SOUTH AFRICAN PRIMARY HEALTHCARE ESSENTIAL MEDICINES LIST
CHAPTER 11: HIV & AIDS
NEMLC RECOMMENDATIONS FOR MEDICINE MANAGEMENT (2016 – 2018)

Medicine amendment recommendations, with supporting evidence and rationale are listed below. Kindly review the medicine amendments in the context of the obstetrics and gynaecology conditions chapter.

NOTE: As the National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults have not been updated as yet, the PHC HIV chapter has been aligned with the *current* NDoH guidelines, 2014. However, the EML Clinical Guide application may be updated once the updated official NDoH HIV Guidelines have been finalised.

MEDICINE AMENDMENTS

At the NEMLC meeting of 12 April 2018, following additional NEMLC recommendations, further amendments were made:

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED/NOT ADDED
HIV INFECTION IN ADULTS		
11.1 Antiretroviral therapy, adults		
Eligibility criteria	ART	Amended
Timing of ART initiation	ART	Same day initiation clarified
Initiating ART in patients with TB co-infection (CD4<50; except TB meningitis)	ART	Timing for initiation amended to 'within 2 weeks'
Time of initiation of ART in TB meningitis		Not amended
Table: ARV dose and common adverse drug reactions	ARVs	Amended - renal adjusted dose included; general information on d4t, ETR, DRV, DTG, RAL included.
1st line: Contraindication to EFV	NVP	Amended - caution added regarding CD4 counts
2nd line: Failing on a TDF-based 1st line regimen and hepatitis B surface antigen positive	Tenofovir	Amended - caution retained & strengthened in hepatitis b co-infection
2nd line: Failing on a d4T/AZT-based 1st line regimen	Stavudine/ zidovudine	Guidance provided for switching from a d4t/AZT-containing ART regimen.
In patients treated for TB with rifampicin regimens there are some important medicine interactions:	Atazanavir	Amended - directions of use in TB added (with referral)
11.2.2 Isoniazid preventive therapy (IPT)		
– *All patients, except pregnant women*	Isoniazid	Duration of preventive therapy amended to 12 months
– *Pregnant women*	Isoniazid	If CD4≥100 cells/microl: IPT deferred until after delivery. If CD4 <100 cells/microl: active TB excluded with symptom screen, then IPT is given.
11.3.3 Candidiasis, oesophageal	ART	Directions for use amended
11.3.4 Cryptococcosis	Algorithm	Amended – urgent referral of all symptomatic pregnant women and asymptomatic pregnant women in the 1st trimester.
11.3.10 Herpes simplex ulcers, chronic	Aciclovir, IV	Not added
HIV INFECTION IN CHILDREN		
11.5 The HIV-exposed infant	HIV infant prophylaxis	Management delineated according to "low-risk", "high-risk" and "unknown risk"
- *Low risk*	Nevirapine	Recommended at birth and then daily for 6 weeks.

- High risk	Nevirapine	Recommended at birth and then daily for 12 weeks.
	Zidovudine	Recommended at birth and then 12 hourly for 6 weeks.
- Unknown risk	Nevirapine	Recommended daily, immediately and then daily for 6 weeks if HIV- positive.
- Mother on lifelong ART, initiated before pregnancy (including TDF + EFV + 3TC/FTC) and failing 1st line and initiated on 2nd line	AZT	*duration of therapy amended*
11.6 Management of HIV-infected children		
Immunisation, deworming and vitamin A programme	Measles vaccine at 6 months	*deleted* BCG vaccine: *directions for use amended*
Antiretroviral therapy	ART	*eligibility criteria amended*
Children requiring fast track (i.e. start ART within 7 days if safe to do so):	ART	*amended - time of initiation of ART in meningitis added (8 weeks)*
First-line regimen **Adolescents > 15 years and > 40 kg:**	TDF + 3TC/FTC + EFV	*caution regarding renal impairment amended*
Adjustment of previous first-line regimens	ddl-containing 2nd line regimen	*directions for switching added*
Treatment failure	1st line ART regimen	*guidance for treatment failure added (with referral)*
11.7 Opportunistic infections, prophylaxis in children	Measles vaccine at 6 months	*deleted* BCG vaccine: *directions for use amended*
11.8.7 Tuberculosis (TB)	Efavirenz, oral	*guidance provided - no dose adjustment required with rifampicin*
HIV PREVENTION		
11.12 Pre-exposure prophylaxis	TDF+FTC	Added with access only at designated sites for duration of therapy of 7 days only
- PrEP follow up and monitoring: ALT monitoring if HepBSAg positive	ALT tests (3 monthly)	Deleted
- Stopping PrEP	TDF+FTC	Caution retained for hepatitis flares on discontinuation of PreP

11.1 ANTIRETROVIRAL THERAPY, ADULTS

ART: *Eligibility criteria amended*

Background:

The South African Minister of health announced in May 2016 that antiretroviral therapy (ART) would be initiated in all individuals diagnosed with HIV infection, regardless of CD4 count, and that this would be implemented in September 2016. This announcement follows current World Health Organization (WHO) recommendations which were recently released[1].

Evidence of efficacy and safety:

Initiation of antiretroviral therapy in adults with a CD4 count of more than 500 cells/mm^3 is supported by observational data and by two randomised controlled trials (RCTs).[2] [3]

Temprano RCT[3]: 2056 Ivory Coast participants with CD4<800 cells/mm^3 were randomised to immediate ART (tenofovir + emtricitabine + efavirenz in ±70%) vs ART deferred till WHO criteria for initiation of ART was reached. Multicentre unblended study which ran from March 2008 to January 2015, during which time WHO criteria for ART initiation changed twice. Factorial design which also included randomisation to 6 months' isoniazid preventative therapy (IPT) or no IPT. The median CD4 count was ±460 cells/mm^3 in all arms at baseline.

[1] World Health Organization *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a Public Health Approach*. Second Edition ed. 2016, Geneva Switzerland

[2] Insight Start Study Group, et al., *Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection.* N Engl J Med, 2015. **373**(9):795-807.

[3] Temprano Anrs Study Group, et al., A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. N Engl J Med, 2015. 373(9):808-22.

- Primary composite endpoint: death from any cause, AIDs defining disease, non-AIDs defining cancer, non-AIDs defining invasive bacterial disease.
- 204 events occurred in 175 patients in 4757 patient years of follow-up.
- 30-month probability of primary end point event was 11.4% for deferred ART vs 6.6% for early ART. ARR of 4.8%; NNT of 20.8 people for 30 months to prevent 1 event. HR for immediate vs deferred ART 0.56 (95% CI 0.41 to 0.76)
- Grade 3 or 4 adverse events occurred in 144 participants: 7.7% in deferred ART group vs 7.1% in the early ART group.

START RCT randomised HIV- infected participants with CD4> 500 cells/mm^3 to immediate ART or deferment until CD4<350 cells/mm^3or an AIDs defining event was present. 4685 patients were followed for a mean of 3 years at 215 sites in 35 countries. The median CD4 was 651 cells/mm^3at baseline.

- Primary composite end point: serious AIDS related event (AIDS related death, AIDS defining event (excluding non-fatal herpes and oesophageal candida), Hodgkins lymphoma)) or serious non-AIDS related event (death from cause other than AIDS, cardiovascular disease (MI/stroke/coronary revascularisation), end stage renal disease, decompensated liver disease, non-AIDS defining cancer).
- Study was stopped early by the data and safety monitoring board.
- Primary end point reached by 42 participants in immediate initiation group (0.6 events/100 person-years of treatment; 1.8% of group) versus 96 participants in deferred initiation group (1.38 events/100 person-years of treatment; 4.1% of group). HR 0.43 (95% CI 0.30 to 0.62). Difference of 0.78 events/100 person-years of treatment. Need to immediately initiate ART in 44 individuals and treat for 3 years to prevent 1 event.
- Grade 4 events occurred in 1.06/100 person-years of treatment in immediate initiation group vs 1.05/100 person-years of treatment in deferred group. Unscheduled hospitalisation 4.02/100 person-years of treatment in immediate initiation group vs 4.40/100 person-years of treatment in the deferred group.

The criteria for starting ART in adults was amended in the STG as follows:

~~» All patients with stage 3 or 4 disease irrespective of CD4 count.~~
~~**OR**~~
~~» All patients with CD4 < 500~~
~~**OR**~~
~~» All pregnant and breastfeeding women, irrespective of CD4 count.~~
~~**OR**~~
~~» Other severe HIV-related conditions or co-morbidity. This group of conditions requires specialist diagnosis and recommendation for ART. Examples of conditions in this category includes but is not limited to:~~
- ~~Immune Thrombocytopenic Purpura and Thrombotic Thrombocytopenic Purpura.~~
- ~~Severe manifestations of the diffuse infiltrative lymphocytic syndrome (e.g. lymphocytic interstitial pneumonitis, polymyositis).~~
- ~~Chronic liver disease due to hepatitis B.~~
- ~~Patients being treated for non-HIV-related malignancies~~

Criteria for starting ART in adults:
» All HIV-infected patients, irrespective of disease stage or CD4 count.

Level of Evidence: I RCT[4]

Timing of ART initiation

ART: *"Same day initiation" clarified*

NDoH circular that was disseminated August 2017 for same day initiation of ART states, "*same day initiation for newly diagnosed who are clinically and psychologically ready for a lifelong commitment*

[4] INSIGHT START Study Group, Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, Sharma S, Avihingsanon A, Cooper DA, Fätkenheuer G, Llibre JM, Molina JM, Munderi P, Schechter M, Wood R, Klingman KL, Collins S, Lane HC, Phillips AN, Neaton JD. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med. 2015 Aug 27;373(9):795-807. doi: 10.1056/NEJMoa1506816. Epub 2015 Jul 20. PubMed PMID: 26192873; PubMed Central PMCID: PMC4569751

to ART". Collaborative meeting with the NDoH Programmatic HIV Chief Director clarified that same day initiation is possible only if there is no clinical contra-indication, and patient has received required pre-counselling and is willing to start ART.

The text of the STG was therefore, amended from:

~~In general, ART should be started as soon as the patient is ready, within 2 weeks of CD4 count result availability. However, with some opportunistic diseases.~~

To:

ART may be started on the same day if the patient has no clinical contraindication, and the patient is willing to start after receiving pre ART counselling. In general, ART should be started as soon as possible, within 2 weeks of CD4 count result availability. For clinical indications for deferring ART initiation, see below.

TIMING OF ART INITIATION

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

ART: *Time of initiation of ART in TB amended*

The text of the STG was amended as follows:

» Start with TB treatment first, followed by ART initiation according to CD4 count (except TB meningitis – see below): » In TB patients with CD4 count > 50 cells/mm^3, ART should be deferred until 8 weeks after initiating TB treatment, which has shown to be safe and reduces the risk of deterioration due to the immune reconstitution inflammatory syndrome (IRIS). » In TB patients with CD4 counts < 50 cells/mm^3 (except TB meningitis), start ART ~~at 2 weeks~~ within 2 weeks after starting TB therapy. » In patients with TB meningitis (irrespective of CD4 count), ART should be deferred until 8 weeks after initiating TB treatment.

Evidence: The systematic review (Uthman et al)[5] 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.

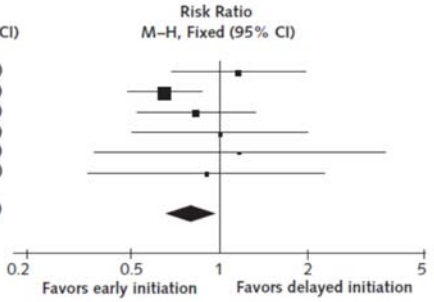
- *Uthman systematic review:* Randomized, controlled trials evaluating early versus delayed ART initiation (1 to 4 weeks vs. 8 to 12 weeks after initiation of TB treatment) or deferred ART initiation (after the end of TB treatment).

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.

[5] 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

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.

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 be amended from "at 2 weeks" to "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*

The recommendation to defer ART 8 weeks after TB meningitis therapy was retained in the STG, as suggested by evidence reviewed in the previous PHC review cycle.

Level of Evidence: I RCT[6]

ANTIRETROVIRAL MEDICINES: DOSE AND COMMON ADVERSE DRUG REACTIONS

The table describing ARVs, dosing and associated ADRs was amended to align with the Adult Hospital Level STGs and EML, 2015 and the SAMF, 2016. The table includes renal adjusted doses from the Adult Hospital Level STGs and EML, 2015. Refer to the chapter for detailed information.

Level of Evidence: III Guidelines

STANDARDISED NATIONAL ART REGIMENS FOR ADULTS AND ADOLESCENTS

1st line: Contraindication to EFV

NVP: *caution added regarding CD4 counts*

The following caution was added to the STG, aligned with the SAMF, 2016:

Nevirapine should not be initiated in women with baseline CD4 count>250 cells/mm^3 or men with baseline CD4 count >400 cells/mm^3.

Level of Evidence: III Guidelines

[6] Török ME, Yen NT, Chau TT et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)--associated tuberculous meningitis. Clin Infect Dis.2011 Jun;52(11):1374-83:

– Immediate ART initiation vs. deferred ART initiation therapy after 8 weeks, does not improve outcome in patients presenting with HIV-associated TB meningitis.

– Significantly more grade 4 adverse events in the immediate ART arm, supporting delayed initiation of ART in HIV-associated TB meningitis (102 vs. 87 in the immediate vs. deferred ART group; p=0.04).

2nd line: Failing on a TDF-based 1st line regimen and hepatitis B surface antigen positive.
TDF: *caution retained for hepatitis B co-infection*
An external comment was received that the following caution was not appropriate:

> * Always check for hepatitis B coinfection before stopping TDF. If patient has chronic hepatitis B, stopping TDF may lead to a fatal hepatitis flare. If hepatitis B positive, TDF should be continued as a fourth medicine in the 2nd line regimen.

However, the evidence that was submitted[7] was insufficient as the study was underpowered, was in pregnant women only, who were Hepatitis B negative, and was funded by pharmaceutical industry.

Additional data suggesting that there is a risk of flares, in patients stopping TDF, if HbsAG positive was discussed: There is data from the SMART[8] and STACCATO[9] RCTs that indicated that people co-infected with hepatitis B who stopped TDF experienced flares. In a Swiss cohort[10], stopping lamivudine caused flares, three patients presented with fulminant hepatitis and one death was recorded.
Recommendation: Caution for tenofovir in hepatitis B co-infection be retained in the STG.
Rationale: Aligned with Adult Hospital Level STGs and EML, 2015.
Level of Evidence: III Guidelines

2nd line: Failing on a d4T/AZT-based 1st line regimen
d4T/AZT: *guidance provided for switching from a d4T/AZT-containing ART regimen.*
Rationale: Aligned with National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults, 2014.
Level of Evidence: III Guidelines

In patients treated for TB with rifampicin regimens there are some important medicine interactions:
Atazanavir: *directions of use in TB added (with referral)*
Management of TB, where rifampicin is contra-indicated (due to concomitant atazanavir), occurs at higher levels of care, with down referral for continuation of care. Guidance was provided in the PHC STG for information purposes on how to manage these cases. Furthermore, information was provided regarding drug-drug interactions of rifampicin with raltegravir and dolutegravir, requiring referral for dose-adjustments of these antiretrovirals.

> » Rifampicin reduces concentrations of some antiretrovirals (e.g. atazanavir) including some antiretrovirals used for 3rd line therapy (raltegravir, dolutegravir and etravirine). Patients on these medicines require referral for rifabutin in place of rifampicin, antiretroviral dose-adjustment or change in the antiretroviral regimen, as appropriate.

Level of Evidence: III Guidelines

11.2.2 ISONIAZID PREVENTIVE THERAPY (IPT)

In patients on ART:
Re: " IPT reduces the risk of TB, irrespective of TST status".

[7] Pan CQ, Duan Z, Dai E, Zhang S, Han G, Wang Y, Zhang H, Zou H, Zhu B, Zhao W, Jiang H; China Study Group for the Mother-to-Child Transmission of Hepatitis B. Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load. N Engl J Med. 2016 Jun 16;374(24):2324-34. https://www.ncbi.nlm.nih.gov/pubmed/27305192
[8] Dore GJ, Soriano V, Rockstroh J, Kupfer B, Tedaldi E, Peters L, Neuhaus J, Puoti M, Klein MB, Mocroft A, Clotet B, Lundgren JD; SMART INSIGHT study group. Frequent hepatitis B virus rebound among HIV-hepatitis B virus-coinfected patients following antiretroviral therapy interruption. AIDS. 2010 Mar 27;24(6):857-65. https://www.ncbi.nlm.nih.gov/pubmed/20216301
[9] Nüesch R, Ananworanich J, Srasuebkul P, Chetchotisakd P, Prasithsirikul W, Klinbuayam W, Mahanontharit A, Jupimai T, Ruxrungtham K, Hirschel B. Interruptions of tenofovir/emtricitabine-based antiretroviral therapy in patients with HIV/hepatitis B virus co-infection. AIDS. 2008 Jan 2;22(1):152-4. https://www.ncbi.nlm.nih.gov/pubmed/18090405
[10] Bellini C, Keiser O, Chave JP, Evison J, Fehr J, Kaiser L, Weber R, Vernazza P, Bernasconi E, Telenti A, Cavassini M; Swiss HIV Cohort Study. Liver enzyme elevation after lamivudine withdrawal in HIV-hepatitis B virus co-infected patients: the Swiss HIV Cohort Study. HIV Med. 2009 Jan;10(1):12-8. https://www.ncbi.nlm.nih.gov/pubmed/18795964

IPT: *recommendation of 12 months IPT retained for patients on ART, irrespective of TST status.*
Clinical trials conducted in South Africa and Cote d'Ivoire have shown that isoniazid preventive therapy (IPT) has an additive effect with ART in preventing incident TB in HIV-infected patients[11] [12]. In the South African trial, there was a 37% reduction in incident TB when patients receiving ART were prescribed IPT (vs placebo) for 12 months. This benefit applied irrespective of tuberculin skin test (TST) status, and the trial was conducted in patients initiating ART[13].

AT THE NEMLC MEETING OF 12 APRIL 2018[14]:
Isoniazid: NEMLC amended the duration of IPT to 12 months, without the necessity of a TST, based on randomised control trial (RCT) data[15]. It was acknowledged that patients are starting ART earlier.
Level of Evidence: I RCT
The text of the STG was updated as follows:

Duration of IPT
- Isoniazid, oral, 300 mg daily for 12 months
  - Educate patients on the symptoms of hepatotoxicity (nausea, vomiting, yellow eyes, brown urine, pain in right upper quadrant).
  - Instruct patient to present early if any of these symptoms arise.
  - Patients should be followed up monthly for the first 3 months.
- Pyridoxine, oral, 25 mg once daily.

Note: TST is not necessary for patients on ART.

Pregnant women
IPT: *initiation of IPT deferred in pregnant women with high CD4 counts.*

Conference on Retroviruses and Opportunistic Infections (CROI) study[16]: A randomised controlled trial of immediate (started during pregnancy) versus deferred (started post-partum) isoniazid for TB prophylaxis in HIV infected women in high TB incidence settings was presented at CROI 2018 in March[17]. The primary outcome of this non-inferiority study was isoniazid-related maternal adverse events ≥ grade 3 or permanent discontinuation due to adverse reaction. The non-inferiority margin was an incidence rate of 5/100 person-years (investigators assumed an incidence rate of 5/100 person-years in the deferred group based on reports in non-pregnant women with HIV).

The primary outcome was reached in 15% of women (74 in the immediate/antepartum group vs 73 in deferred/postpartum group) with an incidence rate of 15.4/100 person-years and 14.9/100 person-years, respectively. This was higher than expected based on data from non-pregnant women.
There was a higher rate of adverse pregnancy outcomes in the group receiving INH during pregnancy (23% vs 17%; p =0.009). TB incidence was low and did not differ between the 2 groups.

In view of these findings administration of isoniazid for prevention of TB to pregnant HIV infected women should be reconsidered, particularly in woman with high CD4 counts. Pregnant women are

[11] Group TAS, Danel C, Moh R, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. N Engl J Med. 2015;373:808–822. https://doi. org/10.1056/NEJMoa1507198
[12] Rangaka MX, Wilkinson RJ, Boulle A, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: A randomised double-blind, placebo-controlled trial. Lancet. 2014;384:682–690. https://doi.org/10.1016/S0140-6736(14)60162-8
[13] Rangaka MX, Wilkinson RJ, Boulle A, Glynn JR, Fielding K, van Cutsem G, Wilkinson KA, Goliath R, Mathee S, Goemaere E, Maartens G. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind placebo-controlled trial. Lancet 2014;384(9944):682-90.http://www.ncbi.nlm.nih.gov/pubmed/24835842
[14] Minutes of the NEMLC meeting of 12 April 2018.
[15]Rangaka MX, Wilkinson RJ, Boulle A, Glynn JR, Fielding K, van Cutsem G, Wilkinson KA, Goliath R, Mathee S, Goemaere E, Maartens G. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind placebo-controlled trial. Lancet 2014;384(9944):682-90.http://www.ncbi.nlm.nih.gov/pubmed/24835842
[16] Gupta et al. Randomized trial of safety of isoniazid preventive therapy during or after pregnancy. CROI Conference Abstract, March 2018.
[17] Gupta et al. Randomized trial of safety of isoniazid preventive therapy during or after pregnancy. CROI Conference Abstract, March 2018. http://www.croiwebcasts.org/console/player/37314?mediaType=audio&&crd_fl=1&ssmsrq=1521455648187&ctms=5000&csmsrq=989

routinely given ART which gives protection against TB acquisition[18]. Although isoniazid prophylaxis gives additional benefit[19] [20] this should be weighed up against the risk of adverse pregnancy outcome.

The RCT was underpowered to detect the incidence of TB or TB deaths in pregnant women with low CD4, but fetal harm was reported (fetal demise, low birth weight, preterm delivery and congenital anomaly).

Lower CD4: Available evidence shows that TB incidence (and thus, risk of TB mortality[21]) increases exponentially with declining CD4.[22] [23] Thus, patients with very advanced HIV disease are at higher risk of TB acquisition.

Cochrane review[24] (12 RCTs) showed that when compared to placebo:

- TB preventive therapy associated with lower incidence of active TB (RR 0.68, 95% CI 0.54 to 0.85).
- IPT reduced mortality amongst those tested TST-positive (RR 0.74, 95% CI 0.55 to 1.00).
- INH plus rifampicin, irrespective of TST status, reduced mortality (RR 0.69, 95% CI 0.50 to 0.95),
- Overall, TB preventive therapy did not reduce all-cause mortality (RR 0.94, 95% CI 0.85 to 1.05).

REALITY RCT[25]*:* The RCT showed that a package of enhanced prophylaxis including TB prophylaxis reduced risk of death in patients with CD4<100. Mortality benefit was mostly shown for cryptococcosis (intervention was a combination of isoniazid, fluconazole and azithromycin). The RCT showed that IPT decreased non-fatal tuberculosis, but not mortality associated with TB (adjusted subhazard ratio (sHR) =0.81, 95% CI 0.52 to 1.25; p=0.34 in this cohort of patients. However, there is limited RCT evidence that compared immediate versus deferred IPT and only the REALITY RCT could be retrieved from the published literature. The study was done in non-pregnant women.

Recommendation: IPT deferral if CD4 ≥100 in pregnant women; whilst where CD4<100, active TB to be excluded with symptom screen and then IPT to be given.
Rationale: A recent 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. The CD4 cut-off of <100 was extrapolated from the REALITY RCT that showed that immediate IPT was associated with a decreased incidence of TB in patients with advanced disease (i.e. CD4<100) who started ART. Although REALITY was not done in pregnant women, it is well known that TB risk and TB mortality increase exponentially with declining CD4 counts. Evidence further suggests that IPT may reduce mortality amongst those tested TST-positive.
Level of Evidence: I Systematic review; Abstract of RCT; Extrapolation from RCT; Expert opinion

[18] Temprano Anrs Study Group, Danel C, Moh R, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *N Engl J Med.* 2015;373(9):808-822.
[19] Temprano Anrs Study Group, Danel C, Moh R, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *N Engl J Med.* 2015;373(9):808-822.
[20] Rangaka MX, Wilkinson RJ, Boulle A, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. *Lancet.* 2014;384(9944):682-690.
[21] UNAIDS. 2016. Global AIDS update 2016. UNAIDS, Geneva. Available at http://www.unaids.org/en/resources/documents/2016/Global-AIDS-update-2016
[22] Ellis PK, Martin WJ, Dodd PJ. CD4 count and tuberculosis risk in HIV-positive adults not on ART: a systematic review and meta-analysis. PeerJ. 2017 Dec 14;5:e4165. https://www.ncbi.nlm.nih.gov/pubmed/29259846
[23] Kaplan R, Hermans S, Caldwell J, Jennings K, Bekker LG, Wood R. HIV and TB co-infection in the ART era: CD4 count distributions and TB case fatality in Cape Town. BMC Infect Dis. 2018 Jul 31;18(1):356. https://www.ncbi.nlm.nih.gov/pubmed/30064368
- Article circulated electronically after the NEMLC meeting: Electronic South African TB registry data – multivariable analysis showed that decreased TB mortality was associated with higher CD4 count - Adjusted HR 0.82 per increase of 50 cells/mm3, 95% CI: 0.81–0.83, p < 001
[24] Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD000171. https://www.ncbi.nlm.nih.gov/pubmed/20091503
[25] 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

The following text was added to the STG:

In pregnant women, starting ART:
» If CD4≥100 cells/microL: defer IPT until after delivery.
» If CD4 <100 cells/microL: exclude active TB with symptom screen, then give IPT

11.3.3 CANDIDIASIS, OESOPHAGEAL

ART: *directions for use amended*

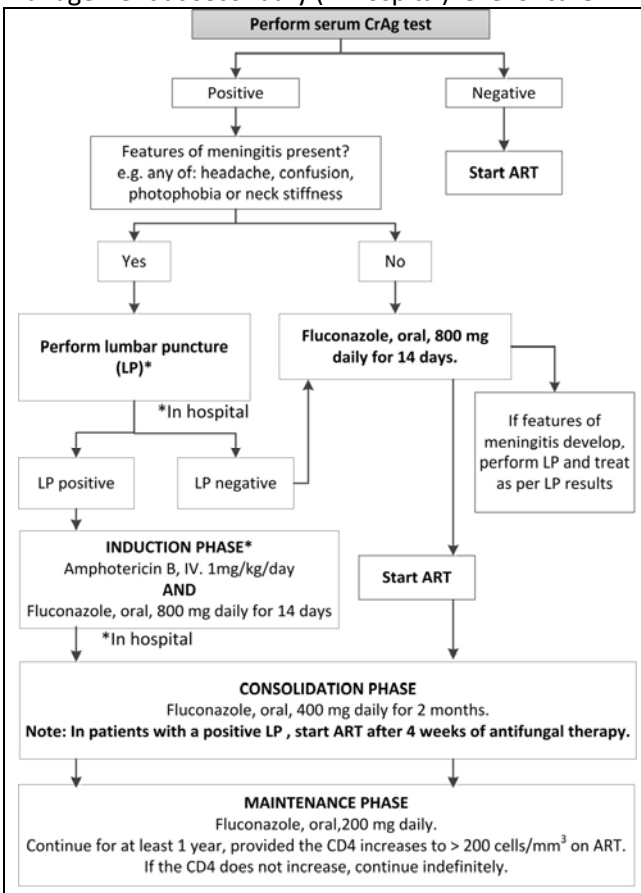
STG text was amended for completeness, aligned with the NDoH HIV Guidelines as follows:

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

Level of Evidence: III Guidelines

11.3.4 CRYPTOCOCCOSIS

The following algorithm, adapted from the Adult Hospital Level STGs and EML, 2015 was included.
Note, that this algorithm is relevant to primary level of care, indicating where treatment is referred for management at secondary (in hospital) level of care.



Note:** The following CrAg+ patients require **urgent referral:
» *Pregnant women who are symptomatic (headache, confusion).*
» *Pregnant women who are asymptomatic, but in the 1st trimester.*

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

Refer to the NEMLC report for chapter 6: Obstetrics & gynaecology conditions, section 6.8: HIV in pregnancy, for detailed information regarding the updated algorithm.

11.3.4.1 CRYPTOCOCCAL INFECTION, PRE- EMPTIVE THERAPY

CrAg positive and any symptom of meningitis

Fluconazole: NEMLC did not accept the recommendation of fluconazole as an initial pre-referral dose as they were of the opinion that this was a sub-acute illness, fluconazole is a fungistatic medicine and the evidence base is low quality[26].

11.3.10 HERPES SIMPLEX ULCERS, CHRONIC

Aciclovir, IV: *not added*

An external comment was received to consider inclusion of aciclovir, IV. However, the STG recommends that non-responders to oral aciclovir be referred to higher level of care for further management.

11.5 THE HIV-EXPOSED INFANT

HIV INFANT PROPHYLAXIS: *management delineated according to "low-risk", "high-risk" and "unknown risk".*

Low-risk category:

Nevirapine, oral: *recommended at birth and then daily for 6 weeks.*

High-risk category:

Zidovudine, oral: *recommended at birth and then 12 hourly for 6 weeks.*
Nevirapine, oral: *recommended at birth and then daily for 12 weeks.*

Unknown risk category:

Nevirapine, oral: *recommended daily, immediately and then daily for 6 weeks if HIV-positive.*

The PMTCT section was aligned with the Paediatric Hospital Level STGs and EML, 2017, except for the duration of AZT for high risk infants – this was reduced from "12 weeks" to "6 weeks". Please see the rationale, below:

High-risk infant prophylaxis: WHO Guidelines[27] recommends combination therapy for infants at high risk of acquiring HIV based on systematic review[28] that shows that "*limited available evidence suggests that using combination ARV regimens in high-risk infants reduces intrapartum transmission and that using prolonged prophylaxis in breastfed infants reduces breastfeeding transmission rates*".

Zidovudine (AZT)

PMTCT: The recommendation for nevirapine and zidovudine for 12 weeks in high risk infants in the Paediatric Hospital Level STGs and EML was not representative of RCT evidence[29]. There were

[26]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

[27] WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, 2016.

[28] 2015 review cited in WHO Guidelines - Updated review: Beste S, Essajee S, Siberry G, Hannaford A, Dara J, Sugandhi N, Penazzato M. Optimal Antiretroviral Prophylaxis in Infants at High Risk of Acquiring HIV: A Systematic Review. Pediatr Infect Dis J. 2018 Feb;37(2):169-175. https://www.ncbi.nlm.nih.gov/pubmed/29319636

[29] Nielsen-Saines K, Watts DH, Veloso VG, Bryson YJ, Joao EC, Pilotto JH, Gray G, Theron G, Santos B, Fonseca R, Kreitchmann R, Pinto J, Mussi-Pinhata MM, Ceriotto M, Machado D, Bethel J, Morgado MG, Dickover R, Camarca M, Mirochnick M, Siberry G, Grinsztejn B, Moreira RI, Bastos FI, Xu J, Moye J, Mofenson LM; NICHD HPTN 040/PACTG 1043 Protocol Team. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. N Engl J Med. 2012 Jun 21;366(25):2368-79. https://www.ncbi.nlm.nih.gov/pubmed/22716975

concerns raised regarding toxicity of prolonged zidovudine in primary care settings, where monitoring of WCC and Hb in infants poses challenges.

Toxicity:

- *Nielsen-Saines et al (2012)[30]:* RCT, where at 6 weeks postpartum, AZT exposure in HIV exposed (3 regimens- monotherapy, plus 2 doses of NVP or with 3TC and nelfinavir) adverse events reported were 20% grade 2 or greater neutropenia, 26% grade 2 or more anaemia; and 12% had serious AEs that were causally related to ARVs, predominantly anaemia and neutropenia.
- *Retrospective case review[31]* showed that AZT associated with neutropenia, anaemia and thrombocytopenia in infants prophylaxis.

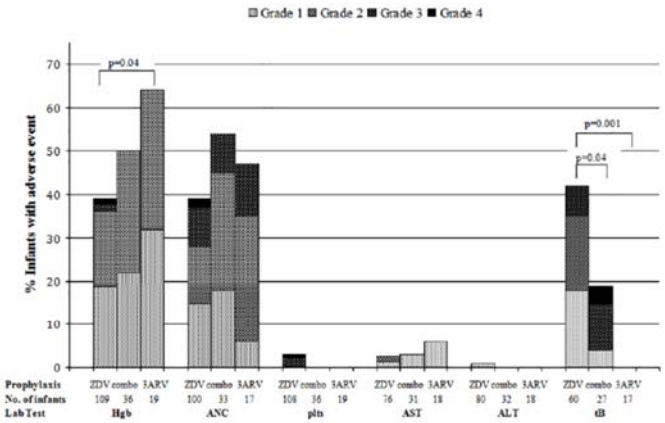


Fig 1. Frequency and severity of laboratory adverse events for infants exposed to zidovudine alone, combination prophylaxis, or three-drug prophylaxis. The maximum grade adverse event within each laboratory test (hemoglobin, Hgb; absolute neutrophil count, ANC; platelets, plts; aspartate aminotransferase, AST; alanine aminotransferase, ALT; total bilirubin, tB) that occurred between days of life 8 through 42 is shown for infants exposed postnatally to zidovudine alone (ZDV), combination antiretroviral prophylaxis (combo), and three-drug prophylaxis containing zidovudine (or stavudine), lamivudine, and nevirapine (3ARV). Significant differences are denoted by p-values.

doi:10.1371/journal.pone.0127062.g001

- Mulenga et al (2016)[32]: Adverse event in the CHAPAS-3 RCT (of HIV-infected children receiving either stavudine-, abacavir- or zidovudine-containing regimen) occurring in the zidovudine group included grade 3 or 4 anaemia (6%) and grade 3 or 4 neutropenia (8%).

Recommendation: Alignment of PMTCT HIV prophylaxis in HIV-exposed infants with the Paediatric Hospital Level STGs and EML, 2017; except that the duration of AZT for high risk infants be reduced from "12 weeks" to "6 weeks".

Rationale: Evidence supports the 6-week duration of AZT in high risk infants. AZT is associated with anaemia and neutropaenia, and as monitoring at primary care is challenging, particularly neutrophil count which requires phlebotomy, the PHC Committee cautioned against AZT course, beyond 6-weeks, at primary level of care.

Level of Evidence: I Systematic review, RCTs, Retrospective case series, Guidelines[33] [34]

[30] Nielsen-Saines K, Watts DH, Veloso VG, Bryson YJ, Joao EC, Pilotto JH, Gray G, Theron G, Santos B, Fonseca R, Kreitchmann R, Pinto J, Mussi-Pinhata MM, Ceriotto M, Machado D, Bethel J, Morgado MG, Dickover R, Camarca M, Mirochnick M, Siberry G, Grinsztejn B, Moreira RI, Bastos FI, Xu J, Moye J, Mofenson LM; NICHD HPTN 040/PACTG 1043 Protocol Team. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. N Engl J Med. 2012 Jun 21;366(25):2368-79. https://www.ncbi.nlm.nih.gov/pubmed/22716975

[31] Smith C, Forster JE, Levin MJ, Davies J, Pappas J, Kinzie K, Barr E, Paul S, McFarland EJ, Weinberg A. Serious adverse events are uncommon with combination neonatal antiretroviral prophylaxis: a retrospective case review. PLoS One. 2015 May 22;10(5):e0127062. https://www.ncbi.nlm.nih.gov/pubmed/26000984

[32] Mulenga V, Musiime V, Kekitiinwa A, Cook AD, Abongomera G, Kenny J, Chabala C, Mirembe G, Asiimwe A, Owen-Powell E, Burger D, McIlleron H, Klein N, Chintu C, Thomason MJ, Kityo C, Walker AS, Gibb DM; CHAPAS-3 trial team. Abacavir, zidovudine, or stavudine as paediatric tablets for African HIV-infected children (CHAPAS-3): an open-label, parallel-group, randomised controlled trial. Lancet Infect Dis. 2016 Feb;16(2):169-79. https://www.ncbi.nlm.nih.gov/pubmed/26481928

[33] Paediatric Hospital Level STGs and EML, 2017.

[34] WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, 2016.

11.5 THE HIV-EXPOSED INFANT

Infant regimens

Mother on lifelong ART, initiated before pregnancy (including TDF + EFV + 3TC/FTC) and failing 1st line and initiated on 2nd line:

AZT: *duration of therapy amended*

The following text was amended for correctness and alignment with the NDoH HIV Guidelines, 2015:

< 4 weeks before delivery

- AZT for 6 weeks + NVP for 12 weeks.

Level of Evidence: III Guidelines

11.6 MANAGEMENT OF HIV-INFECTED CHILDREN

Immunisation, deworming and vitamin A programme

Measles vaccine at 6 months: *deleted*

The following was deleted, aligned with the current EPI schedule:

- ~~Give an additional dose of measles vaccine at 6 months.~~

Level of Evidence: III Guidelines

Antiretroviral therapy

Eligibility for ART

Amended to align with the UTT approach:

Clinical criteria

» Confirmation of diagnosis of HIV infection, irrespective of CD4 count or WHO clinical stage.

~~**AND**~~

~~» Child < 5 years of age irrespective of CD4 count or staging.~~

~~» Child ≥ 5 years with CD4 < 500 or WHO clinical stage III or IV.~~

AND

» No medical contraindication (e.g. major organ dysfunction). If medical contraindications are present refer to hospital for rapid review and planning.

Children requiring fast track (i.e. start ART within 7 days of being eligible if safe to do so):

Amended for correctness and consistency, extrapolated from evidence for Adult timing of 8 weeks prior to ART initiation (See page 6 of this report).

» MDR or XDR-TB except meningitis, in which case wait 8 weeks to initiate ART.

Level of Evidence: II extrapolated RCT[35]

First-line regimen

Adolescents > 15 years and > 40 kg:

TDF + 3TC/FTC + EFV: *caution regarding renal impairment amended*

Amended for correctness, aligned with the NDoH HIV Guidelines, 2015:

Do not use in patients with significant psychiatric co-morbidity, renal compromise (creatinine clearance < ~~50~~ 80 mL/min/1.73m^2), or co-administration of nephrotoxic medicines.

Level of Evidence: III Guidelines

Adjustment of previous first-line regimens

DdI-containing 2nd line regimens: *directions for switching added*

Guidance on switching 2nd line ddi to AZT was included, as follows, aligned with the NDoH HIV Guidelines, 2015:

Change ddI to ABC, irrespective of VL. If receiving ddI and AZT as a second-line regimen, stop the ddI and replace with 3TC.

Level of Evidence: III Guidelines

[35] Török ME, Yen NT, Chau TT et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)--associated tuberculous meningitis. Clin Infect Dis.2011 Jun;52(11):1374-83:

Treatment failure

1st line ART regimen: *Guidance for treatment failure added*

The text of the STG was updated as follows, to reflect the different cut-off values of the various laboratory assays in use.

Viral load (VL)	Response
Lower than detectable limits	» Praise the patient and caregiver(s) and continue 12-monthly VL monitoring.
Detectable, but < 1 000 copies/mL	» Begin step up adherence package. » Repeat VL in 6 months.
>1 000 copies/mL	» Begin step-up adherence package. » Repeat VL in 3 months: – VL lower than detectable limits Return to routine 6–12 monthly monitoring. – VL detectable, but < 1000 copies/mL: Continue step up adherence and repeat VL after 6 months. – VL > 1 000 copies/mL despite stepped up adherence, **and** child is on NNRTI-based regimen: Consult or refer for switch to 2nd line therapy after adherence ensured. – Child is on a PI-based regimen and VL > 1000 copies/mL, despite stepped up adherence: – If the child received an unboosted PI (e.g. ritonavir alone) in the past or received TB treatment while LPV/r (without dose adjusting or adding additional ritonavir) and the VL is > 1000 copies/mL, discuss new regimen with an expert. – Referral for resistance testing is indicated in these situations, but should only be done if the child has been taking ARVs reliably in the last month » VL < 30 000 copies/mL: Continue with same regimen while monitoring VL 3-monthly. Continue stepping up adherence and consult an expert. » VL > 30 000 copies/mL: Refer.

Level of Evidence: III Expert opinion

11.6 MANAGEMENT OF HIV-INFECTED CHILDREN *and* 11.7 OPPORTUNISTIC INFECTIONS, PROPHYLAXIS IN CHILDREN: IMMUNISATION

BCG vaccine: *directions for use amended*

An external comment was received stating that it is not current practice to immunize HIV-infected children who have immune reconstitution on ART with BCG.

The following text was updated for clarity purposes:

» Continue immunisation as in the HIV-uninfected child except:
- ~~Do not give BCG to children with symptomatic HIV unless the child has immune reconstituted on ART.~~
- Do not give BCG.
- See Chapter 13: Immunisation.

Level of Evidence: III Guidelines

11.7 OPPORTUNISTIC INFECTIONS, PROPHYLAXIS IN CHILDREN

Measles vaccine at 6 months: *deleted*

The following was deleted, aligned with the current EPI schedule:

- ~~Give an additional dose of measles vaccine at 6 months.~~

Level of Evidence: III Guidelines

11.8.7 TUBERCULOSIS (TB)

Efavirenz, oral: *guidance provided - no dose adjustment required with rifampicin*

Aligned with Guidelines and text of the STG was cross-referenced to the paediatric ART dosing table, as follows:

If the child needs to take concomitant ART and rifampicin:
» Efavirenz: use the normal recommended dosage as per dosing table on pg 11.38.
» Abacavir and lamivudine: no dose adjustment required.

» Lopinavir/ritonavir: Add additional ritonavir to ensure an equal dose in mg of lopinavir and ritonavir while on rifampicin. For example, for each mL of LPV/r solution (80/20 mg/mL), add 0.75 mL of ritonavir solution (80 mg/mL). See dosing table on pg 11.38.
» Give pyridoxine (vitamin B_6) to all children on TB and ART, to avoid development of peripheral neuropathy.

11.12 PRE-EXPOSURE PROPHYLAXIS

NDoH HIV PrEP Guidelines: The NDoH HIV PrEP Guidelines has not been officially endorsed, as the National Health Council had concluded that it was not cost-effective to roll out this programme, universally, as yet. However, HIV PrEP is currently being provided in a phased manner, starting with commercial sex worker; thereafter, other higher risk groups would be considered. PrEP is currently being provided at *designated sites*.

TDF+FTC (PrEP)

Evidence of efficacy: Fonner *et al*[36] conducted a systematic review of randomized controlled trials (RCTs), open label extension and demonstration projects evaluating tenofovir-containing pre-exposure prophylaxis (PrEP) compared to placebo/no PrEP i.e. delayed PrEP. The review analyses data from 15 RCTS and 3 observational studies, including 19491 participants of which 11901 received active drug. The following populations were included: people who inject drugs, serodiscordant couples, men who have sex with men (MSM), transgender women, women and heterosexual men. The review found PrEP to be effective, with a 51% reduction in risk of HIV infection (95% CI 0.33 to 0.73). Poor adherence resulted in decreased effectiveness. When stratified by mode of acquisition, PrEP showed similar effectiveness across groups: PrEP vs placebo RR of 0.34 (95%CI 0.15 to 0.80) for rectal exposure and RR of 0.54 (95% CI 0.32 to 0.90) for penile/vaginal exposure. PrEP had decreased efficacy in individuals <25 years old, which may be the result of poorer adherence: RR 0.71 (95%CI 0.47 to 1.06). In younger women one study found evidence of efficacy (Partners-PrEP), and one found no evidence for efficacy (FEM PrEP)- this was thought to be due to differences in adherence. There was no increase in proportion experiencing adverse effects in tenofovir arms, but 2 studies found decrease in renal function with tenofovir exposure. Emergence of tenofovir or emtricitabine resistance was low, and there was no evidence for PrEP resulting in risk compensating behaviour.
Note: There was no information on absolute risk reduction, so NNT could not be calculated.
Level of Evidence: I Systematic review

Duration of therapy retained as 7 days: An external comment was received querying the statement *"Note: To reach adequate protective levels in tissues, 7 days of daily dosing are required for anal sex and 20 days for vaginal sex".*
Pharmacokinetic study[37] supports this statement, and cited accordingly in the STG.
Level of Evidence: III Pharmacokinetic study

Stopping TDF+FTC (PrEP): The caution for hepatitis flares on discontinuation of PreP was retained (See discussion on page 4 of this NEMLC report).

PrEP follow up and monitoring: ALT monitoring if HepBSAg positive
ALT monitoring (3-monthly): *deleted*
As patients would be on hepatitis B antiviral therapy, monitoring of ALT levels was not considered necessary.

[36] Fonner VA, Dalglish SL, Kennedy CE, Baggaley R, O'Reilly KR, Koechlin FM, et al. Effectiveness and safety of oral HIV preexposure prophylaxis for all populations. AIDS. 2016;30(12):1973-83.
[37] Patterson KB, Prince HA, Kraft E, Jenkins AJ, Shaheen NJ, Rooney JF, Cohen MS, Kashuba AD. Penetration of tenofovir and emtricitabine in mucosal tissues: implications for prevention of HIV-1 transmission. Sci Transl Med. 2011 Dec 7;3(112):112re4. https://www.ncbi.nlm.nih.gov/pubmed/22158861

The following new STG was added to the chapter:

11.12 Pre-exposure prophylaxis

Consult the most recent National Department of Health Guideline for PrEP eligibility criteria.
PrEP is currently available at designated sites only.

Description

Pre-exposure prophylaxis (PrEP) is the use of antiretroviral medicines by HIV-negative individuals before potential exposure to HIV to prevent them from acquiring HIV infection.

PrEP only protects against HIV infection; it does not offer protection against other STIs or pregnancy.

PrEP should be used as part of a package including condoms, lubricants for anal sex, STI management, screening and management of intimate partner violence, sexual and reproductive health services, medical male circumcision and HIV services, including counseling and testing, HIV management, ART, PEP, and PrEP.

Individuals initiated on PrEP must be:

» HIV-negative.
» At substantial risk of HIV infection.
» Willing and able to adhere to PrEP.
» Prepared to come for repeat HIV testing every 3 months.
» No contra-indications to tenofovir or emtricitabine.
» No suspicion of acute HIV-infection (see clinical features, below).

Clinical features of acute HIV infection

Symptoms	Signs
Malaise, anorexia, myalgia, headache, sore throat, sore glands, rash	Fever, sweating, viral meningitis, generalised lymphadenopathy, hepatosplenomegaly, pharyngitis, truncal rash, orogenital herpetiform ulceration, oral/oesophageal candidiasis, cervical adenopathy

Contra-indications to PREP

» Pre-existing HIV infection.
» Creatinine clearance or eGFR < 60 mL/min.
» Use of nephrotoxic medicines e.g. aminoglycosides.
» Young women/men < 35 kg or < 15 years of age who are not Tanner stage 3 (sexual maturity) or greater.
» Unwilling or unable to adhere to daily PrEP.

PREP regimen

A fixed dose combination formulation of:

- Tenofovir, oral, 300 mg daily.

AND

- Emtricitabine, oral, 200 mg daily.

Note: To reach adequate protective levels in tissues, 7 days of daily dosing are required for anal sex and 20 days for vaginal sex.

Screening investigations before starting PrEP

Investigation	Purpose	Action
HIV test (using algorithm in the HTS guidelines)	Assessment of HIV status.	If HIV-negative, consider PrEP If HIV-positive. Link to treatment and care services.
Creatinine clearance/ eGFR	To identify pre-existing renal disease.	Do not initiate PrEP if creatinine clearance/eGFR < 60 mL/min. Repeat creatinine clearance after two weeks. If renal function returns to normal and other PrEP criteria are met, PrEP may be initiated. Refer for further investigation if renal function remains abnormal.
Hepatitis B surface antigen (HBsAg)	To diagnose chronic hepatitis B infection. To identify those eligible for vaccination against hepatitis B.	Consider vaccination if available for HBsAg-negative. If HBsAg-positive, do ALT prior to PrEP initiation.

ALT if HBsAg-positive		If ALT persistently elevated or other abnormal liver function tests, refer for assessment.
Urine pregnancy test	To identify if pregnant.	Discuss the potential risks of TDF + FTC.
RPR	To diagnose syphilis infection for treatment.	Manage according to STI guidelines.
Syndromic STI screening	To diagnose and treat STI.	Manage according to STI guidelines.

Note:

» If symptoms or signs of acute HIV infection are present, PrEP should be postponed until symptoms subside and a repeat rapid HIV test after 4 weeks remains negative.

» TDF + FTC is active against hepatitis B (HBV) infection. HBV infection is not a contra-indication to PrEP, but will require LFT monitoring. Discontinuation of TDF + FTC in patients with HBV requires referral to a specialist because of a risk of a hepatitis flare.

Hepatitis B immune status and PrEP eligibility

Hepatitis B surface antigen (HBsAg)	Hepatitis B surface antibody (HBsAb)	Action
Negative (-)	Negative (-)	Start PrEP. Vaccinate concurrently if available
Negative (-)	Positive (+)	Start PrEP. No vaccine needed
Positive (+)	N/A	Refer for evaluation, if ALT > 2 times upper limit of normal.

Note:

» PrEP users with chronic hepatitis B infection who develop abnormal liver function tests should be referred for assessment.

PrEP follow up and monitoring

Activity	Frequency
Confirmation of HIV-negative status	At 1 month, then every 3 months
Address side effects	Every visit
Adherence counseling	Every visit
Creatinine clearance	At 1 month, then every 3 months for the first year, then 12-monthly
STI screening and treatment	Every visit
PrEP dispensing	1 month supply, then 3 monthly supply
Behavioural sexual risk reduction counseling	Every visit

PREP SAFETY

Relevant medicine interaction information

Medicine	Interaction information	Advise
Standard TB medicines	No interaction	No need for dose adjustments
MDR-TB medicines	Increase risk of renal side effects	Avoid PrEP. Advise other prevention methods
Hormonal contraception	No interaction	Hormonal contraception does not affect PrEP effectiveness, nor does PrEP affect hormonal contraceptive effectiveness
Nephrotoxic medicines	Increase risk of renal side effects	Avoid PrEP. Advise other prevention methods

Side effects of TDF + FTC combination

Major	Renal toxicity, decreased bone mineral density, extremely small risk of lactic acidosis and hepatic steatosis or steatohepatitis
Minor	Gastrointestinal symptoms (diarrhoea, nausea, vomiting and flatulence), unintentional weight loss

Note:

» Minor side effects are relatively common (approximately 1 in 10 individuals in the first 1-2 months).

» Mild and self-limiting; do not require discontinuation.

» Renal toxicity and decreased bone mineral density usually reversible upon stopping PrEP.

Stopping PREP

PrEP should be stopped if:

» Tests HIV-positive.

» Renal disease develops.

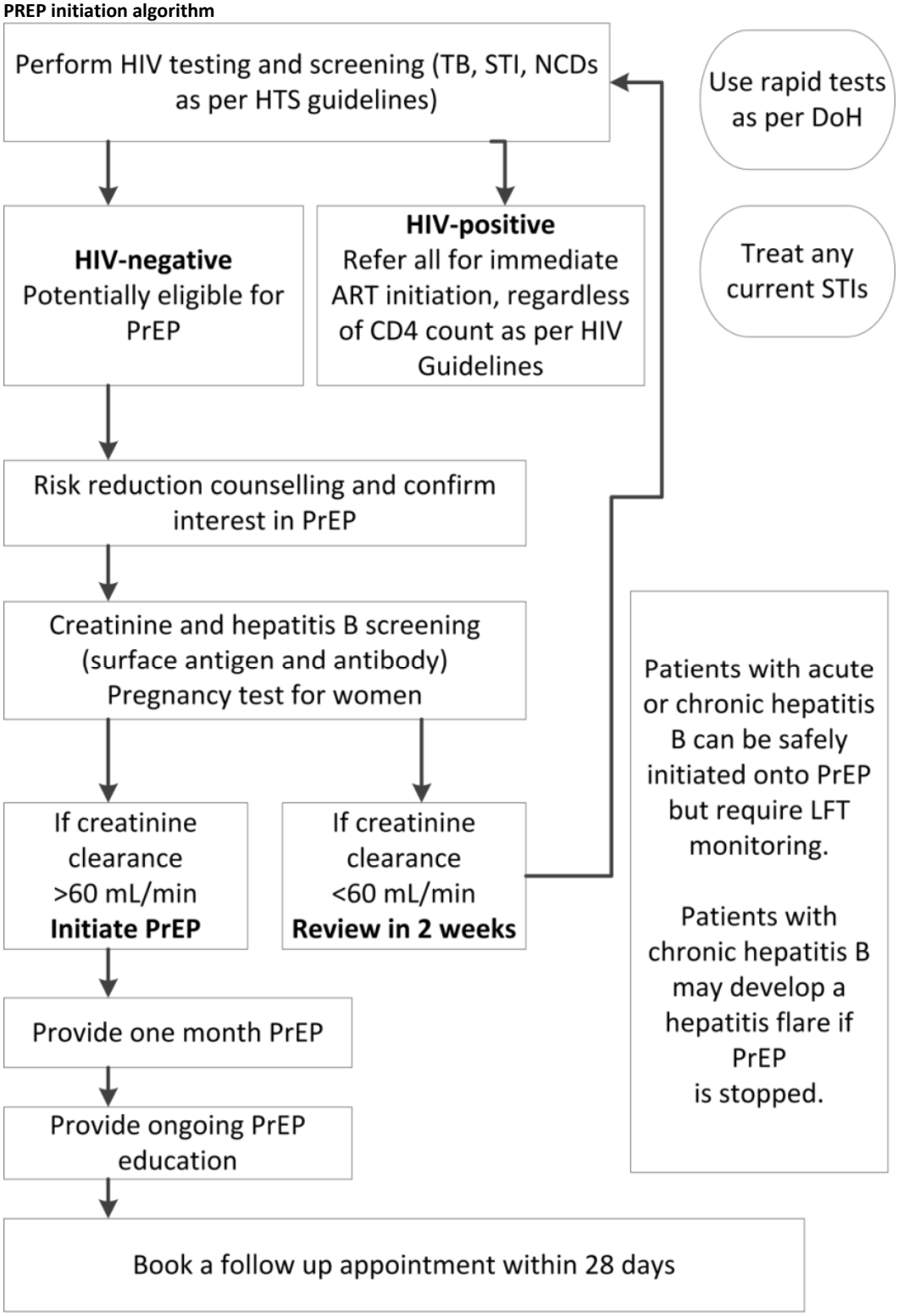
» Non-adherent to PrEP.

» Does not need or want PrEP.
» No longer meets eligibility criteria.
» There are safety concerns where the risks of PrEP use outweigh potential benefit.

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

Note: Patients with chronic HBV may experience a hepatitis flare on discontinuation of PrEP.

PREP initiation algorithm



Referral

» HBsAg-positive, with abnormal ALT.
» Discontinuation of TDF + FTC in patients with HBV.

RILPIVIRINE MEDICINE REVIEW

Rilpivirine, oral: *not added*

Refer to the medicine review, below:

Rilpivirine_for HIV in adults_PHC Revie

Nevirapine: The proposed recommendation of RPV was to replace nevirapine (NVP) which is considered a toxic medicine, was reviewed in the above-mentioned medicine review. However, there is no available head-to-head safety data comparing NVP to RPV. The medicine review used the available data and extrapolated the evidence.

Efavirenz (EFV): RPV is better tolerated than EFV, but RPV is less efficacious than EFV in patients with a viral load (VL)>100 000 copies/mL, which is the VL of about half of South African patients at baseline.

NEMLC Recommendation: Rilpivirine not be recommended to replace NVP as part of the first line ART regimen.

Rationale: RPV is less effective than EFV at high viral loads.

Level of Evidence: III Expert opinion

DOLUTEGRAVIR MEDICINE REVIEW

Dolutegravir, oral: *not added*

Refer to the medicine review for dolutegravir (DTG) as first line in ART-naive HIV-infected adult patients, below:

Dolutegravir for HIV in adults_PHC R

NEMLC Recommendation: DTG not be recommended currently; and that a "watch and wait" approach be taken; as the increasing primary level NRTI resistance throughout Africa renders DTG to be an attractive alternative. In addition, price parity of DTG-containing FDC with the current regimen is recommended.

Rationale: There is limited evidence (phase III RCT) for DTG as part of a first line ART regimen; no outcome data in TB (except a pharmacokinetic study) or pregnancy. However, additional evidence will be forthcoming as trials are underway. DTG has a heightened barrier to resistance, is indicated amongst paediatrics, possibly more tolerable and efficacious than EFV and a number of applications for DTG-FDC containing regimens is still pending at the Medicines Control Council/South African Health Products Regulatory Authority. The currently available DTG-containing FDC is expensive.

Level of Evidence: I Phase III RCT