Diagnosis

Confirmed on lumbar puncture.

GENERAL MEASURES

Therapeutic lumbar puncture is indicated to lower pressure in symptomatic patients and should be done with pressure monitoring. Remove sufficient CSF (maximum 30 mL) to lower pressure to 50% of the opening pressure but not less than 20 cm H_2O.

Therapeutic lumbar puncture should be done daily until there is clinical improvement.

MEDICINE TREATMENT
Induction phase

If flucytosine is available:

- Flucytosine, oral 25 mg/kg for 7 days.

Weight	6 hourly dosing
30-39 kg	750 mg 6 hourly

AMENDED TO:

10.2.4.2. CRYPTOCOCCAL MENINGITIS

B20.5 + (B45.1 + G02.1*)

DESCRIPTION

Cryptococcal meningitis is the commonest manifestation of disseminated cryptococcosis in patients with advanced HIV. Severe headache is common due to raised intracranial pressure.

Diagnosis

Confirmed on lumbar puncture.

GENERAL MEASURES

Therapeutic lumbar puncture is indicated to lower pressure in symptomatic patients and should be done with pressure monitoring. Remove sufficient CSF (maximum 30 mL) to lower pressure to 50% of the opening pressure but not less than 20 cm H_2O.

Continue daily therapeutic lumbar puncture until there is clinical improvement.

MEDICINE TREATMENT
Induction phase

If liposomal amphotericin B and flucytosine are available:

- Liposomal amphotericin B, slow IV infusion over 2 hours, 10 mg/kg in dextrose 5%, single dose.

AND

40-49 kg	1000 mg 6 hourly
50-59 kg	1250 mg 6 hourly
60-69 kg	1500 mg 6 hourly
70-79 kg	1750 mg 6 hourly

Note: Flucytosine requires dose adjustment in renal failure (See Appendix II for preventing, monitoring and management of toxicity).

AND

- Amphotericin B, slow IV infusion, 1 mg/kg daily in dextrose 5 % over 4 hours for 7 days.
  - Ensure adequate hydration to minimise nephrotoxicity. (See Appendix II for preventing, monitoring and management of toxicity).

THEN (i.e. days 8-14 of induction phase):

- Fluconazole, oral 1200mg daily for 7 days.

<u>If flucytosine is not available:</u>

- Fluconazole, oral 1200 mg daily for 14 days.

AND

- Amphotericin B, slow IV infusion, 1 mg/kg daily in dextrose 5 % over 4 hours for 14 days.
  - Ensure adequate hydration to minimise nephrotoxicity. (See Appendix II for preventing, monitoring and management of toxicity).

Consolidation phase

Follow with:

- Fluconazole, oral, 800 mg daily for 8 weeks.

Maintenance phase

- Fluconazole, oral, 200 mg daily.
  - Continue for at least 1 year provided that the CD4 count increases to >200 cells/mm^3 on ART. If the CD4 count does not increase continue treatment indefinitely.

- Commence ART 4–6 weeks after starting antifungal therapy. See section 10.1: Antiretroviral therapy.

Note: Adjunctive corticosteroids have been shown to be detrimental.

REFERRAL

» Focal neurological signs – CT scan required to exclude other pathology e.g. toxoplasmosis.

» Persistent raised intracranial pressure despite daily therapeutic lumbar puncture.

- Flucytosine, oral 25 mg/kg 6 hourly for 14 days (see flucytosine weight-based dosing table below).
  - Flucytosine requires dose adjustment in renal failure (See Appendix II for preventing, monitoring and management of toxicity).

AND

- Fluconazole, oral 1200mg daily for 14 days
  - Fluconazole requires dose adjustment in renal failure.

<u>If liposomal amphotericin B is not available:</u>

- Amphotericin B deoxycholate, slow IV infusion, 1 mg/kg daily in dextrose 5 % over 4 hours for 7 days.
  - Ensure adequate hydration to minimise nephrotoxicity. (See Appendix II for preventing, monitoring and management of toxicity).

<u>AND</u>

- Flucytosine, oral 25 mg/kg 6 hourly for 7 days (see flucytosine weight-based dosing table below).
  - Flucytosine requires dose adjustment in renal failure (See Appendix II for preventing, monitoring and management of toxicity).

THEN (i.e. days 8-14 of induction phase):

- Fluconazole, oral 1200mg daily for 7 days.

<u>If flucytosine is not available:</u>

- Fluconazole, oral 1200 mg daily for 14 days.

AND

- Amphotericin B deoxycholate, slow IV infusion, 1 mg/kg daily in dextrose 5 % over 4 hours for 14 days.
  - Ensure adequate hydration to minimise nephrotoxicity. (See Appendix II for preventing, monitoring and management of toxicity).

Consolidation phase

Follow with:

- Fluconazole, oral, 800 mg daily for 8 weeks.

Maintenance phase

- Fluconazole, oral, 200 mg daily.
  - Continue for at least 1 year provided that the CD4 count increases to >200 cells/mm3 on ART. If the CD4 count does not increase continue treatment indefinitely.

- Commence ART 4–6 weeks after starting antifungal therapy. See section 10.1: Antiretroviral therapy.

Note: Adjunctive corticosteroids have been shown to be detrimental.

Flucytosine weight-based dosing table:

Weight	6 hourly dosing
30-39 kg	750 mg 6 hourly
40-49 kg	1000 mg 6 hourly
50-59 kg	1250 mg 6 hourly
60-69 kg	1500 mg 6 hourly
70-79 kg	1750 mg 6 hourly

REFERRAL

- Focal neurological signs – CT scan required to exclude other pathology e.g. toxoplasmosis.
- Persistent raised intracranial pressure despite daily therapeutic lumbar puncture

Dosing in renal impairment has also been included in Appendix II for preventing, monitoring and management of toxicity, aligned with Guidelines *(note: Appendix II to be published with the final Adult Hospital Level STGs and EML, 2023 edition).* More specifically, an update has been made to drug monograph for amphotericin B deoxycholate (tabulated below).

AMENDED FROM:	**AMENDED TO:**
AMPHOTERICIN B, IV • Amphotericin B, IV, 0.7–1 mg/kg daily, dose and duration of therapy depend on indication for use and infecting organism. ○ Reconstitue in 5% dextrose water only (as incompatibile with saline solution). ○ Administer over a period of 2–6 hours. ○ Ensure adequate hydration to minimise the risk of nephrotoxicity. ***Monitoring*** – Serum potassium, magnesium and creatinine (baseline and twice weekly). Monitoring of serum potassium and creatinine should occur more frequently in neutropenic patients (3 times a week). – Monitor haemoglobin (baseline and weekly). – Careful attention to fluid monitoring of intake and output. – For management of hypokalaemia, see section 7.2.2: Hypokalaemia. ***Management of elevated creatinine*** If creatinine increases by ≥2 fold from baseline value, either omit an amphotericin B dose, or increase pre-hydration to 1 litre 8 hourly. – Once improved, restart at 0.7 mg/kg daily and consider alternate day amphotericin B. – If creatinine remains elevated i.e. ≥2 fold from baseline value, discontinue amphotericin B and continue with fluconazole, oral, 800 mg daily (for fungal infections known to be responsive to fluconazole, e.g. *Cryptococcus*). (Adapted from: WHO. Rapid advice: diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children: Prevention, monitoring and management of amphotericin B toxicity. 2011 [Online] [Accessed March 2016]. http://www.ncbi.nlm.nih.gov/books/NBK299520/pdf/Bookshelf_NBK299520.pdf	**AMPHOTERICIN B DEOXYCHOLATE, IV** • Amphotericin B deoxycholate, IV, 0.7–1 mg/kg daily, dose and duration of therapy depend on indication for use and infecting organism. ○ Reconstitue in 5% dextrose only (as incompatibile with saline solution). Do not reconstitute or dilute with saline or administer through an intravenous line that has previously been used for saline unless first flushed with dextrose solution (5 %,10 % or 20 %) for infusion. ○ Administer over a period of 2–6 hours. ○ Ensure adequate hydration to minimise the risk of nephrotoxicity. ***Monitoring*** – Serum potassium, magnesium and creatinine (baseline and twice weekly). Monitoring of serum potassium and creatinine should occur more frequently in neutropenic patients (3 times a week). – Monitor haemoglobin (baseline and weekly). – Careful attention to fluid monitoring of intake and output. – For management of hypokalaemia, see section 7.2.2: Hypokalaemia. ***Management of elevated creatinine in cryptococcal meningitis*** If creatinine increases by ≥2 fold from baseline value, stop amphotericin B deoxycholate, increase pre-hydration to 1 litre 8 hourly (watch for fluid overload), and switch to fluconazole 600mg daily and flucytosine 25mg/kg (with the flucytosine dosing interval adjusted for eGFR). – Once improved, restart to complete 7 days amphotericin B deoxycholate in total (Adapted from: WHO. Rapid advice: diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children: Prevention, monitoring and management of amphotericin B toxicity. 2011 [Online] [Accessed March 2016] http://www.ncbi.nlm.nih.gov/books/NBK299520/pdf/Bookshelf_NBK299520.pdf

Additionally, new monographs added for flucytosine and liposomal amphotericin (as tabulated below) which will be added to Appendix II of the EML:

LIPOSOMAL AMPHOTERICIN B, IV ○ Liposomal amphotericin B, IV, 10 mg/kg single dose for cryptococcal meningitis – Reconstitute in 5% dextrose only (as incompatible with saline solution). Do not reconstitute or dilute with saline or administer through an intravenous line that has previously been used for saline unless first flushed with dextrose solution (5 %,10 % or 20 %) for infusion. – Administer over a period of 2 hours. – Liposomal amphotericin B contains soya oil. Patients allergic to peanut or soya should not be given liposomal amphotericin B. ***Monitoring in patients with cryptococcal meningitis***

- Anaphylaxis and anaphylactoid reactions have been reported in association with liposomal amphotericin B. If a severe anaphylactic/ anaphylactoid reaction occurs, the infusion should be immediately discontinued and the patient should not receive further infusion.
- Monitor blood glucose levels in diabetic patients - each vial of liposomal amphotericin contains 900mg of sucrose. Furthermore, liposomal amphotericin B must be reconstituted with dextrose 5%.

FLUCYTOSINE, ORAL

- Flucytosine, oral, 25 mg/kg 6 hourly for 14 days for cryptococcal meningitis.

Monitoring

- Flucytosine is partially metabolised to 5-fluorouracil which is potentially teratogenic. Women of child-brearing age should be counselled on effective contraception during treatment and up to one month following discontinuation of treatment. Male patients should be counselled to use effective contraception during treatment and for 3 months following discontinuation of flucytosine treatment.

Management of elevated creatinine

Dosage adjustment is required in patients with renal impariment as tabulated below:

Creatinine Clearance	Single Dose	Dosing Interval
CrCl >40mL/min	25mg/kg	6 hourly
20 ≤ CrCl < 40mL/min	25mg/kg	12 hourly
10 ≤ CrCl < 20mL/min	25mg/kg	24 hourly
CrCl <10mL/min*	25mg/kg	48 hourly

***Adopted from:** Flucytosine | Johns Hopkins ABX Guide (hopkinsguides.com) https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540227/all/Flucytosine?q=flucytosine#3.2 and *Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. South Afr J HIV Med. 2019 Nov 8;20(1):1030. https://pubmed.ncbi.nlm.nih.gov/32201629/ Source: The Sanford guide to antimicrobial therapy 2019 / editors, David N, Gilbert MD, George M, Eliopoulos MD, Henry F, Chambers MD et al. Sperryville, VA, USA: Antimicrobial Therapy, Inc., [2019]).*

10.2.4.2 SYMPTOMATIC, NON-MENINGEAL CRYPTOCOCCOSIS *(STG DELETED)*

Fluconazole, oral: *Deleted*

Amphotericin B, parenteral: *Deleted*

ART: *Deleted*

As all CrAg positive patients are recommended to have a lumbar puncture, regardless of whether symptoms of meningitis are present, this STG has been deleted - guidance has been included in section 10.2.4.1: Cryptococcosis, CSF CrAg negative.

~~**DESCRIPTION**~~

~~Cryptococcal infection confirmed on culture or serum CrAg positive with non-meningeal disease. Any anatomical site may be involved, but the lungs are the commonest site.~~

~~**MEDICINE TREATMENT**~~

~~**Induction phase**~~

- ~~Fluconazole, oral 1200 mg daily for 14 days.~~

~~**AND**~~

- ~~Amphotericin B, slow IV infusion, 1 mg/kg daily in dextrose 5 % over 4 hours for 14 days.~~
  - ~~Ensure adequate hydration to minimise nephrotoxicity. (See Appendix II for preventing, monitoring and management of toxicity).~~

~~**Consolidation phase**~~

~~Follow with:~~

- ~~Fluconazole, oral, 800 mg daily for 8 weeks.~~

~~**Maintenance phase**~~

- ~~Fluconazole, oral, 200 mg daily.~~
  - ~~Continue for at least 1 year provided that the CD4 count increases to >200 cells/mm^3 on ART. If the CD4 count does not increase continue treatment indefinitely.~~
- ~~Commence ART 4–6 weeks after starting antifungal therapy. See section 10.1: Antiretroviral therapy.~~

10.2.6 CYTOMEGALOVIRUS (CMV)

Maintenance treatment

Ganciclovir, parenteral: *Deleted*

Valganciclovir, oral: *Retained*

The option to provide ganciclovir, IV, if valganciclovir, oral could not be tolerated for maintenance treatment of CMV was not considered to be a pragmatic option for public health sector, and was recommended for deletion.

Level of Evidence: IV Expert opinion

NEMLC MEETING OF 24 FEBRUARY 2022:

DISCUSSION:

Ganciclovir, parenteral: The proposal to remove ganciclovir, IV, for maintenance treatment of cytomegalovirus, was based on a value judgment, as it was more pragmatic to administer oral valganciclovir compared to parenteral ganciclovir (the latter requiring hospital admission). However, it is acknowledged that a standardised systematic framework for making value judgements is lacking.

Historically, ganciclovir, parenteral was cheaper than oral valganciclovir – the current price comparison estimated as follows (modelled on a 70kg adult and using UPFS 2020 tariffs for day patient administration of ganciclovir) favours use of oral valganciclovir:

Maintenance treatment regimen	Estimated cost for 30 days
Ganciclovir, IV, 5 mg/kg daily until CD4 count rises to >100 cells/mm3 on ART.	R724.50 + R1602 = R2326.50/day; 30 days **=R69 795.00**
Valganciclovir, oral, 900 mg daily until CD4 count rises to >100 cells/mm3 on ART.	**R 4973.75** (see discussion above)

References: Contract circulars Contract circular HP02-2021AI and HP02-2021AI/01; UPFS 2020 tariffs

10.2.9 PNEUMOCYSTIS PNEUMONIA

Primaquine, oral: *directions for access added*

The STG text was amended to include S21 access of primaquine.

Referral: *Editorial amendment*

The criteria for referral was amended editorially as tabulated below:

AMENDED FROM:

REFERRAL/CONSULTATION

Specialist or tertiary

Intolerance to second line regimen.

AMENDED TO:

REFERRAL/CONSULTATION

Specialist or tertiary

Intolerance to all alternative regimens.

10.5.1 POST-EXPOSURE PROPHYLAXIS, OCCUPATIONAL

Darunavir/ritonavir: *not added*

An external comment was received to consider a darunavir/ritonavir (DRV/r)-containing PEP regimen if lopinavir/ritonavir or atazanavir/ritonavir is not tolerated. However, darunavir/ritonavir is salvage therapy, and not recommended for inclusion on the primary or secondary level EML. Therefore, the STG text was updated as follows:

Lopinavir/ritonavir often causes diarrhoea. If lopinavir/ritonavir is not tolerated switch to atazanavir/ritonavir. Atazanavir/ritonavir often causes unconjugated jaundice, which is benign but may not be tolerated, in which case switch to lopinavir/ritonavir. If both these protease-inhibitors are not well tolerated, consult a specialist.

PEP REGIMENS

Tenofovir disoproxil fumarate (TDF): *Editorial amendments*

TDF contraindicated: *Guidance clarified*

Amendments to the STG were made for improved clarity as tabulated below:

AMENDED FROM:

When PEP is indicated (administered preferably as a fixed-dose combination):

- Tenofovir, oral, 300 mg daily for 4 weeks (provided baseline eGFR is >50 mL/minute).

and

- Lamivudine, oral, 300 mg daily for 4 weeks

and

Dolutegravir, oral 50 mg once daily for 4 weeks.

If DTG is not tolerated:

- Tenofovir, oral, 300 mg daily for 4 weeks (provided baseline eGFR is >50 mL/minute).

and

- Emtricitabine, oral, 200 mg daily for 4 weeks.

and

- Atazanavir/ritonavir 300/100 mg daily for 4 weeks.

Or

- Lopinavir/ritonavir 200/50 mg, oral, 2 tablets 12 hourly for 4 weeks.

If tenofovir is contraindicated or if source patient is known to be failing a tenofovir based regimen, replace tenofovir and emtricitabine with:

- Zidovudine, oral, 300 mg 12 hourly for 4 weeks.

and

- Lamivudine, oral, 150 mg 12 hourly for 4 weeks.

PEP is generally not well tolerated. Adverse effects occur in about half of cases and therapy is discontinued in about a third. Efavirenz is not recommended as it is very poorly tolerated in PEP.

AMENDED TO:

When PEP is indicated (administered preferably as a fixed-dose combination):

- Tenofovir disoproxil fumarate (TDF), oral, 300 mg daily for 4 weeks (provided baseline eGFR is >50 mL/minute. Do not delay initiation of PEP while awaiting baseline eGFR. Re-assess TDF eligibility once results become available).

AND

- Lamivudine, oral, 300 mg daily for 4 weeks

AND

Dolutegravir, oral 50 mg daily for 4 weeks.

If DTG is not tolerated:

- Tenofovir disoproxil fumarate (TDF), oral, 300 mg daily for 4 weeks (provided baseline eGFR is >50 mL/minute).

AND

- Emtricitabine, oral, 200 mg daily for 4 weeks.

AND

- Atazanavir/ritonavir 300/100 mg, 1 tablet, oral daily for 4 weeks.

OR

- Lopinavir/ritonavir 200/50 mg, oral, 2 tablets 12 hourly for 4 weeks.

If TDF is contraindicated or if source patient is known to be failing a TDF- based regimen, replace TDF and emtricitabine with:

- Zidovudine, oral, 300 mg 12 hourly for 4 weeks.

AND

- Lamivudine, oral, 150 mg 12 hourly for 4 weeks.

AND

- Continue third applicable drug (DTG or boosted PI – see above)

PEP is generally not well tolerated. Adverse effects occur in about half of cases and therapy is discontinued in about a third. Efavirenz is not recommended as it is very poorly tolerated in PEP.

PEP for healthcare workers following hepatitis B exposure

Hepatitis B Immunoglobulin: *Amended*

Aligned with the National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020[38] - STG text was updated as follows:

Vaccination status and	Source patient			
	Vaccination status	**HBsAg positive**	**HbsAg negative**	**HBsAg unknown**
	Unvaccinated or	• HBIG, IM, 500 units* • Hep B vaccine	• Initiate Hep B vaccination	• HBIG, IM, 500 units* • Hep B vaccine

[38] National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020. https://www.knowledgehub.org.za/elibrary/national-clinical-guidelines-post-exposure-prophylaxis-pep-occupational-and-non

antibody response status of HCW	vaccination incomplete	(3 doses at monthly intervals)	(month 0, 1 and 6)	(3 doses at monthly intervals)
	Vaccinated **AND** known to have HBsAb ≥ 10 units/mL[#]	No treatment	No treatment	No treatment
	Vaccinated **AND** HBsAb <10 units/mL or level unknown	• HBIG, IM, 500 units * • If HBIG <10 units/mL, repeat HBIG at 1 month • Repeat Hep B vaccine (3 doses at monthly intervals)	No treatment	• HBIG, IM, 500 units* • If HBIG <10 units/mL, repeat HBIG at 1 month • Repeat Hep B vaccine (3 doses at monthly intervals)

* HBIG and first dose of vaccine to be given simultaneously, but at different sites.
[#] If the delay in obtaining HBsAb results is more than 7 days initiate treatment as for vaccinated AND HBsAb < 10 units/mL.
After vaccination ensure the health care worker has a HBsAb > 10 units/mL 1 – 2 months after the last vaccine dose.

Delay in obtaining HBsAb results

Time period of delay: *Amended*

Aligned with the National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020[39]- STG text was updated as follows:

If the delay in obtaining HBsAb results is more than ~~24 hours~~ 7 days initiate treatment as for vaccinated AND HBsAb < 10 units/mL.

10.5.2 NON OCCUPATIONAL POST EXPOSURE PROPHYLAXIS, SEXUAL ASSAULT

HIV PrEP: *Added as a cross reference to the PHC STGs and EML*

For patients at ongoing high risk of HIV acquisition, guidance was provided to transition from PEP to PrEP as follows:

HIV PrEP
If patient is at ongoing high risk of HIV acquisition, commence PrEP after PEP has been completed.
Perform HIV test 4-weeks after initiating PrEP.

Emergency contraception

Copper IUCD: A*dded (as first line option)*

Levonorgestrel, oral: *Retained (as 2nd line option)*

Copper IUCD placed as the first line option as this agent has less drug-drug interactions compared to oral levonorgestrel 1.5mg and is the agent of choice for obese women. Copper IUCD can also be used as a long-acting reversible contraceptive.[40] [41]

Emergency contraception for obese women

Levonorgestrel, oral: *Dose not amended*

An external comment was received that there is no need to double the dose of levonorgestrel for obese women for emergency contraception. Limited data suggests that obese women have an increased risk of pregnancy after use of levonorgestrel and ulipristal acetate emergency contraception compared to those who are not obese.[42] In a pharmacokinetic study with 10 participants, levonorgestrol Cmax in obese participants was half that achieved in participants with normal BMI, and doubling the levonorgestrol dose in obese participants resulted in a similar Cmax to that seen in those with normal BMI[43]. Faculty of Sexual & Reproductive Healthcare (FSRH) Overweight, Obesity and Contraception Guidelines of April 2019, therefore recommends "double-dose (3 mg) of levonorgestrel emergency contraception, if BMI >26 kg/m2 or weight >70 kg". However, the effectiveness of double-dosing in preventing

[39] National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020. https://www.knowledgehub.org.za/elibrary/national-clinical-guidelines-post-exposure-prophylaxis-pep-occupational-and-non

[40] FSRH Guideline (April 2019) Overweight, Obesity and Contraception. BMJ Sex Reprod Health. 2019 Apr;45(Suppl 2):1-69. https://pubmed.ncbi.nlm.nih.gov/31053605/

[41] Turok DK, Jacobson JC, Dermish AI, Simonsen SE, Gurtcheff S, McFadden M, Murphy PA. Emergency contraception with a copper IUD or oral levonorgestrel: an observational study of 1-year pregnancy rates. Contraception. 2014 Mar;89(3):222-8. https://pubmed.ncbi.nlm.nih.gov/24332433/

[42] Jatlaoui TC and Curtis KM. Safety and effectiveness data for emergency contraceptive pills among women with obesity: a systematic review. Contraception 94 (2016) 605–611. https://www.ncbi.nlm.nih.gov/pubmed/27234874

[43] Edelman AB, Cherala G, Blue SW, Erikson DW, Jensen JT. Impact of obesity on the pharmacokinetics of levonorgestrel-based emergency contraception: single and double dosing. Contraception. 2016 Jul;94(1):52-7. https://pubmed.ncbi.nlm.nih.gov/27000996/

pregnancy is unknown.[44] In an randomised pharmacodynamic study with 70 obese participants, doubling the levonorgestrol dose did not result in improved inhibition of ovulation: proportion of women with no follicle rupture within 5 days of levonorgestrol administration was similar with standard and double dosing [45]. This suggests that doubling dose may not be sufficient to improve efficacy of oral levonorgestrol in obese women, although this study did not directly explore effect of double dosing on subsequent rates of pregnancy. Therefore, until new evidence emerges the recommendation of double-dosing of levonorgestrel amongst obese/overweight women will be retained, aligned with Guidelines.[5] Available evidence also suggests that the effectiveness of the copper IUCD is not affected by body weight or BMI. The copper IUCD is therefore the preferred method for emergency contraception in the obese.[46]
Level of Evidence: Guidelines

The caution box in the STG was amended as follows:

CAUTION
Emergency contraceptive tablets must be taken as soon as possible, preferably within 72 hours of unprotected intercourse, and not later than 5 days.
Enzyme inducers (including efavirenz and carbamazepine) cause a significant reduction in levonorgestrel concentrations.
Women on these medicines should preferably have copper IUCD inserted or alternatively double the dose of levonorgestrel.
Women > 80 kg or BMI ≥ 30 should also preferably have copper IUCD inserted or alternatively double the dose of levonorgestrel.

10.5.3 NON OCCUPATIONAL POST EXPOSURE PROPHYLAXIS, INADVERTENT NON-OCCUPATIONAL

Inadvertent (non-occupational) exposure: *Editorial amendment*
The list of examples pertaining to inadvertent, non-occupational exposure was transferred from Section 10.5.2 Non occupational post exposure prophylaxis, sexual assault to Section 10.5.3 Non occupational post exposure prophylaxis, inadvertent non-occupational as not relevant to sexual exposure. The following text was moved from Section 10.5.2 to Section 10.5.3:

Inadvertent (non-occupational) exposure to infectious material from HIV sero-positive persons often requires clinical judgement and includes:
» human bites (requires hepatitis B, but not HIV prophylaxis)
» sharing of needles during recreational drug use
» consensual sexual exposure, burst condoms
» contact sports with blood exposure

[44] FSRH Guideline (April 2019) Overweight, Obesity and Contraception. BMJ Sex Reprod Health. 2019 Apr;45(Suppl 2):1-69. https://pubmed.ncbi.nlm.nih.gov/31053605/
[45] Edelman, Alison B. MD, MPH; Hennebold, Jon D. PhD; Bond, Kise PSM; Lim, Jeong Y. PhD; Cherala, Ganesh PhD; Archer, David F. MD; Jensen, Jeffrey T. MD, MPH Double Dosing Levonorgestrel-Based Emergency Contraception for Individuals With Obesity, Obstetrics & Gynecology: June 9, 2022 - Volume - Issue - 10.1097/AOG.0000000000004717 doi: 10.1097/AOG.0000000000004717
[46] Turok DK, Jacobson JC, Dermish AI, Simonsen SE, Gurtcheff S, McFadden M, Murphy PA. Emergency contraception with a copper IUD or oral levonorgestrel: an observational study of 1-year pregnancy rates. Contraception. 2014 Mar;89(3):222-8. https://pubmed.ncbi.nlm.nih.gov/24332433/