SOUTH AFRICAN PRIMARY HEALTHCARE LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 11: HIV AND AIDS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2020)

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the complete chapter for HIV and AIDS
Note: This primary healthcare chapter has been updated to align to previous NEMLC recommendations as well as the recent NEMLC-approved Adult Hospital Level STGs and EML, 2019 edition and Paediatric Hospital Level HIV and AIDS chapter (2020 draft).

MEDICINE AMENDMENTS

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED
HIV INFECTION IN ADULTS		
11.1 Antiretroviral therapy		
ART regimens	ART	Amended to align with 2019 NDoH HIV Guidelines
Treatment-naïve patients	Tenofovir+emtricitabine+efavirenz, oral	Indication amended
	Tenofovir+lamivudine+dolutegravir, oral	Added
Failing a DTG- based 1st line regimen for > 2 years (TDF+3TC+DTG) - If HBsAg positive	TDF + 3TC/FTC +LPV/r	Added
Dual therapy	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	Amended: guidance on adverse effects updated (associated encephalopathy)
ART: Important drug interactions	InSTI, oral	Guidance added on drug interactions
	Atazanavir, oral	Amended: guidance added on interaction with PPIs/H2 antagonists
Monitoring for adults, whilst on ART	LAM testing	Added as additional test for DS-TB in seriously ill
11.2.2 Tuberculosis preventive therapy (TPT)		
TPT for pregnant women starting ART	Isoniazid, oral	Initiation of TPT deferred in pregnant women with high CD4 counts
11.3.4 Cryptococcosis		
Screening and referral	Lumbar puncture	Indication amended
Lumbar puncture not accessible	Fluconazole, oral	Dose increased and pre-referral first dose added
Asymptomatic and CSF CrAg negative	Fluconazole, oral	Dose amended
11.3.10 Herpes simplex ulcers, chronic	Antiviral (active against herpes simplex))	Added as therapeutic class
	Aciclovir, oral	Retained as the example of antiviral therapeutic class (listed in STG)
	Valaciclovir, oral	Added as a therapeutic alternative
	Famciclovir, oral	Added as a therapeutic alternative
11.3.11 Herpes zoster (shingles)	Antivirals (active against herpes zoster)	Added as therapeutic class
	Aciclovir, oral	Retained as the example of antiviral therapeutic class (listed in STG)
	Valaciclovir, oral	Added as a therapeutic alternative
	Famciclovir, oral	Added as a therapeutic alternative
HIV INFECTION IN CHILDREN		
11.5 The HIV exposed infant		
High-risk Infant prophylaxis	Nevirapine, oral	Duration amended
Cotrimoxazole preventive therapy (CPT)	Cotrimoxazole, oral	Discontinuation time-frame amended
HIV testing	HIV testing	Amended
11.6 The HIV infected infant/child (<10 years)		
Cotrimoxazole preventive therapy (CPT)	Cotrimoxazole, oral	CD4 cut-off for discontinuation amended
First-line ART regimens	Dolutegravir, oral	Added
	Efavirenz, oral	Removed from first-line for newly initiating patients

Side-effects	Guidance on single drug substitution (due to adverse effects)	Added
Antiretroviral medicine dosages by weight bands	ARV weight-band dosing tables	Amended (to include dosing for DTG & LPV/r pellets)
9.2 Tuberculosis and HIV		
Drug interactions	Dolutegravir plus rifampicin	Dosing recommendations added

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

Algorithms aligned to the NDoH 2019 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy, Adolescents, Children, Infants and Neonates and Paediatric Hospital Level HIV chapter, 2020 draft, as appropriate.

A: HIV IN ADULTS/ADOLESCENTS

11.1 ANTIRETROVIRAL THERAPY

ART regimens: *amended to align* to the NDoH 2019 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy, Adolescents, Children, Infants and Neonates (see table on next page)

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

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[1], Guidelines[2]

[1] 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

[2] 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 *»WOCP not actively wishing to conceive* *»Pregnant women ≥6 weeks gestation, and those who make an informed choice to use DTG* 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 + 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		
Management 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 6 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)*	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 atazanavir/ritonavir	Switch lopinavir/ritonavir to atazanavir/ritonavir
Third-line ART		
Failing any 2nd line regimen	Refer to a specialist.	Refer to a specialist.
(Abbreviations: 3TC=lamivudine, ABC=Abacavir, DTG=dolutegravir, FTC=emtricitabine).		

Note: For Contraindications and intolerance to EFV and DTG, the STG has been amended further to recommend TDF+3TC/FTC + LPV/r. This is at variance with the Adult Hospital Level, 2019 edition that recommends TDF+3TC/FTC + NVP. For safety reasons NVP has been deleted.

Level of Evidence: III Expert opinion

Dual therapy

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)[3]. The observational DOLAMA study[4] 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*

Dolutegravir: TB-associated IRIS with dolutegravir was reported to be uncommon, with no discontinuations for IRIS.

Level of Evidence: I RCT[5]

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

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[6]

ART: Important drug interactions

Dolutegravir, oral: *guidance added on drug interactions*

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

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

Atazanavir, oral: *directions for use amended*

[3] 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

[4] 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

[5] 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

[6] 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

Atazanavir needs an acidic gastric environment for dissolution and absorption, and PPIs and H2 antagonists (which decreases gastric pH) probably decreases solubility of atazanvir - however, other pharmacological mechanism for interaction has yet to be determined[7]. The European Medicines Agency had issued a public statement[8] 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

Monitoring for adults, whilst on ART

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

Aligned with section the Adult Hospital Level STGs and EML, 2019 edition.

11.2.2 TUBERCULOSIS PREVENTIVE THERAPY (TPT)

TPT for pregnant women starting ART:

TPT: *initiation of TPT 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 TPT until after delivery.
» If CD4 <350 cells/microL: Exclude active TB with symptom screen, then give TPT.

CD4 cut-off in pregnant women:

Background: WHO Guidelines recommends TPT in all HIV-infected pregnant women. Previous NEMLC-approved PHC recommendation of deferring TPT in pregnancy if CD≥100 cells/mm3 based on the TB APPRISE RCT[9] (n=956) that showed no difference between administering TPT 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[10] 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[11] done in a non-pregnant cohort).

[7] 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

[8] 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

[9] 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

[10] NEMLC report for the Primary Health Care HIV chapter, 2016-8 review.

[11] 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

Kalk et al (2020): Subsequently, a larger local retrospective cohort study[12] (n= 43 971) showed that antenatal TPT 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 (TPT vs no TPT)*
   - Adverse pregnancy outcomes: aOR 0.83; 95%CI 0.78 to 0.87.
   - TPT started after the first trimester: aOR 0.71; 95%CI 0.65 to 0.79.
   - TPT started from first trimester: aOR 0.64; 95%CI 0.55 to 0.75.

ii. *TB risk (TPT vs no TPT)*
   - 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: TPT deferral if CD4 ≥350 in pregnant women; whilst where CD4<350, active TB to be excluded with symptom screen and then TPT given.

Rationale: A RCT of immediate versus delayed TPT 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 study[13] (n= 43 971) showed that antenatal TPT 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] 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)

11.3.4 CRYPTOCOCCOSIS

Screening and referral

Lumbar puncture: *indication amended*

[12] 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

[13] 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

Evidence for routine LP screening: Local South African study[14] 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: The algorithm updated to include LP for screening of cryptococcal meningitis. All patients with a positive CrAg to be referred for a lumbar puncture.
Level of Evidence: III Observational study, Guidelines

LUMBAR PUNCTURE NOT ACCESSIBLE
Pre-referral fluconazole, oral: *dose increased and pre-referral first dose added*
Pragmatic implications of a LPs for all CrAg positive patients may include a delay in treatment, as patients would need referral from primary level. However, as recommended in the updated South African HIV Clinician Society guideline, CrAg +ve patients and patients with symptoms of meningitis should be referred with an initial dose of fluconazole, at the revised, higher recommended dose for fluconazole during the intensive phase of treatment.
Level of Evidence: III Antimicrobial susceptibility study, Expert opinion

When the LP can be performed at PHC level, symptoms and LP results should be assessed to determine if the patient requires admission for Amphotericin B:

- Symptoms and/or CSF CrAg positive on LP: Refer for IV Amphotericin B for either cryptococcal meningitis or non-meningeal cryptococcosis.
- Asymptomatic and CSF CrAg negative on LP: provide oral fluconazole.

LUMBAR PUNCTURE ACCESSIBLE
Asymptomatic and CSF CrAg negative:
Fluconazole, oral: *dose amended*
NICD data on file shared with NDoH[15] 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

STG text was updated from:

~~**CrAg-positive and any symptom of meningitis:**~~
~~Refer patient immediately for lumbar puncture.~~

~~**CrAg-positive and no symptoms of meningitis:**~~
~~**Induction phase**~~
- ~~Fluconazole, oral 800 mg daily for 14 days.~~

~~**Consolidation phase**~~
~~Follow with:~~
- ~~Fluconazole, oral, 400 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 after completion of the induction phase i.e. at 2 weeks.~~

To:

If CSF Crag positive:
Refer for amphotericin B, IV (induction phase) - See Adult Hospital STGs and EML, Section 10.2.4: Cryptococcosis.
Patients may be down referred for secondary prophylaxis; see maintenance phase, below.

[14] 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
15 NICD data on file, pending publication in peer reviewed journal.

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

- Fluconazole, oral, 1200 mg immediately.

No symptoms present **and** CSF CrAg negative (LP):
Treat with fluconazole.

Induction phase

- Fluconazole, oral 1200 mg daily for 14 days.

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.

11.3.10 HERPES SIMPLEX ULCERS, CHRONIC

Aciclovir, oral: *retained as the example of antiviral therapeutic class (listed in STG)*
Valaciclovir, oral: *added as a therapeutic alternative*
Famciclovir, oral: *added as a therapeutic alternative*
Aligned with the Adult Hospital Level STGs and EML, 2019 edition.
Level of Evidence: III Guidelines[16]

11.3.11 HERPES ZOSTER (SHINGLES)

Aciclovir, oral: *retained as the example of antiviral therapeutic class (listed in STG)*
Valaciclovir, oral: *added as a therapeutic alternative*
Famciclovir, oral: *added as a therapeutic alternative*
Aligned with the Adult Hospital Level STGs and EML, 2019 edition.
Level of Evidence: I Systematic review[17]

B: HIV IN CHILDREN

This section was aligned with the 2019 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy, Adolescents, Children, Infants and Neonates; the 2019 Guideline for the Prevention of Mother to Child Transmission (PMTCT) of Communicable Infections and the NEMLC-approved Paediatric Hospital Level HIV chapter (2020 draft).

11.5 THE HIV EXPOSED INFANT

High-risk infant prophylaxis
Nevirapine: *duration amended*
For high risk exposure, nevirapine is recommended for a *minimum* of 12 weeks.
The text was amended as follows:

High Risk
NVP daily for at least 12 weeks and AZT twice daily for 6 weeks. (initiate as soon as possible)

[16] Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015 Jun 5;64(RR-03):1-137. Erratum in: MMWR Recomm Rep. 2015 Aug 28;64(33):924. https://www.ncbi.nlm.nih.gov/pubmed/26042815
[17] McDonald EM, De Kock J, Ram FS. Antivirals for management of herpes zoster including ophthalmicus: a systematic review of high-quality randomized controlled trials. Antiviral Therapy 2012; 17(2): 255-264.https://www.ncbi.nlm.nih.gov/pubmed/22300753

Cotrimoxazole preventive therapy

Cotrimoxazole: *Discontinuation time-frame amended*

The text was amended as follows:

Cotrimoxazole prophylaxis

Discontinuation:

» If birth and 10 week PCR is negative.

~~» If the child has a negative HIV test at least 6 weeks after full cessation of breastfeeding **or**~~

» If HIV infected, as per section 11.6 Management of HIV-infected children

Rationale: A South African study by Daniels et.al.[18] investigated whether receiving no cotrimoxazole prophylaxis was inferior to receiving prophylaxis in incidence grade 3 or 4 common childhood conditions or mortality in breastfed HIV-exposed, HIV uninfected infants. The study included 1570 mother-child pair, 611 infants to cotrimoxazole group and 608 infants to the no cotrimoxazole group. The cumulative probability of the composite primary outcome was 0.114 (95% CI 0.076 to 0.147; 49 events) in the cotrimoxazole group and 0.0795 (95% CI 0.044 to 0.115; 39 events) in the no cotrimoxazole group. This reflected a risk of approximately 3 percentage points lower in the no-cotrimoxazole group. When the initial recommendations for cotrimoxazole prophylaxis were made, there was a high HIV transmission rate, and an inability to identify an infant's HIV status before 18 months. There was also no or limited access to ART in this age group. Currently however transmission rates are low, with earlier HIV identification, and immediate ART once identified. It was thus proposed that discontinuation of the cotrimoxazole in HIV exposed infants can occur if both birth and 10 week PCR are negative.

HIV testing

The Paediatric Hospital Level HIV chapter was aligned to the PMTCT guideline.

The HIV PCR at 18 weeks has fallen away and been replaced with a PCR test at 6 months of age for all HIV-exposed infants in the updated HIV guideline. Guidance on universal HIV testing at 18 months was added.

The testing timelines were updated as follows:

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

- Birth (HIV PCR).
- Repeat at 10-week visit (HIV PCR).
- ~~Do HIV PCR at 18 weeks~~
- Repeat at 6-month visit (HIV PCR)
- At any time when clinical signs indicate possible HIV infection.
- 6 weeks after breastfeeding has stopped.
- ~~18 months (ELISA or HIV rapid test), if the exposed infant has not been shown to be HIV-infected.~~
- Do Universal HIV rapid/ELISA test at 18 months (HIV rapid test for ALL children regardless of HIV exposure, except in those who previously tested HIV positive and are on ART)

Unknown maternal status

The algorithm from the updated PMTCT guidelines (abandoned babies) was added.

Management of high maternal viral load after delivery

Guidance was added for the management of infants of a newly diagnosed mother during breastfeeding and a breastfeeding mother on ART with an elevated VL, and the respective algorithm from the NDoH PMTCT Guideline was added.

11.6 MANAGEMENT OF CHILDREN WITH HIV INFECTION (<10 YEARS)

Cotrimoxazole preventive therapy

Cotrimoxazole prophylaxis: *CD4 cut-off for discontinuing amended*

[18] Daniels B, Coutsoudis A, Moodley-Govender E, Mulol H, Spooner E, Kiepiela P, Reddy S, Zako L, Ho NT, Kuhn L, Ramjee G. Effect of co-trimoxazole prophylaxis on morbidity and mortality of HIV-exposed, HIV-uninfected infants in South Africa: a randomized controlled, non-inferiority trial. Lancet Global Health. 2019, 7: e1717-e1727.

The previous recommendations for cotrimoxazole prophylaxis discontinuation was for patients with CD4 counts of >350 cells/mm^3. However, there is a move to making the CD4 cut-off > 200 cells/mm^3. The US Antiretroviral (ARV) guideline uses 200, supported good evidence base.[19, 20, 21, 22, 23, 24, 25] The cut-off was thus changed to 200 cells/mm^3 .
The discontinuation criteria were amended as follows:

Cotrimoxazole prophylaxis
Discontinuation:
» HIV-infected child > 1 year of age whose immune system is fully reconstituted on ART (i.e. 1–5 year: CD4% > 25% or > 5 years: CD4 count > ~~350~~ 200 cells/mm3 on two tests at least 3–6 months apart).
» Child is HIV-infected with PJP infection: after treatment, continue cotrimoxazole prophylaxis until 5 years of age.

First-line ART Regimens
Dolutegravir: *Added*
Efavirenz: *Removed from first-line for newly initiating patients*
The Paediatric STGs and EML has aligned with the National 2019 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy, Adolescents, Children, Infants and Neonates; and the 2019 Guideline for the Prevention of Mother to Child Transmission of Communicable Infections. The algorithms from this guideline were amended to be incorporated into this chapter.

The first-line ART regimen was amended as follows:

Age/weight	First-line regimen
0 - 1 month	AZT/3TC/NVP
≥ 4 weeks and ≥ 42 weeks gestational age (3 kg – 20 kg)	ABC/3TC/LPV/r
< 10 years of age (20 kg – 35 kg)	ABC/3TC/DTG
≥10 years (≥35Kg)	FDC (TDF/3TC/DTG)

Dolutegravir plus an optimised NRTI backbone has been shown to be safe, well tolerated and efficacious in a children aged 12 - < 18 years treatment experienced HIV-1 infected adolescents.[26] Dolutegravir is currently only available as a 50 mg tablet (no paediatric formulations). The WHO recommends the use of 50mg dolutegravir from ≥ 20 kg.
Data presented at the Conference on Retroviruses and Opportunistic Infections (CROI) May 2019 found that the adult dose of a 50mg tablet daily can be used in children from 20kg and the strategy was endorsed in the 2019 WHO Guidelines.[27]

Regimens/algorithms
The algorithms for the switching of therapy, viral load management and the tables related to first and second line regimens was included in the STG.

Side-effects
The following narrative was added, aligned with the Paediatric Hospital Level HIV chapter (2020 draft):

[19] Nachman S, Gona P, Dankner W, et al. The rate of serious bacterial infections among HIV-infected children with immune reconstitution who have discontinued opportunistic infection prophylaxis. *Pediatrics*. Apr 2005;115(4):e488-494. Available at http://www.ncbi.nlm.nih.gov/pubmed/15772172.
[20] Furrer H, Egger M, Opravil M, et al. Discontinuation of primary prophylaxis against Pneumocystis carinii pneumonia in HIV-1-infected adults treated with combination antiretroviral therapy. Swiss HIV Cohort Study. *N Engl J Med*. Apr 29 1999;340(17):1301-1306. Available at http://www.ncbi.nlm.nih.gov/pubmed/10219064.
[21] Schneider MM, Borleffs JC, Stolk RP, Jaspers CA, Hoepelman AI. Discontinuation of prophylaxis for Pneumocystis carinii pneumonia in HIV-1-infected patients treated with highly active antiretroviral therapy. Lancet.Jan 16 1999;353(9148):201-203. Available at http://www.ncbi.nlm.nih.gov/pubmed/9923876.
[22] Dworkin MS, Hanson DL, Kaplan JE, Jones JL, Ward JW. Risk for preventable opportunistic infections in persons with AIDS after antiretroviral therapy increases CD4+ T lymphocyte counts above prophylaxis thresholds. *J Infect Dis*. Aug 2000;182(2):611-615. Available at http://www.ncbi.nlm.nih.gov/pubmed/10915098.
[23] Ledergerber B, Mocroft A, Reiss P, et al. Discontinuation of secondary prophylaxis against Pneumocystis carinii pneumonia in patients with HIV infection who have a response to antiretroviral therapy. Eight European Study Groups. *N Engl J Med*. Jan 18 2001;344(3):168-174. Available at http://www.ncbi.nlm.nih.gov/pubmed/11188837.
[24] Lopez Bernaldo de Quiros JC, Miro JM, Pena JM, et al. A randomized trial of the discontinuation of primary and secondary prophylaxis against Pneumocystis carinii pneumonia after highly active antiretroviral therapy in patients with HIV infection. Grupo de Estudio del SIDA 04/98. *N Engl J Med*. Jan 18 2001;344(3):159-167. Available at http://www.ncbi.nlm.nih.gov/pubmed/11172138.
[25] Urschel S, Ramos J, Mellado M, et al. Withdrawal of Pneumocystis jirovecii prophylaxis in HIV-infected children under highly active antiretroviral therapy. *AIDS*. Dec 2 2005;19(18):2103-2108. Available at http://www.ncbi.nlm.nih.gov/pubmed/16284459.
[26] Viani RM, et.al. Long-term safety and efficacy of dolutegravir in treatment-experienced adolescents with human immunodeficiency virus infection: Results of the IMPAACT P1093 Study. J Pediatric Infec Dis Soc. 2019.
[27] Bollen P, et.al. Adult dolutegravir 50mg tablets in children living with HIV weighing 20 – 25 kg. CROI. March 2019, Abstract number: 830. https://www.croiconference.org/sessions/adult-dolutegravir-50mg-tablets-children-living-hiv-weighing-20

Note: Children may occasionally need to change a medicine from the first line regimen to one from the second line regimen because of intolerance or a serious adverse reaction. There is no need to change an entire regimen for a single adverse drug reaction.

» A single drug substitution can only be made if the viral load is undetectable or if the change is made in the first six months of starting a regimen.

» Refer or consult a doctor with antiretroviral experience.

Antiretroviral medicine dosages by weight bands

ARV Weight-band dosing table was amended to include dosing for DTG and LPV/r oral pellets formulation.

11.8.7 TUBERCULOSIS

Dolutegravir plus rifampicin-containing treatment: *dosing recommendations added.*

Text amended as follows:

If the child needs to take concomitant ART and rifampicin:

» **Dolutegravir: use DTG twice daily**

» ……..