SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 10: HIV AND AIDS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2017 -2019)

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the chapter for HIV and AIDs.

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED
10.1 Antiretroviral therapy	ART regimens	Amended to align with 2019 NDoH HIV Guidelines
- TB co-infection; CD4<50 (except TB meningitis)	ART	Time of initiation of ART in TB – *"initiate ART within 2 weeks of starting TB treatment"*
- TB meningitis	ART	*Time of initiation of ART in TB meningitis not amended – "defer ART until 8 weeks after initiating TB treatment"*
-Treatment-naïve patients	Tenofovir+emtricitabine+efavirenz, oral	Indication amended
	Tenofovir+lamivudine+dolutegravir, oral	Added
- Dual therapy	Efavirenz + lopinavir/ritonavir, oral	Retained
	Lamivudine + dolutegravir, oral	Added
- ART: Dosing and important adverse effects	Dolutegravir, oral	Guidance added on dosing and adverse effects
	Raltegravir, oral	Guidance added on dosing and adverse effects
	Efavirenz, oral	Guidance on adverse effects updated (associated encephalopathy)
- ARV-rifampicin drug interactions	InSTI, oral	Guidance added on interaction with rifampicin
- Protease inhibitor(s) – rifampicin interaction	Rifabutin, oral	Dose amended
- ARV – PPI/ H2 antagonist interaction	Atazanavir, oral	Guidance added on interaction with PPIs/H2 antagonists
- Drug interactions with dolutegravir	Dolutegravir, oral	Guidance added on drug interactions
- Monitoring for adults, whilst on ART	LAM testing	Added as additional test for DS-TB in seriously ill
- Evidence review	Tenofovir alafenamide (TAF), oral	Not added
10.1.2 Immune reconstitution inflammatory syndrome (IRIS)	Prednisone, oral	Added for prevention of IRIS in high risk patients
10.2.1 Tuberculosis preventive therapy (TPT)		
- Isoniazid monotherapy	Isoniazid, oral	Retained, duration of therapy and indication(s) amended
- Rifapentine-isoniazid therapy (3HP monthly regimen)	Rifapentine, oral	Not added (as 3HP)
	Isoniazid, oral	Not added (as 3HP)
- Pregnant women	Isoniazid, oral	Initiation of TPT deferred in pregnant women with high CD4 counts.
10.2.2 Oppurtunistic infection prophylaxis, with cotrimoxazole	Cotrimoxazole, oral	CD4 cut-off for OI prophylaxis retained as 200 cells/mm^3
10.2.4 Cryptococcosis	Algorithm	Amended
	Lumbar puncture	Indication amended
	Fluconazole, oral	Dose increased
	CD4 threshold	Not increased from 100 to 200 cells/mm^3
10.2.4.1 Asymptomatic cryptococcosis, CrAg positive	Fluconazole, oral	Dose increased
10.2.4.2 Symptomatic, non-meningeal cryptococcosis	Fluconazole, oral	Dose increased
	Amphotericin B liposomal, IV	Not added
10.2.4.3 Cryptococcal meningitis	Amphotericin B, IV	Dose not amended
	Amphotericin B liposomal, IV	Not added
	Flucytosine	Not added
	Fluconazole, oral	Dose increased
10.5.1 Post-exposure prophylaxis, occupational *and* **10.5.2 Non occupational post exposure prophylaxis , sexual assault** *and* **10.5.3 Non occupational post exposure prophylaxis, inadvertent non-occupational**	Tenofovir+lamivudine+dolutegravir, oral	Added
	Tenofovir + emtricitabine + atazanavir/ritonavir or lopinavir/ritonavir	Retained and indication amended (WOCP, pregnant <6 weeks gestation and intolerant to DTG)

Note: Prof G Maartens (as clinical editor) assisted with the update of this chapter.

STG narrative was generally aligned to the NDoH 2019 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy, Adolescents, Children, Infants and Neonates

Following was edited to include a url link to the updated 2019 guidelines:

Consult the most recent HIV Guidelines from the National Department of Health. https://www.knowledgehub.org.za/elibrary/2019-art-clinical-guidelines-management-hiv-adults-pregnancy-adolescents-children-infants

10.1 ANTIRETROVIRAL THERAPY

ART regimens: *amended to align with 2019 NDoH HIV Guidelines*

TIMING OF ART INITIATION

Previous NEMLC decisions upheld relating to timing of ART initiation[1].

Co-infected TB

i) INITIATING ART IN PATIENTS WITH TB CO-INFECTION (CD4<50; EXCEPT TB MENINGITIS)

ART: *Time of initiation of ART in TB – "initiate ART within 2 weeks of starting TB treatment"*

Evidence: The systematic review (Uthman et al)[2] showed that exposure/timing definitions of early ART are different across studies; there was approximately a two -fold increase in IRIS with early ART, but that there was a benefit of early ART in patients with CD4 < 50.

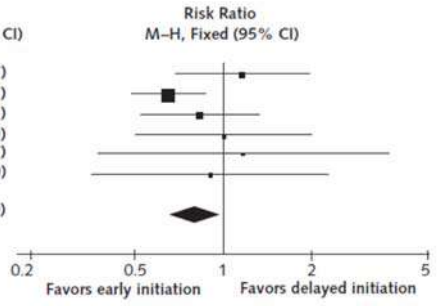
- *Uthman systematic review:* Randomized, controlled trials evaluating early versus delayed ART initiation (1 to 4 weeks vs. 8 to 12 weeks after initiation of TB treatment) or deferred ART initiation (after the end of TB treatment).

a) Mortality

Figure 3. All-cause mortality comparing early versus delayed initiation of ART.

Study, Year (Reference)	Events/Total, *n/N* Early ART	Delayed ART	Weight, %	Risk Ratio M–H, Fixed (95% CI)
Amogne et al, 2015 (27)	41/323	17/155	12.8	1.16 (0.68–1.97)
Blanc et al, 2011 (25 [CAMELIA])	59/332	90/329	50.6	0.65 (0.49–0.87)
Havlir et al, 2011 (26 [STRIDE])	31/405	37/401	20.8	0.83 (0.53–1.31)
Abdool Karim et al, 2011 (24 [SAPiT])	15/214	15/215	8.4	1.00 (0.50–2.00)
Manosuthi et al, 2012 (28 [TIME])	6/79	5/77	2.8	1.17 (0.37–3.67)
Sinha et al, 2012 (29)	9/88	7/62	4.6	0.91 (0.36–2.30)
Total	1441	1239	100.0	0.81 (0.66–0.99)
Total events	161	171		

Heterogeneity: $X^2 = 4.77$ ($P = 0.44$); $I^2 = 0\%$
Test for overall effect: $Z = 2.06$ ($P = 0.04$)



ART = antiretroviral therapy; CAMELIA = Cambodian Early Versus Late Introduction of Antiretrovirals; M-H = Mantel-Haenszel; SAPiT = Starting ART at Three Points in TB; STRIDE = Immediate Versus Deferred Start of Anti-HIV Therapy in HIV-Infected Adults Being Treated for Tuberculosis; TIME = Appropriate Timing of HAART in Co-infected HIV/TB Patients.

b) TB-IRIS

Among 1450 participants who received early ART, 253 (17.5%) developed TB-IRIS compared with 103 of 1239 (8.3%) in the delayed ART group (6 trials; RR, 2.31 [CI, 1.87 to 2.86]; I2 = 19%) early ART was associated with a higher incidence of TB-IRIS than delayed ART.

[1] Minutes of the NEMLC meeting of 5 July 2018.

[2] TB patients with CD4 count < 50 cells/mm^3: Uthman OA, Okwundu C, Gbenga K, Volmink J, Dowdy D, Zumla A, Nachega JB. Optimal timing of antiretroviral therapy initiation for HIV-infected adults with newly diagnosed pulmonary tuberculosis: A Systematic Review and Meta-analysis. Ann Intern Med. 2015 Jul 7;163(1):32-9. http://www.ncbi.nlm.nih.gov/pubmed/26148280

c) RCTs in the review

TRIAL	EARLIER ART	LATER ART
Amogne et al, 2015 (27) PMID: 25966339 1wk,4wk,12wk	Median7d(range4-48)	28d(r21-45) and 56d(r48-74)
Blanc et al, 2011 (25 [CAMELIA]) PMID: 22010913]	2 weeks (+/- 4 days)	8 weeks (+/- 4 days)
Havlir et al, 2011 (26 [STRIDE]) PMID: 22010914	Within 2 weeks	8-12 weeks
Abdool Karim et al, 2011 (24 [SAPiT]) PMID: 22010915] (within 4 weeks of TB init vs within 4 weeks of cont phase initiation arms presented in this paper)	21 d(IQR 15-29)	94d (IQR 77 to 127)
Manosuthi et al, 2012 (28 [TIME]) PMID: 22592586]	At 4 weeks	At 12 weeks
Mfinanga et al, 2014 (18 [TB-HAART]) PMID: 24810491	After 2 weeks	After 6 months
Sinha et al, 2012 (29) [PMID: 22846195]	2-4 weeks	8-12 weeks

Recommendation:

- Timing of ART in patients co-infected with TB recommended as "*within 2 weeks".*

Rationale: Systematic review showed mortality benefit of ART in patients that were severely immunocompromised (i.e. CD4<50). This review included a range of ART start times (1- 4 weeks). The 3 largest studies in the systematic review included patients started on ART before 2 weeks in the "early ART" arm.

Level of Evidence: III Systematic review

ii) INITIATING ART IN PATIENTS WITH TB MENINGITIS CO-INFECTION

ART: *Time of initiation of ART in TB meningitis not amended – "defer ART until 8 weeks after initiating TB treatment"*

Discrepancy between the STGs and the NDoH HIV Guidelines was noted with respect to the following:

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

The NDoH HIV Guidelines recommends deferring ART until 4–8 weeks after start of TB treatment, from a pragmatic perspective. However, NEMLC recommended that the current STG text be retained, based on level I evidence[3].

Level of Evidence: I RCT

Neural tube defects

Following narrative added, aligned with 2019 HIV Guidelines:

Women of childbearing potential should be given all necessary information on DTG- and EFV-containing regimens, including the benefits and potential risks of neural tube defects (NTDs) with DTG use during periconception period, as well as known risks of EFV-based regimens.

"DTG may increase the risk of neural tube defects (NTDs). The absolute risk is very low and translates into a risk difference of 2 additional NTDs per 1000 periconception exposures to DTG (0.3% risk), compared to EFV ART at conception (0.1% risk). DTG should be avoided periconception and in the first 6 weeks of pregnancy. The neural tube closes by the end of the sixth week of pregnancy (fourth week post-conception). DTG appears to be safe if started after the neural tube has closed. Thus, there is no risk of NTDs with TLD use after this period. Women of childbearing potential (WOCP) should be counseled regarding the risk of NTDs and be allowed to make an informed choice. Contraception is recommended for all women who do not currently wish to become pregnant".

Level of Evidence: III Surveillance study[4], Guidelines[5]

Treatment-naïve patients

Tenofovir + emtricitabine + efavirenz, oral: *indication amended*

Tenofovir + lamivudine + dolutegravir, oral: *added*

Refer to the NEMLC-approved medicine review (dolutegravir for HIV-infected patients commencing first-line antiretroviral therapy updated 11 February 2019), below:

Dolutegravir_HIV-Adults_Medicine revie

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

[3] Török ME, Yen NT, Chau TT, Mai NT, Phu NH, Mai PP, Dung NT, Chau NV, Bang ND, Tien NA, Minh NH, Hien NQ, Thai PV, Dong DT, Anh do TT, Thoa NT, Hai NN, Lan NN, Lan NT, Quy HT, Dung NH, Hien TT, Chinh NT, Simmons CP, de Jong M, Wolbers M, Farrar JJ. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)--associated tuberculous meningitis. Clin Infect Dis. 2011 Jun;52(11):1374-83. http://www.ncbi.nlm.nih.gov/pubmed/21596680

[4] Zash R, Holmes L, Diseko M, Jacobson DL, Brummel S, Mayondi G, Isaacson A, Davey S, Mabuta J, Mmalane M, Gaolathe T, Essex M, Lockman S, Makhema J, Shapiro RL. Neural-Tube Defects and Antiretroviral Treatment Regimens in Botswana. N Engl J Med. 2019 Aug 29;381(9):827-840. https://www.ncbi.nlm.nih.gov/pubmed/31329379

[5] NDoH 2019 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy, Adolescents, Children, Infants and Neonates, 2019.

ART Regimens: Aligned to the 2019 HIV Guidelines, as appropriate:

	PREVIOUS RECOMMENDATION	2019 RECOMMENDATION
First-line ART		
Treatment-naïve patients	Tenofovir + emtricitabine + efavirenz	Tenofovir + lamivudine + dolutegravir *Pregnant women in the 1st trimester or WOCP who make an informed choice to use EFV:* Tenofovir + emtricitabine + efavirenz
Contraindications and intolerance to EFV	Tenofovir + emtricitabine + nevirapine	Tenofovir + lamivudine + dolutegravir
Contraindications and intolerance to EFV and DTG	n/a	Tenofovir + lamivudine/emtricitabine + nevirapine
Contraindications to EFV and NVP	Tenofovir + emtricitabine + lopinavir/ritonavir	Tenofovir + lamivudine + dolutegravir
Contraindications to EFV, NVP and DTG	n/a	Tenofovir + emtricitabine/lamivudine + lopinavir/ritonavir
Contraindication to TDF	Abacavir + lamivudine + efavirenz or nevirapine	Abacavir + lamivudine + dolutegravir/efavirenz
Contraindication to TDF and ABC intolerance	Zidovudine + lamivudine + efavirenz or nevirapine	Zidovudine + lamivudine + dolutegravir/efavirenz
***NOTE:* In the unlikely scenario where there is intolerance/ contraindication to all currently available NRTIs (TDF, AZT and ABC) – dual therapy may be used - Specialist consult**	Efavirenz + lopinavir/ritonavir	Dolutegravir + lamivudine
Second-line ART		
Managament of low grade viraemia (VL = 50-999 copies/mL)	n/a	Enhance adherence counselling and repeat VL at 3 months. VL remains at 50-999 copies/mL, enhance adherence counselling, etc and repeat VL months later. Persistent low grade viraemia, manage as virological failure, below
Management of virological failure		
Failing a TDF-based/ NNRTI-based 1st line regimen	Zidovudine + lamivudine + lopinavir/ritonavir (PLUS tenofovir, if HBsAg positive).	Zidovudine + lamivudine/emtricitabine + dolutegravir. (**PLUS** tenofovir, if HBsAg positive). If dolutegravir contraindicated/ not tolerated: Zidovudine + lamivudine/emtricitabine + lopinavir/ritonavir
Failing a d4T/AZT-based 1st line regimen	TDF + FTC and LPV/r	n/a
Failing a DTG-based 1st line regimen for >2 years *(TDF+3TC+DTG)* • Resistance testing maybe required	n/a	Zidovudine + lamivudine/emtricitabine + lopinavir/ritonavir If HBsAg positive: Tenofovir + emtricitabine/lamivudine + lopinavir/ritonavir
Dyslipidaemia or diarrhoea associated with LPV/r	Switch lopinavir/ritonavir to atazanivr/ritonavir	Switch lopinavir/ritonavir to atazanivr/ritonavir
Third-line ART		
Failing any 2nd line regimen	Refer to a specialist.	Refer to a specialist.
(Abbreviations: 3TC=lamivudine, ABC=Abacavir, cobi=cobicistat, DTG=dolutegravir, EVG=elvitegravir, FTC=emtricitabine, TAF=tenofovir alafenamide).		

Dual therapy
Efavirenz + lopinavir/ritonavir, oral: *retained*
Lamivudine + dolutegravir, oral: *added*

Updated recommendation is based the results of two large Phase 3 RCTs that showed that 3TC + DTG was noninferior to DTG +TDF + FTC in terms of virologic efficacy in treatment-naïve patients. No drug resistance was seen in either treatment group (GEMINI studies I and II)[6]. The observational DOLAMA study[7] showed that dual therapy, 3TC + DTG, is a safe, effective and cost-effective option in pretreated and virologically stable HIV-positive patients to triple therapy DTG + ABC + 3TC and EVG/cobi + FTC + TAF.
Level of Evidence: I RCTs, Observational study

ART: Dosing and important adverse effects
Dolutegravir, oral: *guidance added on dosing and adverse effects*
Raltegravir, oral: *guidance added on dosing and adverse effects*
Aligned with SAMF, 2016, relevant package inserts and electronic medicine compendium.
Level of Evidence: III Guidelines

Dolutegravir: TB-associated IRIS with dolutegravir was reported to be uncommon, with no discontinuations for IRIS.
Level of Evidence: I RCT[8]

Efavirenz, oral: *guidance on adverse effects updated (associated encephalopathy)*
Case series suggests that efavirenz may be associated with severe reversible ataxia and encephalopathy; likely presenting in genetic slow metabolizers.
Level of Evidence: III Case series[9]

A: Important drug interactions to consider in patients treated for TB with rifampicin regimens:

- *Integrase strand transfer inhibitor (InSTI)*

InSTI, oral: *guidance added on interaction with rifampicin*
Aligned with aligned with NDoH 2019 HIV Guidelines.
Level of Evidence: III Guidelines

- *Protease inhibitors*

Rifabutin, oral: *dose amended*
The dose of rifabutin corrected from “150 mg 3 times a week” to “150 mg daily”.

Medicines Information Centre at the University of Cape Town has been informed of the error in the SAMF, 2016 edition (dosing of “150 mg 3 times a week).

Rifabutin concentrations are increased when rifabutin is taken together with protease inhibitors (PIs)[10]. Pharmacokinetic study[11] in healthy subjects showed that rifabutin 150 mg once daily alone vs rifabutin 150 mg twice weekly with atazanavir/ritonavir, Cmax, AUC and Cmin increased 149%, 48% and 40%, respectively; and active metabolite, 25-O-desacteyl rifabutin Cmax, AUC and Cmin increased 6.77-, 9.90- and 10.45-fold, respectively). Subjects experienced severe declines in neutrophil counts when rifabutin was given with atazanavir/ritonavir than alone and study was stopped. Post-hoc simulation analysis showed that rifabutin 150 mg thrice weekly with atazanavir/ritonavir was comparable to rifabutin 300 mg daily, dose necessary for reducing rifamycin resistance in

[6] Cahn P, Madero JS, Arribas JR, Antinori A, Ortiz R, Clarke AE, et al; GEMINI Study Team. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. Lancet. 2019 Jan 12;393(10167):143-155. https://www.ncbi.nlm.nih.gov/pubmed/30420123
[7] Hidalgo-Tenorio C, Cortés LL, Gutiérrez A, Santos J, Omar M, Gálvez C, et al. DOLAMA study: Effectiveness, safety and pharmacoeconomic analysis of dual therapy with dolutegravir and lamivudine in virologically suppressed HIV-1 patients. Medicine (Baltimore). 2019 Aug;98(32):e16813. https://www.ncbi.nlm.nih.gov/pubmed/31393412
[8] Dooley KE, Kaplan R, Mwelase N, Grinsztejn B, Ticona E, Lacerda M, Sued O, Belonosova E, Ait-Khaled M, Angelis K, Brown D, Singh R, Talarico CL, Tenorio AR, Keegan MR, Aboud M; INSPIRING study group. Dolutegravir-Based Antiretroviral Therapy for Patients Co-Infected with Tuberculosis and Hiv: A Multicenter, Noncomparative, Open-Label, Randomized Trial. Clin Infect Dis. 2019 Mar 28. pii: ciz256. https://www.ncbi.nlm.nih.gov/pubmed/30918967
[9] Variava E, Sigauke FR, Norman J, Rakgokong M, Muchichwa P, Mochan A, Maartens G, Martinson NA. Brief Report: Late Efavirenz-Induced Ataxia and Encephalopathy: A Case Series. J Acquir Immune Defic Syndr. 2017 Aug 15;75(5):577-579. https://www.ncbi.nlm.nih.gov/pubmed/28520619
[10] SAMF, 2016
[11] Zhang J, Zhu L, Stonier M, Coumbis J, Xu X, Wu Y, Arikan D, Farajallah A, Bertz R. Determination of rifabutin dosing regimen when administered in combination with ritonavir-boosted atazanavir. J Antimicrob Chemother. 2011 Sep;66(9):2075-82. https://www.ncbi.nlm.nih.gov/pubmed/21712242

HIV/TB co-infected patients and it was concluded that the benefit of rifabutin 150 mg thrice weekly outweigh the risks of neutropenia in non-HIV-infected subjects, provided that there is close monitoring for safety and tolerability monitoring.

Centers for Disease Control and Prevention subsequently updated recommendations to rifabutin 150 mg daily (when co-adminsitered with PIs)[12] as pharmacokinetic study of rifabutin 150mg thrice weekly with atazanavir/ritonavir in HIV/TB co-infected patients[13] suggest that rifabutin dosage may be inadequate with peak rifabutin concentrations below the lower therapeutic limit (<0.3 µg/ml) in some patients, while others had trough concentrations below the minimal inhibitory concentration against Mycobacterium tuberculosis (0.06 µg/ml). However, safety data with this dose and combination is limited and patients would require monitoring for rifabutin-related toxicities.

Lan et al (2014)[14] showed that when co-adminsitered with lopinavir/ritonavir, rifabutin 150 mg daily was associated with a 32% mean increase in rifabutin average steady state concentration vs rifabutin 300 mg alone; whilst rifabutin 150 mg thrice weekly showed a decrease by 44%. 2-5 fold increases of the 25-O-desacetyl-rifabutin metabolite were observed with both dosing regimens. The authors conclude that rifabutin 150 mg daily dosing may be preferred when co-administered with lopinavir/ritonavir,

Level of Evidence III: Pharmacokinetic studies, Guidelines

B: Other drug interactions

- *Atazanavir*

Atazanavir needs an acidic gastric environment for dissolution and absorption, and these agents (which decreases gastric pH) probably decreases solubility of atazanvir - however, other pharmacological mechanism for interaction has yet to be determined[15]. The European Medicines Agency had issued a public statement[16] of this interaction recommending that atazanavir not be co-administered with any PPI, irrespective of dose; – as an unpublished open-label pharmacokinetic study showed that 40mg omeprazole reduced atazanavir C_{MAX} by 72% and AUC by 76%. Co-administering 8 oz of cola (to reduce gastic pH) nor increasing dose of atazanavir to 400 mg resulted in therapeutic levels of atazanavir.

Recommendation: Guidance be provided that atazanavir not be co-administered with PPIs or H2 antagonists to reduce gastric acidity. If these agents are required, atazanavir to be changed to an alternative protease inhibitor.

Rationale: Pharmacokinetic study showed a significant interaction between omeprazole and atazanavir with a reduction in AUC of 76%, unresolved by boosting atazanavir or ritonavir. Atazanavir needs an acidic gastric environment for dissolution and absorption, and as PPIs and H2-antagonists decreases gastric pH these agents have been recommended not to be used with atazanavir. (Editorial recommendation that guidance be included in the STG in tabulated format, “Drug interactions with boosted PIs”).

Level of evidence: III Pharmacokinetic study, Expert opinion

C: Drug interactions with dolutegravir

Dolutegravir, oral: *guidance added on drug interactions*

Following was added to the STG text, aligned with NDoH 2019 HIV Guidelines:

[12] Centers for Disease Control and Prevention. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis [online]. 2013. www.cdc.gov/tb/TB_HIV_Drugs/default.htm

[13] Ramachandran G, Bhavani PK, Hemanth Kumar AK, Srinivasan R, Raja K, Sudha V, Venkatesh S, Chandrasekaran C, Swaminathan S. Pharmacokinetics of rifabutin during atazanavir/ritonavir co-administration in HIV-infected TB patients in India. Int J Tuberc Lung Dis. 2013 Dec;17(12):1564-8. https://www.ncbi.nlm.nih.gov/pubmed/24200269

[14] Lan NT, Thu NT, Barrail-Tran A, Duc NH, Lan NN, Laureillard D, Lien TT, Borand L, Quillet C, Connolly C, Lagarde D, Pym A, Lienhardt C, Dung NH, Taburet AM, Harries AD. Randomised pharmacokinetic trial of rifabutin with lopinavir/ritonavir-antiretroviral therapy in patients with HIV-associated tuberculosis in Vietnam. PLoS One. 2014 Jan 22;9(1):e84866. https://www.ncbi.nlm.nih.gov/pubmed/24465443

[15] University of Liverpool HIV Drug Interaction online tool. https://www.hiv-druginteractions.org/checker
- cited: Khanlou H, Farthing C. Co-administration of atazanavir with proton-pump inhibitors and H2 blockers. J Acquir Immune Defic Syndr. 2005 Aug 1;39(4):503. https://www.ncbi.nlm.nih.gov/pubmed/16010179

[16] European Medicines Agency. Public Statement: Important new pharmacokinetic data demonstrating that REYATAZ(atazanavir sulfate) combined with NORVIR (ritonavir) and omeprazole should not be co-administered, 21 December 2004. https://www.ema.europa.eu/en/documents/public-statement/important-new-pharmacokinetic-data-demonstrating-reyataz-atazanavir-sulfate-combined-norvir_en.pdf

DRUG INTERACTIONS WITH DOLUTEGRAVIR		
Interacting medicine	**Effect of co-administration**	**Recommendation**
Preparations containing polyvalent cations (Mg^{2+}, Ca^{2+}, Fe^{2+}, Al^{3+}, Zn^{2+}) Antacids Sucralfate Multivitamins Nutritional supplements	Significant reduction in concentration of DTG	Magnesium- and aluminum-containing preparations should be taken 6 hours before or 2 hours after DTG. Calcium- and iron- containing preparations can be taken with DTG together with food. **Note:** Iron and calcium should be taken at least 4 hours apart from one another.
Anitconvulsants: Carbamazepine Phenobarbital Phenytoin	Significant reduction in concentration of DTG	Avoid co-administration if possible. Consider valproate or lamotrigine. *For carbamazepine:* Double DTG dose to 50 mg 12 hourly.
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.

Level of Evidence: III Guidelines

Monitoring for adults, whilst on ART

LAM testing: *added as additional test for DS-TB in seriously ill*

Aligned with section 16.9: Tuberculosis, pulmonary.

EVIDENCE REVIEW OF TENOFOVIR ALAFENAMIDE

Tenofovir alafenamide oral: *not added*

Refer to the NEMLC-approved medicine review (tenofovir alafenamide, oral for HIV 1-infected adults, February 2020), below:

Tenofovir alafenamide (TAF) fc

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: TAF not be considered for inclusion in the Adult Hospital Level EML, currently.

Note:

- Based on the best available evidence, TAF is no better in efficacy than TDF and may have small safety benefits whose clinical relevance is still uncertain. TAF can be considered in first line regimens in the future should the TAF/FTC co-formulation or FDCs be licensed in RSA (FTC/TAF/DTG) – for patients with contraindications to TDF i.e. advanced renal disease.
- There is very limited clinical experience of TAF in pregnancy and we therefore do not recommend TAF use in pregnancy.
- The potential for the interaction of TAF with rifampicin exists and concurrent therapy still needs further evaluation.

Rationale:

- The efficacy and safety of TAF-containing regimens vs. TDF-containing regimens have been mostly evaluated in the context of the coformulation of elvitegravir, cobicistat, emtricitabine and darunavir. There is insufficient data where it has been evaluated in standard formulation used in LMICs.
- The synthesis shows that TAF is no more effective than TDF. TAF overall, shows slightly lower toxicity in these studies especially with regard to renal and bone health markers – the clinical significance of these differences in markers is not clear. However, these findings should be interpreted cautiously as in most studies TAF was co-formulated with cobicistat, where the TAF dose is reduced from 25mg to 10mg. The is a need for trials comparing or evaluating efficacy and especially safety of TAF head for head in standard coformulations used in low middle-income countries.

- Emerging observational data suggests switching from TDF to TAF may cause a statistically significant worsening of the lipid profile that may have clinical relevance. This is likely seen in patients with cardiovascular risk factors such as older age and high BMI. The lower concentrations of TDF in plasma from TAF as compared with TDF, and the lipid-lowering effect of TDF may explain the increases in total cholesterol in the TAF group compared with the TDF group. It may be important to weigh the possible benefit of lipid changes associated with TDF against the possible benefit of TAF for bone and kidney.

Level of Evidence: I Systematic Reviews and Meta-Analysis of Randomized Clinical Trials[17] [18] [19] [20] [21]

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.

10.1.2 IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

Severe IRIS manifestations (e.g. compression of major structures by enlarging lymph nodes, expanding CNS tuberculomata, worsening meningitis)

Prednisone, oral: *added for prevention of severe IRIS in high risk patients*
Recent RCT[22] supports current recommendation of prednisone: "Prednisone treatment during the first 4 weeks after the initiation of ART for HIV infection resulted in a lower incidence of tuberculosis-associated IRIS than placebo, without evidence of an increased risk of severe infections or cancers",

Effect size:

- Tuberculosis-associated IRIS in prednisone vs placebo group: 39/120 (32.5%) vs 56/120 (46.7%); RR 0.70; 95% CI 0.51 to 0.96; p=0.03; ARR 14.2% (95% CI 1.9 to 26.4%); NNT 8 (95% CI 4 to 53).

Level of Evidence: I RCT

Recommendation: Prednisone for prevention of severe IRIS in high risk patients (CD4 ≤ 100 cells/micromol) and had been receiving antituberculosis treatment for <30 days before initiating ART, noting that steroids should not be used in patients with Kaposi sarcoma.

10.2.1 TUBERCULOSIS PREVENTIVE THERAPY (IPT)

A: ISONIAZID
LTBI Regimens:
A. Isoniazid monotherapy
Isoniazid, oral: *retained, duration of therapy and indication(s) amended*
Aligned with PHC STGs and EML, 2018.

Duration of therapy:
Refer to the medicine review: Isoniazid preventive therapy for PLHIV on ART (November 2018):

[17] Tao X, Lu Y, Zhou Y, Zhang L, Chen Y. Efficacy and safety of the regimens containing tenofovir alafenamide versus tenofovir disoproxil fumarate in fixed-dose single-tablet regimens for initial treatment of HIV-1 infection: A meta-analysis of randomized controlled trials. Int J Infect Dis. 2020 Jan 24.
[18] Tao X, Lu Y, Zhou Y, Huang Y, Chen Y. Virologically suppressed HIV-infected patients on TDF-containing regimens significantly benefit from switching to TAF-containing regimens: A meta-analysis of randomized controlled trials. Int J Infect Dis. 2019 Oct; 87:43-53.
[19] Tamuzi JL, Tshimwanga JL, Bulabula AN, Muyaya LM. Tenofovir Alafenamide versus Tenofovir Disoproxil Fumarate: Systematic Review and Meta-Analysis. Int J Pul & Res Sci. 2018;2:555600.
[20] Gotham D, Hill A, Pozniak AL. Candidates for inclusion in a universal antiretroviral regimen: tenofovir alafenamide. Curr Opin HIV AIDS. 2017 Apr
[21] Vitoria M, Ford N, Clayden P, Pozniak AL, Hill AM. When could new antiretrovirals be recommended for national treatment programmes in low-income and middle-income countries: results of a WHO Think Tank. Curr Opin HIV AIDS. 2017 Apr.
[22] Meintjes G, Stek C, Blumenthal L, Thienemann F, Schutz C, Buyze J, Ravinetto R, van Loen H, Nair A, Jackson A, Colebunders R, Maartens G, Wilkinson RJ, Lynen L; PredART Trial Team. Prednisone for the Prevention of Paradoxical Tuberculosis-Associated IRIS. N Engl J Med. 2018 Nov 15;379(20):1915-1925. https://www.ncbi.nlm.nih.gov/pubmed/30428290

Isoniazid TB prophylaxis in PLHIV

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on this evidence review, the Adult Hospital Level Committee recommends a single six month course of INH within one month of initiating ART independent of CD4 cell count or TST status. Patients already on ART who have never received IPT may also benefit from IPT[5].
Rationale: Evidence of efficacy and safety with decreased TB incidence rate[5,6,8]. Badie *et al* showed that 6 months provided sustained response up to 6 years post treatment[7].
Level of evidence: I RCTs

NEMLC MEETING OF 21 FEBRUARY 2019:
Available evidence for IPT in PLHIV: Most of the evidence for isoniazid prevention therapy (IPT) in people living with HIV (PLHIV) was from the pre-ART era. Two RCTs done in PLHIV: i)RCT in Khayelitsha by Rangaka et al, 20146 of PLHIV either starting or established on ART comparing 12 months of isoniazid vs placebo; ii) Temprano RCT by Danel et al, 20157, where IPT; ART and IPT+ART were evaluated either starting early or late.
Previous NEMLC recommendation: In the PHC STGs and EML, 2018 IPT was simplified to 12 months, from the previous complex algorithm requiring TST, based on the Khayelitsha RCT.
Evidence for 6 months IPT: The Adult Hospital Level Committee's recommendation to change duration of IPT to 6 months based on a mortality benefit from the Temprano RCT, raised a concern. The Temprano RCT was done in West Africa, where the incidence of TB is lower compared to South Africa. It was stated that greater mortality benefit of 6 months IPT compared to 12 months IPT was biologically implausible, unless IPT is very toxic, however this is not the case.
Network meta-analysis of individual patient data (including South African data) is currently underway in the USA which should further inform decision-making on duration of IPT in PLHIV.
WHO recommendation of 36 months was discussed, noting that the evidence base was from the pre-ART era. IPT with ART was reported to be more durable than IPT without ART.
Recommendation: Previous NEMLC recommendation of IPT in PLHIV be retained as 12 months duration, until further evidence is forthcoming.
Rationale: Biologically plausible that 12 months rather than six months IPT would have greater benefit.
Despite the lack of data comparing duration of IPT therapy, available evidence in the local South African setting suggests that 12 months IPT would be reasonable.
Level of Evidence: I RCT

B: RIFAPENTINE
Following negotiations between UNITAIDs, Sanofi-Aventis South Africa (Pty) Ltd had reduced the price of rifapentine 150 mg, 24 tablets to R109.40 (55% reduction in price) – the current price on contract circular HP01-2019TB, w.e.f.7 November 2019.

Medicine review for rifapentine as part of the 3HP regimen for TB prophlaxis in PLHIV, has been updated using the updated tender price of rifapentine (Medicine review: Rifapentine (as part of Isoniazid-rifapentine short course TLTBI regimen for Adult persons living with HIV (PLHIV) on ART in a high burden TB country, November 2019).

Rifapentine (3HP) as TPT in PLHIV -Adu

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Direct medicine price comparison shows that 3HP is still cost-prohibitive: 12H = R211.44 vs 3HP = R350.84 (Price parity will occur when rifapentine 150mg, 24 tablets is reduced further to ***R62.93***).

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).

New indications:

Additional indications proposed for 3HP to be tabled at a quorum NEMLC meeting for review, includes:

ii) Children < 5 years of age (though safety in <2 years of age is uncertain) – for review by Paediatric ERC

iii) Virologically suppressed on TEE & switching to TLD; or virologically suppressed on TLD – for review by Adult ERC

Refer to the medicine review for 3HP use in patients who are virally suppressed on TLD, or virally suppressed on TEE and switching to TLD (Medicine review: Rifapentine (as part of Isoniazid-rifapentine short course TLTBI regimen for Adult persons living with HIV (PLHIV) on DTG-containing regimen in a high burden TB country, November 2019):

Rifapentine (3HP) as TPT in PLHIV on D

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

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*

NEMLC MEETINGS OF 11 APRIL 2019 AND 5 DECEMBER 2019:

The NEMLC recommended that 3HP prophylaxis could be considered as an alternative to 12H for Adult PLHIV on an efavirenz- or raltegravir-based ART regimen. However, 3HP was cost-prohibitive for inclusion to the Adult Hospital Level STGs and EML as a TPT regimen for PLHIV.

Rationale: There is reasonable evidence that the shorter 1HP and 3HP regimens are effective. However, there is no evidence of superior efficacy and safety over the current 12H standard of care; there are trends towards a slightly better side-effect profile for rifapentine-containing regimens, though it was uncertain whether the laboratory-confirmed (as opposed to clinically-evident) hepatoxic adverse effects would be relevant in the real-world setting. Furthermore, more data is required regarding drug-drug interactions (including in ART-naïve patients initiated on a DTG-containing regimen). Rifapentine is also considered too expensive and when there is price parity with 12H and adequate safety data (as provided by the TB Impact study and NDoH Demonstration study), the medicine could be further reviewed for possible inclusion in the EML.

Level of Evidence: I Meta-analysis[23], RCTs (moderate quality)[24] [25] [26]

Review indicators: *New evidence of efficacy and safety; Price*

[23] Njie GJ, Morris SB, Woodruff RY, Moro RN, Vernon AA, Borisov AS. Isoniazid-Rifapentine for Latent Tuberculosis Infection: A Systematic Review and Meta-analysis. Am J Prev Med. 2018 Aug;55(2):244-252

[24] Sterling TR, Scott NA, Miro JM, Calvet G, La Rosa A, Infante R, et al. Three months of weekly rifapentine and isoniazid for treatment of Mycobacterium tuberculosis infection in HIV-coinfected persons. AIDS. 2016;30(10):1607-15.

[25] Swindells S, Ramchandani A, Gupta A, et al. One month of rifapentine plus isoniazid to prevent HIV-related tuberculosis. N Eng J Med 2019; 380(11): 1009-1011.

[26] Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, et al. New regimens to prevent tuberculosis in adults with HIV infection. N Engl J Med. 2011;365(1):11-20.

Rifapentine, oral: *not added as 3 HP regimen*
Isoniazid, oral: *not added as 3HP regimen*
Non-inferiority trials suggests that 3HP prophylaxis is not inferior to 12H in PLHIV. However, 3HP is more expensive than 12H (even at a 55% reduction in the current price of rifapentine). Despite preliminary evidence suggesting that rifapentine can safely be used in patients on ART who are virally suppressed; peer reviewed publication of the Dolphin trial results is awaited.

In pregnant women, starting ART:
IPT: *initiation of IPT deferred in pregnant women with high CD4 counts.*

Following text was added to the STG:

In pregnant women, starting ART: » If CD4 ≥350 cells/microL: Defer IPT until after delivery. » If CD4 <350 cells/microL: Exclude active TB with symptom screen, then give IPT.

CD4 cut-off in pregnant women:
Background: WHO Guidelines recommends IPT in all HIV-infected pregnant women. Previous NEMLC-approved PHC recommendation of deferring IPT in pregnancy if CD≥100 cells/mm3 based on the TB APPRISE RCT[27] (n=956) that showed no difference between administering IPT antepartum vs postpartum for primary endpoint (mortality rate and incidence of active TB), but increased adverse pregnancy outcomes were reported (as a secondary endpoint). The mean CD4 was 500 cells/mm3 in the study with few TB events, and for local context, NEMLC previously recommended[28] a CD4 cut-off of 100 cells/mm^3 due to high incidence of TB in the South African setting (and extrapolated from the REALITY RCT[29] done in a non-pregnant cohort).

Kalk et al (2020): Subsequently, a larger local retrospective cohort study[30] (n= 43 971) showed that antenatal IPT is safe (adverse pregnancy outcomes defined as miscarriage, stillbirth, neonatal death, low birth weight) with greatest benefit against active TB when CD4 ≤350 cells/mm3.

Results of the study:

i. Adverse pregnancy outcomes (IPT vs no IPT)
- Adverse pregnancy outcomes: aOR 0.83; 95%CI 0.78 to 0.87.
- IPT started after the first trimester: aOR 0.71; 95%CI 0.65 to 0.79.
- IPT started from first trimester: aOR 0.64; 95%CI 0.55 to 0.75.

ii. TB risk (IPT vs no IPT)
- Risk of TB: aHR 0.71; 95%CI 0.63 to 0.81; absolute risk-difference 1518/100000.
- CD4 count ≤350cells/mm3: aHR 0.51; 95%CI 0.41 to 0.63.
- CD4 count >350cells/mm3: aHR 0.93; 95%CI 0.76 to 1.13.

Recommendation: IPT deferral if CD4 ≥350 in pregnant women; whilst where CD4<350, active TB to be excluded with symptom screen and then IPT given.
Rationale: A RCT of immediate versus delayed IPT initiation in pregnant woman found that isoniazid exposure in pregnancy was associated with increased risk of adverse pregnancy outcome (fetal demise, low birth weight, preterm delivery and congenital anomaly). Isoniazid should therefore be deferred until after delivery, except in women who are severely immunocompromised and have low CD4s. Subsequently, a local retrospective cohort

[27] Gupta A, Montepiedra G, Aaron L, Theron G, McCarthy K, Bradford S, Chipato T, Vhembo T, Stranix-Chibanda L, Onyango-Makumbi C, Masheto GR, Violari A, Mmbaga BT, Aurpibul L, Bhosale R, Mave V, Rouzier V, Hesseling A, Shin K, Zimmer B, Costello D, Sterling TR, Chakhtoura N, Jean-Philippe P, Weinberg A; IMPAACT P1078 TB APPRISE Study Team. Isoniazid Preventive Therapy in HIV-Infected Pregnant and Postpartum Women. N Engl J Med. 2019 Oct 3;381(14):1333-1346. https://www.ncbi.nlm.nih.gov/pubmed/31577875
[28] NEMLC report for the Primary Health Care HIV chapter, 2016-8 review.
[29] Post FA, Szubert AJ, Prendergast AJ, Johnston V, Lyall H, Fitzgerald F, Musiime V, Musoro G, Chepkorir P, Agutu C, Mallewa J, Rajapakse C, Wilkes H, Hakim J, Mugyenyi P, Walker AS, Gibb DM, Pett SL; Reduction of EArly mortaLITY in HIV-infected adults and children starting antiretroviral therapy (REALITY) Trial Team . Causes and Timing of Mortality and Morbidity Among Late Presenters Starting Antiretroviral Therapy in the REALITY Trial. Clin Infect Dis. 2018 Mar 4;66(suppl_2):S132-S139. https://www.ncbi.nlm.nih.gov/pubmed/29514234
[30] Kalk E, Heekes A, Mehta U, de Waal R, Jacob N, Cohen K, Myer L, Davies MA, Maartens G, Boulle A. Safety and Effectiveness of Isoniazid Preventive Therapy in HIV-Positive Pregnant Women on Art: An Observational Study using Linked Population Data. Clin Infect Dis. 2020 Jan 4. pii: ciz1224. https://www.ncbi.nlm.nih.gov/pubmed/31900473

study[31] (n= 43 971) showed that antenatal IPT is safe with greatest benefit against active TB when CD4 ≤350 cells/mm3.

Level of Evidence: II Cohort study

Table 4. Cox proportional hazard model for risk of TB disease stratified by CD4 count

variable	aHR CD4 ≤ 350 cells/µl (27.6%)	aHR CD4 > 350 cells/µl (46.9%)	CD4 Missing (25.6%)
Age (per 10 year increase)	0.97 (0.87 – 1.08)	0.79 (0.69 – 0.90)	0.85 (0.73 – 0.98)
1st recorded pregnancy	0.81 (0.72 – 0.91)	1.00 (0.86 – 1.16)	1.09 (0.92 – 1.30)
ART prior pregnancy	0.98 (0.85 – 1.13)	0.93 (0.77 – 1.11)	1.45 (1.01 – 2.10)
History of TB disease	2.56 (2.23 – 2.93)	3.10 (2.61 – 3.69)	2.16 (1.78 – 2.61)
VL > 50 copies/ml	Ref	Ref	Ref
VL < 50 copies/ml	0.59 (0.52 – 0.68)	0.76 (0.65 – 0.87)	0.50 (0.41 – 0.91)
VL missing	1.15 (0.97 – 1.37)	0.81 (0.61 – 1.09)	0.91 (0.71 – 1.15)
First ANC visit in primary care[a]	1.07 (0.93 – 1.23)	0.93 (0.79 – 1.10)	0.92 (0.75 – 1.11)
[illegible]	[illegible]	[illegible]	0.69 (0.53 – 0.89)
Any IPT	0.51 (0.41 – 0.63)	0.93 (0.76 – 1.13)	0.83 (0.63 – 1.08)

[illegible] e therapy; VL –HIV viral load

[a] first antenatal visit at a primary health care facility (Midwife Obstetric Unit as opposed to hospital)

[b] delivery in a primary health care facility (Midwife Obstetric Unit as opposed to hospital)

10.2.2 OPPURTUNISTIC INFECTION PROPHYLAXIS, WITH COTRIMOXAZOLE

Cotrimoxazole, oral: *CD4 cut-off for opportunistic infection (OI) prophylaxis retained as 200 cells/mm³*

Refer to the medicine review, cotrimoxazole for opportunistic infections in HIV – CD4 cut-off (May 2017):

Cotrimoxazole for OI in HIV-CD4 cut-o

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation

Based on the evidence gathered from the technical review, the Adult Hospital Level expert review committee does not support the current recommendations by the WHO[32] for cotrimoxazole prophylaxis among adult HIV-infected patients. The current recommendation be retained in the STGs and EML: Cotrimoxazole for HIV-infected patients with CD4 < 200 cells/ml and/or advanced HIV disease (WHO stages 2, 3, and 4).

Rationale: The impact and benefit of cotrimoxazole prophylaxis on morbidity and mortality among HIV-infected patients with CD4 ≤ 350 cells/mm3 and regions with high infectious disease (irrespective of CD4) has been demonstrated in a good quality systematic review and meta-analysis and individual randomized controlled trials. However, local South African data showed no benifit of cotrimoxazole prophylaxis when CD4 count >200 cells/mm³ in patients who were not WHO clinical stage III or stage IV.

Although cotrimoxazole is inexpensive, widely available and has been demonstrated to be cost-effective, long term safety data of cotrimoxazole use in adults and pregnant women are scanty.

Level of Evidence: I Meta-analysis, Systematic reviews and metanalyses [33] [34] [35], Observational study[36]

[31] Kalk E, Heekes A, Mehta U, de Waal R, Jacob N, Cohen K, Myer L, Davies MA, Maartens G, Boulle A. Safety and Effectiveness of Isoniazid Preventive Therapy in HIV-Positive Pregnant Women on Art: An Observational Study using Linked Population Data. Clin Infect Dis. 2020 Jan 4. pii: ciz1224. https://www.ncbi.nlm.nih.gov/pubmed/31900473

[32] World Health Organization. Guidelines on Post-Exposure Prophylaxis for HIV and the Use of Co-Trimoxazole Prophylaxis for HIV-Related Infections Among Adults, Adolescents and Children: Recommendations for a Public Health Approach: December 2014 supplement to the 2013 consolidated gu. Geneva; 2014 Dec.

[33] Suthar AB, Vitoria MA, Nagata JM, Anglaret X, Mbori-Ngacha D, Sued O, Kaplan JE, Doherty MC. Co trimoxazole prophylaxis in adults, including pregnant women, with HIV: a systematic review and meta-analysis. Lancet HIV. 2015 Apr;2(4): e137-50.

NEMLC MEETING OF 29 JUNE 2017:

NEMLC accepted this evidence review and the proposal as recommended by the Adult Hospital Level Expert Review Committee, above.

The NEMLC also acknowledged that despite meta-analyses and WHO Guidelines recommending cotrimoxazole prophylaxis in people on antiretroviral treatment (ART) with CD4 counts <350 cells/mm^{3}in low-income and middle-income countries, the majority of the studies (mix of observational and randomised controlled trials) were performed in countries with a high burden of malaria. The South African observational cohort study by Hoffman et al., showed that cotrimoxazole prophylaxis reduced mortality overall (adjusted HR 0.64, 0.57 to 0.72; p<0.001), where CD4 count was <200 cells/mm^3 (adjusted HR 0.64, 0.56 to 0.72) or in those with WHO clinical stage 3 or 4 conditions. Mortality was not significantly reduced where CD4 count was >200 cells/mm3 (HR 0.92, 0.42 to 2.0, p=0.08) or in those with WHO clinical stage 1 or 2 conditions.

Other considerations:

Adherence: Sterling et al[37] showed that for the outcome of active Tuberculosis, per protocol analysis failed to show non-inferiority of 3HP; whilst MITT demonstrated non- inferiority of 3HP – indicating that MITT analyses assumes all patients are compliant; and thus negating the adherence argument of 3HP vs Isoniazid (INH) monotherapy (H). In addition most of the trial protocols included directly observed treatment (DOT) in 3HP arm and not the control arm.

Fixed dose combination: There is no fixed dose combination formulation for HP, which has programmatic implications specifically impacting patient adherence and completion rates. However, a WHO pre-qualified FDC product is expected to be available from October 2019, and would probably be SAHPRA-registered thereafter.

Rifampicin: Evidence[38] suggests that daily INH+ rifampicin for 3 months (3RH) is also as effective as 6-12 months INH as preventive therapy. INH+rifampicin is available as a FDC and is cheaper than 3HP; though the intermittent dosing of 3HP is preferred as it is well tolerated. Network meta-anaysis[39] showed that there was no difference between 3HP and 3RH; but there are case reports[40] of increased postpartum and neonatal bleeding associated with rifampicin in pregnancy.

Global market for rifapentine has been limited, and it was reported that South Africa's contribution (due to the high TB burden of disease) to the global market would result in higher volumes consumed and thus a lower more affordable price globally. A NDoH programmatic decision has been taken to commit to uptake of rifapentine programmatically; however, the NEMLC has not recommended inclusion of rifapentine on the national EML, until the price of rifapentine is reduced with price parity between 12H and 3HP (evidence shows that 3HP is non-inferior to 12H).

Rifapentine studies: The following are underway:

- *TB impact study:* South Africa is a site of a multi-country TB Impact study of 3HP by Aurum Institute. A key research question that the TB Impact study will answer is what the impact would be to use 3HP in patients newly initiated on a DTG-containing regimen.
- *Demonstration study* to be funded in South Africa by the Global Fund, that will address programmatic aspects including safety issues with pharmacovigilance monitoring.

Therapeutic categorisation: 3HP is not considered therapeutically equivalent to 12H, pending evidence awaited to answer questions (see studies above) to further inform decision-making.

[34]SaadaniHassani A, Marston BJ, Kaplan JE. Assessment of the impact of cotrimoxazole prophylaxis on key outcomes among HIV-infected adults in low- and middle-income countries: a systematic review. J Acquir Immune DeficSyndr. 2015 Apr 15;68 Suppl3:S257-69. doi: 10.1097/QAI.0000000000000486. Review. Erratum in: J Acquir Immune DeficSyndr. 2015 Jun 1;69(2):e84.

[35] Forna F, McConnell M, Kitabire FN, Homsy J, Brooks JT, Mermin J, et al. Systematic review of the safety of trimethoprim-sulfamethoxazole for prophylaxis in HIV-infected pregnant women: implications for resource-limited settings. AIDS Rev. 2006;8(1):24–36.

[36]Hoffmann CJ, Fielding KL, Charalambous S, Innes C, Chaisson RE, Grant AD, Churchyard GJ. Reducing mortality with cotrimoxazole preventive therapy at initiation of antiretroviral therapy in South Africa.AIDS. 2010 Jul 17;24(11):1709-16.

[37] Sterling TR, Scott NA, Miro JM, Calvet G, La Rosa A, Infante R, et al. Three months of weekly rifapentine and isoniazid for treatment of Mycobacterium tuberculosis infection in HIV-coinfected persons. AIDS. 2016;30(10):1607-15.

[38] Ena J, Valls V. Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: a meta-analysis. Clin Infect Dis. 2005 Mar 1;40(5):670-6. https://www.ncbi.nlm.nih.gov/pubmed/15714411

[39] Njie GJ, Morris SB, Woodruff RY, Moro RN, Vernon AA, Borisov AS. Isoniazid-Rifapentine for Latent Tuberculosis Infection: A Systematic Review and Meta-analysis. Am J Prev Med. 2018 Aug;55(2):244-252

[40] Joint Formulary Committee (2017) British National Formulary. 55th Ed., London: British Medical Association and Royal Pharmaceutical Society of Great Britain.

10.2.4 CRYPTOCOCCOSIS

Lumbar puncture: *indication amended*

Updated guidelines recommends that all CrAg +ve PLHIV require a lumbar puncture to diagnose cryptococcal meningitis, as mortality from cryptococcal meningitis reported to be the highest in Sub-Saharan Africa (75%)[41] .CrAg +ve test can remain positive for prolonged period of time, and thus retesting should not be required. However, from a pragmatic perspective, only CrAg +ve PLHIV with symptoms of meningitis recommended for lumbar puncture. Algorithm updated - adapted from the updated South African HIV Clinician Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons, 2019[42](with adaptation) and WHO for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children[43].

Level of Evidence: III Guidelines

NEMLC MEETING OF 5 DECEMBER 2019:

Cryptococcal algorithm: NEMLC noted that algorithm in the PHC STGs and EML, 2018 and the draft Adult Hospital Level STGs and EML would differ (regarding the need for lumbar puncture in asymptomatic CrAg+ve patients), and queried the need to provide guidance for patients not consenting to a lumbar puncture.

NEMLC Recommendation: Algorithm for the management of cryptococcosis be amended to consider the above pragmatic implications.

Response to NEMLC recommendation (5 December 2019):

Evidence for routine LP screening: Local South African study[44] showed that an estimated third of asymptomatic CrAg-positive patients had cryptococcal meningitis; 31/90 asymptomatic patients (34%; 95% CI, 95% CI 25% to 45%) and 70/78 patients with headache only (90%; 95% CI 81% to 96%) were confirmed to have cryptococcal meningitis.

Significant association of blood CrAg titer was reported with concurrent cryptococcal meningitis in asymptomatic patients ($p<0.001$) and in patients with headache only ($p = 0.003$); OR for concurrent cryptococcal meningitis was 34.5 (95% CI 8.3 to 143.1; $p<0.001$).

After adjusting for antifungal therapy, HR for death in asymptomatic patients with confirmed concurrent cryptococcal meningitis was 2.00 (95% CI 0.83 to 4.78; $p =0.12$).

Recommendation: Thus, the algorithm updated to include LP for screening of cryptococcal meningitis. Pragmatic implications may include delay in treatment, as patients would need referral from primary level for LPs. However, as recommended in the updated South African HIV Clinician Society guideline, CrAg +ve patients and patients with symptoms of meningitis could be referred with an initial dose of fluconazole.

Level of Evidence: III Observational study, Guidelines

Algorithm is a simplified adaptation of the updated South African HIV Clinician Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons, 2019[45] and WHO for the diagnosis,

41 Rajasingham R, Smith RM, Park BJ, Jarvis JN, Govender NP, Chiller TM, Denning DW, Loyse A, Boulware DR. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. Lancet Infect Dis. 2017 Aug;17(8):873-881. doi: 10.1016/S1473-3099(17)30243-8. https://www.ncbi.nlm.nih.gov/pubmed/28483415

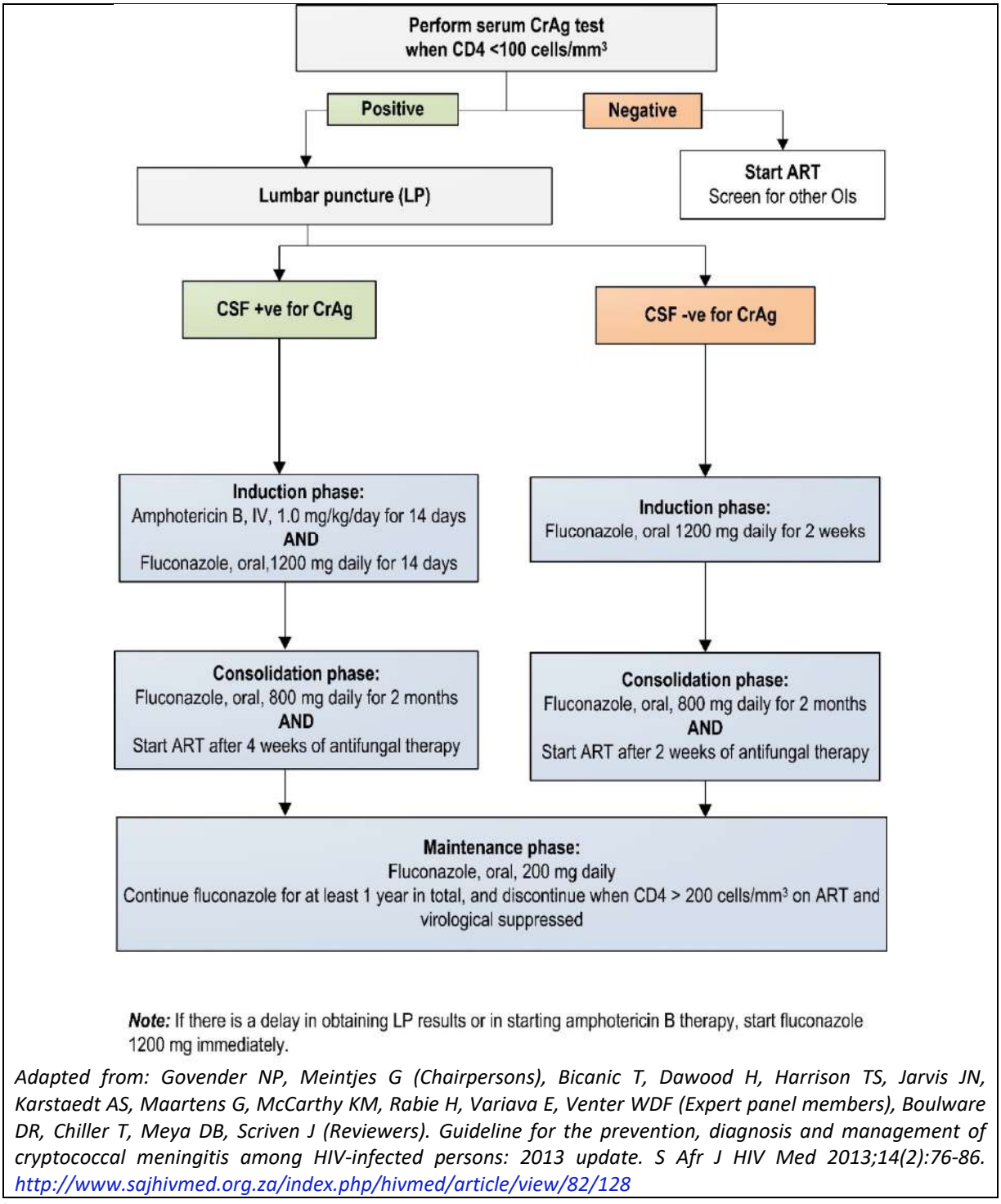
42 Govender NP, Meintjes G (Chairpersons), Bicanic T, Dawood H, Harrison TS, Jarvis JN, Karstaedt AS, Maartens G, McCarthy KM, Rabie H, Variava E, Venter WDF(Expert panel members), Boulware DR, Chiller T, Meya DB, Scriven J (Reviewers). Guideline for the prevention, diagnosis and management of cryptococcal meningitis among HIV-infected persons: 2013 update. S Afr J HIV Med 2013;14(2):76-86. http://www.sajhivmed.org.za/index.php/hivmed/article/view/82/128

43 WHO. Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, March 2018. https://www.who.int/hiv/pub/guidelines/cryptococcal-disease/en/

44 Wake RM, Britz E, Sriruttan C, Rukasha I, Omar T, Spencer DC, Nel JS, Mashamaite S, Adelekan A, Chiller TM, Jarvis JN, Harrison TS, Govender NP. High Cryptococcal Antigen Titers in Blood Are Predictive of Subclinical Cryptococcal Meningitis Among Human Immunodeficiency Virus-Infected Patients. Clin Infect Dis. 2018 Feb 10;66(5):686-692. https://www.ncbi.nlm.nih.gov/pubmed/29028998

45 Govender NP, Meintjes G (Chairpersons), Bicanic T, Dawood H, Harrison TS, Jarvis JN, Karstaedt AS, Maartens G, McCarthy KM, Rabie H, Variava E, Venter WDF(Expert panel members), Boulware DR, Chiller T, Meya DB, Scriven J (Reviewers). Guideline for the prevention, diagnosis and management of cryptococcal meningitis among HIV-infected persons: 2013 update. S Afr J HIV Med 2013;14(2):76-86. http://www.sajhivmed.org.za/index.php/hivmed/article/view/82/128

prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children[46]. The algorithm, recommended for use at secondary level was updated to:



Adapted from: Govender NP, Meintjes G (Chairpersons), Bicanic T, Dawood H, Harrison TS, Jarvis JN, Karstaedt AS, Maartens G, McCarthy KM, Rabie H, Variava E, Venter WDF (Expert panel members), Boulware DR, Chiller T, Meya DB, Scriven J (Reviewers). Guideline for the prevention, diagnosis and management of cryptococcal meningitis among HIV-infected persons: 2013 update. S Afr J HIV Med 2013;14(2):76-86. http://www.sajhivmed.org.za/index.php/hivmed/article/view/82/128

Level of Evidence: III Guidelines

Fluconazole, oral: *dose increased*

NICD data on file shared with NDoH[47] showed that fluconazole MIC_{50} and MIC_{90} values twice as high in 2017 (2 and 4 µg/ml, respectively) vs 2007-2008 (1 and 2 µg/ml, respectively). There are no breakpoints for fluconazole, but doses may be required for treatment of cryptococcosis and cryptococcal meningitis.

Level of Evidence: III Antimicrobial susceptibility study, Expert opinion

[46] WHO. Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, March 2018. https://www.who.int/hiv/pub/guidelines/cryptococcal-disease/en/

47 NICD data on file, pending publication in peer reviewed journal.

CD4 threshold: *not increased from 100 to 200 cells/mm3*

WHO 2018 Guideline recommendation[48]*: "Screening for cryptococcal antigen followed by pre-emptive antifungal therapy among cryptococcal antigen–positive people to prevent the development of invasive cryptococcal disease is recommended before initiating or reinitiating ART for adults and adolescents living with HIV who have a CD4 cell count <100 cells/mm3 (strong recommendation; moderate-certainty evidence) and may be considered at a higher CD4 cell count threshold of <200 cells/mm3 (conditional recommendation; moderate certainty evidence)".* The conditional recommendation was made in recognition of the higher prevalence of cryptococcal antigen observed at lower CD4 cell counts[49] and the availability of cost–effectiveness data to support screening at this threshold.

Ford et al: Systematic review of observational studies showed a statistically significant decrease in mortality among both people with a CD4 cell count <100 cells/mm3 (mortality rate ratio 0.75, 95%CI 0.58 to 0.95) and those with a CD4 cell count of 100–200 cells/mm3 (mortality rate ratio 0.56, 95% CI 0.32to 0.97).[50]

NICD report: Please see attached report from NICD submitted for NEMLC consideration:

NICD_Briefing report for NEMLC_C

(Available on request)

The above has been reviewed by the Adult Hospital Level Committee and the following has been concluded:

- The HIV Programme needs to review this data and implications.
- The literature points towards the mortality benefit of CrAg screening and pre-emptive treatment being retained among those with a CD4 count 101-200 cells/µl as shown in a post-hoc analysis of data from a single randomized clinical trial. Unpublished NHLS CD4 test volume data, August 2018-July 2019, indicate approximately 280,000 persons had CD4s<100 cells/µl and approximately 300,000 had a CD4 between 100 cells/µl and 200 cells/µl.
- From an implementation perspective, screening all persons with CD4 <200 cells/µl would lead to doubling of tests done.
- It is noted that as per the report, the following are recommended which the Adult Hospital Level Committee concurs with:
  - Conduct a pilot CrAg screening project to determine the current prevalence of new antigenaemia among persons with a CD4 count <200 cells/µl.
  - Conduct a full-scale costing and cost-effectiveness study using South African data comparing screening at a CD4 threshold of <200 cells/µl versus <100 cells/µl and various implementation scenarios.

Recommendations: The Adult Hospital Level Committee recommends that until there is sufficient data to inform a higher CD4 threshold, treatment protocol to retain the CD4 threshold as is (i.e. 100 cells/mm3).

10.2.4.1 ASYMPTOMATIC CRYPTOCOCCOSIS, CRAG POSITIVE

Fluconazole, oral: *dose increased*

See rationale above (section 10.2.4 Cryptococcosis)

[48] WHO. Guidelines for the diagnosis, prevention and management of cryptococcal disease in hiv-infected adults, adolescents and children supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, March 2018. https://www.who.int/hiv/pub/guidelines/cryptococcal-disease/en/

[49] 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. https://www.ncbi.nlm.nih.gov/pubmed/29514236

[50] 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. https://www.ncbi.nlm.nih.gov/pubmed/29514236

10.2.4.2 SYMPTOMATIC, NON-MENINGEAL CRYPTOCOCCOSIS

Amphotericin, liposomal: *not added*
See rationale and medicine review, below (section 10.2.4.3 Cryptococcal meningitis)

Fluconazole, oral: *dose increased*
See rationale above (section 10.2.4 Cryptococcosis)

10.2.4.3 CRYPTOCOCCAL MENINGITIS

Amphotericin B, IV: *dose not amended*
Flucytosine: *not added*
Amphotericin, liposomal: *not added*
Fluconazole, oral: *dose increased*

Amphotericin B, IV: *dose not amended*
Aligned with ACTA study[51] where amphotericin B was administered at a dose of 1 mg/kg.
Recommendation: Dose of amphotericin B retained as 1 mg/kg.
Rationale: Dose studied in ACTA trial.
Level of Evidence: I RCT

Amphotericin B, liposomal: *not added*
Price in comparison to amphotericin B makes this agent cost-prohibitive. Refer to the medicine review, liposomal amphotericin B for Cryptococcal meningitis, November 2018.

Liposomal Amphotericin B for c

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: The current evidence, although limited and of moderate risk of bias, shows that liposomal amphotericin 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. However, liposomal amphotericin B is not currently considered affordable for inclusion on the Adult Hospital Level EML. As there may be a need for consideration of liposomal amphotericin B in mucormycosis, the National Essential Medicines List Committee (NEMLC) recommends that this be investigated for tertiary level of care.

Level of Evidence: II Systematic review and meta-analysis of low to moderate quality RCTs
Review indicator: Price

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, shows that liposomal amphoteracin B is as efficacious as amphoteracin B deoxycholate in the management of cryptococcal meningitis, it is currently not affordable.

Flucytosine: *not added*

i. Evidence review

Refer to the medicine review: Flucytosine for cryptococcal meningitis, November 2018.

[51] Molloy SF, et al: ACTA Trial Study Team. Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa. N Engl J Med. 2018 Mar 15;378(11):1004-1017. https://www.ncbi.nlm.nih.gov/pubmed/29539274

Flucytosine for cryptococcal mening

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

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 requiredto 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[52]

Level of Evidence: I Systematic Review[53]

NEMLC MEETING 6 DECEMBER 2018:

The NEMLC accepted the Adult Hospital Level Recommendations for flucytosine.

Flucytosine has been shown to be efficacious, but is currently not registered and is only available through section 21 application but inequitable access is a concern. Concerns of blanket S21 approvals were raised – these should essentially be reserved for emergency situations and not used by suppliers to circumvent registration processes. Donations through non-governmental organisations should also be considered with caution as SAHPRA regulatory oversight would be amiss.

Recommendations:

- Economic evaluation be undertaken through the Adult Hospital level Committee.

ii. Economic analysis

Flucytosine cost-effectiveness analysis (CEA) and budget impact analysis (BIA) was commissioned. Refer to health economics report: Flucytosine as induction therapy in the treatment of cryptococcal meningitis in HIV infected adults (June 2019):

Flucytosine Health Economics and Budg

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

NEMLC MEETING OF 11 JULY 2019:

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

Review indicators: SAHPRA registration; price reduction

Additional matters for consideration:

- *Fluconazole arm:* Base model derived from ACTA trial where fluconazole, oral was administered in hospital. However, in clinical practice patients could possibly be managed out-of-hospital.

[52] Molloy SF, Kanyama C, Heyderman RS, Loyse A, Kouanfack C, Chanda D, et al. Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa. N Engl J Med [Internet]. 2018;378(11):1004–17. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1710922

[53] Tenforde MW, Shapiro AE, Rouse B, Jarvis JN, Li T, Eshun-Wilson I, et al. Treatment for HIV-associated cryptococcal meningitis. Cochrane database Syst Rev. 2018 Jul;7:CD005647.

- *CEA sensitivity analysis:* Model is sensitive to infusion fees and hospital length of stay (LOS).
- *Cost of flucytosine:* Price sourced from a buy-out price procured through the Western Cape Pharmaceutical Services; noting that internationally, generics are available.
- *BIA sensitivity analysis:* Model is sensitive to flucytosine cost, hospital LOS, infusions fees.
- *Real-world data:* As the model was based on RCT evidence, real-world study should be conducted to confirm model outputs.
- *MSF UNITAID Programme:* Launched at various sites throughout the country to create demand and a sustainable market, but initially creating inequitable access throughout the country.

Fluconazole, oral: *dose increased*
See rationale above (section 10.2.4 Cryptococcosis).

10.5.1 POST-EXPOSURE PROPHYLAXIS, OCCUPATIONAL *and* **10.5.2 NON OCCUPATIONAL POST EXPOSURE PROPHYLAXIS , SEXUAL ASSAULT** *and* **10.5.3 NON OCCUPATIONAL POST EXPOSURE PROPHYLAXIS , INADVERTENT EXPOSURE**

Tenofovir + lamivudine + doluegravir, oral: *added*
Tenofovir + emtricitabine + atazanir/ritonavir or lopinavir/ritonavir: *retained and indication amended (WOCP, pregnant <6 weeks gestation and intolerant to DTG)*

Ford et al (2015) systematic review of very low quality data[54], assessed safety and efficacy of 2- vs 3- based ART regimens for PEP (occupational and non-occupational. Efficacy of various PEP regimens could not be determined, but PEP completion rates were report to be highest for the TDF-based regimens (>71.1%) vs AZT-based regimen (59.1%); and discontinuation due to ADRs reported to be lowest for the TDF+FTC+RAL regimen (1.9%). Authors suggest use of co-formulated TDF with 3TC/FTC as backbone with third ARV selection dependent on availability and resources (RAL recommended in the context of high-income settings).

Raltegravir: Compared with TDF+FTC+ LPV/r regimens, alternative ARVs reported to have fewer adverse effects and less drug-drug interactions[55]. Open label RCT comparing TDF+FTC+ LPV/r to TDF+FTC+RAL[56] showed that fewer adverse events associated with RAL-based regimen with higher adherence rates; but one participant who had received RAL-based regimen, with multiple high-risk exposures, sero-coneverted at 90-day follow-up.

Dolutegravir: Open-label, single-arm, non-randomized study assessed the safety and tolerability of a single PEP regimen, TDF+FTC+DTG, in men who have sex with men[57].

Recommendation: TDF with 3TC/FTC be recommended as PEP backbone with 3rd ARV, DTG; except in WOCP, pregnant women <6 weeks gestation where alternative option protease inhibitor to be considered.
Rationale: There is limited evidence of efficacy for integrase strand transfer inhibitors as prevention of HIV prophylaxis treatment. DTG is preferred in a number of guideline[58] [59], due to the higher barrier to resistance, daily dosing and better tolerability; noting that completion of treatment contributes to the effectiveness of PEP therapy.

[54] Ford N, Shubber Z, Calmy A, Irvine C, Rapparini C, Ajose O, et al. Choice of antiretroviral drugs for postexposure prophylaxis for adults and adolescents: A systematic review. Clinical Infectious Diseases. 2015;60 Suppl 3:S170–6. https://www.ncbi.nlm.nih.gov/pubmed/25972499
[55] Mulka L, Annandale D, Richardson C, Fisher M, Richardson D. Raltegravir-based HIV postexposure prophylaxis (PEP) in a real-life clinical setting: Fewer drug-drug interactions (DDIs) with improved adherence and tolerability. Sexually Transmitted Infections. 2016;92(2):107. https://www.ncbi.nlm.nih.gov/pubmed/26892929
[56] Leal L, Leon A, Torres B, Inciarte A, Lucero C, Mallolas J, et al. A randomized clinical trial comparing ritonavir-boosted lopinavir versus raltegravir each with tenofovir plus emtricitabine for post-exposure prophylaxis for HIV infection. Journal of Antimicrobial Chemotherapy. 2016;71(7):1987–93. https://www.ncbi.nlm.nih.gov/pubmed/26994089
[57] McAllister JW, Towns JM, McNulty A, Pierce AB, Foster R, Richardson R, et al. Dolutegravir with tenofovir disoproxil fumarate-emtricitabine as HIV postexposure prophylaxis in gay and bisexual men. AIDS. 2017;31(9):1291–5. https://www.ncbi.nlm.nih.gov/pubmed/28301425
[58] Goldschmidt RH. CDC Releases Updated Guidelines for Postexposure Prophylaxis After Sexual, Injection Drug, or Other Nonoccupational Exposures to HIV. Am Fam Physician. 2016 Sep 1;94(5):392-3. https://www.ncbi.nlm.nih.gov/pubmed/27583430
[59] Canadian guideline on HIV pre-exposure prophylaxis and nonoccupational postexposure prophylaxis. CMAJ. 2018 Jun 25;190(25):E782. https://www.ncbi.nlm.nih.gov/pubmed/29941442

The risk of NTDs associated with DTG precludes use of DTG-based regimen in WOCP or pregnant women<6 weeks gestation[60].

Level of Evidence: III Observational studies

Report prepared by TD Leong: Secretariat to the Adult Hospital Level Committee (2017-2020)

- ***Note:*** *Information was sourced from NEMLC ratified minutes and NEMLC-approved documents.*

[60] Zash R, Holmes L, Diseko M, Jacobson DL, Brummel S, Mayondi G, Isaacson A, Davey S, Mabuta J, Mmalane M, Gaolathe T, Essex M, Lockman S, Makhema J, Shapiro RL. Neural-Tube Defects and Antiretroviral Treatment Regimens in Botswana. N Engl J Med. 2019 Aug 29;381(9):827-840. https://www.ncbi.nlm.nih.gov/pubmed/31329379