CHAPTER 10
HIV AND AIDS

Comprehensive guidelines are available for ART and the care of adults and children with HIV infection in the 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates.[i]

10.1 ANTIRETROVIRAL THERAPY

B24

Antiretroviral therapy (ART) consists of combinations of antiretroviral medicines that are capable of suppressing HIV replication (defined as an undetectable viral load). Continued use of ART with a detectable viral load results in the development of resistance to some or all of the medicines in the regimen. High levels of adherence are essential for long-term success with ART.

The current recommended first-line ART regimen contains two nucleoside reverse transcriptase inhibitors (NRTIs) together with an integrase strand transfer inhibitor (InSTI) dolutegravir (DTG). Previously a non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz or nevirapine, together with two NRTIs, were recommended for first-line ART. DTG is better tolerated than the NNRTIs and has a much higher barrier to the development of resistance.
DTG, together with two NRTIs, is now also recommended in a patient who has failed an NNRTI-based (formerly first-line) regimen. Previously a protease inhibitor (PI), together with two NRTIs, was recommended for second-line ART, but DTGis better tolerated than PIs. Switching people established on ART to the newer DTG-based ART regimens need to be carefully done to reduce the risk of the emergence of resistance (refer to National Department of Health HIV Guidelines and “Switching existing clients to DTG-containing regimens” section in Table 10.1: ART regimens).

ELIGIBILITY FOR ART

Eligibility to start ART:
All adults with confirmed HIV infection, irrespective of CD4 count or WHO clinical stage.

LoE: Ia[#]

Immediate initiation:
ART should be initiated immediately in pregnancy and during breastfeeding.

LoE:IIa[#]

Timing of ART initiation:

» Where a patient is willing and ready, ART should be initiated on the same day as HIV diagnosis, except in patients with TB or cryptococcal meningitis (see Timing of ART initiation below).

» In TB co-infection, start with TB treatment first, followed by ART initiation according to CD4 count (except TB meningitis – see below):
  - CD4 <50 cells/mm^3: initiate ART within 2 weeks of starting TB treatment.
  - CD4 ≥50 cells/mm^3: defer ART until 8 weeks after starting TB treatment, as this does not increase the risk of mortality and reduces the risk of deterioration due to immune reconstitution inflammatory syndrome (IRIS).

LoE:Ia[iv]

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

LoE:IIIa[v]

» In patients with cryptococcal meningitis, defer ART until 4–6 weeks after starting antifungal treatment (earlier initiation has been shown to increase the risk of death).

LoE:IIIa[vi]

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

LoE:IVb[vii]

PSYCHOSOCIAL INDICATORS OF READINESS FOR ART

It is essential that patients have good insight into the need for long-term therapy and high levels of adherence. Pay careful attention to adherence planning. Encourage patients to disclose their HIV status to somebody to act as a treatment supporter. If this is not possible then the patient should join a support group.

Manage depression.

Active substance abuse/alcoholism is an impediment to adherence and, if possible, should be addressed prior to initiating ART.

LoE:IIIb[viii]

ART REGIMENS

INITIATING ART	
Treatment-naïve patients	Individuals ≥30kg: TDF + 3TC + DTG ("TLD") *LoE:IIa*[ix] **Note***:* DTG-based regimens are now recommended as first line ART in all women of child-bearing potential. *LoE:IIa*[x] Patients on rifampicin-based TB treatment: TDF + FTC + EFV **OR**

	TDF + 3TC + DTG *plus* additional dose of DTG 50 mg 12 hours later. The extra DTG dose can be stopped two weeks after completion of TB therapy. *LoE:IIIb*[xi] (Also see AH STG Section 6.6: HIV in pregnancy.)
Contraindications/ intolerance to DTG	TDF + 3TC/FTC + EFV
Contraindications to EFV and DTG	Start protease inhibitor-based regimen: TDF + 3TC/FTC + ATV/r *LoE:IIb*[xii] **Note:** if patient requires rifampicin-based TB treatment, substitute ATV/r with LPV/r 800/200 mg 12-hourly. **Note:** There is an increased risk of ALT/AST elevations and gastrointestinal disorders. LPV/r dose should be gradually titrated upward over 1-2 weeks (e.g. 600/150 mg and then 800/200 mg). The LPV/r can be switched back to ATV two weeks after completion of TB therapy.
Contraindication to TDF » eGFR <50 mL/minute.	If chronic hepatitis B coinfection and eGFR 30-50 ml/min: TAF + FTC + DTG. Other scenarios: ABC + 3TC + DTG *LoE:IIIb*[xiii]
Contraindication to TDF/TAF and ABC intolerance/hypersensitivity	AZT + 3TC with DTG
Note: In the unlikely scenario where there is intolerance/contraindication to all currently available NRTIs, the following alternative dual-therapy regimens may be used **after** consulting a specialist: • DTG + 3TC (if no resistance/intolerance to 3TC and VL <500 000 copies/mL) • EFV + LPV/r *LoE:IIb*[xiv] • DTG + LPV/r	

VIROLOGICAL FAILURE

Management of viraemia on TLD	<u>If plasma VL >50 copies/mL:</u> » Address adherence, tolerability, medicine interactions & psychosocial factors. » Repeat VL test 3 months later. <u>If plasma VL remains > 50:</u> » Assess adherence, tolerability, medicine interactions & psychosocial factors again. » If on TLD <2 years, or persistent low-level viraemia (50-999 copies/mL), or adherence suboptimal, repeat VL at next scheduled visit (i.e. in 6 months' time). » If on TLD >2 years and ≥2 consecutive VL ≥1000 copies/mL (or 1 VL ≥1000 copies/mL plus CD4 <200 or opportunistic infection), discuss with an HIV expert* whether a resistance test is indicated (as a rule it is not, and efforts to resolve adherence issues should be intensified instead).
SWITCHING EXISTING CLIENTS TO DTG-CONTAINING REGIMENS	
Patient on: » **TDF/FTC/EFV** » **ABC/3TC/EFV (or NVP)** » **AZT/3TC/EFV (or NVP)** » **AZT/3TC/DTG** » **Any LPV/r- or ATV/r-containing regimen for <2 years** » **Any LPV/r- or ATV/r-containing regimen with latest VL <1000 copies/mL**	Switch to DTG-containing regimen regardless of VL result: TDF + 3TC + DTG ("TLD") If contraindications to DTG or TDF, use alternative regimen as for first line above. *LoE:IIb*[xv]
Patient on: » **ATV/r or LPV/r regimen for >2 years and ≥2 consecutive viral loads ≥1000 copies/mL**	If adherence >80%, discuss with an HIV expert* to authorise and interpret a resistance test before switching. If adherence < 80%, switch to DTG-containing regimen: TDF + 3TC + DTG ("TLD") If contraindications to DTG or TDF, use alternative regimen as for first line above. *LoE:IIb*[xvi]
CLIENTS WITH DTG RESISTANCE	

Any DTG resistance shown on genotype authorised by HIV expert	Discuss case with an HIV expert*. The regimen will be determined by an Expert Committee based on the pattern of resistant mutations and the prior history of antiretroviral exposure. Darunavir/ritonavir is included on the Essential Medicines List for adults as a special access item; as recommended by the National ARV Drug Resistance Committee (ADReC), previously called the TLART committee), following a genotype resistance test. Application for 3rd line using the standard motivation form may be required (available on request from TLART@health.gov.za or download from https://www.health.gov.za/nhi-edp-stgs-eml/).
RIFAMPICIN-BASED TB TREATMENT	
Rifampicin-based TB treatment	<u>If on DTG:</u> Add DTG 50 mg 12 hours after TLD dose. *LoE:IIIb*[xvii] <u>If on ATV/r</u>: Switch ATV/r to LPV/r 800/200 mg 12 hourly (i.e. double dose). **Note:** There is an increased risk of ALT/AST elevations and gastrointestinal disorders. LPV/r dose should be gradually titrated upward over 1-2 weeks. The LPV/r can be switched back to ATV/r two weeks after completion of TB therapy.

ABC=Abacavir, ATV/r=Atazanavir/ritonavir, AZT=Zidovudine, 3TC=Lamivudine, DTG= Dolutegravir, EFV=Efavirenz FTC=Emtricitabine, LPV/r=Lopinavir/ritonavir, TDF=Tenofovir disoproxil fumarate TAF= Tenofovir alafenamide

Table 10.1: ART regimens

*For advice from an HIV expert, approach an HIV Hotline, an infectious disease specialist, or the Third Line ART committee.

<u>HIV Hotlines:</u>

» National HIV & TB Health Care Worker Hotline: **0800 212 506**

» Right to Care Paediatric, Adolescent and Adult HIV Helpline: **082 352 6642**

» KZN Paediatric Hotline: **0800 006 603**

Note:

» Always check hepatitis B surface antigen (HBsAg) before stopping TDF.

» If patient has chronic hepatitis B, stopping TDF may lead to a fatal hepatitis flare.
» Continue TDF if HBsAg positive.

RE-INITIATING ART IN PATIENTS WHO HAVE INTERRUPTED TREATMENT

» Do VL, recommence ART regimen unless there is a clinical indication to defer ART, repeat VL at 3 months. Recommence previous regimen (unless patient would qualify for a switch to TLD anyway as per above, in which case start DTG-based regimen, e.g. TLD).
» If VL does not to decrease to <1000 copies/mL at 3 months, manage as per virological failure above.

LoE:IIIb[xviii]

ART: DOSING AND IMPORTANT ADVERSE EFFECTS				
Generic name	**Class**	**Usual dose**	**Renal adjusted dose**	**Important adverse drug reactions (ADRs) and timing**
Tenofovir disoproxil fumarate (TDF)	NRTI	300 mg daily	Avoid in renal impairment (eGFR <50 mL/min)	» Acute kidney injury (rare - weeks to months). » Decline in eGFR (months to years). » Fanconi syndrome (rare – months to years). » Reduced bone mineral density (months to years).
Abacavir (ABC)	NRTI	600 mg daily	Dose adjustment not required	» Hypersensitivity reaction (1 to 6 weeks) fever, rash, constitutional symptoms, gastrointestinal symptoms and respiratory symptoms.
Zidovudine (AZT)	NRTI	300 mg 12 hourly	eGFR <10 mL/min: 300 mg daily	» Anaemia, neutropenia (weeks to months). » Gastro-intestinal upset. » Headache. » Myopathy (rare). » Hyperlactataemia / steatohepatitis (medium risk - months). » Lipoatrophy (months to years).
Lamivudine (3TC)	NRTI	300 mg daily (or 150 mg 12 hourly)	eGFR 10-30 mL/min: 150 mg daily eGFR <10 mL/min: 50 mg daily	» Anaemia due to pure red cell aplasia (rare).
Emtricitabine (FTC)	NRTI	200 mg daily	eGFR 15-29 mL/min:	» Palmar hyperpigmentation. » Anaemia due to pure red cell aplasia (rare).

			200 mg every 3 days <u>eGFR <15 mL/min:</u> 200 mg every 4 days Note: FTC is not available as a single-ingredient formulation.	*LoE:IVb*[xix]
Efavirenz (EFV)	NNRTI	600 mg at night	Dose adjustment not required	» Central nervous system symptoms: vivid dreams, problems with concentration, confusion, mood disturbance, psychosis (days to weeks). » Encephalopathy, often with cerebellar features (uncommon – months to years). *LoE:IVb*[xx] » Rash (1 to 6 weeks). » Hepatitis (weeks to months) » Gynaecomastia.
Tenofovir alafenamide (TAF)	NRTI	25 mg daily If co-formulated with FTC, avoid if eGFR <30 ml/min. If used as a single agent, avoid if eGFR <15 ml/min and not on haemodialysis.		» Acute kidney injury. » Fanconi syndrome. » Reduced bone mineral density.
Lopinavir/ ritonavir (LPV/r)	Boosted PI	400/100 mg 12 hourly **OR** 800/200 mg daily (only if PI-naïve)	Dose adjustment not required	» Gastrointestinal upset. » Dyslipidaemia (weeks). » Rash and/or Hepatitis (1 to 6 weeks).
Atazanavir/ ritonavir (ATV/r)	Boosted PI	ATV 300 mg with ritonavir 100 mg daily	Dose adjustment not required	» Unconjugated hyperbilirubinaemia (common, but benign). » Dyslipidaemia (low risk). » Hepatitis (rare - 1 to 6 weeks). » Renal stones (uncommon).
Dolutegravir (DTG)	InSTIs	50 mg once daily	Dose adjustment not required	» Hypersensitivity (rare, weeks). » Insomnia (common). » Headache (common). » Other neuropsychiatric symptoms. » Nausea, diarrhoea (common). » Hepatitis (uncommon). » Increase in serum creatinine (<30 mmol/L within the first few weeks of DTG initiation) due to inhibition

				of creatinine secretion by DTG; this is clinically insignificant as glomerular filtration rate is not reduced but will modestly affect eGFR which is determined using serum creatinine.

Table 10.2: Dosing and important adverse effects associated with ART
The time-onset information with respect to adverse drug reactions (ADRs) serves as an estimate. Patients may present with ADRs with the onset deviating from that indicated in the table.

LoE:IIIb[xxi]

ART: DRUG-DRUG INTERACTIONS

Information can be accessed from:

» https://www.hiv-druginteractionslite.org/checker.
» http://www.mic.uct.ac.za/ download the ARV/EML interaction checker.
» Product Information Leaflets (PILs).

ART INTERACTIONS WITH RIFAMPICIN AND RECOMMENDATIONS FOR ADMINISTRATION			
Class	**ARV**	**Interaction with rifampicin**	**Dose of ARV with rifampicin**
NRTI	3TC/FTC/ TDF/ AZT/ABC	No clinically significant pharmacokinetic interactions.	No dose adjustment required.
NNRTI	EFV	Non-significant change (EFV concentrations may increase in patients who are genetic slow metabolisers of EFV and are on isoniazid which also inhibits EFV metabolism).	No dose adjustment required (600 mg at night).
PI	LPV/r	LPV plasma concentrations significantly decreased.	Double the dose of LPV/r to 800/200 mg 12 hourly. **Note:** There is an increased risk of ALT/AST elevations and gastrointestinal disorders. Dose should be gradually titrated upward over 1-2 weeks. Adjusted dose should be continued for 2 weeks after rifampicin is stopped.
	All other PIs	Marked reduction in PI concentrations.	Do not prescribe concomitantly – replace rifampicin with rifabutin 150 mg daily (see monitoring instructions below).
InSTI	DTG	Significant reduction in concentration of DTG.	Dose increased to 50 mg 12 hourly*.

**Dose adjustments should be continued for 2 weeks after rifampicin is stopped*
Table 10.3: ART interactions with rifampicin and dose-adjustment recommendations.

LoE:IIIb[xxii]

In patients on atazanavir or darunavir, or if double dose LPV/r is not tolerated, replace rifampicin with:

- Rifabutin, oral, 150 mg daily.
  - Monitor FBC monthly for anaemia and neutropenia.

- Monitor clinically for symptoms of uveitis (e.g. pain, photophobia, variable loss of vision, circumcilliary injection, a miotic pupil) – immediately stop rifabutin pending ophthalmology opinion.

LoE:IIIb[xxiii]

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 Mineral supplements	Significant reduction in concentration of DTG	Magnesium- and aluminium-containing preparations should be taken 6 hours before or 2 hours after DTG. Calcium- and iron- containing preparations can be taken concomitantly with DTG when administered with food. **Note:** Iron and calcium should be taken at least 4 hours apart from one another.
Anticonvulsants: 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	May increase metformin concentration	*Metformin initiation:* Initiate metformin at a low dose (500-1000mg total daily dose), titrating up as needed. Do not exceed 2 g daily. *DTG initiation:* If patient stabilised on metformin dose ≤2 g daily, retain metformin dose and monitor for side effects. If patient stabilised on >2 g daily, reduce dose of metformin to ≤2 g daily and monitor. *Patients with renal impairment:* Close monitoring of renal function required. Do not co-prescribe if eGFR <30 mL/min. See Appendix II for further guidance on patients with renal impairment.
Rifampicin	Significant reduction in concentration of DTG	Double DTG dose to 50 mg 12 hourly.

Table 10.4: Drug interactions with DTG

LoE:IIIb[xxiv]

DRUG INTERACTIONS WITH BOOSTED PIs		
Interacting medicine	**Effect of co-administration**	**Recommendation**
Substrates of cytochrome P450 3A4 (e.g. most statins, calcium channel blockers, most SSRIs, most benzodiazepines)	Significant increase in levels of *CYP3A4* substrates	Avoid co-administration or use lower doses of *CYP3A4* substrates (always consult interaction resources).

Anticonvulsants: Carbamazepine Phenobarbital Phenytoin	Significant reduction in concentration of PI	Avoid co-administration. Consider valproate or lamotrigine.
Proton pump inhibitors	Significant reduction in ATV levels	Avoid co-administration. *LoE:IIIb*[xxv]
Rifampicin	Significant reduction in levels of PI	Double LPV/r dose. Avoid co-administration of other PIs (replace rifampicin with rifabutin).

Table 10.5: Drug interactions with boosted PIs

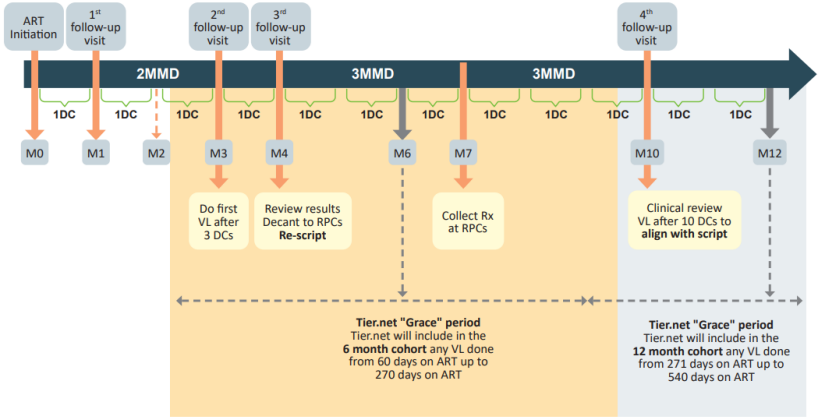
MONITORING ON ART	
Baseline evaluation	» Confirm HIV positive result with second test. » WHO staging. » Check CD4 count. *LoE:IVb*[xxvi] » <u>If CD4 <200 cells/mm^3:</u> – Check cryptococcal antigen (if positive, perform LP regardless of whether symptoms are present or not). – Initiate cotrimoxazole prophylaxis (see Section 10.2.2: Cotrimoxazole prophylaxis). – Reflex CrAg testing is done on the CD4 sample if CD4 <100 cells/mm^3. If patient's CD4 is 100-199, a serum CrAg test must be ordered separately. » Screen for pregnancy or ask if planning to conceive. » Screen for mental health, STIs and NCDs. » Screen for TB using the WHO screening questionnaire (any one of cough, fever, night sweats, or weight loss). » Sputum TB-NAAT* in all who can produce sputum, regardless of symptoms. » Urine LAM for inpatients or outpatients who are symptomatic if CD4 <200, or advanced HIV disease or current serious illness. » If planning to use TDF: check creatinine (avoid TDF if eGFR <50 mL/minute). » Haemoglobin *LoE:IIIb*[xxvii] » Check HBsAg (if positive, TDF should form part of the regimen). » Cervical cancer screening. *TB-NAAT: TB Nucleic Acid Amplification Tests (e.g. GeneXpert Ultra MTB/RIF). *LoE:IIb*[xxviii]
On ART	» Monitoring schedule has been adapted to minimise the number of visits required per annum. » VL at 3 and 10 months after initiating ART and every 12 months thereafter, if virologically suppressed. Align timing with client's scripting cycle.

	» CD4 at 10 months after initiating ART (align with VL). Stop CD4 count monitoring when >200 cells/mm^3 and virologically suppressed. If virological or clinical failure occurs, or if client returns >90 days after missing an appointment, then a CD4 count should be done as cotrimoxazole may need to be commenced/ recommenced. Repeat CD4 count every 6 months if VL remains ≥1000 copies/mL. » If on TDF: creatinine at month 3, month 10, and every 12 months thereafter. Align with VL monitoring schedule. » If on AZT: FBC and differential count at 1 and 3 months after initiating AZT, then only if clinically indicated. » ALT if symptoms of hepatitis develop. » If on a protease inhibitor (PI): cholesterol and triglycerides at 3 months after initiating PI. If above acceptable range, do fasting cholesterol and TGs and if still above acceptable range, obtain expert advice.

Table 10.6: Monitoring on ART

HIV VIRAL LOAD MONITORING SCHEDULE

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



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

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

DC: Dispensing cycle; MMD: Multi-month dispensing; RPCs: Repeat prescription collection strategies

Figure 10.1: Incorporated from the NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates.

10.1.1 MANAGEMENT OF SELECTED ANTIRETROVIRAL ADVERSE DRUG REACTIONS

Dyslipidaemia E78.0-5 + (Y41.5 + B24)
The protease inhibitors can cause significant dyslipidaemia. Fasting lipids should be done 3 months after starting protease inhibitors. LPV/r is associated with a higher risk of dyslipidaemia (especially hypertriglyceridaemia) than ATV/r.

Patients on LPV/r with the following should switch to ATV/r and repeat the fasting lipids in three months:
» triglycerides >10 mmol/L,
» total cholesterol >6 mmol/L with a high risk (i.e. >20% risk of developing a CVD event in 10 years).

Patients with persistent dyslipidaemia despite switching to ATV/r may need lipid lowering therapy. Criteria for initiating lipid lowering therapy are the same as for HIV seronegative patients. (See Section 3.1: Ischaemic heart disease and atherosclerosis, prevention.)

Many statins (including simvastatin) cannot be used with protease inhibitors, as protease inhibitors inhibit the metabolism of the statin resulting in extremely high blood levels.

Patients, who fail to respond to lifestyle modification and have hypertriglyceridemia >10 mmol/L, treat with a fibric acid derivative, e.g.:
- Bezafibrate, oral, 400 mg at night.

OR
If LDL cholesterol is raised (see Section 3.1: Ischaemic heart disease and atherosclerosis, prevention):
- Atorvastatin, oral, 10 mg daily (do not exceed this dose due to a drug interaction with PIs).

Anaemia and neutropenia D64.9/D70 + (Y41.5 + B24)
AZT causes macrocytosis and can cause anaemia and neutropenia (note that it does not cause thrombocytopenia). AZT does not need to be stopped with mild anaemia and/or neutropenia, but must be stopped and replaced with an alternative medication if:
» anaemia is symptomatic,
» anaemia is severe (Hb <8.0 g/dL), or
» the neutrophil count is below 0.75×10^9/L.
Lamivudine and emtricitabine can cause pure red cell aplasia, but this is rare.

Hypersensitivity L27.0-1 + (Y41.5 + B24)
Note that pre-existing dermatological conditions (especially papulopruritic eruptions and acne) may worsen after commencing ART due to immune reconstitution inflammatory syndrome; see Section 10.1.2: Immune

reconstitution inflammatory syndrome (IRIS)) – this is not a hypersensitivity reaction and ART should be continued.

Other medicines, notably cotrimoxazole, can also cause hypersensitivity.

Hypersensitivity rashes occur commonly in the 8-week period after starting EFV. NNRTI-associated rashes can be severe and life-threatening.

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

Patients with lesions affecting the mucous membranes, or with significant blistering, likely have Stevens Johnson syndrome or toxic epidermal necrolysis, and will require admission.
With mild rashes EFV can be continued with careful observation and the rash will often subside.
If rash worsens or does not improve within a week discontinue EFV.
DTG can cause systemic hypersensitivity syndrome with rash, but this is very uncommon. DTG should be permanently discontinued if this occurs.
ABC can cause a rash as part of a systemic hypersensitivity reaction, which is confined to people who are *HLA-B*5701* positive. ABC should be permanently discontinued if this occurs. *LoE:IVb*[xxix]

Hyperlactataemia E87.2 + (Y41.5 + B24)
Symptomatic hyperlactataemia occurs due to mitochondrial toxicity of NRTIs. The estimated risk of symptomatic hyperlactataemia differs among the NRTIs, with zidovudine having moderate risk and the other NRTIs very low risk.

Risk factors for hyperlactataemia include:
» females,
» obesity,
» prolonged use of NRTIs (> 3 months), or
» development of NRTI-induced fatty liver.

Clinical symptoms of hyperlactataemia are non-specific and may include:
» nausea
» vomiting
» abdominal pain
» weight loss
» malaise
» tachycardia
» liver dysfunction (due to steatosis)

A high index of suspicion is necessary. Send blood for lactate levels (check with your local laboratory for specimen requirements for lactate). Alternatively, point of care finger prick lactate monitoring can be done. Check the serum bicarbonate level if lactate is elevated to confirm metabolic acidosis.
Patients with mild hyperlactataemia (lactate 2.5–5 mmol/L):

Alter therapy, selecting NRTIs that are less associated with hyperlactataemia.
Note: The resolution of hyperlactataemia may take a few months.

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

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

Hepatotoxicity K71.9 + (Y41.5 + B24)
All currently available antiretrovirals are potentially hepatotoxic. EFV has the highest risk. NRTIs uncommonly cause acute hepatitis, but may result in steatohepatitis after prolonged use, which manifests with mildly elevated liver enzymes, affecting GGT and alkaline phosphatase more than the transaminases, and ALT more than AST. Patients on atazanavir may develop jaundice due an unconjugated hyperbilirubinaemia, which is not accompanied by liver injury. This is a cosmetic issue and the atazanavir can be substituted if the patient is unable to tolerate the jaundice. However, all protease inhibitors can rarely cause hepatitis, so it is important to exclude this in patients developing jaundice on ATV/r. DTG can cause a hepatitis, but this is rare.

Other potentially hepatotoxic medicines prescribed in PLHIV include anti-tuberculous therapy, fluconazole and cotrimoxazole. Cotrimoxazole, amoxicillin/clavulanate, and macrolides may cause cholestatic hepatitis that may take months to resolve.

The exclusion of viral hepatitis is important in the work-up of drug-induced liver injury (DILI). Testing for hepatitis A, B and C should be undertaken. Hepatitis B is common, and flares of viral hepatitis may occur after ART initiation (i.e. IRIS). Furthermore, life threatening flares may occur when antiretrovirals that are also active against hepatitis B (i.e. TDF, 3TC and FTC) are withdrawn.

Other potential causes include disseminated TB, IRIS, alcohol, alternative remedies, fatty liver, sepsis and HIV cholangiopathy.

Investigations:
» Request an ALT.
» Request viral hepatitis screen, full liver function tests and INR in patients with any of the following criteria:
    - ALT >5 x upper limit of normal (ULN).
    - Jaundice.
    - Other symptoms of hepatitis (e.g. right upper quadrant pain, nausea or vomiting).

» Perform a liver ultrasound if GGT or ALP are significantly elevated or if conjugated bilirubin is elevated, to exclude:
  - Extrahepatic biliary obstruction.
  - Fatty liver due to NRTIs.
  - Disseminated TB.

Management:

Upper Limit of Normal (ULN)	<2.5 x ULN	2.5 – 5 x ULN	> 5 x ULN
ALT	Repeat in 2 weeks	Repeat in 1 week	Stop ART

*Stop the relevant medicines at lower levels if symptoms of hepatitis (right upper quadrant pain, nausea / vomiting) or jaundice are present.
Table 10.7: Management of hepatotoxicity associated with ART

If ART is considered to be the cause, substitute ART as follows:
» If the hepatitis occurred on efavirenz, substitute with DTG or a boosted PI.
» If hepatitis occurred on PI, substitute with DTG.
» NRTI fatty liver – discontinue AZT (if relevant) and replace with safer NRTI (TDF or ABC) – if not on AZT and hepatitis is severe switch to NRTI-sparing regimen (see footnote in Table 10.1: ART regimens, located in Section 10.1: Antiretroviral therapy. Importantly, consult a specialist).

Hepatitis in patients on ART and anti-tuberculosis therapy
Drug-induced liver injury (DILI) is a known adverse effect of anti-tuberculosis therapy and ART and is a common problem in HIV/TB co-infected patients. First-line TB medicines associated with DILI include isoniazid (INH), rifampicin (RIF) and pyrazinamide (PZA). Anti-tuberculosis therapy commonly causes transient, mild, asymptomatic elevations in serum aminotransferase levels that may not necessarily require discontinuation of therapy.

If hepatitis develops, as defined above, stop all antiretrovirals, cotrimoxazole and all potentially hepatotoxic TB medicines (i.e. INH, RIF and PZA).

TB immune reconstitution inflammatory syndrome (TB-IRIS) should be considered in the differential diagnosis (see Section 10.1.2: Immune reconstitution inflammatory syndrome (IRIS)). This condition presents shortly after ART initiation in patients with TB. The GGT and ALP are elevated to a greater degree than the transaminases. Mild jaundice with a conjugated hyperbilirubinaemia and tender hepatosplenomegaly may be present.

Investigations:
» Request an ALT.
» Request viral hepatitis screen, full liver function tests and INR in patients if ALT >5 x ULN and/or jaundice and/or symptoms of hepatitis are present.
» Perform a liver ultrasound if GGT or ALP are significantly elevated or if conjugated bilirubin is elevated, to exclude extrahepatic biliary obstruction.
» Reassess the grounds for TB diagnosis.
» Check if patient is on intensive or continuation phase of TB treatment.

Management:

» Stop TB therapy, initiate background TB therapy and continue throughout rechallenge:
  - Linezolid, oral 600 mg daily. R (Amikacin, IV/IM, 15 mg/kg daily A is an alternative if Hb <8g/dL, but only for short term use).
  - Levofloxacin, oral, 750–1000 mg daily W or Moxifloxacin, oral, 400 mg daily. W
  - Ethambutol, oral, 800–1200 mg daily.
» Stop cotrimoxazole prophylaxis.
» Stop ART as described above.
» Repeat ALT and bilirubin in 2 days (inpatient) or 7 days (outpatient).
» When ALT is <100 IU/L and total bilirubin is less than twice the upper limit of normal, start TB medicine rechallenge as follows:

Day 1:	• Rifampicin, oral 600 mg daily. W ○ If <60 kg: rifampicin, oral 450 mg daily.
Day 3:	» Check ALT.
Day 4–6:	**ADD** • Isoniazid, oral 300 mg daily.
Day 7:	» Check ALT.
Day 8:	» Stop moxifloxacin/levofloxacin and linezolid (continue ethambutol). Consider pyrazinamide rechallenge only in cases of TB meningitis or intolerance/resistance to other medicines. • Pyrazinamide, oral 25 mg/kg daily.
Day 10:	» Check ALT. » Thereafter, monitor ALT twice weekly for the first 3 weeks, then every two weeks for a month, then monthly until 3 months. • Restart ART 2 weeks after completing rechallenge of TB therapy. ○ Monitor ALT every 2 weeks for 2 months after ART rechallenge.

Table 10.8: Management of drug-induced liver injury (DILI) *LoE:IVb*[xxx]

» If drug rechallenge is unsuccessful, then manage as per algorithm in Figure 10.2.

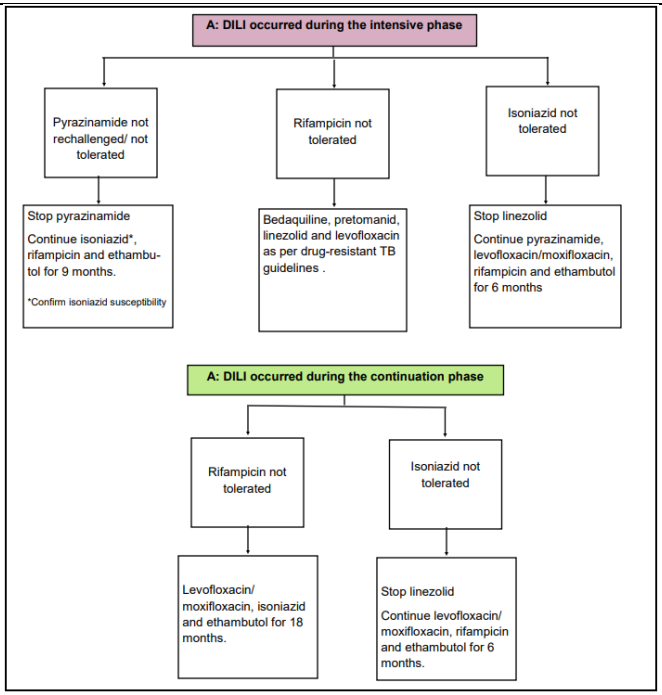


Figure 10.2: Management of TB if drug re-challenge unsuccessful

10.1.2 IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

D89.3 + (Y41.5 + B24)

DESCRIPTION

IRIS occurs when improving immune function unmasks a previously occult opportunistic disease ("unmasking IRIS") or causes paradoxical deterioration of an existing opportunistic disease ("paradoxical IRIS"). IRIS is more common in patients with advanced HIV disease, particularly those with a CD4 count <100 cells/mm^3. IRIS nearly always presents during the first 3 months of ART, with the median time of onset being about two weeks. The diagnosis of paradoxical IRIS is often difficult as new opportunistic diseases, or drug resistance of the organism causing the opportunistic infection, need to be excluded.

TB is the commonest opportunistic disease involved in IRIS reactions in South Africa. Paradoxical TB IRIS presents as recurrence or worsening of TB symptoms/signs, or new manifestations. The commonest presentation is with

enlarging lymph nodes, often with extensive caseous necrosis. Lung infiltrates or effusions may worsen or develop. It is important to exclude multi-drug resistance in all patients with suspected paradoxical TB IRIS.

Other common IRIS manifestations include:
» Inflammatory reactions to skin diseases, especially acne and Kaposi's sarcoma.
» Worsening cryptococcal meningitis.
» Flares of hepatitis B or C.

GENERAL MEASURES

Counselling is important to ensure that the patient understands that IRIS does not mean failure of ART.
Management of IRIS is mainly symptomatic, e.g. aspiration of TB lymph nodes or effusions.
Continue ART and therapy for the opportunistic infection.

MEDICINE TREATMENT

For pain and fever:

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

OR

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals.

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

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 1.5 mg/kg daily for 2 weeks.
  - Then 0.75 mg/kg daily for 2 weeks.

Prophylaxis for paradoxical TB IRIS in high-risk patients (CD4 ≤100 cells/mm^3) who have had antituberculosis treatment for <30 days before initiating ART:

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 40 mg daily for 2 weeks.
  - Then 20 mg daily for 2 weeks. *LoE:IIa*[xxxi]

Note: Do not use steroids in patients with Kaposi sarcoma.

10.2 OPPORTUNISTIC DISEASES

10.2.1 TUBERCULOSIS PREVENTIVE THERAPY (TPT)

Z29.2 + (B24)

DESCRIPTION

Patients with HIV infection at any CD4 count are more susceptible to TB infection than HIV-negative patients. TPT is an effective intervention for reducing the incidence of TB in HIV-infected patients

Eligibility

All HIV-infected patients, irrespective of CD4 count, tuberculin skin test status, and ART status.

Exclusions

- » Suspected or confirmed TB
- » Liver Disease
- » Previous MDR- or XDR-TB
- » Painful peripheral neuropathy
- » Alcohol use disorder

Note:

- » Exclude TB prior to initiating TPT by screening for the following:
  - Cough (any duration)
  - Fever
  - Weight loss
  - Night sweats
- » Do not initiate TPT in patients if any of the above is present. These patients require further investigation for active TB.

Ideally start TPT together with ARVs: *LoE:IIb*[xxxii]

- TPT, e.g.:
- Isoniazid, oral, 300 mg daily for 12 months.
  - Educate patients on the symptoms of hepatotoxicity (nausea, vomiting, yellow eyes, brown urine, and pain in right upper quadrant) associated with TPT.

Note: For adults and adolescents initiating a DTG-containing ART regimen, isoniazid daily for 12 months is the preferred regimen. For patients who are already virally suppressed on a DTG-based regimen, a weekly combination of isoniazid (900mg if weight >30 kg) plus rifapentine (900mg if weight >30 kg) for three months may be preferred. Do not use rifapentine-containing TPT in patients on protease inhibitor-based ART, or in women on hormonal contraceptives. *[See the therapeutic interchange database for details regarding the rifapentine-containing TPT regimen.]*

LoE:IIb[xxxiii]

ADD

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

NOTE: **For pregnant women living with HIV:**

- If CD4 count > 200 cells/mm^3 and initiating ART, defer TPT until after delivery.
- If CD4 count ≤ 200 cells/mm^3 and initiating ART, offer 12 months of daily isoniazid as TPT, after excluding active tuberculosis disease.
- Ensure that routine screening against TB is conducted at each antenatal visit.

LoE:IIb[xxxiv]

10.2.2 OPPORTUNISTIC INFECTION PROPHYLAXIS, WITH COTRIMOXAZOLE

Z29.2 + (B24)

DESCRIPTION

Primary prophylaxis reduces the probability of developing many infections, e.g.:

» Pneumocystis pneumonia
» toxoplasmosis
» bacterial pneumonia
» bacteraemia
» cystoisosporiasis

LoE:IIa[xxxv]

Indications for primary prophylaxis:

» WHO Clinical stage III or IV.
» CD4 count <200 cells/mm^3.

MEDICINE TREATMENT

Prophylaxis

- Cotrimoxazole, oral, 160/800 mg daily. A

LoE:IIa[xxxvi]

Note:

Discontinue prophylaxis once the CD4 >200 cells/mm^3 (as measured at the routine CD4 count done at 1 year on ART). If the CD4 count was >200 cells/mm^3 when cotrimoxazole was commenced (e.g. patients with TB), continue for 6 months**.**

LoE:IIIb[xxxvii]

10.2.3 CANDIDIASIS OF OESOPHAGUS/TRACHEA/BRONCHI

B20.4

DESCRIPTION

Mucosal candidiasis involving the oesophagus/trachea/bronchi is AIDS-defining (WHO clinical stage 4). Oesophagitis is by far the commonest manifestation.

Clinical features: symptoms of pain or difficulty on swallowing. Oral thrush is present in most patients.

GENERAL MEASURES

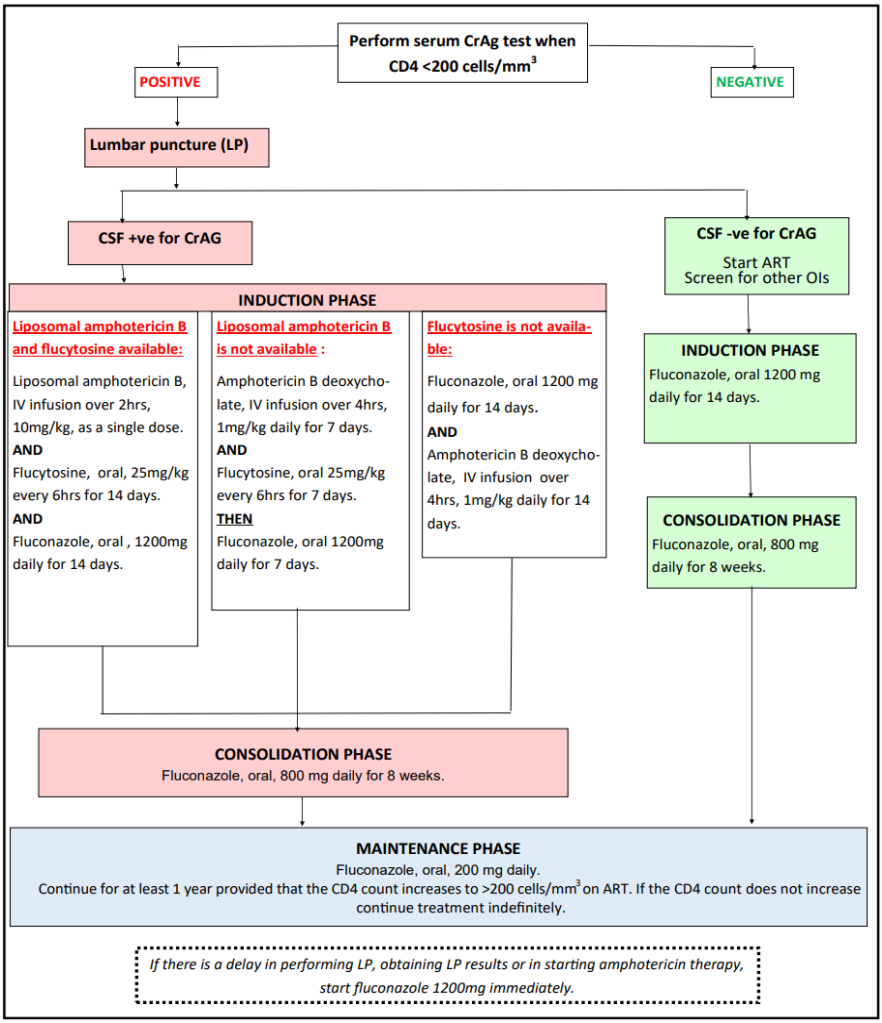
Maintain adequate hydration.

MEDICINE TREATMENT

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

Note: Primary or secondary fluconazole prophylaxis for mucosal candidiasis is not recommended.

10.2.4 CRYPTOCOCCOSIS



Adapted from: Govender NP, Meintjes G, Mangena et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med 2019;20(1):a1030. https://doi.org/10.4102/sajhivmed.v20i1.1030

Figure 10.3: Algorithm for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons

10.2.4.1 CRYPTOCOCCOSIS, CSF CRAG NEGATIVE

(B45.0-3/B45.7-9) + B20.5

DESCRIPTION

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

LoE:IIa[xxxviii]

MEDICINE TREATMENT

<u>If cryptococcal meningitis is excluded by negative CSF CrAg:</u>
Commence ART immediately - see Section 10.1: Antiretroviral therapy.

LoE:IIIa[xxxix]

Induction phase

- Fluconazole, oral 1200 mg daily for 14 days.

Consolidation phase

Follow with:

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

Maintenance phase

LoE:IIIb[xl]

- 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.

CAUTION

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

» All pregnant women <20 weeks gestation exposed to fluconazole should have an ultrasound scan to detect congenital abnormalities. *LoE:IIIb*[xli]

» Although fluconazole is excreted into breast milk at concentrations similar to maternal plasma concentrations, the dose that the infant is exposed to with doses <400 mg is similar to the dose used in systemic treatment in infants. The benefits will likely outweigh the risks, even with higher doses, though this can be discussed with a specialist.

LoE:IVb[xlii]

10.2.4.2 CRYPTOCOCCAL MENINGITIS

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

DESCRIPTION

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

Diagnosis

Confirmed on lumbar puncture.

GENERAL MEASURES

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

Continue daily therapeutic lumbar puncture until there is clinical improvement.

MEDICINE TREATMENT

Induction phase

If liposomal amphotericin B and flucytosine are available: *LoE:IVb[xliii]*

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

AND

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

AND *LoE:IIa[xliv]*

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

If liposomal amphotericin B is not available:

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

AND

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

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

- Fluconazole, oral 1200 mg daily for 7 days. *LoE:IVb*[xlv]

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

- Fluconazole, oral 1200 mg daily for 14 days.

AND *LoE:IIa*[xlvi]

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

Consolidation phase

Follow with: *LoE:IIIa*[xlvii]

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

Maintenance phase *LoE:Ia*[xlviii]

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

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

LoE:IIIa[xlix]

Note: Adjunctive corticosteroids have been shown to be detrimental. *LoE:Ia*[l]

Flucytosine weight-based dosing:

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

Table 10.9: Flucytosine weight-based dosing

REFERRAL

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

» Persistent raised intracranial pressure despite daily therapeutic lumbar puncture.

10.2.5 CRYPTOSPORIDIOSIS DIARRHOEA

A07.2 + (B20.8)

DESCRIPTION

Chronic diarrhoea due to *Cryptosporidium parvum*. Disease lasting >4 weeks is AIDS-defining (WHO clinical stage 4).

GENERAL MEASURES

Rehydration with oral rehydration solution (ORS).

MEDICINE TREATMENT

There is no specific antimicrobial therapy for cryptosporidiosis. As with other opportunistic diseases, it responds well to ART.

Antimotility agents are partially effective, e.g.:

- Loperamide, oral, 4 mg initially, followed by 2 mg as required up to four times daily.

10.2.6 CYTOMEGALOVIRUS (CMV)

B20.2

DESCRIPTION

CMV disease outside the reticulo-endothelial system is an AIDS-defining illness (WHO clinical stage 4).
CMV disease is seen in patients with CD4 counts <100 cells/mm^3.
The commonest manifestations are:

» retinitis,
» GIT ulceration,
» pneumonitis, and
» polyradiculitis.

GIT and other organ involvement must be diagnosed on biopsy.
CNS disease must be diagnosed by PCR of CSF.
The diagnosis of CMV retinitis should be confirmed by an ophthalmologist.
Note: CMV serology (IgM and IgG), antigenaemia (pp65), or PCR on blood are not helpful in the diagnosis of CMV disease in HIV-infected adults.

MEDICINE TREATMENT

Valganciclovir is the treatment of choice, but this agent is toxic and expensive and should only be used by a specialist familiar with its use.
To prevent recurrent disease, commence patients on ART as soon as possible after initiating valganciclovir (see Section 10.1: Antiretroviral therapy).
Maintenance therapy is only applicable to CNS disease and retinitis.
Monitor FBC regularly during therapy. Avoid other medicines associated with bone marrow suppression, particularly zidovudine.

Biopsy-proven GIT disease or pneumonitis

- Valganciclovir, oral, 900 mg 12 hourly for the first 3 weeks. Specialist initiated.

OR

If unable to tolerate oral medication:

- Ganciclovir, IV, 5 mg/kg 12 hourly for 14 days. Specialist initiated.

CNS disease

Initial treatment:

- Valganciclovir, oral, 900 mg 12 hourly for the first 3 weeks. Specialist initiated.

OR

If unable to tolerate oral medication:

- Ganciclovir, IV, 5 mg/kg 12 hourly for 14 days. Specialist initiated.

Maintenance treatment:

Only patients with a good clinical response should be considered for maintenance.

Valganciclovir, oral, 900 mg daily until CD4 count rises to >100 cells/mm^3 on ART, if available. Specialist initiated.

Note: Maintenance treatment is not indicated unless there has been a relapse.

REFERRAL/CONSULTATION

Specialist or tertiary

All patients.

10.2.7 CYSTOISOSPORIASIS

A07.3 + (B20.8)

DESCRIPTION

Diarrhoea due to *Cystoisospora belli*. Disease lasting >4 weeks is AIDS-defining (WHO clinical stage 4).

GENERAL MEASURES

Rehydration with oral rehydration solution (ORS).

MEDICINE TREATMENT

- Cotrimoxazole 160/800 mg, oral, 2 tablets 12 hourly for 10 days. A

OR

If allergic to cotrimoxazole:

- Ciprofloxacin, oral, 500 mg 12 hourly for 10 days. W

Secondary prophylaxis:
Continue for at least 6 months and until CD4 count increases to >200 cells/mm^3 on ART.

- Cotrimoxazole 160/800 mg, oral daily.

10.2.8 MYCOBACTERIOSIS – DISSEMINATED NON-TUBERCULOUS

B20.0

DESCRIPTION

Disseminated infection due to non-tuberculous mycobacteria, usually *Mycobacterium avium* complex.
Diagnosis must be by culture from sterile sources, e.g. blood, tissue or bone marrow. Note that culture from a single sputum specimen is not adequate to make the diagnosis as this often reflects colonisation rather than disease.
Non-tuberculous mycobacteria can cause limited pulmonary disease, which is diagnosed if the sputum culture is positive repeatedly and there is a worsening pulmonary infiltrate.
Disseminated disease is AIDS-defining (WHO clinical stage 4).

MEDICINE TREATMENT

- Azithromycin, oral, 500 mg daily. W

AND *LoE:IIIa*[#]

- Ethambutol, oral, 15–20 mg/kg daily.

Treatment can be stopped when treatment has been continued for at least 12 months **AND** the CD4 count has increased to >100 cells/mm^3 on ART.

10.2.9 PNEUMOCYSTIS PNEUMONIA

B20.6

DESCRIPTION

Interstitial pneumonitis due to *Pneumocystis jirovecii* (formerly *carinii*). AIDS-defining illness (WHO clinical stage 4).

MEDICINE TREATMENT

<u>All patients:</u>

- Cotrimoxazole 80/400 mg, oral, 6 hourly for 21 days. A
  - <60 kg three tablets
  - ≥60 kg four tablets

Monitor FBC and potassium when on high dose therapy.
OR

If vomiting:

- Cotrimoxazole, IV, 6 hourly for 21 days. A
  - <60 kg 240/1200 mg
  - ≥60 kg 320/1600 mg

For hypoxic patients (PaO_2 <70 mmHg [<9.33 kPa], A-a gradient >35, or sats <92%):

- Oxygen by face mask or CPAP as necessary.

AND

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 80 mg daily for 5 days, then taper over 14 days. (Refer to Appendix II for an example of a dose reduction regimen.)

Cotrimoxazole intolerance and desensitisation

Attempt desensitisation in patients with a history of cotrimoxazole intolerance, unless hypersensitivity reaction was life-threatening, e.g. Stevens-Johnson syndrome (see Section 4.6: Erythema Multiforme, Stevens Johnson Syndrome, Toxic Epidermal Necrolysis). Unless rash is severe or associated with systemic symptoms, continue treatment with careful observation for deterioration.

Desensitisation should be attempted using cotrimoxazole suspension 240 mg/5 ml. Dilute the suspension appropriately and consult with your pharmacist if necessary. DO NOT administer antihistamines or steroids.

Time (hours)	Cotrimoxazole dose (mL of 240mg/5mL suspension
0	0.0005
1	0.005
2	0.05
3	0.5
4	5
5	Two single strength tablets (each tablet = 80/400 mg) followed by full dose

Table 10.10: Desensitisation of cotrimoxazole

Alternatively, in case of intolerance and unsuccessful desensitisation:

- Clindamycin, oral, 600 mg 8 hourly for 21 days.

AND

- Primaquine, oral, 15 mg daily for 21 days.
  - Exclude G6PD deficiency before initiating therapy.
  - Primaquine is only available via the Section 21 application process.

If primaquine is not available, consider:

- Clindamycin, oral, 600 mg 8 hourly for 21 days. A

AND

- Dapsone, oral, 100 mg daily for 21 days.

Secondary prophylaxis
Continue for at least 6 months and until CD4 count increases to >200 cells/mm^3 on ART.

- Cotrimoxazole 160/800 mg, oral daily. A

Alternatively, in case of intolerance to cotrimoxazole:

- Dapsone, oral, 100 mg daily.

REFERRAL/CONSULTATION

Specialist or tertiary
Intolerance to all alternative regimens.

10.2.10 CEREBRAL TOXOPLASMOSIS

B58 + (B20.8)

DESCRIPTION

Intracranial space-occupying lesions, with ring contrast enhancement on imaging, due to *Toxoplasma gondii*. AIDS-defining illness (WHO clinical stage 4).

The diagnosis of toxoplasmosis is very unlikely if either the serum toxoplasma IgG is negative or the CD4 count is >200 cells/mm^3.

Diagnosis is confirmed by a clinical response to therapy, which occurs in 7–14 days. CT scan improvement usually occurs within 14–21 days. Interpreting the response to therapy may be difficult if steroids have been given concomitantly. Steroid therapy should only be given for life-threatening peri-lesional oedema.

MEDICINE TREATMENT

- Cotrimoxazole 160/800 mg, oral, 2 tablets 12 hourly for 28 days, followed by 1 tablet 12 hourly for 3 months. A

Secondary prophylaxis
Continue for at least 6 months and until CD4 count increases to > 200 cells/mm^3 on ART.

- Cotrimoxazole 160/800 mg, oral, 2 tablets daily. A

See guidance on cotrimoxazole desensitisation in Section 10.2.9: Pneumocystis pneumonia.

REFERRAL/CONSULTATION

Specialist or tertiary
Intolerance to cotrimoxazole.
Note: Attempt desensitisation first (see Section 10.2.9: Pneumocystis pneumonia).

10.3 HIV AND KIDNEY DISEASE

N28.9 + (B23.8)

DESCRIPTION

A number of kidney disorders are associated with HIV infection.
Acute kidney injury due to sepsis, dehydration or nephrotoxicity from medicines occurs commonly.

The commonest chronic kidney disorder is HIV-associated nephropathy (HIVAN).
Typical features of HIVAN are:

» Heavy proteinuria.
» Rapidly progressive chronic kidney disease with preserved kidney size on imaging.

Early detection of kidney disease is important in order to implement interventions that may slow kidney disease progression, and for adjusting the dose of relevant medicines.
Risk factors for HIV renal disease:

» CD4 count <200 cells/mm^3.
» Use of nephrotoxic medications.
» Comorbidity such as diabetes mellitus, hypertension, or hepatitis C virus co-infection.
» ART may slow progression of HIVAN.

Screening for renal disease in HIV

» Tests should include:
  – Urine dipstick for haematuria and proteinuria (request urine protein:creatinine ratio if proteinuria is detected; discuss with a specialist if >0.15 g/mmol).
  – Serum creatinine and eGFR.

Dose adjustment of ART in renal impairment: Refer to Table 10.2: Dosing and important adverse effects associated with ART in Section 10.1: Antiretroviral therapy.

10.4 KAPOSI SARCOMA (KS)

B21.0

DESCRIPTION

Kaposi Sarcoma (KS) is a malignancy of lymphatic endothelial origin associated with Human Herpes Virus-8, also known as KS Herpes Virus, infection.
KS may involve the skin, oral cavity, lymph nodes or viscera (especially lung and GIT).
Most patients have multiple lesions.
Lymphoedema is a common complication.
10–20% of cases of visceral KS will have no oral or skin involvement.
KS is an AIDS-defining illness (WHO clinical stage 4).

Although most cases are diagnosed on the typical macroscopic appearance of skin and oral lesions, biopsy confirmation is necessary for atypical lesions and consideration for chemotherapy. One important differential diagnosis is bacillary angiomatosis, which develops more rapidly.

MEDICINE TREATMENT

All patients with KS should be commenced on ART (see Section 10.1: Antiretroviral therapy) and cotrimoxazole prophylaxis (see Section 10.2.2: Opportunistic infection prophylaxis, with cotrimoxazole) regardless of CD4 count. Many patients with limited mucocutaneous KS will have complete resolution or substantial regression on ART alone.

REFERRAL

Prior to referral, all patients must be started on ART.

» Radiotherapy/intralesional chemotherapy for symptomatic local lesions.
» Systemic chemotherapy is indicated in patients with poor prognostic factors:
  - more than 25 skin lesions,
  - rapidly progressive disease,
  - visceral involvement,
  - extensive oedema, or
  - "B" symptoms, i.e. fever, night sweats, significant constitutional symptoms.
» Failure of KS to respond to ART.

10.5 POST-EXPOSURE PROPHYLAXIS

National HIV Health Care Worker Hotline: 0800 212 506 or 021 406 6782.

10.5.1 POST-EXPOSURE PROPHYLAXIS, OCCUPATIONAL

S61.0 + (W46.22 + Z20.6 + Z29.8)

DESCRIPTION

Antiretroviral therapy may prevent the risk of acquiring HIV following a significant occupational exposure.

It is essential to document occupational exposures adequately for possible subsequent compensation.

Other blood borne infections (hepatitis B and C) should also be tested for in the source patient and appropriate prophylaxis instituted in the case of hepatitis B.

Assessing the risk of occupational exposures

The risk of acquiring HIV following occupational exposure is determined by the nature of the exposure and the infectiousness of the source patient. High-risk exposures involve exposure to a larger quantity of viruses from the source patient, either due to exposure to larger quantity of blood or because the amount of virus in the blood is high.

Any one of the following is associated with an increased risk of HIV transmission:

» deep percutaneous sharps injuries,
» percutaneous exposure involving a hollow needle that was used in a vein or artery,
» visible blood on the sharp instrument involved in a percutaneous injury,
» the source patient has terminal AIDS or is known to have a high viral load, i.e. >100 000 copies/mL.

In instances when the risk of infection is extremely low or non-existent, post-exposure prophylaxis (PEP) is not indicated, as the risks of PEP will far outweigh the benefits. PEP is **NOT** indicated when:

» The material the healthcare worker was exposed to is not infectious for HIV in the occupational setting, e.g. vomitus, urine, faeces or saliva, unless these are visibly blood stained.
» The exposure was on intact skin.
» The source patient is HIV negative, unless there are clinical features to suggest seroconversion illness, in which case PEP should be commenced until further tests are done – consult with a virologist or infectious diseases specialist.
» The healthcare worker is HIV infected, as this person should be assessed for ART initiation.

PEP REGIMENS

PEP should be commenced as soon as possible after the injury. Do not delay initiating PEP while awaiting confirmatory test results on the source patient and health care worker. PEP should be considered up to 72 hours after exposure and, in exceptional circumstances involving high-risk exposures, PEP may be considered up to 7 days after exposure.

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

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

AND

- Lamivudine, oral, 300 mg daily for 4 weeks

AND

Dolutegravir, oral 50 mg daily for 4 weeks. *LoE:IIIa*[lii]

If DTG is not tolerated:

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

AND

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

AND *LoE:IIIb*[lii]

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

OR

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

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

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

AND

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

AND

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

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

Zidovudine often causes nausea and headache and so should only be given if TDF is contraindicated.

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

Recommendations for post exposure prophylaxis (PEP) after occupational exposure to infectious material (includes blood, CSF, semen, vaginal secretions and synovial/pleural/ pericardial/ peritoneal/amniotic fluid) from HIV seropositive patients are given in the table, below.

Exposure	**HIV Status of source patient**	
	Negative	**Unknown or Positive**
Intact skin	no PEP	no PEP
Mucosal splash **or** **non-intact skin** **or** **percutaneous injury**	no PEP	PEP: • TDF+3TC+DTG **OR** • Other 3-drug regimen

Table 10.11: PEP for healthcare worker following occupational HIV exposure

When the source patient is known to be failing ART, modify the PEP regimen:

» If the patient is on zidovudine, use TDF

» If the patient is on TDF, use zidovudine.

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

Table 10.12: PEP for healthcare workers following hepatitis B exposure

LoE:IVb[liv]

* HBIG and first dose of vaccine to be given simultaneously, but at different sites.

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

After vaccination ensure the health care worker has a HBsAb > 10 units/mL 1 – 2 months after the last vaccine dose.

LoE:IVb[liv]

Test	**Source patient**	**Exposed health care worker**			
	Baseline	**Baseline**	**2 weeks**	**6 weeks**	**4 months**
HIV	Rapid test **PLUS** ELISA	Rapid test **PLUS** ELISA		ELISA	ELISA
Hepatitis B	Surface antigen	Surface antibody**			Surface antigen and surface antibody**
Hepatitis C	HCV antibody	HCV antibody*		HCV PCR*	
Syphilis	RPR/ TP antibody	RPR/TP antibody*			RPR/TP antibody*
Creatinine		If TDF part of PEP	If TDF part of PEP		
FBC		If AZT part of PEP	If AZT part of PEP		

Table 10.13: Investigations and monitoring in occupational exposures

*Only if source patient was positive (in the case of syphilis, source patient must be RPR positive)

**Only if source patient was positive AND health care worker unvaccinated or HBsAb <10 units/mL

10.5.2 NON-OCCUPATIONAL POST EXPOSURE PROPHYLAXIS, SEXUAL ASSAULT

Z29.8

PEP should be offered to rape survivors who present within 72 hours (management is the same as for occupational HIV exposure. See Section 10.5.1: Post-exposure prophylaxis, occupational).
A patient presenting ≥72 hours since the alleged incident should not be given PEP but should be counselled about the possible risk of transmission, with HIV testing provided at the time of presentation and 4 months later. Rape survivors who test HIV seropositive should be initiated on ART– see Section 10.1: Antiretroviral therapy.
Other important aspects of care for the rape survivor should not be forgotten, i.e. contraception, treatment for sexually transmitted infections, counselling and forensic specimens.

Emergency contraception after pregnancy is excluded
Do a pregnancy test in all women and female adolescents. Children must be tested and given emergency contraception from Breast Tanner Stage III. If unsure of staging, give emergency contraception when you detect any breast development (DO NOT REGARD MENARCHE AS AN INDICATION).

- Copper IUCD, e.g.:
- Cu T380A, inserted as soon as possible after unprotected intercourse and not later than 5 days.

LoE:IIIb[lvi]

OR

- Levonorgestrel 1.5 mg, oral, as a single dose as soon as possible after unprotected intercourse, and not later than 5 days.
  - If the woman vomits within 2 hours, repeat the dose.
  - Advise women that their period should be on time; very rarely it is delayed but it should not be more than 7 days late. If this occurs, they should come back for a pregnancy test.

LoE:Ia[lvii]

CAUTION

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

LoE:IIIb[lviii]

An anti-emetic:

LoE:IVb[lix]

- Metoclopramide oral, 10 mg 8 hourly as needed.

STI prophylaxis

- Ceftriaxone, IM, 250 mg as a single dose. W
  - For ceftriaxone IM injection: Dissolve ceftriaxone 250 mg in 0.9 mL lidocaine 1% without epinephrine (adrenaline).

AND

- Azithromycin, oral, 1 g as a single dose. W

LoE:IIIb[lx]

AND

- Metronidazole, oral, 2 g immediately as a single dose. A

HIV PrEP

If patient is at ongoing high risk of HIV acquisition, commence PrEP after PEP has been completed.

Perform HIV test 4 weeks after initiating PrEP. See PHC STGs and EML, Section 11.11: Pre-exposure prophylaxis (PrEP).

10.5.3 NON-OCCUPATIONAL POST EXPOSURE PROPHYLAXIS, INADVERTENT NON-OCCUPATIONAL

Z29.8

Inadvertent (non-occupational) exposure to infectious material from HIV sero-positive persons often requires clinical judgement and includes:

» human bites (requires hepatitis B, but not HIV prophylaxis),
» sharing of needles during recreational drug use,
» consensual sexual exposure, burst condoms,
» contact sports with blood exposure.

LoE:IVb[lxi]

For those who require PEP, management of inadvertent (non-occupational) HIV exposure is the same as for occupational HIV exposure. See Section 10.5.1: Post-exposure prophylaxis, occupational.

References:

[i]South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management

[i]South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management IV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[ii]Eligibility for ART: 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. http://www.ncbi.nlm.nih.gov/pubmed/26192873

Eligibility for ART: TEMPRANO ANRS 12136 Study Group. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. N Engl J Med. 2015 Aug 27;373(9):808-22. http://www.ncbi.nlm.nih.gov/pubmed/26193126

Eligibility for ART- Immediate initiation of ART: Rosen S, Maskew M, Fox MP, Nyoni C, Mongwenyana C, Malete G, Sanne I, Bokaba D, Sauls C, Rohr J, Long L. Initiating Antiretroviral Therapy for HIV at a Patient's First Clinic Visit: The RapIT Randomized Controlled Trial. PLoS Med. 2016 May 10;13(5):e1002015. https://www.ncbi.nlm.nih.gov/pubmed/27163694

Eligibility for ART- Immediate initiation of ART: National Department of Health: National Consolidated Guidelines for the Management of HIV in Adults, Adolescents, Children and Infants and Prevention of Mother-to-Child Transmission, June 2020. https://www.knowledgehub.org.za/elibrary/national-consolidated-guidelines-management-hiv-adults-adolescents-children-and-infants

[iii] Immediate initiation of ART, pregnant and breastfeeding women: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Dolutegravir in pregnant women and women of child-bearing potential (WOCP), 17 June 2021.
https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Immediate initiation of ART, pregnant and breastfeeding women: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

[iv]Timing of ART initiation (pulmonary TB): 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

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

[vi] Timing of ART initiation (cryptococcal meningitis): Eshun-Wilson I, Okwen MP, Richardson M, Bicanic T. Early versus delayed antiretroviral treatment in HIV-positive people with cryptococcal meningitis. Cochrane Database Syst Rev. 2018 Jul 24;7(7):CD009012. https://pubmed.ncbi.nlm.nih.gov/30039850/

Timing of ART initiation (cryptococcal meningitis): National Department of Health: National Consolidated Guidelines for the Management of HIV in Adults, Adolescents, Children and Infants and Prevention of Mother-to-Child Transmission, June 2020. https://www.knowledgehub.org.za/elibrary/national-consolidated-guidelines-management-hiv-adults-adolescents-children-and-infants

Timing of ART initiation (cryptococcal meningitis): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

[vii] Timing of ART initiation (asymptomatic cryptococcosis): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Timing of ART initiation (asymptomatic cryptococcosis): Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, Rabie H, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. South Afr J HIV Med. 2019 Nov 8;20(1):1030. https://pubmed.ncbi.nlm.nih.gov/32201629/

[viii]Psychosocial indicators of readiness for ART: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

[ix]Dolutegravir, oral (first-line ART): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Dolutegravir in HIV-infected patients commencing first-line antiretroviral therapy, updated 27 July 2021 (including addendum of use of dolutegravir with rifampicin).
https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Dolutegravir, oral (first-line ART): Rutherford GW, Horvath H. Dolutegravir Plus Two Nucleoside Reverse Transcriptase Inhibitors versus Efavirenz Plus Two Nucleoside Reverse Transcriptase Inhibitors As Initial Antiretroviral Therapy for People with HIV: A Systematic Review. PLoS One. 2016 Oct_13;11(10):e0162775. https://www.ncbi.nlm.nih.gov/pubmed/27736859

Dolutegravir, oral (first-line ART): South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[x] Dolutegravir, oral (first-line ART in pregnancy/ WOCP): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Dolutegravir in pregnant women and women of child-bearing potential (WOCP), 17 June 2021.
https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Dolutegravir, oral (risk of NTDs): National Department of Health. Notice: Updated guidance of dolutegravir in pregnancy, 29 June 2021 (Reference: 2021/06/29/EDP/01). https://www.knowledgehub.org.za/e-library

[xi] Dolutegravir, oral (first-line ART with concomitant rifampicin): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Dolutegravir in HIV-infected patients commencing first-line antiretroviral therapy, updated 27 July 2021 (including addendum of use of dolutegravir with rifampicin).
https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Dolutegravir, oral (first-line ART with concomitant rifampicin): Dooley KE, Sayre P, Borland J, Purdy E, Chen S, Song I, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. J Acquir Immune Defic Syndr 2013; 62(1):21-27. https://pubmed.ncbi.nlm.nih.gov/23075918/

Dolutegravir, oral (first-line ART with concomitant rifampicin): Dooley KE, Kaplan R, Mwelase N, Grinsztejn B, Ticona E, Lacerda M, et al. Dolutegravir-based Antiretroviral Therapy for Patients Coinfected With Tuberculosis and Human Immunodeficiency Virus: A Multicenter, Noncomparative, Open-label, Randomized Trial. Clin Infect Dis 2020; 70(4):549-556. https://pubmed.ncbi.nlm.nih.gov/30918967/

[xii] National Department of Health: Affordable Medicines, EDP-PHC/Adult Hospital level. Medicine Review: Atazanavir/ritonavir vs lopinavir/ritonavir in HIV, 27July2021.
https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xiii] Abacavir: Cruciani M, Mengoli C, Malena M, Serpelloni G, Parisi SG, Moyle G, Bosco O. Virological efficacy of abacavir: systematic review and meta-analysis. J Antimicrob Chemother. 2014 Dec;69(12):3169-80.http://www.ncbi.nlm.nih.gov/pubmed/25074854

[xiv] Dual therapy – dolutegravir/lamivudine: 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

Dual therapy – dolutegravir/lamivudine: 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

[xv] South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[xvi] South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[xvii]Dolutegravir, oral (double-dose with concomitant rifampicin): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Dolutegravir in HIV-infected patients commencing first-line antiretroviral therapy, updated 27 July 2021 (including addendum of use of dolutegravir with rifampicin).
https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Dolutegravir, oral (double-dose with concomitant rifampicin): Dooley KE, Sayre P, Borland J, Purdy E, Chen S, Song I, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. J Acquir Immune Defic Syndr. 2013 Jan 1;62(1):21-7. https://pubmed.ncbi.nlm.nih.gov/23075918/

Dolutegravir, oral (double-dose with concomitant rifampicin): Dooley KE, Kaplan R, Mwelase N, Grinsztejn B, Ticona E, Lacerda M, et al; International Study of Patients with HIV on Rifampicin ING study group. Dolutegravir-based Antiretroviral Therapy for Patients Coinfected With Tuberculosis and Human Immunodeficiency Virus: A Multicenter, Noncomparative, Open-label, Randomized Trial. Clin Infect Dis. 2020 Feb 3;70(4):549-556. https://pubmed.ncbi.nlm.nih.gov/30918967/

[xviii] South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[xix]Emtricitabine, oral (red cell aplasia adverse drug reaction): Cohen K, Viljoen C, Njuguna C, Maartens G. Emtricitabine-associated red cell aplasia. AIDS. 2019 May 1;33(6):1095-1096. https://www.ncbi.nlm.nih.gov/pubmed/30946164

[xx]Efavirenz, oral (encephalopathy adverse drug reaction): 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

[xxi] Dosing of ART and ADRs: Dosing of ART and ADRs: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Dosing of ART and ADRs: South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

Dosing of ART and ADRs: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

Dosing of ART and ADRs: Datapharm Ltd. Electronic medicines compendium (emc). [Internet][Accessed 28 November 2019] https://www.medicines.org.uk/emc/

Dosing of ART (renal impairment): Dosing of ART and ADRs: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Dosing of ART (renal impairment): Lucas GM, Ross MJ, Stock PG, Shlipak MG, Wyatt CM, Gupta SK, et al.; HIV Medicine Association of the Infectious Diseases Society of America. Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2014 Nov 1;59(9):e96-138. http://www.ncbi.nlm.nih.gov/pubmed/25234519

Dosing of ART (renal impairment): Meintjes G, Moorhouse MA, Carmona S, Davies N, Dlamini S, van Vuuren C, Manzini T, et al. Adult antiretroviral therapy guidelines 2017. South Afr J HIV Med. 2017 Jul 15;18(1):776. doi: 10.4102/sajhivmed.v18i1.776. https://pubmed.ncbi.nlm.nih.gov/29568644/

[xxii] ART-rifampicin drug interaction: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

ART-rifampicin drug interaction: South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[xxiii]Rifabutin: Zhang J, Zhu L, Stonier M, Coumbis J, Xu X, Wu Y, Arikan D, Farajallah A, Bertz R. Determination of rifabutin dosing regimen when administered in combination with ritonavir-boosted atazanavir. J Antimicrob Chemother. 2011 Sep;66(9):2075-82. http://www.ncbi.nlm.nih.gov/pubmed/21712242

Rifabutin (dosing): Lan NT, Thu NT, Barrail-Tran A, Duc NH, Lan NN, Laureillard D, et al. Randomised pharmacokinetic trial of rifabutin with lopinavir/ritonavir-antiretroviral therapy in patients with HIV-associated tuberculosis in Vietnam. PLoS One. 2014 Jan 22;9(1):e84866. http://www.ncbi.nlm.nih.gov/pubmed/24465443

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

[xxiv] Drug interactions with dolutegravir: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Drug interactions with dolutegravir: South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[xxv] Atazanavir-PPI/H2-anatagonist interaction: University of Liverpool HIV Drug Interaction online tool. https://www.hiv-druginteractions.org/checker

Atazanavir-PPI interaction: 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

Atazanavir-PPI interaction: 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

[xxvi] Screen for Cryptococcus antigen: South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[xxvii]Urine dipstick: Han TM, Naicker S, Ramdial PK, Assounga AG. A cross-sectional study of HIV-seropositive patients with varying degrees of proteinuria in South Africa. Kidney Int. 2006 Jun;69(12):2243-50. http://www.ncbi.nlm.nih.gov/pubmed/16672914

[xxviii] LAM urine testing (DS-TB): Bjerrum S, Schiller I, Dendukuri N, Kohli M, Nathavitharana RR, Zwerling AA, et al. Lateral flow urine lipoarabinomannan assay for detecting active tuberculosis in people living with HIV. Cochrane Database Syst Rev. 2019 Oct 21;10:CD011420. https://www.ncbi.nlm.nih.gov/pubmed/31633805

LAM urine testing (DS-TB): National Department of Health. Guidance on the use of the lipoarabinomannan lateral flow assay (LF-LAM) for the diagnosis of tuberculosis in people living with HIV, July 2017. https://www.knowledgehub.org.za/

[xxix]Abacavir: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022

[xxx]Management of drug-induced liver injury: Jong E, Conradie F, Berhanu R, Black A, John MA, Meintjes G, Menezes C. Consensus Statement: Management of drug-induced liver injury in HIV-positive patients treated for TB. S Afri HIV Med 2013;14(3): 113-119.http://www.sajhivmed.org.za/index.php/hivmed/article/view/63

Management of drug-induced liver injury: Sharma SK, Singla R, Sarda P, Mohan A, Makharia G, Jayaswal A, Sreenivas V, Singh S. Safety of 3 different reintroduction regimens of antituberculosis drugs after development of antituberculosis treatment-induced hepatotoxicity. Clin Infect Dis. 2010 Mar 15;50(6):833-9. https://www.ncbi.nlm.nih.gov/pubmed/20156055

[xxxi]Prednisone, oral (TB-IRIS on ART): Meintjes G, Stek C, Blumenthal L, Thienemann F, Schutz C, Buyze J, et al; PredART Trial Team. Prednisone for the Prevention of Paradoxical Tuberculosis-Associated IRIS. N Engl J Med. 2018 Nov 15;379(20):1915-1925. https://www.ncbi.nlm.nih.gov/pubmed/30428290

[xxxii]TB preventive therapy (therapeutic class): Affordable Medicines, EDP- Adult Hospital level. Medicine Review: Isoniazid TB prophylaxis in PLHIV, November 2018. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

TB preventive therapy (therapeutic class): Rangaka MX, Wilkinson RJ, Boulle A, Glynn JR, Fielding K, van Cutsem G, et al. 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

TB preventive therapy (therapeutic class): Affordable Medicines, EDP- Adult Hospital level. Medicine Review: Rifapentine (3HP) as TPT in PLHIV, November 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

TB preventive therapy (therapeutic class): Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Rifapentine (3HP) as TPT in PLHIV on DTG-regimens, November 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xxxiii] Rifapentine-containing regimen (3HP): Affordable Medicines, EDP- Adult Hospital level. Medicine Review: Rifapentine (3HP) as TPT in PLHIV, November 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Rifapentine-containing regimen (3HP): Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Rifapentine (3HP) as TPT in PLHIV on DTG-regimens, November 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xxxiv] IPT in pregnancy: Affordable Medicines, EDP- Adult Hospital level. Medicine Review: Evidence review: IPT in pregnancy_v1.2_15 April 2024_final approved. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xxxv]Cotrimoxazole, oral (pregnancy): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Evidence summary: Is co-trimoxazole safe to use in pregnancy, March2024. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Cotrimoxazole, oral (pregnancy): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

[xxxvi]Cotrimoxazole, oral: Grimwade K, Swingler, G. Cotrimoxazole prophylaxis for opportunistic infections in adults with HIV. Cochrane Database Syst Rev. 2003;(3):CD003108. http://www.ncbi.nlm.nih.gov/pubmed/12917946

Cotrimoxazole, oral: South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[xxxvii]Cotrimoxazole, oral (criteria for discontinuation): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Cotrimoxazole, oral (criteria for discontinuation): South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[xxxviii]CrAg screening (CD4 < 100 cells/mm^3): Meya DB, Manabe YC, Castelnuovo B, Cook BA, Elbireer AM, Kambugu A, et al. Cost-effectiveness of serum cryptococcal antigen screening to prevent deaths among HIV-infected persons with a CD4+ cell count < or = 100 cells/microL who start HIV therapy in resource-limited settings. Clin Infect Dis. 2010 Aug 15;51(4):448-55. http://www.ncbi.nlm.nih.gov/pubmed/20597693

CrAg screening (CD4 < 100 cells/mm^3): Ford N, Shubber Z, Jarvis JN, Chiller T, Greene G, Migone C, Vitoria M, Doherty M, Meintjes G. CD4 Cell Count Threshold for Cryptococcal Antigen Screening of HIV-Infected Individuals: A Systematic Review and Meta-analysis. Clin Infect Dis. 2018 Mar 4;66(suppl_2):S152-S159. https://pubmed.ncbi.nlm.nih.gov/29514236/

CrAg screening (CD4 < 100 cells/mm^3): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

[xxxix] ART (delayed): Makadzange AT, Ndhlovu CE, Takarinda K, Reid M, Kurangwa M, Gona P, Hakim JG. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-saharan Africa. Clin Infect Dis. 2010 Jun 1;50(11):1532-8.http://www.ncbi.nlm.nih.gov/pubmed/20415574

ART (delayed): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

ART (delayed): Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med 2019;20(1):a1030. https://doi.org/10.4102/sajhivmed.v20i1.1030

[xl]Fluconazole, oral (cryptococcosis): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Fluconazole, oral (cryptococcosis): Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal

disease among HIV-infected persons: 2019 update. S Afr J HIV Med 2019;20(1):a1030. https://doi.org/10.4102/sajhivmed.v20i1.1030

Fluconazole, oral (cryptococcosis): NICD data on file.

[xli] Fluconazole, oral (pregnancy): Mølgaard-Nielsen D, Pasternak B, Hviid A. Use of oral fluconazole during pregnancy and the risk of birth defects. N Engl J Med. 2013 Aug 29;369(9):830-9. http://www.ncbi.nlm.nih.gov/pubmed/23984730

Fluconazole, oral (pregnancy): Mølgaard-Nielsen D, Svanström H, Melbye M, Hviid A, Pasternak B. Association Between Use of Oral Fluconazole During Pregnancy and Risk of Spontaneous Abortion and Stillbirth. JAMA. 2016 Jan 5;315(1):58-67. http://www.ncbi.nlm.nih.gov/pubmed/26746458

Fluconazole, oral (pregnancy): Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med 2019;20(1):a1030. https://doi.org/10.4102/sajhivmed.v20i1.1030

[xlii] Fluconazole, oral (breastfeeding): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

Fluconazole, oral (breastfeeding): Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med 2019;20(1):a1030. https://doi.org/10.4102/sajhivmed.v20i1.1030

[xliii] Liposomal amphotericin: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Liposomal Amphotericin B_ cryptococcal meningitis_Adults Review_Update_23 January 2024_final approved.

[xliv]Flucytosine, oral: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Flucytosine for cryptococcal meningitis, 15 November 2018. https://www.knowledgehub.org.za/e-library

Flucytosine, oral: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Health economic and budget impact analysis: Flucytosine as induction therapy in the treatment of cryptococcal meningitis in HIV infected adults, June 2019. https://www.knowledgehub.org.za/e-library

https://www.nejm.org/doi/full/10.1056/NEJMoa2111904

Flucytosine, oral: Tenforde MW, Shapiro AE, Rouse B, Jarvis JN, Li T, Eshun-Wilson I, Ford N. Treatment for HIV-associated cryptococcal meningitis. Cochrane Database Syst Rev. 2018 Jul 25;7(7):CD005647. https://pubmed.ncbi.nlm.nih.gov/30045416/

Flucytosine, oral: Miot J, Leong T, Takuva S, Parrish A, Dawood H. Cost-effectiveness analysis of flucytosine as induction therapy in the treatment of cryptococcal meningitis in HIV-infected adults in South Africa. BMC Health Serv Res. 2021 Apr 6;21(1):305. https://pubmed.ncbi.nlm.nih.gov/33823842/

[xlv]Fluconazole, oral: Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update

[xlvi]Fluconazole, oral (induction phase): Tenforde MW, Shapiro AE, Rouse B, Jarvis JN, Li T, Eshun-Wilson I et al. Treatment for HIVassociated cryptococcal meningitis. Cochrane Database Syst Rev. 2018;7;CD005647. https://pubmed.ncbi.nlm.nih.gov/30045416/

Fluconazole, oral (induction phase): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Fluconazole, oral (induction phase): Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med 2019;20(1):a1030. https://doi.org/10.4102/sajhivmed.v20i1.1030

[xlvii]Fluconazole, oral (consolidation phase): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Fluconazole, oral (consolidation phase): Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med 2019;20(1):a1030. https://doi.org/10.4102/sajhivmed.v20i1.1030

[xlviii]Fluconazole, oral (maintenance phase): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Fluconazole, oral (maintenance phase): Bozzette SA, Larsen RA, Chiu J, Leal MA, Jacobsen J, Rothman P, Robinson P, Gilbert G, McCutchan JA, Tilles J, et al. A placebo-controlled trial of maintenance therapy with fluconazole after treatment of cryptococcal meningitis in the acquired immunodeficiency syndrome. California Collaborative Treatment Group. N Engl J Med. 1991 Feb 28;324(9):580-4. https://pubmed.ncbi.nlm.nih.gov/1992319/

Fluconazole, oral (maintenance phase): Powderly WG, Saag MS, Cloud GA, Robinson P, Meyer RD, Jacobson JM, Graybill JR, Sugar AM, McAuliffe VJ, Follansbee SE, et al. A controlled trial of fluconazole or amphotericin B to prevent relapse of cryptococcal meningitis in patients with the acquired immunodeficiency syndrome. The NIAID AIDS Clinical Trials Group and Mycoses Study Group. N Engl J Med. 1992 Mar 19;326(12):793-8. https://pubmed.ncbi.nlm.nih.gov/1538722/

Fluconazole, oral (maintenance phase): Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med 2019;20(1):a1030. https://doi.org/10.4102/sajhivmed.v20i1.1030

[xlix] ART (delayed): Makadzange AT, Ndhlovu CE, Takarinda K, Reid M, Kurangwa M, Gona P, Hakim JG. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-saharan Africa. Clin Infect Dis. 2010 Jun 1;50(11):1532-8.http://www.ncbi.nlm.nih.gov/pubmed/20415574

ART (delayed): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

[l]Steroids and HIV-associated Cryptococcal Meningitis Treatment: Beardsley J, Wolbers M, Kibengo FM, Ggayi AB, Kamali A, Cuc NT, et al. Adjunctive dexamethasone in HIV-associated cryptococcal meningitis. N Engl J Med 2016;374:542-54. https://www.ncbi.nlm.nih.gov/pubmed/26863355

[li]Azithromycin: Dunne M, Fessel J, Kumar P, Dickenson G, Keiser P, Boulos M, Mogyros M, White Jr AC, Cahn P, O'Connor M, Lewi D, Green S, Tilles J, Hicks C, Bissett J, Schneider MM, Benner R. A randomized, double-blind trial comparing azithromycin and clarithromycin in the treatment of disseminated Mycobacterium avium infection in patients with human immunodeficiency virus. Clin Infect Dis. 2000 Nov;31(5):1245-52. Erratum in: Clin Infect Dis 2001 May 1;32(9):1386. http://www.ncbi.nlm.nih.gov/pubmed/11073759

Azithromycin: Ward TT, Rimland D, Kauffman C, Huycke M, Evans TG, Heifets L. Randomized, open-label trial of azithromycin plus ethambutol vs. clarithromycin plus ethambutol as therapy for Mycobacterium avium complex bacteremia in patients with human immunodeficiency virus infection. Veterans Affairs HIV Research Consortium. Clin Infect Dis. 1998 Nov;27(5):1278-85. http://www.ncbi.nlm.nih.gov/pubmed/9827282

[lii] Dolutegravir-based PEP regimen: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Dolutegravir-based PEP regimen: McAllister JW, Towns JM, McNulty A, Pierce AB, Foster R, Richardson R, et al. Dolutegravir with tenofovir disoproxil fumarate-emtricitabine as HIV postexposure prophylaxis in gay and bisexual men. AIDS. 2017;31(9):1291–5. https://www.ncbi.nlm.nih.gov/pubmed/28301425

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

[liii]Protease-inhibitor- based PEP regimen: Ford N, Shubber Z, Calmy A, Irvine C, Rapparini C, Ajose O, et al. Choice of antiretroviral drugs for postexposure prophylaxis for adults and adolescents: A systematic review. Clinical Infectious Diseases. 2015;60 Suppl 3:S170–6. https://www.ncbi.nlm.nih.gov/pubmed/25972499

Protease-inhibitor- based PEP regimen: National Department of Health. National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020. https://www.knowledgehub.org.za/elibrary/national-clinical-guidelines-post-exposure-prophylaxis-pep-occupational-and-non

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

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

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

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

[lvii]Levonorgestrel 1.5 mg oral (emergency contraception): Shen J, Che Y, Showell E, Chen K, Cheng L. Interventions for emergency contraception. Cochrane Database Syst Rev. 2019 Jan 20;1(1):CD001324. https://pubmed.ncbi.nlm.nih.gov/30661244/

[lviii]Levonorgesterol, oral - emergency contraception (double dose): Carten ML, Kiser JJ, Kwara A, Mawhinney S, Cu-Uvin S. Pharmacokinetic interactions between the hormonal emergency contraception, levonorgestrel (Plan B), and Efavirenz. Infect Dis Obstet Gynecol. 2012;2012:137192. http://www.ncbi.nlm.nih.gov/pubmed/22536010

Levonorgesterol, oral - emergency contraception (double dose): Tittle V, Bull L, Boffito M, Nwokolo N. Pharmacokinetic and pharmacodynamic drug interactions between antiretrovirals and oral contraceptives. ClinPharmacokinet. 2015 Jan;54(1):23-34. http://www.ncbi.nlm.nih.gov/pubmed/25331712

Levonorgesterol, oral - emergency contraception (double dose): Jatlaoui TC and Curtis KM. Safety and effectiveness data for emergency contraceptive pills among women with obesity: a systematic review. Contraception 94 (2016) 605–611. https://www.ncbi.nlm.nih.gov/pubmed/27234874

Levonorgesterol, oral - emergency contraception (double dose): FSRH Guideline (April 2019) Overweight, Obesity and Contraception. BMJ Sex Reprod Health. 2019 Apr;45(Suppl 2):1-69. https://pubmed.ncbi.nlm.nih.gov/31053605/

[lix] Metoclopramide, oral: National Department of Health, Essential Drugs Programme: Primary Health Care STGs and EML, 2020. http://www.health.gov.za/

[lx]STI prophylaxis: Workowski KA, Bachmann LH, Chan PA, Johnston CM, Muzny CA, Park I, Reno H, Zenilman JM, Bolan GA. Sexually Transmitted Infections Treatment Guidelines, 2021. MMWR Recomm Rep. 2021 Jul 23;70(4):1-187. https://pubmed.ncbi.nlm.nih.gov/34292926/

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

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

SOUTH AFRICAN NATIONAL DEPARTMENT OF HEALTH
NEMLC SUMMARY REPORT ON UPDATES MADE TO THE
THE STANDARD TREATMENT GUIDELINES AND ESSENTIAL MEDICINE LIST GUIDANCE PRODUCTS
AHC Chp 10 HIV and AIDS

Document Version Control

Report Version	Date	Detail
V1.0	*27/11/2025*	• *Inclusion of Darunavir/Ritonavir* for *adults as a special access item; as recommended by the National ARV Drug Resistance Committee (ADReC)* • *Update – guidance on IPT in pregnancy*
V1.0	*29/01/2026*	• *Retention of DTG dosing Key*

Summary Tables

Medicine Amendments

Medicine amendment recommendations, with supporting evidence and rationale are listed below. If appropriate can include non-medicine amendments if appropriate (for example if item has a large impact on how medicine is accessed). Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG). Include updates post initial publication first or mark/highlight appropriately.

STG/SECTION	GUIDANCE PRODUCTS (Tick relevant)				MEDICINE / MANAGEMENT	ADDED / DELETED / AMENDED	TI* CONSIDERATIONS (if applicable)
	PHC STGs & EML	AH STG & EML	PaedH STG & EML	TQ EML			
Report v1.0: Antiretroviral therapy - Inclusion of Darunavir/Ritonavir for adults as a special access item							
Section 10.1 Antiretroviral therapy		√	√		Darunavir/ritonavir, oral - included on the Essential Medicines List for adults as a special access item; as recommended by the National ARV Drug Resistance Committee (ADReC), previously called the Third Line ART committee), following a genotype resistance test, for use on a named patient basis.	Added	n/a
Report Version 1.0 : TPT in pregnancy							
Section 10.2.1	√	√			Isoniazid	Amended	n/a

*Therapeutic Interchange

Report V1.0

AH HIV Chapter 10

NOTE

The PHC and AH HIV chapters are in the process of being updated to align with the recently updated National Consolidated Guidelines for the Prevention and Management of HIV in Adults, Adolescents, Children, Infants and Pregnant and Breastfeeding Women (Jan 2025).

Section 10.1 Antiretroviral therapy

Darunavir/ritonavir for adults as a special access item

Darunavir/ritonavir (DRV/r), oral: Added

A systematic review commissioned by the WHO showed that: DRV/r had better overall safety outcomes compared with other PIs in adults (very low to moderate level of evidence). In pregnant women (based on observational data) DRV/r has good safety and viral efficacy in pregnancy. The committee through a historical use review[1] of the evidence suggested (conditionally) that DRV/r be included on the Essential Medicines List for adults as a special access item; as recommended by the National ARV Drug Resistance Committee (ADReC), previously called the Third Line ART committee, (by the (TLART committee), following a genotype resistance test, for use on a named patient basis.

Very low to moderate level of evidence

The STG was updated as follows:

CLIENTS WITH DTG RESISTANCE	
Any DTG resistance shown on genotype authorised by HIV expert	Discuss case with an HIV expert*. The regimen will be determined by an Expert Committee based on the pattern of resistant mutations and the prior history of antiretroviral exposure. Darunavir/ritonavir is included on the Essential Medicines List for adults as a special access item; as recommended by the National ARV Drug Resistance Committee (ADReC), (previously called the TLART committee), following a genotype resistance test. Application for 3rd line using the standard motivation form may be required (available on request from TLART@health.gov.za or download from https://www.health.gov.za/nhi-edp-stgs-eml/).

ARV Fixed Dose Combination Preparations

List of ARV Fixed Dose Combination Preparations: Removed

In alignment with other STG chapters, a list of ARV fixed dose combination preparations was removed from the chapter as the list is dynamic and applied to a specific tender cycle.

ART: Drug-drug interactions

Table 10.3 ART interactions with rifampicin and dose-adjustment recommendations: Editorial amendment

A description to a key (*) which was omitted in editing in the previous review cycle was added to Table 10.3 ART interactions with rifampicin and dose-adjustment recommendations shown in excerpt of table 10.3 below.

[1] Medicine review_PHL_ South African National Department of Health
Historically Accepted Use Review of Darunavir Ritonavir _ Human Immunodeficiency Virus Infections_202506

Table 10.3 ART interactions with rifampicin and dose-adjustment recommendations

ART INTERACTIONS WITH RIFAMPICIN AND RECOMMENDATIONS FOR ADMINISTRATION			
Class	**ARV**	**Interaction with rifampicin**	**Dose of ARV with rifampicin**
InSTI	DTG	Significant reduction in concentration of DTG.	Dose increased to 50 mg 12 hourly*.
**Dose adjustments should be continued for 2 weeks after rifampicin is stopped*			

The DTG dosing key stipulating that the increased DTG dose should continue for 2 weeks after rifampicin cessation was reviewed. The review was informed by the publication of a study exploring virologic suppression in patients on rifampicin-containing TB regimens, randomised to either single dose i.e. standard DTG dose or double dose DTG.[2] In this study virological suppression was similar in the 2 arms (At week 24, 43 (83%, 95% CI 70–92) of 52 participants in the supplemental dolutegravir arm and 44 (83%, 95% CI 70–92) of 53 participants in the placebo arm had virological suppression) and DTG resistance was not detected in those failing. However, the study was not powered to compare virological suppression between the 2 groups. Patients who had previously failed an ART regimen were excluded. Many patients currently on DTG in South Africa have had prior ART exposure (before commencing DTG) and may be at higher risk for the development of DTG resistance, especially if concentrations are reduced by concomitant rifampicin treatment. In view of these concerns the committee were against revising the dosing recommendations for DTG with rifampicin until more data on risk of resistance in treatment-experienced patients becomes available. The key in the STG, is intended to address DTG dosing two weeks post rifampicin treatment and not DTG dosing during rifampicin treatment, which is a separate broader discussion. The committee recommended that a change to the key not be made at this time as an isolated change would likely result in confusion as the 2 week recommendation post rifampicin is standard for all such interactions. Therefore the suggestion was to retain the key i.e. retain the current DTG dosing instruction guidance for the 2 weeks post rifampicin cessation in the STGs, until more data is available.

The historical STG recommendation that the '*DTG dose adjustments should be continued for 2 weeks after rifampicin is stopped'*, is retained.

Section 10.2 Opportunistic diseases

Section 10.2.1 Tuberculosis preventative therapy (TPT)

TPT in pregnant women living with HIV (PWHIV)

ISONIAZID: Guidance amended

On 25 January 2025, the NDoH released a circular jointly issued by the NEMLC and NDoH TB program recommending that TPT be avoided in all pregnant women. This consensus recommendation was informed by concerns with the complexity of implementing guidance for the use of TPT in pregnant women that was stratified based on HIV status and CD4 count. Concerns with the approach of avoiding TPT in all pregnant women, were subsequently raised by clinicians at the SA HIV Clinicians Society Conference (Aug 2025), and a poll taken after debate, indicated strong support from clinicians for a CD4 count-guided approach to IPT initiation in pregnant women living with HIV. This prompted further

[2] Griesel R, Zhao Y, Simmons B, Omar Z, Wiesner L, Keene CM, Hill AM, Meintjes G, Maartens G. Standard-dose versus double-dose dolutegravir in HIV-associated tuberculosis in South Africa (RADIANT-TB): a phase 2, non-comparative, randomised controlled trial. Lancet HIV. 2023 Jul;10(7):e433-e441. doi: 10.1016/S2352-3018(23)00081-4. Epub 2023 May 22. PMID: 37230101; PMCID: PMC10322729

collaboration between the NDoH TB and HIV programs with the resultant alignment of a package of care for people with Advanced HIV Disease[3], defined as any client (including pregnant women) with a CD4 count < 200 cells/mm^3, or WHO Stage 3 or 4 clinical conditions. This package contains several elements, including:

- systematic TB screening and investigation, and IPT if TB is excluded,
- screening for cryptococcal antigenaemia,
- screening and management of serious bacterial infections,
- CPT prophylaxis,
- ART,
- Adherence support, and
- Intensified follow-up.

Pregnant women with CD4<200 cells/mm^3 are eligible for this package of care for advanced HIV disease. This package therefore, provides opportunity to reconsider CD4 count stratification in deciding on administration of IPT in pregnancy, and alignment with the Advanced HIV Disease definition (i.e., CD4 < 200), will facilitate implementation as part of a comprehensive care package. The NEMLC supports a CD4 count-stratified approach as informed by the evidence review undertaken and programmatic support with implementation.

NEMLC Recommendation:

See the NEMLC recommendation below. A copy of the complete evidence review[4] may be found at the end of this report or on the NHI website.

[3] NDoH. 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. Accessible online https://knowledgehub.health.gov.za/elibrary/2023-art-clinical-guidelines-management-hiv-adults-pregnancy-and-breastfeeding-adolescents

[4] NEMLC Evidence review. TPT in pregnancy. V2.0_27 Nov 2025

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

ERC Recommendation 13 November 2025: We recommend that pregnant women living with HIV, with:

- CD_4 counts ≤ 200 cells/mm³ and starting ART, receive 12 months of IPT after exclusion of active tuberculosis disease.
- CD_4 counts > 200 cells/mm³ and starting ART, IPT should be deferred to the post-partum period.

Rationale: The benefit of IPT in preventing tuberculosis disease at CD4 counts ≤ 350 cells/m³(low certainty evidence) outweighs the increased risk of adverse pregnancy outcomes. However, in pregnant women with higher CD_4 counts, the increased risk of miscarriage after first trimester IPT exposure (low certainty evidence) and increased risk of low birth weight and underweight for age after second trimester IPT exposure (moderate certainty evidence) outweighs any potential benefit (moderate certainty evidence). However, a CD4 cut off of 350 was not deemed programmatically feasible. The current programmatic "package of care" for patients with advanced HIV (CD4< 200), for which pregnant women are eligible, includes IPT. The ERC therefore suggests administering 12 months of IPT for all pregnant women with newly diagnosed HIV with a CD4< 200, co-initiated with ART, after screening for active TB, as part of the AHD package of care

Level of Evidence:

Risk of adverse pregnancy outcomes after first trimester exposure (low certainty evidence from observational studies and cohort studies nested in randomised controlled trials)

Risk of adverse pregnancy outcomes after second trimester exposure (moderate certainty evidence from a randomized controlled trial)

Evidence of benefit at CD_4 ≤ 350 cells/mm³ (low certainty evidence from an observational study)

Review indicator: New high quality evidence of benefit or harm.

NEMLC RECOMMENDATION (MEETING 27 November 2025): NEMLC supports the ERC recommendation as detailed above (dated 13 Nov 2025).

Monitoring and evaluation considerations, and research priorities:

Pregnant women should be routinely screened for TB at every antenatal visit.

Strenthening of pharmacovigilance systems, with implementaiton of measures for identifying signals of drug-related harm in pregnant women.

STG Update: AH Chp 10 Section 10.2.1 Tuberculosis preventative therapy (TPT)

AMENDED FROM:

NOTE: For pregnant women:

- Defer TPT until after delivery.
- Ensure that routine screening against TB is conducted at each antenatal visit.

AMENDED TO:

NOTE: For pregnant women living with HIV:

- If CD4 count > 200 cells/mm³ and initiating ART, defer TPT until after delivery
- If CD4 count ≤ 200 cells/mm³ and initiating ART, offer 12 months of isoniazid as TPT, after excluding active tuberculosis disease
- Ensure that routine screening against TB is conducted at each antenatal visit.

South African National Department of Health
HISTORICALLY ACCEPTED USE REVIEW OF DARUNAVIR
Committee: Third Line Antiretroviral Therapy (TLART) Committee

Executive Summary

Date: June 2025

Reviewers: Dr M Reddy[1], Dr R Lancaster[2]
[1]Pharmaceutical Consultant: Health Technology Assessment and Policy, National Department of Health, [2]Essential Drugs Programme, National Department of Health
Declarations: MR and RL have no have no interests to declare on the topic.

Acknowledgments: Dr J Taylor[3], Dr Leon Levin[4], Dr N Davies[4], Prof H Rabie[4], Prof G Meintjies[5] & the TLART Committee
[3]Pharmacology Registrar: Division of Clinical Pharmacology, Department of Medicine, University of Cape Town
[4]Third Line Antiretroviral Therapy (TLART) Committee, National Department of Health
[5]Professor of Medicine, University of Cape Town

Medicine(s) (INN): Darunavir (DRV); darunavir/ritonavir (DRV/r) (Note – ritonavir must accompany darunavir)
Medicine(s) (ATC): J05AE10; J05AR26
Indication/s (ICD10 code/s): Human immunodeficiency virus (HIV) (B20)
Patient population/s: HIV-1 infected adults and children with virological failure and laboratory proven resistance to protease inhibitors (PI) and/or integrase-strand transfer inhibitors (INSTI)
Prevalence of condition/s: An estimated 8 million people were living with HIV in South Africa in 2024, representing 12.7% of the national population[1]. Of patients on TLD2 around 1 to 3% will develop resistance to dolutegravir[2], thus requiring Third Line Antiretroviral (TLART) management.
Level of Care: Hospital level, through specialist recommendation.
Prescriber Level: Doctor prescribed (Initiation by TLART Committee)
Current Standard(s) of Care: Third-line ART managed via an algorithm including darunavir/ritonavir (DRV/r) for the following indications:

- Patient is on 2nd line DTG regimen (i.e., ABC/3TC/DTG **OR** TLD **OR** AZT/3TC/DTG)**,** is PI naïve and has developed DTG resistance.*
- Patient is on 2nd line PI regimen (possibly previously on NNRTI-based regimen) and has developed LPV/r or ATV/r resistance (score ≥15) and DRV/r score 10-59 and no prior integrase inhibitor exposure.**
- Patient is on 2nd line DTG regimen, has developed DTG resistance and has prior ATV/r or LPV/r exposure, but no resistance test was done at time of switch to DTG regimen. */**

*Once daily DRV/r vs ** Twice Daily. If history suggests possible DRv/r cross resistance (prolonged non-suppression on ATV/r or LPV/r then increase dose to twice daily)

DRV/r is not indicated in any second line regimens.

Background:

Darunavir (combined with ritonavir) has been part of the third line ART regimens since October 2013[3], however it has never officially been reviewed/approved by the National Essential Medicines List Committee (NEMLC) for inclusion on the South African Essential Medicines List (EML); for use in HIV-1 infected adults and children with virological failure and laboratory proven resistance to protease inhibitors (PI) and/or integrase-strand transfer inhibitors (INSTI). To retain darunavir/ritonavir on the National Department of Health (NDoH) pharmaceutical tender for TLART use, it was recommended that a recommendation for inclusion on the EML be made by NEMLC.

A review of the use of DRV/r in second-line ART was conducted by NEMLC in 2021 and DRV/r was not recommended over LPV/r. The review found that DRV/r-containing ART regimens were associated with higher viral suppression rates and were better tolerated than LPV/r. However, at the time, DRV/r was considered unaffordable and there were additional concerns regarding the supply. The review also noted that DRV/r-containing regimens would not be suitable for patients on a PI-based regimen who require rifampicin-based tuberculosis treatment. DRV/r was recommended for inclusion on the therapeutic interchange database as an alternative to LPV/r and ATV/r for patients not on TB-rifampicin-based tuberculosis treatment. [4]

The TLART Committee ART algorithm is currently under review (as per discussions held with the TLART committee on the 26 and 28 August 2025) and will omit any reference to 2nd line treatment use. Decisions reached by the TLART committee were confirmed for named patient, restricted use only after a resistance test and not for 2nd line access.

Methods:

A search for World Health Organization (WHO) clinical practice guidelines outlining clinical evidence for optimising third-line antiretroviral therapy.

An AGREE II (Appraisal of Guidelines, for Research, and Evaluation)[5] assessment was conducted independently in duplicate (RL & MR) on the selected guideline to evaluate the process of guideline development and quality of reporting.

The AGREE II appraisal outcome is presented in Annexure 1. In summary the WHO Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach (July 2021) guideline can be considered a high-quality clinical practice guideline (AGREE II score of 84% overall and 83% for rigour of development) and was considered up-to-date and relevant to the committee's question.

Results:

A WHO meeting report (26 & 27 November 2023) on "Optimization of second-line and third-line antiretroviral therapy for people living with HIV" was identified[6]. A part objective of this working group was to discuss darunavir/ritonavir (DRV/r) as the preferred PI option in second-line and third-line ART for adults, pregnant women and children, based on updated evidence for DRV/r following a systematic review and meta-analysis commissioned by the WHO.

The WHO recommends that:

- Third-line regimens include new drugs with minimal risk of cross-resistance to previously used ART regimens, such as INSTIs and second-generation nonnucleoside reverse-transcriptase inhibitors (NNRTIs) and PIs.
- For individuals for whom a DTG-based first-line regimen and an ATV/r or LPV/r second-line regimen has failed, DRV/r in combination with two nucleoside reverse-transcriptase inhibitors (NRTIs) with the possible addition of DTG is a suitable third-line ART option.

WHO TLART recommendations for DRV/r include:

- Adults (including pregnant women)
- Adolescents,
- Paediatric patients over the age of 3 years

The Food and Drug Administration (FDA) does not recommend the use of DRV/r in children less than 3 years of age OR <10 kg.[7]

Summary of Evidence:

The following is a summary of the evidence cited in the WHO meeting report:

Systematic review and network meta-analysis on the use of DRV/r in second-line or first and second-line ART for adults and pregnant women (commissioned by WHO):

- No clear differences between DRV/r and ATV/r or LPV/r; limited comparative effectiveness data (2016 systematic review and network meta-analysis conducted).[8]
    - Estimated efficacy of ritonavir-boosted darunavir (800 mg/100mg once daily) was too imprecise to determine non-inferiority compared to than with both atazanavir and lopinavir plus two NRTIs
    - No significant differences between regimens with respect to
        - Continuations
        - AIDS-defining illnesses
        - WHO stage 3-4 disease
        - Mortality
- DRV/r use in TB: DRV/r interacts with rifampicin-based TB treatment.[6]

- A systematic review commissioned by WHO (See **Table 1** below extracted from the WHO meeting report (26 & 27 November 2023) showed that:
    - ATV/r and DRV/r tended to be more effective and tolerable than LPV/r, in second-line only studies and in combined first- and second-line studies
    - ATV/r had more favourable lipid outcomes than DRV/r in combined first- and second-line studies
    - DRV/r had better overall safety outcomes compared with other PIs in second-line only studies and in combined first- and second-line studies
- Pregnant Women *(based on observational data):*

- Higher risk of negative pregnancy outcomes, preterm births and small for- gestational-age births among women receiving LPV/r-based regimens (second line studies AND combined first and second line studies).
- Differences between ATV/r and DRV/r were less evident.
- Trend towards improved viral suppression for women on DRV/r-based regimens.
- DRV/r has good safety and viral efficacy in pregnancy, with some new comparative data suggesting superior viral efficacy of DRV/r (given in twice-daily dosing) compared to ATV/r.
- In later pregnancy, once-daily DRV/r is associated with a greater decrease in both total and unbound plasma concentrations of darunavir compared to twice-daily DRV/r.
- US FDA Administration recommends DRV/r 600/100 mg twice daily dosing.[9]
- European Medicines Agency recommends DRV/r 800/100 mg once-daily dosing in pregnancy.[10]
- International HIV clinical guidelines currently recommend DRV/r 600/100 mg twice-daily dosing for pregnant women, except if the woman becomes pregnant on DRV/r once-daily dosing and has suppressed viral loads. [11,12]

Table 1; Comparative efficacy and safety of regimens containing atazanavir/ritonavir, darunavir/ritonavir and lopinavir/ritonavir (Taken from *Optimization of second-line and third-line antiretroviral therapy for people living with HIV: meeting report, 27-28 November 2023*)

	DRV/r + NRTIs versus LPV/r + NRTIs			ATV/r + NRTIs versus LPV/r + NRTIs			DRV/r + NRTIs versus ATV/r + NRTIs		
Comparison	Effect (95% CI)	Absolute effects	Overall quality of evidence	Effect (95% CI)	Absolute effects	Overall quality of evidence	Effect (95% CI)	Absolute effects	Overall quality of evidence
Viral suppression <50 copies/mL at 24 weeks	1.26 (0.85, 1.89)	49 per 1000 (–38 to 122)	⊕⊕⊕ Moderate	1.21 (0.97, 1.49)	40 per 1000 (–6 to 78)	⊕ Very low	1.11 (0.90, 1.37)	22 per 1000 (–22 to 63)	⊕⊕ Low
Viral suppression <50 copies/mL at 48 weeks	1.27 (0.95, 1.71)	48 per 1000 (–10 to 101)	⊕⊕⊕ Moderate	1.33 (1.08, 1.61)	55 per 1000 (16 to 87)	⊕ Very low	1.23 (1.00, 1.50)	41 per 1000 (1 to 75)	⊕ Very low
Viral suppression <50 copies/mL at 96 weeks	2.45 (1.65, 3.64)	150 per 1000 (92 to 195)	⊕⊕⊕ Moderate	1.37 (1.08, 1.76)	62 per 1000 (16 to 104)	⊕⊕ Low	1.49 (1.14, 1.96)	76 per 1000 (26 to 121)	⊕⊕⊕ Moderate
CD4 24-week change	–	36.02 cells/mL (–63.27, –8.83)	⊕⊕ Low	–	4.87 cells/mL (–23.07, 13.56)	⊕⊕ Low	–	12.46 cells/mL (–31.2, 6.24)	⊕⊕ Low
CD4 48-week change	–	17.71 cells/mL (–34.98, –0.62)	⊕⊕ Moderate	–	1.83 cells/mL (–13.37, 9.34)	⊕ Very low	–	16.23 cells/mL (–29.29, –3.42)	⊕⊕ Low
CD4 96-week change	–	17.3 cells/mL (–41.66, 8.82)	⊕⊕ Low	–	4.29 cells/mL (–24.9, 16.49)	⊕⊕ Low	–	17.3 cells/mL (–41.66, 8.82)	⊕⊕ Low
Discontinuations	0.56 (0.29, 1.05)	59 per 1000 (–101 to 7)	⊕⊕⊕ Moderate	0.70 (0.55, 0.89)	46 per 1000 (–72 to –16)	⊕⊕ Low	0.73 (0.57, 0.93)	42 per 1000 (–68 to –10)	⊕⊕ Low
Discontinuations due to adverse events	0.63 (0.18, 2.04)	14 per 1000 (–35 to 39)	⊕⊕ Low	0.63 (0.40, 1.00)	19 per 1000 (–32 to 0)	⊕⊕ Low	0.58 (0.38, 0.89)	21 per 1000 (–34 to –5)	⊕⊕⊕ Moderate
Overall adverse event (any grade)	0.74 (0.55, 0.99)	50 per 1000 (–108 to –2)	⊕⊕⊕ Moderate	0.91 (0.71, 1.16)	14 per 1000 (–56 to 21)	⊕⊕ Low	0.39 (0.27, 0.55)	182 per 1000 (–267 to –105)	⊕⊕⊕ Moderate

Overall severe adverse events	0.82 (0.47, 1.42)	24 per 1000 (–74 to 51)	⊕⊕⊕ Moderate	1.07 (0.81, 1.41)	9 per 1000 (–24 to 48)	⊕⊕ Low	0.68 (0.41, 1.09)	41 per 1000 (–80 to 11)	⊕⊕ Low
Overall severe adverse events (treatment related)	1.15 (0.34, 4.25)	16 per 1000 (–81 to 257)	⊕⊕ Low	1.69 (0.33, 12.04)	70 per 1000 (–82 to 508)	⊕⊕ Low	0.59 (0.42, 0.82)	48 per 1000 (–71 to –21)	⊕⊕⊕ Moderate
Weight gain 48-week change	–	2.31 Kg (1.14, 3.52)	⊕⊕⊕ Moderate	–	2.02 Kg (1.17, 2.81)	⊕⊕⊕ Moderate	–	0.30 Kg (–1.09, 1.71)	⊕⊕ Low
Hypertension (any grade)	0.82 (0.36, 1.89)	4 per 1000 (–19 to 23)	⊕⊕⊕ Moderate	–	–	–	–	–	–
Total cholesterol 48-week change	–	1.13 mmol/L (–1.79, –0.46)	⊕⊕⊕ Moderate	–	0.51 mmol/L (–0.68, –0.34)	⊕⊕⊕ Moderate	–	0.56 mmol/L (–1.43, 0.17)	⊕ Very low
Fasting glucose 48-week change	–	0.12 mmol/L (–0.06, 0.29)	⊕⊕ Low	–	0.13 mmol/L (–0.01, 0.26)	⊕⊕ Low	–	0.12 mmol/L (–0.06, 0.29)	⊕⊕ Low
High-density lipoprotein 48-week change	–	0.28 mmol/L (–0.61, 0.06)	⊕⊕⊕ Moderate	–	0.07 mmol/L (–0.12, –0.01)	⊕⊕ Low	–	0.15 mmol/L (–0.38, 0.07)	⊕ Very low
Low-density lipoprotein 48-week change	–	0.46 mmol/L (–1.07, 0.17)	⊕⊕⊕ Moderate	–	0.36 mmol/L (–0.49, –0.23)	⊕⊕ Low	–	0 mmol/L (–0.01, 0.01)	⊕ Very low
Triglycerides 24-week change	–	0.04 mmol/L (–0.05, –0.02)	⊕⊕⊕ Moderate	–	0.85 mmol/L (–1.11, –0.58)	⊕⊕⊕ Moderate	–	0.04 mmol/L (–0.05, –0.02)	⊕⊕ Low
Triglycerides 48-week change	–	1.55 mmol/L (–2.4, –0.71)	⊕⊕⊕ Moderate	–	0.72 mmol/L (–0.94, –0.49)	⊕⊕⊕ Moderate	–	1.19 mmol/L (–2.81, 0.31)	⊕ Very low
Mortality	1.64 (0.43, 6.41)	22 per 1000 (–22 to 164)	⊕⊕⊕ Moderate	0.80 (0.35, 1.80)	6 per 1000 (–22 to 25)	⊕ Very low	0.87 (0.39, 1.88)	4 per 1000 (–20 to 28)	⊕ Very low

Second-Line Studies Only	Combined first- and second-line studies

Kanters et al[13] reviewed the estimated efficacy of ritonavir-boosted darunavir (800/100 mg once daily) was too imprecise to determine non-inferiority. Overall, regimens did not differ significantly with respect to continuations.

Limitation: Includes second-line only and combined first- and second-line studies. No studies of DRV/r as TLART included.

Table 2: Comparison of pharmacokinetic parameters of darunavir/ritonavir at different doses during late pregnancy (Taken from Optimization of second-line and third-line antiretroviral therapy for people living with HIV: meeting report, 27-28 November 2023)

DRV dosage	Area under the curve: total DRV	Area under the curve: unbound DRV	Trough: total DRV	Trough Unbound DRV	Trough level below: EC_{50} wild-type virus[a] EC_{50} resistant virus[b]	Viral load <50 copies/mL at delivery (pooled)	Mother-to-child transmission
DRV/r 600/100 mg twice daily *(14–16)*	17–26% ↓	7–8% ↓	11–28% ↓	11% ↓	0/40 (0%) 0/6 (0%)	26/44 (59%)	1/52 (2%)
DRV/r 800/100 mg four times daily *(15,16–18)*	31–39% ↓	20–24% ↓	42–57% ↓	24–38% ↓	3/99 (3%) 7/50 (14%)	81/100 (81%)	0/95 (0%)

DRV/r 800/100 mg twice daily (↑ dose) versus 600/100 mg twice daily postpartum *(19)*	36% ↓		53% ↓		80% (20/25)	0/24 (0%)
DRV/cobicistat 800/150 mg four times daily *(20,21)*	50–56% ↓	40% ↓	79–89% ↓	88%↓	86% (30/35)	

DRV = darunavir, DRV/r = darunavir/ritonavir, EC_{50} = half maximal effective concentration.
[a] EC_{50} wild-type virus = 0.055 ng/mL (55 mg/L). [b] EC_{50} resistant virus = 0.55 ng/mL (550 mg/L).

** DRV/r 800/100mg twice daily in third trimester versus 600/100mg twice daily postpartum*

Systematic review of the safety of darunavir/ritonavir for children (3 to 18 years) and adolescents living with HIV[6]

- Total of 14 studies included comparing ATV/r, DRV/r, DTG and LPV/r.
  - 2 randomized clinical trials (CHAPAS-4 and SMILE)[14],[15]:
    - CHAPAS-4 (Child Antiretroviral Therapy in South Africa) - an open-label RCT that included > 900 children aged 3–15 years
    - 232 children were randomised to DRV/r containing second-line regimens and efficacy and safety outcomes compared to those randomised to LPV/r or ATV/r containing second-line regimens.
    - SMILE (**Strategy for Maintenance of HIV suppression with integrase inhibitor + darunavir/ritonavir in children)**, an open-label RCT included > 300 children aged 6–18 years comparing a switch to once-daily INSTI + DRV/r (158 children receiving DRV/r and INSTI) vs continuing standard NNRTI or PI-based regimens in virologically suppressed children virologically
  - 5 single-arm trials and,
  - 7 observational studies.
- DRV/r had the best efficacy and safety among the boosted PI options:
  - No deaths due to DRV/r.
  - Few drug-related severe adverse events.
  - Few discontinuations.
  - Small increases in total and LDL cholesterol.
  - Viral suppression (viral load <400 copies/mL) were satisfactory (**>85% suppression rates).** in both;
    - CHAPAS-4
      - At week-96, 88.3% of those randomised to DRV/r had VL <400 copies/mL
      - DRV/r-based regimens were reported to be as good as and trending towards being superior to ATV/r- and LPV/r-based regimens.
      - At week-96, 88.3% DRV/r, 84.3% ATV/r and 80.7% LPV/r had VL <400 copies/mL
    - SMILE
      - The study showed that switching to an INSTI plus DRV/r is highly efficacious and non-inferior virologically in maintaining virological suppression at 48 weeks.

- By 48 weeks, 8 INSTI + DRV/r vs. 12 current standard-of-care (SOC) triple ART (2NRTI + boosted PI/NNRTI) had confirmed HIV-RNA ≥50 copies/mL; difference (INSTI + DRV/r-SOC) −2.5% (95% CI: −7.6, 2.5%), showing non-inferiority[16].

In June 2024, Laurus Labs in conjunction with the Clinton Health Access Initiative (CHAI) and UNITAID for generic development filed for tentative USA FDA approval of film coated paediatric DRV/r (120/20 mg).[17]

The AGREE II appraisal outcome is presented in Annexure 1. In summary the WHO Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach (July 2021) guideline, which recommends DRV/R as TLART option, can be considered a high-quality clinical practice guideline (AGREE II score of 84% overall and 83% for rigour of development) and was considered up-to-date and relevant to the committee's question.

Conclusion and recommendations of WHO meeting report (26 & 27 November 2023):

- DRV/r should be the preferred boosted PI for third-line therapy.
- Concerns about the genetic barrier of resistance (higher for DRV/r than for ATV/r).
- Side-effects, drug–drug interactions and the need for research to address gaps in the guidelines.
- Concerns raised about the availability and cost of third-line therapies.
- Clarity required regarding the optimal dosing of DRV/r for pregnant women.
- Dosing and formulations need to be optimized for DRV/r in children.
- Recommended that ATV/r be an alternative.
- Recommended that LPV/r should be reserved for special circumstances (such as drug interactions and stock-outs) or phased out.

Historically accepted use Criteria

SECTION A		
	Criteria	**Comment**
1	The medicine is included in the World Health Organization (WHO) Model Essential Medicines List, either as a core or complementary item, for the indication requested.	YES: X / NO: ***https://list.essentialmeds.org/?query=darunavir**
2	The medicine is currently registered by South African Health Products Regulatory Authority (SAHPRA).	YES: X / NO:
3	A documented rapid literature review identified no new safety concerns or new evidence of lack of efficacy.	YES: X / NO: *See above: Summary of Evidence*
4	The anticipated costs and usage are not likely to result in a substantial impact on the budget.	YES: X / NO: *Comment: small population*

SECTION B		
1	There is evidence prior to 2007* of safety and efficacy for the recognised indication (a systematic review/meta-analysis, or at least one critically appraised controlled trial.) *Information after 2007 would need to be subject to standard review processes for a new inclusion.*	YES: X / NO: *See above: Summary of Evidence*
OR		
2	It is included as part of standard of care in a critically appraised clinical practice guideline (CPG) of adequate quality, for the particular indication. Refer to Annexure 1 AGREE II assessment of the "Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, 2021 update". Geneva: World Health Organization; 2021	YES: X / NO: *See above: CPG recommendations*
AND		
3	It is currently used in practice for this indication.	YES: X / NO: *Comment: Part of the third line antiretroviral therapy treatment bundle since October 2013.*[3]

Modified Evidence to Decision Framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [ ] Small [x] None [ ]	***Systematic review and network meta-analysis on the use of darunavir/ritonavir for adults and pregnant women (commissioned by the WHO):*** *A systematic review commissioned for the WHO meeting report (26 & 27 November 2023) showed that:* ○ *DRV/r had better overall safety outcomes compared with other PIs* ***Pregnant Women (based on observational data):*** • *Trend towards improved viral suppression for women on DRV/r-based regimens.* • *DRV/r has good safety and viral efficacy in pregnancy, with some new comparative data suggesting superior viral efficacy of DRV/r (given in twice-daily dosing) compared to ATV/r.* ***Systematic review of the safety of darunavir/ritonavir for children (3 to 18 years) and adolescents living with HIV*** • *DRV/r had the best efficacy and safety among the boosted PI options:* ○ *No deaths due to DRV/r* ○ *Few drug-related severe adverse events* ○ *Few discontinuations.*

		○ *Small increases in total and LDL cholesterol* ○ *Viral suppression (viral load <400 copies/mL) were satisfactory in both CHAPAS-4 and SMILE (>85% suppression rates).* ○ *In CHAPAS-4, DRV/r-based regimens were reported to be as good as and trending towards being superior to ATV/r- and LPV/r-based regimens* *Lower certainty evidence*
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large ☐ Moderate ☐ Small ☒ None ☐	***Systematic review and network meta-analysis on the use of darunavir/ritonavir for adults and pregnant women (commissioned by the WHO):*** *A systematic review commissioned for the WHO meeting report (26 & 27 November 2023) showed that:* ○ *DRV/r had better overall safety outcomes compared with other PIs* ***Pregnant Women (based on observational data):*** • *DRV/r has good safety and viral efficacy in pregnancy* ***Systematic review of the safety of darunavir/ritonavir for children (3 to 18 years) and adolescents living with HIV*** • *DRV/r had the best safety among the boosted PI options:* ○ *No deaths due to DRV/r* ○ *Few drug-related severe adverse events* ○ *Few discontinuations.* ○ *Small increases in total and LDL cholesterol*
QUALITY OF EVIDENCE	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☐ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect **Very low to moderate**	*Very Low to Moderate – see Table 1 above*
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☒ Favours control ☐ Intervention = Control *or* Uncertain ☐	*See Table 1 above*

THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [ ] No [X]	*There is no alternative.* *DRV/r is used when there is resistance to other PIs such as ATV and LPV.*
FEASIBILITY	**Is implementation of this recommendation feasible?** Yes [x] No [ ] Uncertain [ ]	*Darunavir is already part of the third line ART regimens in South Africa since October 2013 and recommended by the WHO as part of the TLART.* *However, lack of a readily available DRV/r paediatric formulation in South Africa and drug-drug interactions with DRV/r and rifampicin-based TB therapy will limit feasibility of implementation.*
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [X] Uncertain [ ]	*Medicines Health Product List (MHPL -June 2025)* Darunavir, Ritonavir; 400mg, 50mg; Tablet; 56 Tablets — R397.40 Darunavir; 150mg; Tablet; 240 Tablets — R816.44 Darunavir; 600mg; Tablet; 56 Tablets — R862.08 Darunavir; 75mg; Tablet; 480 Tablets — R910.05 Ritonavir; 100mg; Tablet; 56 Tablets — 91.81 Ritonavir; 100mg; Suspension; 30 Sachets — 62.31
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [X] Major [ ] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	*The are challenges of administering DRV/r to people with tuberculosis (TB) considering interactions with rifampicin-based TB treatment.* *Paediatric formulations are registered and available in the country: 150mg and 75mg.*
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [X] Uncertain [ ]	

RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

Recommendation: It is suggested that darunavir/ritonavir be included on the Essential Medicines List for adults and children as a special access item; as recommended by the TLART committee, following a genotype resistance test, for use on a named patient basis as per TLART treatment algorithm. *Rationale: A systematic review commissioned by the WHO showed that: DRV/r had better overall safety outcomes compared with other PIs in adults (very low to moderate level of evidence). In pregnant women (based on observational data) DRV/r has good safety and viral efficacy in pregnancy. Finally, a WHO commissioned systematic review of the safety of darunavir/ritonavir for children (3 to 18 years) and adolescents living with HIV showed that DRV/r had the best safety among the boosted PI options.* **Level of Evidence: Very Low ((Uncertain)** **Review indicator: Change in resistance, safety and efficacy?**
NEMLC RECOMMENDATION (16 October 2025): NEMLC accepted the ERC suggestion and recommended that darunavir/ritonavir be included on the Essential Medicines List for adults and children as a special access item; as recommended by the TLART committee, following a genotype resistance test, for use on a named patient basis as per TLART treatment algorithm.
Monitoring and evaluation considerations: Patientoutcomes as well as patterns of resistance
Research priorities: Monitor response in TLART named patients

Annexures

Annexure 1: Duplicate AGREE II Appraisal

AGREE II assessment scores																							
Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach																							
Scoring the guidelines																							
	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	7	7	7	7	4	7	6	7	7	7	7	7	7	4	7	7	7	4	5	4	2	3	7	6
Appraiser 2	7	4	7	7	6	7	6	6	5	6	7	7	6	1	6	6	6	6	7	7	6	6	7	6
Item Total	14	11	14	14	10	14	12	13	12	13	14	14	13	5	13	13	13	10	12	11	8	9	14	12
Domain Total	39			38			96								39			41				23		276
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	**92%**			**89%**			**83%**								**92%**			**69%**				**79%**		**84%**

Overall assessment: The Guideline is recommened for use in this context

Score: (e.g. domain 1)

Maximum possible score = 7 (highest score) x no. of items x no. of appraisers

Minimum possible score = 1 (lowest score) x no. of items x no. of appraisers

Score for each domain

$$\frac{\text{Obtained score - minimum possible score}}{\text{Maximum possible score - minimum possible score}} \times 100$$

References

[1] Stats SA. 2024 Mid-year population estimates. 30 July 2024. Available at: https://www.statssa.gov.za/?p=17440.

[2] Citation: Chu, C.; Tao, K.; Kouamou, et al. Prevalence of Emergent Dolutegravir Resistance Mutations in People Living with HIV: A Rapid Scoping Review. Viruses 2024, 16, 399. https://doi.org/10.3390/ v16030399

[3] National Department of Health. HIV Drug Resistance Regimens 2024 For the management of protease inhibitor (PI) and dolutegravir (DTG) resistance.

[4] National Department of Health: Affordable Medicines, EDP Primary Health Care and Adult Hospital level. Medicine Review: Darunavir/ritonavir vs lopinavir/ritonavir for adult hiv patients, 27 July 2021. http://www.health.gov.za/. https://accessmedicine.mhmedical.com/content.aspx?bookid=1944&sectionid=143516493

[5] Appraisal Of Guidelines For Research & Evaluation II. Available at: https://www.agreetrust.org/wp-content/uploads/2013/10/AGREE-II-Users-Manual-and-23-item-Instrument_2009_UPDATE_2013.pdf. Accessed 19 April 2024.

[6] Optimization of second-line and third-line antiretroviral therapy for people living with HIV: meeting report, 27-28 November 2023. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO.

[7] Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, 2021 update. Geneva: World Health Organization; 2021 https://iris.who.int/handle/10665/342899.

[8] Kanters S, Socias ME, Paton NI, Vitoria M, Doherty M, Ayers D et al. Comparative efficacy and safety of second-line antiretroviral therapy for treatment of HIV/AIDS: a systematic review and network meta-analysis. Lancet HIV. 2017;4:e433–41. doi: 10.1016/S2352-3018(17)30109-1.

[9] Recommendations for the use of antiretroviral drugs during pregnancy and interventions to reduce perinatal HIV transmission in the United States. Washington (DC): Clinicalinfo; 2024 (https://clinicalinfo.hiv.gov/en/guidelines/perinatal/safety-toxicity-arv-agents-protease-inhibitorsdarunavir- prezista).

[10] Darunavir Viatris (previously Darunavir Mylan). Amsterdam: European Medicines Agency; (https://www.ema.europa.eu/en/medicines/human/ EPAR/darunavir-mylan).

[11] EACS guidelines version 12.0, October 2023. Brussels: European AIDS Clinical Society; 2023 (https://www.eacsociety.org/media/guidelines-12.0.pdf, accessed 13 June 2024).

[12] Gandhi RT, Bedimo R, Hoy JF, Landovitz RJ, Smith DM, Eaton EF. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2022 recommendations of the International Antiviral Society – USA Panel. JAMA. 2023;329:63–84. doi: 10.1001/jama.2022.22246.

[13] Kanters SR which did revie Estimated efficacy of ritonavir-boosted darunavir (800 mg once daily) was too imprecise to

[14] Musiime V, Szubert AJ, Bwakura Dangarembizi A, Chabala C, Doerholt K, Dukakia N et al. Increasing second-line antiretroviral therapy options for children with HIV in Africa: week-96 efficacy and safety results of the CHAPAS-4 randomised trial. 12th IAS Conference on HIV Science, Brisbane, Australia, 23–26 July 2023 (Oral Abstract 5764; https://programme.ias2023.org/Abstract/ Abstract/?abstractid=5764, accessed 13 June 2024).

[15] Compagnucci A, Chan MK, Saidi Y, Cressey TR, Bamford A, Riault Y et al. Nucleoside/nucleotide reverse transcriptase inhibitor sparing regimen with once daily integrase inhibitor plus boosted darunavir is non-inferior to standard of care in virologically suppressed children and adolescents living with HIV – Week 48 results of the randomised SMILE Penta-17-ANRS 152 clinical trial. eClinicalMedicine 2023;60:102025. doi: 10.1016/j.eclinm.2023.102025.

[16] SMILE-PENTA17-ANRS 152 Trial Group. Nucleoside/nucleotide reverse transcriptase inhibitor sparing regimen with once daily integrase inhibitor plus boosted darunavir is non-inferior to standard of care in virologically-suppressed children and adolescents living with HIV - Week 48 results of the randomised SMILE Penta-17-ANRS 152 clinical trial. EClinicalMedicine. 2023 Jun 2;60:102025. doi: 10.1016/j.eclinm.2023.102025. PMID: 37304494; PMCID: PMC10251070.

[17] The Clinton Health Access Initiative. 2024 HIV Market Report. Issue 15, December 2024. The state of HIV treatment, testing, and prevention in low- and middle-income countries. Available from: https://www.clintonhealthaccess.org/wp-content/uploads/2024/12/2024-HIV-Market-Report_12.20.24.pdf

PHC/Adult Hospital Expert Review Committee: Evidence Summary Isoniazid Preventive Therapy in Pregnancy

Date: 9 November 2023
Updated: 13 November 2025 (Version 2.0)
Reviewer(s): Dr Jessica Taylor, Prof. Karen Cohen
Affiliation: University of Cape Town, Groote Schuur Hospital
Author affiliation and conflict of interest details: JT and KC have no interests pertaining to isoniazid. KC is a co-author on the paper by Kalk et al.

Oversight Group Support: Zahiera Adam

Research Question: What is the efficacy and safety of isoniazid preventive therapy in pregnant women?

1. Background and timeline of NEMLC recommendations

Tuberculosis disease during pregnancy and the post-partum period is associated with adverse maternal, pregnancy, infant outcomes.(1) There is consensus regarding the benefit of treating active tuberculosis disease during pregnancy. Additionally, there is consensus regarding the benefit of isoniazid preventive therapy (IPT) in non-pregnant people living with HIV (PLWHIV) to prevent tuberculosis disease.(1)

In PLWHIV not on ART, tuberculosis preventive therapy is reported to reduce the risk of tuberculosis disease by 33% (RR 0.67; 95% CI 0.51 to 0.87), with the reduction in risk reaching 64% in those with proven latent tuberculosis infection on skin testing (RR 0.36; 95% CI 0.22 to 0.61)(2). In a South African study of PLWHIV who were predominantly on ART, 12 months of IPT was associated with 37% reduction in risk of tuberculosis (3226.5 person-years of follow up; HR 0.63; 95% CI 0.41 to 0.94). This protective effect was demonstrated even in those with negative tuberculin skin tests (TST)(aHR 0.43; 95% 0.21 to 0.86) or interferon gamma release assays (IGRA)(aHR 0.43; 95% CI 0.20 to 0.96). However, no difference in all-cause mortality was reported (IPT 0.9 per 100 person-years vs. placebo 1.2 per 100 person-years; HR 0.72; 95% CI 0.34 to 1.34; p = 0.32).(3) The 2018 NEMLC medicine review titled "Isoniazid Preventive Therapy" reported a number needed to treat (NNT) to avert 1 case of tuberculosis disease of 33 in non-pregnant PLWHIV.(4) Additionally, this review indicated that IPT is associated with a mortality benefit in a long-term follow-up study across all CD_4 counts and irrespective of baseline latent tuberculosis infection (aHR 0.61; 95% CI 0.39 to 0.94; NNT 57).(4, 5) However, there remains a lack of consensus regarding the safety and efficacy of IPT in pregnant women living with HIV. Safety is of particular importance in the setting of prophylactic treatment, where the acceptable threshold for potential harm is much lower.

In the 2014 primary healthcare (PHC) standard treatment guidelines (STG), IPT was recommended for all PLWHIV. The duration of IPT recommended, ranged from 6 – 36 months depending on the results and availability of TST and whether or not the patient was taking highly active antiretroviral therapy (HAART). In addition, 12 months of IPT was recommend for all HIV positive pregnant women.(6)

In 2018, the decision was taken to simplify this recommendation to 12 months of IPT for all PLWHIV regardless of TST testing or HAART, based on the results of the locally conducted clinical trial of IPT versus placebo in participants on ART mentioned previously.(3) In the same year preliminary data from the TB APPRISE randomized controlled trial (RCT) reported increased adverse pregnancy outcomes associated with IPT use during pregnancy as compared to the post-partum period, and no difference in tuberculosis disease or mortality. As a result, NEMLC recommended that a caution be added to the STG regarding the use of IPT in pregnant women living with HIV with high CD_4 counts. (1)

After further deliberation, based on the evidence of potential harm associated with IPT use in pregnancy, and after consideration of the potential benefit of IPT in the high tuberculosis prevalence setting of South Africa, a CD_4 cut off for IPT initiation in pregnancy was recommended. The recommendation was that IPT be deferred until after delivery in women living with HIV with CD_4 counts of < 100 cells/mm^3. This CD_4 count was extrapolated from the REALITY RCT, which showed an association between IPT and a reduction in incident tuberculosis disease in non-pregnant patients with advanced HIV (CD_4 < 100 cells/mm^3) starting ART. (7)

Following this, data emerged from a locally conducted, retrospective cohort study in the Western Cape, which reported the benefit of antenatal IPT in preventing incident tuberculosis in women living with HIV with CD_4 counts ≤ 350 cells/mm^3, as well as encouraging safety data, leading to a change in the previously recommended CD_4 count criteria. In the Adult Hospital HIV Chapter (2017 – 2019) and the Primary Healthcare HIV Chapter (2020), it was recommended that pregnant women living with HIV and with a CD_4 count cells/mm^3 < 350 receive 12 months of IPT, while in those with CD_4 counts ≥ 350 cells/mm^3, IPT be deferred till after delivery (see Appendix 1 Textbox 1). (8)

Currently, in high tuberculosis incidence settings, the World Health Organisation (WHO) recommends 36 months of IPT in PLWHIV with unknown or positive TST, irrespective of CD_4 count, history of previous treatment for tuberculosis or pregnancy (conditional recommendation, low quality evidence).(9) This recommendation is based on data from non-pregnant population.

In February 2023, the South African Tuberculosis programme released national guidelines for the treatment of tuberculosis infection, recommending 12 months of IPT for all HIV positive pregnant women, irrespective of CD_4 count. Additionally in these programmatic guidelines, in HIV negative pregnant women, with a history of close contact with a person with active tuberculosis disease, a 3-month treatment regimen consisting of isoniazid and rifampicin is recommended. (10) A CD4 count-based risk stratified approach was assessed by the NDoH TB program as not feasible to implement. Therefore NEMLC and the NDoH TB program jointly decided in March 2024 to defer TPT in all pregnant women with HIV (See Appendix 1 Textbox 2).

Local clinicians raised concerns about deferring TPT in pregnant women living with HIV (PWLHIV), particularly women with advanced HIV and a higher risk of incident TB. In August 2025, a debate on use of IPT in pregnancy was held at the SA HIV Clinicians Society Conference. A poll taken after the debate indicated strong support from clinicians for a CD4 count-guided approach to IPT initiation in pregnancy. The 2023 update of the Consolidated ART Guideline[1] clearly outlines a specific package of care for people with Advanced HIV Disease, defined as any client (including pregnant women) with a CD4 count < 200 cells/mm^3, or WHO Stage 3 or 4 clinical conditions. This comprehensive package of care now provides opportunity to reconsider a CD4 count risk stratification approach to IPT in PWLHIV, in line with the latest available evidence for benefit and harms. After collaborative engagement between the NDoH TB program, the HIV program and NEMLC, joint recommendation was made, as follows:

- PWLHIV with CD4 counts ≤ 200 cells/mm^3 and starting ART should receive 12 months of TPT after exclusion of active tuberculosis disease.
- In PWH with CD4 counts > 200 cells/mm3 and starting ART, TPT should be deferred to the post-partum period.

This document aims summarizes evidence for safety and efficacy of IPT to date, as well as programmatic implementation feasibility concerns to inform recommendations and decision-making.

2. Literature Search

A rapid review of the literature was conducted. PubMed was searched with the following search terms:

("isoniazid"[MeSH Terms] OR "isoniazid"[All Fields] OR "isoniazide"[All Fields]) AND ("prevention and control"[MeSH Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR ("preventive"[All Fields] AND "therapy"[All Fields]) OR "preventive therapy"[All Fields])

[1] NDoH. 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. Accessible online https://knowledgehub.health.gov.za/elibrary/2023-art-clinical-guidelines-management-hiv-adults-pregnancy-and-breastfeeding-adolescents

AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields] OR "pregnancies"[All Fields] OR "pregnancy s"[All Fields])

One hundred and thirty-two articles were identified in the initial search. Systematic reviews, randomized clinical trials, and observational studies with comparator groups, published in English, were eligible for inclusion. Furthermore, studies were required to compare isoniazid monotherapy in pregnant women to placebo/no treatment/delayed treatment, and report on safety (adverse pregnancy outcomes, infant outcomes, hepatotoxicity) and/or efficacy (tuberculosis disease and mortality), to be included.

In the screening stage, only 3 studies conducted in HIV-negative populations were identified. Two of these were single-arm retrospective cohort studies comparing outcomes to historical cohorts only, and were therefore not eligible for inclusion.(11, 12) The third study conducted in HIV-negative women examined pregnancy outcomes in women who became pregnant in RCT's that compared weekly rifapentine-isoniazid (3-HP) to IPT, or self-administered 3-HP to directly observed 3-HP. In this study, rates of fetal loss in IPT and 3-HP exposed pregnancies were compared to each other, and overall, to a historical American cohort.(11) This study was also not considered for further inclusion.

Therefore, after screening of the titles and abstracts, 8 studies were identified, none of which were conducted in pregnant women without HIV.

The relevant studies identified for inclusion are summarized in table 1.

Table 1.

	Study Name/Author	Study Type	Name of Publication	Year of Publication
1.	Hamada et al.	Systematic Review	The safety of isoniazid tuberculosis preventive treatment in pregnant and postpartum women: systematic review and meta-analysis(13)	2020
2.	Gupta et al. (TB-APPRISE)	Randomized Controlled Trial	Isoniazid Preventive Therapy in HIV-Infected Pregnant and Postpartum Women(1)	2019
2.1	Theron et al. (TB-APPRISE)	Randomized Controlled Trial	Individual and Composite Adverse Pregnancy Outcomes in a Randomized Trial on Isoniazid Preventative Therapy Among Women Living with Human Immunodeficiency Virus(14)	2020
2.2	Cherkos et al. (TB-APPRISE)	Randomized Controlled Trial	Effect of pregnancy versus postpartum maternal isoniazid preventive therapy on infant growth in HIV-exposed uninfected infants: a post-hoc analysis of the TB APPRISE trial(15)	2023
3.	Taylor et al.	Prospective cohort study nested in randomized controlled trial.	Pregnancy Outcomes in HIV-Infected Women Receiving Long-Term Isoniazid Prophylaxis for Tuberculosis and Antiretroviral Therapy(16)	2013
4.	Gupta et al. (BRIEF-TB)	Prospective cohort study nested in randomized controlled trial.	Adverse Pregnancy Outcomes Among Women with Human Immunodeficiency Virus Taking Isoniazid Preventive Therapy During the First Trimester(17)	2023
5.	Salazar-Austin et al. (TSHEPISO)	Prospective cohort study	Isoniazid Preventive Therapy and Pregnancy Outcomes in Women Living with Human Immunodeficiency Virus in the Tshepiso Cohort (18)	2020
6.	Kalk et al.	Retrospective cohort study	Safety and Effectiveness of Isoniazid Preventive Therapy in Pregnant Women Living with Human Immunodeficiency Virus on Antiretroviral Therapy: An Observational Study Using Linked Population Data(8)	2020

3. Evidence Summary

3.1 TB-APPRISE(1, 14, 15)

TB-APPRISE was a multicenter, double-blind, placebo controlled non-inferiority trial that enrolled pregnant women living with HIV between 14 – 34 weeks' gestation. All women were enrolled from high tuberculosis prevalence countries, defined as ≥ 60 cases per 100 000. However, only 20% of participants were enrolled from South Africa, which has twice the tuberculosis prevalence than some of the other countries of enrollment. Women were randomized to receive either IPT immediately for 28 weeks followed by placebo, or placebo immediately followed by IPT initiated from 12-weeks post-partum. Women with a recent exposure to a close contact with active tuberculosis, and therefore at higher risk of progression to tuberculosis disease, were excluded.

A total of 956 women were enrolled in the study with 477 randomized to the immediate IPT group and 479 to the deferred IPT group. The median CD_4 count was 493 cells/mm^3 and all but one of the participants were receiving HAART[2]. The HAART regimen included efavirenz in 85.1% of all participants and 63.1% of participants had an undetectable HIV viral load at enrollment. Thirty percent of the enrolled study participants had positive IGRA results indicative of latent tuberculosis infection.

A relatively high attrition rate was reported with 171 women (17.9%) discontinuing the trial prematurely, 88 in the immediate IPT group and 83 in the deferred IPT group. No significant difference in patient-reported adherence or by assessment of pill count were noted between the immediate and deferred groups.

Approximately, one third of participants were exposed to IPT or placebo from the second trimester into the third trimester. The remaining two thirds of participants were exposed to IPT or placebo in third trimester only.

The primary outcome was a composite safety outcome of maternal adverse events of grade 3 or higher that were possibly, probably, or related to isoniazid or placebo or permanent discontinuation of the trial due to toxic effects. The primary outcome event occurred at an incidence rate of 15.03 events per 100 person-years in the immediate IPT group as compared to 14.93 events per 100 person-years in the deferred group (rate difference 0.10; 95% CI -4.77 to 4.98). The predefined noninferiority criterion was met for the primary outcome event.

In terms of efficacy, only 6 cases of incident tuberculosis were reported throughout the trial, 3 cases in each arm. As a result, no significant difference in incident tuberculosis between the immediate IPT and the deferred group was reported (incidence rate: 0.60 vs. 0.59 per 100 person-years; rate difference 0.01; 95% CI -0.94 to 0.96). Six deaths occurred during the trial, 2 in the immediate IPT group and 4 in the deferred group. A large proportion of the deaths occurred due to liver failure (66.67%). No significant difference in mortality rate between the immediate IPT group and the deferred group was reported (incidence rate 0.40 vs. 0.78 per 100 person-years; rate difference -0.39; 95% CI -1.33 to 0.5).

Of the 956 women enrolled in the study, 926 women had pregnancy outcome data. The composite adverse pregnancy outcome included stillbirth (fetal death ≥ 20 weeks' gestation), spontaneous abortion (pregnancy loss <20 weeks' gestation), low birth weight (<2500 g), preterm delivery (delivery < 37 weeks' gestation), or major congenital anomalies in an infant. The composite adverse pregnancy outcome occurred more frequently in the immediate IPT group as compared to the deferred group (23.6% vs. 17.0%; risk difference 6.7 percentage points; 95% CI 0.8 to 11.9; p = 0.01). Individually, the outcomes of stillbirth, spontaneous abortion, and low birth weight infant occurred more frequently in the immediate IPT group than in the deferred group, but the between group differences failed to reach statistical significance.

Theron et al. conducted a secondary analysis of the pregnancy outcome data from 925 mother-infant pairs[3] from the TB-APPRISE study.(14) Important covariates adjusted for in the multivariable logistic regression models included maternal age at delivery, CD_4 quartile, suppressed HIV viral load, timing of ART initiation, HBsAg status,

[2] HAART refers to treatment regimens consisting of three or more antiretroviral drugs.

[3] 926 women with pregnancy outcome and excluding 1 induced abortion. Therefore, 925 women who had at least 1 live birth or fetal demise were analysed.

maternal mid upper arm circumference (MUAC), IGRA status, noninfectious pregnancy complications, infectious pregnancy complications, twin versus singleton pregnancy, current smoking status, and hospitalization.

The study reported that the adjusted odds of a composite of fetal demise, preterm delivery, low birth weight infant or congenital anomaly were 1.63 times higher among women randomized to immediate IPT arm (23.6% vs. 17.0%; aOR 1.63; 95% CI 1.15 to 2.31; p = 0.007; NNTH 16) (refer Table 2). Immediate IPT was also associated with increase odds of composite adverse outcomes that included neonatal death (composite 2) and early neonatal death (composite 3). When examining the individual components of the composite outcomes, no association was detected between IPT study arm and perinatal mortality or preterm delivery. However, after adjusting for other covariates, immediate IPT was associated with a 58% increase in the odds of a low-birth-weight infant (14.4% vs. 10.3%; aOR 1.58; 95% CI 1.02 to 2.46; p = 0.041; NNTH 25).

Table 2. Summary of Composite Adverse Pregnancy Outcomes by Treatment Group and Adjusted Odds Ratio Estimates from Theron et al.

Outcome	Immediate INH, n/N (%)	Deferred INH, n/N (%)	Unadjusted OR (95% CI), by study arm	Adjusted OR (95% CI), by study arm
Composite 1: fetal demise, PTD, LBW, or congenital anomaly	106/449 (23.6)	78/460 (17.0)	1.51 (1.09–2.10)	1.63 (1.15–2.31)
Composite 2: fetal demise, PTD, LBW, or neonatal death (<28 days)	105/450 (23.3)	78/459 (17.0)	1.48 (1.07–2.06)	1.62 (1.14–2.30)
Composite 3: fetal demise, PTD, LBW, or early neonatal death (<7 days)	105/450 (23.3)	73/459 (15.9)	1.61 (1.15–2.24)	1.74 (1.22–2.49)
Perinatal death 1: fetal demise or neonatal death	23/459 (5.0)	20/466 (4.3)	1.18 (.64–2.17)	1.32 (.69–2.53)
Perinatal death 2: fetal demise or early neonatal death	21/459 (4.6)	13/466 (2.8)	1.67 (.83–3.38)	1.84 (.87–3.85)
LBW: <2500 grams at birth	62/430 (14.4)	46/446 (10.3)	1.46 (.97–2.20)	1.58 (1.02–2.46)
PTD: <37 weeks gestation at delivery	48/442 (10.9)	40/458 (8.7)	1.27 (.82–1.98)	1.35 (.85–2.15)

Multivariable model for composite outcomes by study arm.

Abbreviations: CI, confidence interval; LBW, low birth weight; OR, odds ratio; PTD, preterm delivery.

Cherkos et al. conducted a post hoc analysis of data from the TB APPRISE RCT, analyzing only 898 HIV-exposed but uninfected live born babies with at least one follow-up after birth.(15) After adjusting for maternal BMI, maternal age, HAART regimen, HIV viral load, CD_4 count, level of education, and household food security, they reported that infants born to mothers randomized to the immediate IPT arm had a 1.60 times greater risk of low birth weight than infants born to mothers in the deferred IPT arm (aRR 1.60; 95% CI 1.07 to 2.41). No significant association between treatment arm and preterm birth (aRR 1.31; 95% CI 0.87 to 1.97) or small-for-gestational-age was reported (aRR 0.97; 95% CI 0.71 to 1.32). Additionally, infants born to mothers randomized to immediate IPT experienced a 47% increased risk of becoming underweight in the first 12 weeks of life (aHR 1.47; 95% CI 1.06 to 2.03), and a 34% increased risk of becoming underweight in the first 48 weeks of life (aHR 1.34; 95% CI 1.01 to 1.78). No association between IPT treatment arm and stunting or wasting was reported. These findings were particularly pronounced in male infants, suggesting modification of the effect of antenatal IPT by sex.

Pertinent results from all 3 publications arising from the TB-APPRISE RCT are summarized in Table 3 below.

Table 3. Summary of all publications arising from TB-APPRISE RCT

Efficacy(1)	Maternal Adverse Events(1)	Adverse pregnancy outcomes(1, 14)	Infant Growth(15)
INCIDENT TB: IG 0.60 vs. DG 0.59 Rate difference: 0.01 per 100 person-years (95% CI -0.94 to 0.96) **MORTALITY:** IG 0.40 vs. DG 0.78 Rate difference: -0.39 per 100 person-years (95% -1.33 to 0.56)	**≥ GRADE 3 AE OR AE LEADING TO TREATMENT DISCONTINUATION:** IG 15.03 vs. DG 14.93 Rate difference: 0.10 per 100 person-years (95% CI -4.77 to 4.98)	**STILLBIRTH, SPONT. ABORTION, LBW, PRETERM, CONGENTIAL ANOMALIES** IG 23.6% vs DG 17% Risk difference: 6.7 (95% CI 0.8 to 11.9) aOR 1.63 (95% CI 1.15 to 2.31)	**LBW:** aRR 1.60 (95% CI 1.07 to 2.41) **PRETERM:** aRR 1.31 (95% CI 0.87 to 1.97) **SGA:** aRR 0.97 (95% CI 0.71 to 1.32) **UNDERWEIGHT by 12 weeks:** aHR 1.47 (95% CI 1.06 to 2.03)

		STILLBIRTH, SPONT. ABORTION, LBW, PRETERM, NEONATAL DEATH (28 days): aOR 1.62 (95% CI 1.14 to 2.30) **STILLBIRTH, SPONT. ABORTION, LBW, PRETERM, NEONATAL DEATH (7 days):** aOR 1.74 (95% CI 1.22 to 2.49)	**UNDERWEIGHT by 48 weeks:** aHR 1.34 (95% CI 1.01 to 1.78)
IG – immediate group; DG – deferred group; SGA – small for gestational age; LBW – birth weight < 2.5kg; SGA –small for gestational age or weight < 10th percentile for gestational age; aOR – adjusted odds ratio; CI – confidence interval			

3.2. Taylor et al. (16)

Taylor et al. conducted a nested cohort study of women living with HIV who became pregnant while enrolled in a double-blind, randomized, placebo-controlled tuberculosis prevention trial. In the trial, conducted in Botswana, all participants received 6 months of IPT, after which they were randomized to either continue IPT or changed to placebo for a further 30 months. Women, not yet on HAART[4], who became pregnant during the trial with CD_4 counts of > 200 cells/mm^3 received zidovudine prophylaxis from 34 weeks' gestation. Whereas those who became pregnant CD_4 counts ≤ 200 cells/mm^3 were referred to initiate HAART.

One hundred and ninety-six pregnancies occurred during the trial, of which 103 pregnancies[5] were exposed to isoniazid (52.6%) and 93 were not. Almost all (99%) of IPT-exposed pregnancies were exposed from the first trimester, with only 68% of women having ongoing exposure throughout the pregnancy. Thirty seven percent of pregnant women received HAART during pregnancy, with the remainder receiving only zidovudine-based prophylaxis. The median CD_4 count at baseline for women who became pregnant during the trial was 368 cells/mm^3. Approximately 16% of the cohort had CD_4 counts below 200 cells/mm^3. No statistical comparison of the baseline characteristics of the pregnancies exposed to IPT compared to those unexposed was provided.

In this study, adverse pregnancy outcome was defined as preterm delivery (≤ 37 weeks' gestation), low birth weight (<2500g), stillbirth (delivery of an infant with no signs of life at ≥ 28 weeks' gestation), spontaneous abortion (spontaneous termination of pregnancy < 24 weeks' gestation), neonatal mortality (death of a term infant within 28 days of delivery), or any noted congenital abnormality. Isoniazid exposure during pregnancy was not associated with increased odds of an adverse pregnancy outcome (aOR 0.6; 95% CI 0.3 to 1.1), after adjusting for ART regimen, maternal CD_4 count, maternal age, and BMI. Furthermore, no maternal deaths, isoniazid-associated hepatitis or other severe isoniazid-associated events were reported in the 103 women who were exposed to IPT in pregnancy during the trial.

3.3. Gupta et al. (BRIEF-TB trial)(17)

BRIEF-TB was an open-label, randomized, non-inferiority trial, comparing a weight-based 1-month isoniazid plus rifapentine regimen (1HP) with the standard 9-month IPT for tuberculosis prevention among PLWHIV. The trial was conducted from 2012 to 2017, and enrolled participants from ten high tuberculosis prevalence countries[6] (including South Africa). All those who were randomized to receive IPT and became pregnant during the trial were analysed as part of the planned secondary analysis by Gupta et al. Pregnancies were classified as being unexposed[7] (n = 89) or exposed to IPT (possibly or definitely)(n = 39)[8]. Based on the study definition of exposure, all pregnancies exposed to IPT were conceived while taking IPT, with fewer women having ongoing exposure in the second and third trimesters. To note, although the data that informed this study was collected prospectively under trial conditions, which pregnancies were exposed or not exposed to IPT was not determined by randomization.

[4] HAART refers to treatment regimens consisting of three or more antiretroviral drugs.

[5] In 103 women

[6] High tuberculosis prevalence defined as ≥ 60 cases per 100 000 population.

[7] Pregnancies were classified as IPT unexposed if pregnancy outcome occurred > 45 weeks after the final isoniazid dose.

[8] Pregnancies were classified as definitely exposed to IPT if the positive pregnancy test, pregnancy outcome, or estimated date of conception based on gestational age at birth occurred on or before the date of last dose of isoniazid.

Once again a composite adverse pregnancy outcome of spontaneous abortion (fetal demise before 20 weeks' gestation), ectopic pregnancy, or stillbirth (fetal demise at or beyond 20 weeks' gestation) was defined. For live births, low birth weight (< 2500 g) and preterm delivery (delivery before 37 weeks gestational age) were outcomes of interest. Analyses were adjusted for maternal CD_4 count, ART use, hepatitis B surface antigen positivity, age, and latent tuberculosis infection. However, other important confounders associated with poor pregnancy outcomes such as maternal smoking status, BMI or obstetric history were not measured or adjusted for. The median CD_4 count for the cohort was 534 cells/$mm^{3.}$ Thirty eight percent of the IPT-exposed women were receiving HAART at enrolment, increasing to 79% by pregnancy outcome. Thirty four percent of the unexposed women were receiving HAART at enrolment, increasing to 96% at pregnancy outcome. The difference in proportion of women receiving HAART at pregnancy outcome by IPT exposure was statistically significant (79% vs. 96%; p = 0.007).

A total of 29 pregnancies ended in an adverse pregnancy outcome: 25 spontaneous abortions, 2 stillbirths and 2 ectopic pregnancies. The composite pregnancy outcome occurred in 33% of pregnancies exposed to IPT and 18% of pregnancies not exposed to IPT. Crudely, the proportion of spontaneous abortions and stillbirths was 2-fold higher in the pregnancies exposed to IPT as compared to those unexposed. When adjusted for baseline covariates mentioned previously, IPT exposure in pregnancy was associated with an almost 2-fold increased risk of the adverse composite outcome (aRR 1.90; 95% CI 1.01 to 3.54; p = 0.04)(Refer Table 4). In an analysis adjusted for the same covariates, but measured closest to the pregnancy outcome, the association was no longer statistically significant (aRR 1.45; 95% CI 0.75 to 2.80; p = 0.27). No association was reported between IPT exposure in pregnancy and low birth weight (RR 1.01; 95% CI 0.29 to 3.56) or preterm delivery (RR 0.87; 95% CI 0.32 to 2.42).

Table 4. Results from Regression Model of Relative Risk of Adverse Pregnancy Outcome by IPT exposure from Gupta et al. 2023.

	No./Total N (%)		Unadjusted		Adjusted for Covariates Measured at Enrollment		Adjusted for Covariates Measured at Pregnancy Outcome	
Outcome	IPT-exposed	Unexposed	RR (95% CI)	*P*	aRR (95% CI)	*P*	aRR (95% CI)	*P*
Composite adverse outcome[a] (excludes induced abortion as adverse outcome)								
Primary analysis (n = 128)	13/39 (33)	16/89 (18)	1.85 (.99, 3.47)	.05	1.90 (1.01, 3.54)	.04	1.45 (.75, 2.80)	.27
Restricted risk set analysis (n = 122[b])	13/36 (36)	16/86 (19)	1.94 (1.04, 3.61)	.04	1.98 (1.08, 3.65)	.03	1.52 (.83, 2.81)	.18
Extended composite adverse outcome (includes induced abortion as adverse outcome)	16/39 (41)	19/89 (21)	1.92 (1.11, 3.33)	.02	1.98 (1.15, 3.41)	.01	1.47 (.84, 2.55)	.18
Preterm delivery <37 wks gestational age (n = 68[c])	4/20 (20)	11/48 (23)	0.87 (.32, 2.42)	.80	…	…	…	…
Low birth weight <2500 g (n = 74[c])	3/22 (14)	7/52 (13)	1.01 (.29, 3.56)	.98	…	…	…	…

Models adjusted for maternal age, CD4 count, antiretroviral use and latent tuberculosis status.

Abbreviations: aRR, adjusted relative risk; CI, confidence interval; IPT, isoniazid prevention therapy; RR, relative risk.

[a]Any event resulting in a non-live birth, other than induced abortion; individual component outcomes were spontaneous abortion (<20 wks), stillbirth (≥20 wks), and ectopic pregnancy.

[b]Excluded six pregnancies that ended in induced abortion (3 in each exposure group).

[c]Assessed among live births for which data were available; adjusted analyses not undertaken because of small number of events.

3.4. Salazar- Austin et al. TSHEPISO Cohort(18)

Salazar-Austin et al. conducted a secondary analysis of data collected prospectively from a cohort of pregnant women living with HIV in Soweto (TSHEPISO cohort), between 2011 and 2014. The study enrolled pregnant women of at least 18 years of age living with HIV, and of at least 13 weeks' gestation. As part of the study, enrolled women who were investigated for and identified as having tuberculosis disease were subsequently matched to 2 pregnant women living with HIV but without tuberculosis. All pregnant women enrolled without tuberculosis disease were offered IPT. In this study, maternal, pregnancy, and infant outcomes among those women living with HIV without tuberculosis disease, who did or did not use IPT for tuberculosis prevention during pregnancy, were analyzed.

All outcomes assessed in the study were self-reported but confirmed using clinic and hospital records or the road-to-health-chart where available. A participant was considered exposed to IPT if she self-reported use of isoniazid for tuberculosis prevention for any duration while pregnant. A large proportion of the study was conducted during the

time when according to South African guidelines pregnant women were only eligible for efavirenz-based HAART if their CD_4 count was less than 350 cells/mm^3.

The study enrolled 155 women without tuberculosis disease, and 71 were considered IPT exposed (46%) and 84 (54%) unexposed. Pregnancy outcomes were available for 69 of the women exposed to IPT (97%) and 82 (98%) of women unexposed to IPT. Significantly less long-term outcome data, relating to tuberculosis disease and mortality, were available for women unexposed to IPT (76%), as compared to the IPT exposed group (92%), and only a complete case analysis was performed.

Baseline characteristics were similar between the two groups. The CD_4 count at enrollment for the IPT exposed participants was 373 cells/mm^3 compared to 364 cells/mm^3 in the unexposed group. Approximately 26.49% of the cohort received zidovudine with or without single dose nevirapine at delivery for prevention of mother to child transmission. In the unexposed group, 87% were receiving HAART at delivery, compared to only 65% of the IPT exposed group (although this difference was not statistically significantly). As a result, only 39% of the IPT exposed group were virally suppressed, as compared to 55% of the unexposed group, prior to delivery. Almost all participants initiated IPT in the second or third trimester, with only 2 participants reporting initiation in the first trimester. No participants were taking IPT at the time of conception.

In this study the composite adverse pregnancy outcome consisted of fetal demise (spontaneous abortion < 28 weeks or stillbirth ≥ 28 weeks gestational age), low birth weight (< 2500g), prematurity (<37 weeks) and/or major congenital abnormality). Crudely, this outcome occurred less frequently in the IPT-exposed pregnancies, but the difference was not statistically significant (IPT exposed 16% vs. unexposed 28%; p = 0.08). The absolute increase in the composite adverse pregnancy outcome in the unexposed group was driven by preterm delivery (IPT exposed 10% vs. unexposed 22%, p = 0.06).

There was no difference in the composite outcome consisting of maternal, fetal, or infant death, or tuberculosis disease occurring within 1 year of delivery between those exposed to IPT and those unexposed (IPT exposed 3% vs. unexposed 4%; p = 1.0). In the adjusted logistic regression, women unexposed to IPT had 2.5-fold greater odds of having an adverse pregnancy outcome after controlling for CD_4 count at baseline, ARV regimen, HIV viral load, maternal age, BMI, and anemia (aOR 2.5; 95% CI 1.0 to 6.5; p = 0.048).

In this non-randomized study, it is possible that women who opted to take IPT were healthier with better health-seeking behavior than those who declined IPT, impacting on the association of IPT with decreased adverse pregnancy outcomes. This is illustrated by the greater proportion of missing outcome events for the unexposed group, and the larger number of participants in the unexposed group qualifying for HAART at the time. Additional, important confounders of adverse pregnancy outcomes such as maternal smoking status, alcohol use, and obstetric history and risk factors were not measured or adjusted for. Additionally, the self-reported measure of exposure to IPT does not exclude participants prescribed IPT, who did not take the treatment, contributing to misclassification bias.

3.5 Kalk et al.

Kalk et al. conducted a large retrospective cohort study in the Western Cape, using routine electronic health data from the public sector. The cohort comprised 43 971 pregnant women living with HIV who initiated ART during or prior to a pregnancy between 1 January 2015 and 31 December 2017. The objective of the study was to analyze differences in tuberculosis incidence, mortality, and pregnancy outcomes between those women who received IPT during pregnancy and those who did not, over 12 months of post pregnancy outcome follow-up. At the time, South African guidelines recommended 12 months of IPT for all PLWHIV regardless of CD_4 count and including pregnant women. Additionally, all pregnant women living with HIV were eligible for HAART.

IPT was dispensed during pregnancy in 16.6% of the cohort. The median CD_4 count for the cohort was 422, with only 9.7% of the cohort having CD_4 counts <200. At antenatal presentation, there were noteworthy and statistically significant differences in the characteristics of women by antenatal IPT exposure. More women exposed to antenatal IPT group were receiving HAART prior to falling pregnant (77.9% vs 71.6%; p < 0.001). A larger proportion of women exposed to antenatal IPT group had CD_4 counts greater than 500 cells/mm^3 compared to those who were not exposed to IPT (29.1% vs 26.7%). Similarly, a greater proportion of the antenatal IPT exposed group were virologically

suppressed (63.9% vs. 56.1%; p < 0.001). A history of previous tuberculosis disease was also less common in the IPT exposed women (10.6% vs. 13.0%; p < 0.001). These differences may indicate that the cohort that received IPT antenatally was more clinically stable, healthier, or at lower risk of tuberculosis disease than those who did not.

Tuberculosis developed in 1 002 (2.3%) women across the cohort. Only 1% of the women that received antenatal IPT developed tuberculosis, compared to 2.5% of the women who did not receive IPT (Risk difference -1 518 cases per 100 000; 95% CI -1 799 to -1 238 per 100 000). Furthermore, antenatal IPT was associated with a 29% reduction in risk of tuberculosis (aHR 0.71; 95% CI 0.63 to 0.81) after adjusting for maternal age, CD_4 count, history of tuberculosis disease, HIV viral load, and duration of HAART prior to delivery. When stratified by CD_4 count, the benefit of IPT in terms of reduction in incident tuberculosis was greatest in those with $CD_4 \leq 350$ cells/mm^3 (aHR 0.51; 95% CI 0.41 to 0.63), with no reduction in risk of tuberculosis in those with $CD_4 > 350$ cells/mm^3 (aHR 0.93; 95% CI 0.76 to 1.13). Additionally, the reduction in tuberculosis risk persisted even when IPT was started after 14 weeks gestation compared to no IPT (aHR 0.63; 95% CI 0.54 to 0.74). In 75.7% of those that developed tuberculosis during the study, the diagnosis occurred close to the time of the pregnancy outcome or soon thereafter, with 35.6% occurring within 3 months following the pregnancy outcome. After adjustment for covariates listed previously, IPT was not associated with a reduction in maternal mortality (aHR 0.75; 95% CI 0.46 to 1.22) but was associated with severe liver injury (aHR 1.51; 95% CI 1.18 to 1.93).

In the study, the composite adverse pregnancy outcome included miscarriage (loss of products of conception before 27 weeks' gestation), stillbirth (delivery of a fetus with no signs of life after 27 completed weeks' gestation), neonatal death (death of an infant within 28 days of birth), or low birth weight (< 2500 g). Antenatal IPT exposure was associated with a 17% reduction in the odds of adverse pregnancy outcome in the adjusted analysis (aOR 0.83; 95% CI 0.78 to 0.87). The mechanism of this protective effect is postulated to be related to the reduction in tuberculosis disease. However, other important confounders of adverse pregnancy outcomes, such as maternal BMI, smoking status, alcohol use and obstetric history were not adjusted for. When components of the composite outcome were examined individually, stillbirth (aOR 0.80; 95% CI 0.63 to 1.00) and miscarriage (aOR 0.83; 95% CI 0.68 to 1.00) appeared to be largely responsible for the effect.

When analyzed by timing of IPT exposure in pregnancy, IPT exposure starting after 14 weeks gestation was associated with reduced adverse pregnancy outcomes as compared to no IPT exposure (refer Table 5). This effect was driven largely by the reduction in miscarriage, with much smaller reductions in low birth weight and stillbirth.

Table 5. Multivariable analysis for individual pregnancy outcomes by timing of IPT exposure in pregnancy from Kalk et al.

	aOR (95% CI) IPT < 14 weeks versus none	aOR (95% CI) IPT > 14 weeks versus none	aOR (95% CI) IPT < 14weeks versus IPT > 14weeks (<14weeks=ref)
Poor outcome composite	1.04 (0.94 – 1.16)	0.71 (0.65 – 0.79)	0.64 (0.55 – 0.75)
Misc	1.39 (1.11 – 1.75)	0.33 (0.22 – 0.48)	0.21 (0.13 – 0.35)
SB	0.97 (0.68 – 1.37)	0.71 (0.53 – 0.94)	0.73 (0.44 – 1.19)
NND	1.16 (0.76 – 1.77)	0.83 (0.56 – 1.21)	0.84 (0.45 – 1.56)
LBW (livebirths)	1.10 (0.97 – 1.18)	0.90 (0.83 – 0.98)	0.91 (0.79 – 1.04)

IPT – INH preventive therapy; LBW – Low birth weight < 2500g; Misc – miscarriage; NND – neonatal death; SB – stillbirth

Adjusted for maternal age, first recorded pregnancy, ART prior to pregnancy, history of TB disease, CD category, VL suppression category, booking and/or delivery in primary care.

IPT exposure from after 14 weeks of gestation compared to IPT exposure prior 14 weeks gestation was also associated with a reduction in odds of an adverse pregnancy outcome (aOR 0.64; 95% CI 0.55 to 0.75). Again, this reduction in adverse outcome was driven by the reduction in miscarriage (refer Table 5). However, although the study defined any loss before 27 weeks as a miscarriage, risk of miscarriage decreases significantly with advancing gestation. (19) Therefore, survival bias is introduced in the cohort of women exposed to IPT after 14 weeks of gestation. For any women to be classified as IPT exposed after 14 weeks gestation, the pregnancy must have been viable and survived

until 14 weeks gestation. These pregnancies would have therefore, already passed the period of greatest risk, explaining the apparent reduction in miscarriage events reported when compared to no IPT or IPT initiated prior to 14 weeks.

In those exposed to IPT prior to 14 weeks gestation compared to no IPT exposure, no significant difference in the composite adverse pregnancy outcome were reported (aOR 1.04; 95% CI 0.94 to 1.16)(refer Table 3). However, examination of the individual components of the composite outcome, reveal a statistically significantly increased odds of miscarriage associated with first trimester exposure to IPT (aOR 1.39; 95% CI 1.11 to 1.75).

3.6. Hamada et al.

Hamada et al. conducted a systematic review and meta-analysis of the safety of IPT in pregnancy. Randomized and non-randomized studies of pregnant or postpartum women, regardless of HIV status, where the intervention was preventive treatment with daily isoniazid alone for 6 months or longer, and the comparator was another preventive treatment regimen or no preventive treatment (including deferred provision until postpartum in the comparison group) were included. Additionally, to be included, studies needed to have reported on the following outcomes: permanent drug discontinuation due to adverse drug reaction; grade 3 or grade 4 drug related toxic effects; death from any cause; hepatotoxicity; in utero fetal death; neonatal death; preterm delivery/prematurity; intrauterine growth restriction; low birth weight or congenital anomalies. In the systematic review, randomized and non-randomized studies, including those without a comparator group were eligible for inclusion.

The systematic review was assessed as "low quality", using the AMSTAR 2 appraisal tool as the description of the included studies did not contain adequate detail (e.g. duration of follow up), as sources of funding for studies included in the review were not reported, and as they did not provide a list of excluded studies (although the reasons for exclusion were described).

Databases were searched from inception until 15 May 2019. Nine studies were included after full text review(1, 11, 12, 16, 18, 20-23), of which only 1 study was a randomized controlled trial.(1) This RCT was assessed to have some concern for bias due to missing outcome data, and is previously summarized in section 3.1. The outcomes from this RCT relating to infant growth emerged after this systematic review was conducted, and were not included in this analysis. (15)

Of the 8 non-randomized studies included, three had no control/comparator arm and did not contribute to any of the pooled analyses.(12, 21, 23) Another 2 non-randomized studies conducted comparisons between IPT and other preventive regimens, rather than placebo/no treatment/deferred treatment, and are not summarized further here. (11, 20). The three remaining non-randomized studies were considered to be at serious risk of bias, specifically related to confounding.(8, 16, 18) These three studies are summarized in sections 3.2, 3.4 and 3.5 above. Notably, the data included in the systematic review from the study by Kalk et al. was derived from the analysis of the same cohort data published in 2020, but from a conference abstract presented in 2018.(8, 22) Furthermore, the analysis of the BRIEF-TB trial is not included in this systematic review as it was published in 2023. (17)

Due to significant heterogeneity between study types, data from the RCT and non-randomized studies could not be pooled for the outcome hepatotoxicity. Similarly, for maternal death, the RCT by Gupta et al. and pooled analysis of 2 non-randomized studies by Kalk et al. and Salazar-Austin et al. are reported separately and indicated no association with IPT use in pregnancy (Refer Table 6).

Table 6. Summary of evidence regarding IPT use in pregnant women living with HIV with GRADE assessment by Hamada et al.[9]

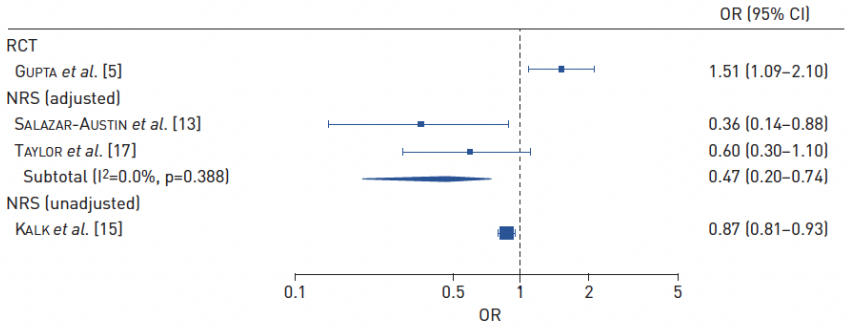
[9] The table contains a correction of an error detected in the review process and confirmed with the primary author of the systematic review.

Outcomes	Studies	Anticipated absolute effects (95% CI)[¶¶]		Relative effect (95% CI)	Participants	Certainty of the evidence (GRADE)
		Risk with no IPT or a placebo	Risk with IPT			
Composite pregnancy outcomes (low birth weight, preterm delivery, spontaneous abortion, stillbirth, or congenital anomaly	One RCT: Gupta *et al.* [5]	170 per 1000	236 per 1000 (182 300)	OR 1.51 (1.09 2.10)	909	⊕⊕⊕◯ (Moderate)[#]
Composite pregnancy outcomes (low birth weight, preterm delivery, spontaneous abortion, stillbirth, neonatal mortality, or congenital anomaly)	Two observational studies: Salazar Austin *et al.* [13] Taylor *et al.* [17]	360 per 1000	209 per 1000 (101 294)	OR 0.471 (0.199 0.742)	347	⊕◯◯◯ (Very low)[#,¶]
Maternal death	One RCT: Gupta *et al.* [5]	6 per 1000	2 per 1000 (0 20)	Risk ratio 0.33 (0.03 3.21)	956	⊕⊕◯◯ (Low)[+]
Maternal death	Two observational studies: Salazar Austin *et al.* [13] Kalk et al. [15]	3 per 1000	2 per 1000 (1 3)	Risk ratio 0.65 (0.39 1.07)	52097	⊕⊕◯◯ (Low)[¶]
Grade 3 or 4 AEs related to study treatment	One RCT: Gupta *et al.* [5]	46 per 1000	71 per 1000 (42 120)	Risk ratio 1.55 (0.92 2.61)	956	⊕⊕⊕◯ (Moderate)[#]
Hepatotoxicity	One RCT: Gupta *et al.* [5]	23 per 1000	38 per 1000 (18 79)	Risk ratio 1.64 (0.78 3.44)	956	⊕⊕⊕◯ (Moderate)[#,§]
Hepatotoxicity	One observational study: Kalk *et al.* [15]	3 per 1000	3 per 1000 (2 4)	Risk ratio 1.01 (0.68 1.51)	58242	⊕⊕◯◯ (Low)[f,##]
Discontinuation of study drug due to toxicity	One RCT: Gupta *et al.* [5]	17 per 1000	23 per 1000 (9 57)	Risk ratio 1.38 (0.56 3.40)	956	⊕⊕⊕◯ (Moderate)[§]

CI: confidence interval; RCT: randomised controlled trial; OR: odds ratio; AE: adverse event. [#]: optimal information size was not met; [¶]: bias due to confounding was considered serious (important confounders were not fully accounted for); [+]: large CI, including both appreciable benefits and harms, and very few events; [§]: CI included both appreciable benefits and harms; [f]: confounding was not accounted for and bias due to measurement of hepatotoxicity was considered serious (since liver function tests were performed only if clinically indicated, which was likely to be influenced by knowledge of the receipt of IPT); [##]: very large sample size and CI of absolute effect was very narrow; [¶¶]: the risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

The results for adverse pregnancy outcomes were inconsistent across the included studies. Once again, due to significant heterogeneity, data from the RCT could not be pooled with the non-randomized studies. However, the adjusted estimates from the studies by Taylor et al. and Salazar-Austin et al. were pooled, and suggested that IPT use in pregnancy is associated with a reduction in adverse pregnancy outcomes (OR 0.47; 95% CI 0.20 to 0.74).(16, 18) The estimates from the study by Kalk et al. were unadjusted and could not be pooled with the other non-randomized studies, but suggested the same direction of effect (Refer figure 1 and table 6).

Figure 1. Forest plot for composite adverse pregnancy outcomes in pregnant women with HIV by IPT exposure from Hamada et al.



A summary of evidence for the safety of IPT use in pregnant women with HIV is presented in Table 6 with accompanying GRADE certainty of evidence assessment.

4 Summary of Evidence

Important differences in study design, population and tuberculosis prevalence between the studies discussed are summarized in Table 7. Key points to note from the evidence

- There is a signal of increased spontaneous miscarriage after first trimester exposure to IPT, compared to no exposure in pregnant women living with HIV on HAART, with relatively high CD_4 counts, in some observational studies. (8, 17)

- In an RCT, there was an association between IPT exposure in second and third trimester and low birth weight (<2500g), that may continue to impact infant growth at week 12 and week 48 of life in pregnant women living with HIV on HAART and with relatively high CD_4 counts.(1, 14, 15)
- In an RCT of women living with HIV on ART, with high CD_4 counts, and without recent close contact to an active tuberculosis case, the risk of developing tuberculosis is similar when IPT is given antenatally versus delayed to 12 weeks post-partum.(1)
- In observational data from a high TB prevalence setting, there is a reduction in incident tuberculosis disease in pregnant women on ART with CD_4 counts ≤ 350 cells/mm^3 who received IPT during pregnancy, but not for those with CD4 counts >350 cells//mm^3. (8)
- Antenatal IPT did not reduce in maternal mortality in the RCT or observational studies.(1, 8, 18)
- Risk of IPT-associated hepatotoxicity may be higher during pregnancy and the postpartum period than in non-pregnant woman (1).
- The reduction in tuberculosis disease seen with antenatal IPT use in women with low CD_4 counts may be an explanation for the better pregnancy outcomes seen in observational studies. None of the observational studies were adjusted for important confounders of adverse pregnancy outcomes. (8, 16, 18)
- All the above data were from women living with HIV, and the majority of those on ART were on efavirenz containing regimens.
- We found no comparative data exploring benefits and risks of IPT in HIV-negative pregnant women.

5. Feasibility considerations

5.1 Deliberations with the NDoH TB program in March 2024

Following engagement with the NDoH program guideline team and other stakeholders on the 7th March 2024, the following matters were raised for local consideration:

- The TB program team raised concerns with the complexity of multiple guidance for pregnant women at various CD4 counts initiating ART and for pregnant women already established on ART.
    - Especially considering the number of pregnant women starting ART below various CD4 thresholds has not yet been determined.
    - A simplified recommendation applicable to all pregnant patients with HIV would be preferred for ease of implementation.
- It was noted that the evidence of benefit in terms of reduction of TB disease was demonstrated in low-quality observational data from South Africa. But that there was no difference in reduction of TB disease between antenatal IPT and IPT deferred to the postpartum period in data from an RCT. However, it was highlighted that the median CD4 from this RCT was 500, which is much higher than what is observed locally
- The strong signals of harm highlighted by the review were noted.

In light of the above, the group proposed that the following recommendation be considered by NEMLC:

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

This recommendation was adopted by NEMLC in November 2024.

5.2 Deliberations with the NDoH TB program in October 2025

In 2023 the NDoH HIV Programme updated the Consolidated ART Guideline10 to clearly outline a specific package of care for people with Advanced HIV Disease (AHD), defined as any client (including pregnant women) with a CD4 count < 200 cells/mm3, or WHO Stage 3 or 4 clinical conditions. This package contains several elements, including:

- systematic TB screening and investigation, and IPT if TB is excluded,

[10] NDoH. 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. Accessible online https://knowledgehub.health.gov.za/elibrary/2023-art-clinical-guidelines-management-hiv-adults-pregnancy-and-breastfeeding-adolescents

- screening for cryptococcal antigenaemia,
- screening and management of serious bacterial infections,
- CPT prophylaxis,
- ART,
- Adherence support, and
- Intensified follow-up.

Pregnant women with CD4<200 cells/mm^3 are also eligible for this package of care for advanced HIV disease. As this package includes IPT, this provides an opportunity to reconsider CD4 count-based stratification to inform the administration of IPT in pregnancy, aligned with the AHD definition (i.e., CD4 < 200). This would allow the benefit of IPT for PWH at higher risk of TB, while minimising the programmatic complexity as the intervention will be nested within the newly established AHD programme, rather than a stand-alone intervention.

The TB programme have therefore suggested revisiting inclusion of a CD4 cut off, but used the AHD definition i.e. CD4<200 to guide initiation of IPT, so that IPT is administered to PWLWHA as part of the AHD package of care.

Table 7. Summary of important differences between studies reviewed.

Study Author, Study Type	N	% on HAART on entry into study	Median CD4 (cells/mm^3)	% Viral Load Suppressed	% on efavirenz based HAART	% participants confirmed with latent TB infection	TB Prevalence by Geographic Location of enrolment	% participants initiated on IPT by trimester	Effect
Gupta et al. Randomized controlled trial	956	100%	493	62.83%	85.1%	30% positive IGRA	Zimbabwe: 33.37% (344 per 100 000) (24) South Africa: 19% (681 per 100 000)(8) Uganda 17.36% (401 per 100 000)(24) Botswana: 12.55% (305 per 100 000)(25)	No 1st trimester IPT initiation. IPT initiation between 14 – 24 weeks: 33.6% IPT initiation >24 weeks: 66.4%	Increased adverse pregnancy outcome, specifically low birth weight, after second/third trimester exposure. Increased risk of underweight for infant exposed antenatally.
Kalk et al. Retrospective cohort study	43 971	76.8%	422 CD_4 < 200: 9.7%	57.4%	Not reported	Not reported.	South Africa: 100% (681 per 100 000)(8)	IPT initiation < 14 weeks: 36.2% IPT initiation ≥ 14 weeks: 63.8%	Decreased adverse pregnancy outcomes. IPT < 14 weeks associated with increased miscarriage compared to no IPT.
Taylor et al. Nested prospective cohort study	196	(Pre-universal ART) 37%	368 CD_4< 200: 16%	Not reported	Not reported	Not reported.	Botswana: 100% (305 per 100 000)(25)	1st trimester IPT initiation: 99%	No association.
Gupta et al. 2023 Nested prospective cohort study	128	(Pre-universal ART) 35%	534	Not reported	64% in IPT exposed group at pregnancy outcome 87% in unexposed group at pregnancy outcome.	20% positive TST (but testing limited by shortage of reagents)	South Africa: 28.12% (681 per 100 000)(8) Botswana: 26.56% (305 per 100 000)(25) Haiti: 18.75% (254 per 100 000)(26) Kenya: 10.16% (558 per 100 000)(24)	1st trimester IPT initiation: 100% (All IPT exposed pregnancies were conceived while taking isoniazid.)	Increased adverse pregnancy outcomes, specifically miscarriage, after first trimester exposure.
Salazar Austin et al. Prospective cohort study	155	71.52% on HAART	364 - 373 (No IPT vs. IPT)	47.68%	60.26 %	Not reported.	South Africa: 100% (681 per 100 000)(8)	1st trimester IPT initiation: 3% 2nd trimester IPT initiation: 48% 3rd trimester IPT initiation: 49%	Decreased adverse pregnancy outcomes.

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

ERC Recommendation 13 November 2025: We recommend that pregnant women living with HIV, with:

- CD_4 counts ≤ 200 cells/mm^3 and starting ART, receive 12 months of IPT after exclusion of active tuberculosis disease.
- CD_4 counts > 200 cells/mm^3 and starting ART, IPT should be deferred to the post-partum period.

Rationale: The benefit of IPT in preventing tuberculosis disease at CD4 counts ≤ 350 cells/m^3(low certainty evidence) outweighs the increased risk of adverse pregnancy outcomes. However, in pregnant women with higher CD_4 counts, the increased risk of miscarriage after first trimester IPT exposure (low certainty evidence) and increased risk of low birth weight and underweight for age after second trimester IPT exposure (moderate certainty evidence) outweighs any potential benefit (moderate certainty evidence). However, a CD4 cut off of 350 was not deemed programmatically feasible. The current programmatic "package of care" for patients with advanced HIV (CD4< 200), for which pregnant women are eligible, includes IPT. The ERC therefore suggests administering 12 months of IPT for all pregnant women with newly diagnosed HIV with a CD4< 200, co-initiated with ART, after screening for active TB, as part of the AHD package of care

Level of Evidence:

Risk of adverse pregnancy outcomes after first trimester exposure (low certainty evidence from observational studies and cohort studies nested in randomised controlled trials)

Risk of adverse pregnancy outcomes after second trimester exposure (moderate certainty evidence from a randomized controlled trial)

Evidence of benefit at CD_4 ≤ 350 cells/mm^3 (low certainty evidence from an observational study)

Review indicator: New high quality evidence of benefit or harm.

NEMLC RECOMMENDATION (MEETING 27 November 2025): NEMLC supports the ERC recommendation as detailed above (dated 13 Nov 2025).

Monitoring and evaluation considerations, and research priorities:

Pregnant women should be routinely screened for TB at every antenatal visit.

Strenthening of pharmacovigilance systems, with implementaiton of measures for identifying signals of drug-related harm in pregnant women.

References

1. Gupta A, Montepiedra G, Aaron L, Theron G, McCarthy K, Bradford S, et al. Isoniazid Preventive Therapy in HIV-Infected Pregnant and Postpartum Women. N Engl J Med. 2019;381(14):1333-46. 10.1056/NEJMoa1813060.
2. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database of Systematic Reviews. 2010(1). 10.1002/14651858.CD000171.pub3. https://doi.org//10.1002/14651858.CD000171.pub3.
3. Rangaka MX, Wilkinson RJ, Boulle A, Glynn JR, Fielding K, van Cutsem G, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. Lancet. 2014;384(9944):682-90. 10.1016/s0140-6736(14)60162-8.
4. Black A, Dawood H. NEMLC. Adult Hospital level Medication Review Process. Isoniazid Preventive Therapy. . 2018.
5. Badje A, Moh R, Gabillard D, Guéhi C, Kabran M, Ntakpé JB, et al. Effect of isoniazid preventive therapy on risk of death in west African, HIV-infected adults with high CD4 cell counts: long-term follow-up of the Temprano ANRS 12136 trial. Lancet Glob Health. 2017;5(11):e1080-e9. 10.1016/s2214-109x(17)30372-8.
6. South African National Department Of Health. Standard Treatment Guidelines and Essential Medicines List for South Africa. Primary Health Care Level 2014.
7. Hakim J, Musiime V, Szubert AJ, Mallewa J, Siika A, Agutu C, et al. Enhanced Prophylaxis plus Antiretroviral Therapy for Advanced HIV Infection in Africa. New England Journal of Medicine. 2017;377(3):233-45. 10.1056/NEJMoa1615822. https://www.nejm.org/doi/full/10.1056/NEJMoa1615822.
8. Kalk E, Heekes A, Mehta U, de Waal R, Jacob N, Cohen K, et al. Safety and Effectiveness of Isoniazid Preventive Therapy in Pregnant Women Living with Human Immunodeficiency Virus on Antiretroviral Therapy: An Observational Study Using Linked Population Data. Clin Infect Dis. 2020;71(8):e351-e8. 10.1093/cid/ciz1224.
9. WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment: Module 1: prevention. WHO Guidelines Approved by the Guidelines Review Committee. Geneva2020.
10. South African National Department of Health. National Guidelines on the Treatment of Tuberculosis Infection. 2023. https://knowledgehub.health.gov.za/elibrary/national-guidelines-treatment-tuberculosis-infection.
11. Moro RN, Scott NA, Vernon A, Tepper NK, Goldberg SV, Schwartzman K, et al. Exposure to Latent Tuberculosis Treatment during Pregnancy. The PREVENT TB and the iAdhere Trials. Ann Am Thorac Soc. 2018;15(5):570-80. 10.1513/AnnalsATS.201704-326OC. https://www.ncbi.nlm.nih.gov/pubmed/29393655.
12. Franks AL, Binkin NJ, Snider DE , Rokaw WM, Becker S. Isoniazid hepatitis among pregnant and postpartum Hispanic patients. Public Health Rep. 1989;104(2):151-5.
13. Hamada Y., Figueroa C., Martín-Sánchez M., Falzon D., Kanchar A. The safety of isoniazid tuberculosis preventive treatment in pregnant and postpartum women: systematic review and meta-analysis. Eur Respir J. 2020;55(3). 10.1183/13993003.01967-2019.
14. Theron G., Montepiedra G., Aaron L., McCarthy K., Chakhtoura N., Jean-Philippe P., et al. Individual and Composite Adverse Pregnancy Outcomes in a Randomized Trial on Isoniazid Preventative Therapy Among Women Living With Human Immunodeficiency Virus. Clin Infect Dis. 2021;72(11):e784-e90. 10.1093/cid/ciaa1482.
15. Cherkos A. S., LaCourse S. M., Enquobahrie D. A., Richardson B. A., Bradford S., Montepiedra G., et al. Effect of pregnancy versus postpartum maternal isoniazid preventive therapy on infant growth in HIV-exposed uninfected infants: a post-hoc analysis of the TB APPRISE trial. EClinicalMedicine. 2023;58:101912. 10.1016/j.eclinm.2023.101912. https://www.ncbi.nlm.nih.gov/pubmed/36969345.
16. Taylor AW, Mosimaneotsile B, Mathebula U, Mathoma A, Moathlodi R, Theebetsile I, et al. Pregnancy Outcomes in HIV-Infected Women Receiving Long-Term Isoniazid Prophylaxis for Tuberculosis and Antiretroviral Therapy. Infectious Diseases in Obstetrics and Gynecology. 2013;2013:195637. 10.1155/2013/195637. https://doi.org/10.1155/2013/195637.
17. Gupta A., Hughes M. D., Cruz J. L., Avihingsanon A., Mwelase N., Severe P., et al. Adverse Pregnancy Outcomes among HIV-infected Women Taking Isoniazid Preventive Therapy During the First Trimester. Clin Infect Dis. 2023. 10.1093/cid/ciad583. https://www.ncbi.nlm.nih.gov/pubmed/37768207.
18. Salazar-Austin N, Cohn S, Lala S, Waja Z, Dooley KE, Hoffmann CJ, et al. Isoniazid Preventive Therapy and Pregnancy Outcomes in Women Living With Human Immunodeficiency Virus in the Tshepiso Cohort. Clin Infect Dis. 2020;71(6):1419-26. 10.1093/cid/ciz1024.
19. Tong S, Kaur A, Walker SP, Bryant V, Onwude JL, Permezel M. Miscarriage risk for asymptomatic women after a normal first-trimester prenatal visit. Obstet Gynecol. 2008;111(3):710-4. 10.1097/AOG.0b013e318163747c.
20. Singh P, Moulton LH, Barnes GL, Gupta A, Msandiwa R, Chaisson RE, et al. Pregnancy in Women With HIV in a Tuberculosis Preventive Therapy Trial. J Acquir Immune Defic Syndr. 2022;91(4):397-402. 10.1097/QAI.0000000000003078. https://www.ncbi.nlm.nih.gov/pubmed/36000934.
21. Tiam A, Machekano R, Gounder CR, Maama-Maime LB, Ntene-Sealiete K, Sahu M, et al. Preventing tuberculosis among HIV-infected pregnant women in Lesotho: the case for rolling out active case finding and isoniazid preventive therapy. J Acquir Immune Defic Syndr. 2014;67(1):e5-e11. 10.1097/qai.0000000000000209.
22. Kalk EK, Heekes A, Mehta U. Programmatic review of safety and effectiveness of isoniazid preventive therapy in HIV infected pregnant women on ART in routine care. Reproductive Toxicology. 2018; 80: 155.

23. Chang AH, Polesky A, Bhatia G. House calls by community health workers and public health nurses to improve adherence to isoniazid monotherapy for latent tuberculosis infection: a retrospective study. BMC Public Health. 2013;13(1):894. 10.1186/1471-2458-13-894. https://doi.org/10.1186/1471-2458-13-894.

24. Law I, Floyd K, The African TB Prevalence Survey Group. National tuberculosis prevalence surveys in Africa, 2008–2016: an overview of results and lessons learned. Tropical Medicine & International Health. 2020;25(11):1308-27. https://doi.org/10.1111/tmi.13485. https://onlinelibrary.wiley.com/doi/abs/10.1111/tmi.13485.
25. Tembo BP, Malangu NG. Prevalence and factors associated with multidrug/rifampicin resistant tuberculosis among suspected drug resistant tuberculosis patients in Botswana. BMC Infectious Diseases. 2019;19(1):779. 10.1186/s12879-019-4375-7. https://doi.org/10.1186/s12879-019-4375-7.
26. Delva GJ, Francois I, Claassen CW, Dorestan D, Bastien B, Medina-Moreno S, et al. Active Tuberculosis Case Finding in Port-au-Prince, Haiti: Experiences, Results, and Implications for Tuberculosis Control Programs. Tuberc Res Treat. 2016;2016:8020745. 10.1155/2016/8020745.

APPENDIX 1: HISTORIC ERC/NEMLC RECOMMENDATIONS

Textbox 1: ERC/NEMLC Recommendation (2017-2019 review cycle)

NEMLC Recommendation: *IPT deferral if CD4 ≥350 in pregnant women; whilst where CD4<350, active TB to be excluded with symptom screen and then IPT given.*

Rationale:

A RCT of immediate versus delayed IPT initiation in pregnant woman found that isoniazid exposure in pregnancy was associated with increased risk of adverse pregnancy outcome (fetal demise, low birth weight, preterm delivery and congenital anomaly). Isoniazid should therefore be deferred until after delivery, except in women who are severely immunocompromised and have low CD4s. Subsequently, a local retrospective cohort study[31] (n= 43 971) showed that antenatal IPT is safe with greatest benefit against active TB when CD4 ≤350 cells/mm3.

Level of Evidence: II Cohort Study

Textbox 2: ERC/NEMLC Recommendation (2020-2024 review cycle)

Multi stakeholder engagement meeting recommendation- 7 March 2024:

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

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

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

ERC Recommendation: Mar 2024

The ERC recommends that pregnant women living with HIV, with:

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

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

Level of Evidence:

Risk of adverse pregnancy outcomes after first trimester exposure (low certainty evidence from observational studies and cohort studies nested in randomised controlled trials)

Risk of adverse pregnancy outcomes after second trimester exposure (moderate certainty evidence from a randomized controlled trial)

Evidence of benefit at CD_4 ≤ 350 cells/mm^3 (low certainty evidence from an observational study)

Review indicator: New high quality evidence of benefit or harm.

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