CHAPTER 10
HIV AND AIDS

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

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. Previously a non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz or nevirapine, together with two NRTIs, were recommended for first-line ART. Dolutegravir is better tolerated than the NNRTIs and has a much higher barrier to the development of resistance.

Dolutegravir, together with two NRTIs, is also recommended in second-line ART after failing an NNRTI-based first-line regimen. Previously a protease inhibitor (PI), together with two NRTIs, was recommended for second-line ART, but dolutegravir is better tolerated than PIs. Switching people established on ART to the newer dolutegravir-based ART regimens needs to be carefully done to reduce the risk of the emergence of resistance (refer to National Department of Health HIV Guidelines).

ELIGIBILITY FOR ART

Eligibility to start ART:

All adults with confirmed HIV infection, irrespective of CD4 count or WHO clinical stage.

LoE: Ia[i]

Immediate initiation:

ART should be initiated immediately in pregnancy and during breastfeeding.

LoE:IIa[ii]

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, which does not increase the risk of mortality and reduces the risk of deterioration due to IRIS.

LoE:Ia[iii]

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

LoE:IIIa[iv]

» 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[v]

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

LoE:IVb[vi]

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. Give 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[vii]

ART REGIMENS

1ST LINE ART	
Treatment-naïve patients	Men and women ≥35kg: TDF + 3TC + DTG *LoE:IIa*[viii] **Note***:* DTG-based regimens are now recommended as first line ART in all women of childbearing potential. *LoE:IIa*[ix] Patients with TB: TDF + FTC + EFV Alternative if EFV not available: TDF + 3TC + DTG *plus* additional dose of DTG 50mg 12 hours later. *LoE:IIIb*[x]

	(Also see section 6.7: 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*[xi] **Note:** if patient requires rifampicin-based TB treatment, substitute ATV/r for LPV/r to 800/200 mg 12-hourly. The LPV/r can be switched to ATV two weeks after completion of TB therapy.
Contraindication to TDF » eGFR <50 mL/minute.	Replace TDF + 3TC/FTC with either ABC + 3TC (preferred) **or** AZT + 3TC *LoE:IIIb*[xii]
Contraindication to TDF and ABC intolerance » eGFR <50 mL/minute. » Use of additional nephrotoxic agent e.g. aminoglycoside. » Hypersensitivity.	AZT + 3TC with DTG **or** EFV
Note: In the unlikely scenario where there is intolerance/contraindication to all currently available NRTIs, an alternative dual-therapy regimen may be used, e.g. DTG + 3TC (if no resistance/intolerance to 3TC and VL <500 000 copies/mL) **or** EFV + LPV/r **or** DTG + LPV/r may be used. Consult a specialist. *LoE:IIb*[xiii]	
2ND LINE ART	
Management of viraemia on 1st line ART	If plasma VL between 50–999 copies/mL: » Address adherence, tolerability, medicine interactions & psychosocial factors. » Repeat VL test 3 months later. If plasma VL ≥ 1000 copies/mL: » Assess adherence, tolerability, medicine interactions & psychosocial factors. Repeat VL test 3 months later If plasma VL 50-999 copies/mL: » Continue enhanced adherence support. » Repeat VL test 6 months later. If plasma VL remains at 50-999 copies/mL i.e. persistent low grade viraemia: » Manage as virological failure below.

Management of virological failure on 1st line ART **Note:** Always check hepatitis B surface antigen (HBsAg) before stopping TDF*:* » If patient has chronic hepatitis B, stopping TDF may lead to a fatal hepatitis flare. » If HBsAg positive, TDF should be continued in the 2nd line regimen.	Indications for changes to 2nd line therapy and the 2nd line regimens are different for NNRTI-based and DTG-based 1st line regimens.
Failing a NNRTI-based 1st line regimen *(TDF+3TC/FTC+EFV/NVP)*	<u>If plasma VL confirmed ≥1000 copies/mL (on 2 tests), and adherence issues addressed:</u> Change regimen to 2nd line therapy TDF + 3TC + DTG. *LoE:IIb*[xiv] <u>If DTG contraindicated/ not tolerated and ***not*** on rifampicin-based TB treatment:</u> TDF + 3TC/FTC + ATV/r *LoE:IIb*[xv] <u>If TDF contraindicated/not tolerated:</u> AZT + 3TC + DTG <u>If AZT and TDF contraindicated/ not tolerated (e.g. anaemia and renal impairment):</u> ABC + 3TC + DTG
Failing a DTG- based 1st line regimen for >2 years *(TDF+3TC+DTG)* » Resistance testing for adults and adolescents failing a DTG-based regimen and who meet the definition of confirmed virological failure may be authorized by an expert on a case-by-case basis.	<u>If plasma VL confirmed ≥1000 copies/mL for >2 years:</u> TDF + 3TC/FTC +ATV/r <u>If HBsAg positive:</u> ensure patient is on TDF-containing regimen. *LoE:IIb*[xvi]
Rifampicin-based TB treatment	<u>If on DTG:</u> Add DTG 50 mg - DTG needs to be given at a dose of 50 mg 12 hourly. *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.
3RD LINE ART	
Failing any 2nd line regimen	Refer to a specialist.

	Resistance to ATV/r or LPV/r and/or DTG must be shown on genotype antiretroviral resistance test in order to qualify for 3rd line – this test is expensive and should only be done in patients with at least 2 years exposure to a PI and objective evidence of good adherence. Application for 3rd line using the standard motivation form is required (available from TLART@health.gov.za or from https://www.righttocare.org/) – the regimen will be determined by an Expert Committee based on the pattern of resistant mutations and the prior history of antiretroviral exposure.

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

Table 10.1: ART regimens

Currently available ARV FDC preparations on contract:

- ABC 600 mg + 3TC 300 mg
- TDF 300 mg + FTC 200 mg
- AZT 300 mg + 3TC 150 mg
- LPV 100 mg + ritonavir 25 mg
- LPV 200 mg + ritonavir 50 mg
- TDF 300 mg + FTC 200 mg + EFV 600 mg
- TDF 300mg + DTG 50 mg + 3TC 300 mg
- ATV 300mg + ritonavir 100mg
- ABC 600mg + 3TC 300mg + DTG 50mg

Source: Contract circular HP13-2022ARV http://www.health.gov.za/

RE-INITIATING ART IN PATIENTS WHO HAVE INTERRUPTED TREATMENT

» Recommence previous regimen.
» Do VL, recommence ART regimen, repeat at 3-6 months.
» If VL does not to decrease to <1000 copies per mL at 6 months, manage virological failure according to the specific regiment (refer to ART regimens table).

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 (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 10-50 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 30-50 mL/min: 200 mg every 2 days eGFR 15-29 mL/min: 200 mg every 3 days eGFR <15 mL/min: 200 mg every 4 days	» Palmar hyperpigmentation. » Anaemia due to pure red cell aplasia (rare). *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.
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	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, diarrhea (common) » Hepatitis (uncommon) » Increase in serum creatinine 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.

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]

Table 10.2: Dosing and important adverse effects associated with ART

ART: DRUG-DRUG INTERACTIONS

Information can be accessed from:

» https://www.hiv-druginteractionslite.org/checker
» http://www.mic.uct.ac.za/ and download the ARV/EML interaction checker.
» Package inserts.

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 due to inhibition by isoniazid)	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.*
	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 aluminum-containing preparations should be taken 6 hours before or 2 hours after DTG. Calcium- and iron- containing preparations can be taken with DTG together with food. **Note:** Iron and calcium should be taken at least 4 hours apart from one another.
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	Significant increase in metformin levels	Administer metformin to a maximum of 500 mg 12 hourly.
Rifampicin	Significant reduction in concentration of DTG	Double DTG dose to 50 mg 12 hourly.

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	
At HIV Diagnosis	» Confirm HIV positive result with antibody test. » WHO staging. » Check CD4 count. – CD4 <100 cells/mm^3: Check cryptococcal antigen (If positive, perform LP regardless of whether symptoms are present or not). – CD4 <200 cells/mm^3: *LoE:IVb*[xxvi] Initiate cotrimoxazole prophylaxis. » 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). If positive, investigate for TB with a sputum Xpert MTB/RIF Ultra ®. Also do urine LAM if severely ill or CD4 ≤100 cells/mm^3 » In pregnancy do sputum XpertMTB/RIF Ultra® in all. *LoE:IIb*[xxvii]
Prior to initiating ART	» If planning to use TDF: check creatinine (avoid TDF if eGFR <50 mL/minute). » If planning to use AZT: check FBC (avoid AZT if Hb <8 g/dl). *LoE:IIIb*[xxviii] » Check HBsAg (if positive, TDF should form part of the regimen).
On ART	» VL at 6 and 12 months after initiating ART and every 12 months thereafter, if virologically suppressed. » CD4 at 12 months after initiating ART. Stop CD4 count monitoring when >200 cells/mm^3 and virologically suppressed. If virological or clinical failure occurs, 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 3, 6 and 12 months after initiation, and every 12 months thereafter. » If on AZT: FBC and differential count at 3 and 6 months after initiating AZT, then every 12 months. » ALT if symptoms of hepatitis develop. » If on a protease inhibitor (PI): Fasting cholesterol and triglycerides at 3 months after initiating PI.

Table 10.6: Monitoring on ART

10.1.1 MANAGEMENT OF SELECTED ANTIRETROVIRAL ADVERSE DRUG REACTIONS

E78.4/K71.9 + (Y41.5 + B24)

Dyslipidaemia E78.4 + (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 who:
» develop triglycerides >10 mmol/L;or
» have a total cholesterol >6 mmol/L with a high risk (>20% risk of developing a CVD event in 10 years)
» should switch to ATV/r and repeat the fasting lipids in three months.

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 section3.1: 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
AZT causes macrocytosis and can cause anaemia and neutropenia (but 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
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: Management of

selected antiretroviral adverse drug reactions) – 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, 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
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
» abdominal pain
» malaise
» liver dysfunction (due to steatosis)
» vomiting
» weight loss
» tachycardia

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

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

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

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

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 to in HIV-infected patients include anti-tuberculous therapy, fluconazole and cotrimoxazole. Cotrimoxazole, amoxicllin/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. Furthermore, life threatening flares may occur when antiretrovirals that are also active against hepatitis B (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 if ALT >5 x upper limit of normal (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.
- 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 (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 not requiring discontinuation of therapy.

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

TB immune reconstitution inflammatory syndrome (TB-IRIS) should be considered in the differential diagnosis (see section 10.1.2: Management of selected antiretroviral adverse drug reactions). 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 and initiate background TB therapy and continue throughout rechallenge:

- Linezolid, oral 600 mg daily (amikacin, IV/IM, 15 mg/kg daily is an alternative, but only for short term use).
- Moxifloxacin, oral, 400 mg daily or levofloxacin 750–1000 mg daily.
- Ethambutol, oral, 800–1200 mg daily.

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

Day 1:	• Rifampicin, oral 600 mg daily. o 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. 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. o 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 10.1.

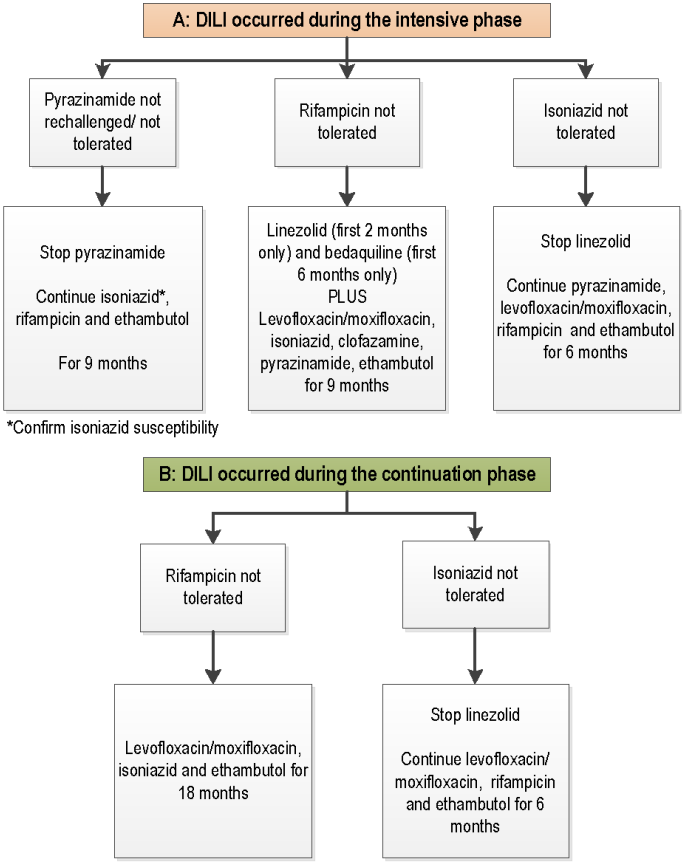


Figure 10.1: Management of TB if drug rechallenge unsuccessful

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, which has an unusual inflammatory presentation ("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 needs to be excluded.

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

Counseling 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, 1 g 4–6 hourly when required.
  - Maximum dose: 15 mg/kg/dose.
  - Maximum daily dose: 4 g in 24 hours.

OR

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

Treating 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.

Preventing paradoxical TB IRIS in high risk patients (CD4 ≤100 cells/mm^3) and 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)

Patients with HIV infection are more susceptible to TB infection than HIV-uninfected patients at any CD4 count. 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:
- » TB must be excluded prior to initiating TPT by screening for the following:
  - Cough (any duration)
  - Fever
  - Weight loss
  - Night sweats
- » TPT should not be initiated in patients if any of the above is present. These patients require further investigation for active TB.

Ideally start TPT together with ARVs:
- TPT, e.g.:
- Isoniazid, oral, 300 mg daily for 12 months. *LoE:IIb*[xxxii]

Note: Ideally start TPT together with ARVs. However, if a rifapentine-containing TPT regimen is available, it should only be initiated together with an EFV-based ART regimen. A rifapentine-containing TPT regimen can be used with a DTG-based ART regimen in patients who are already virally suppressed. Do not use in patients on protease inhibitor-based ART, or in women on oral or 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 12 months.
  - Educate patients on the symptoms of hepatotoxicity (nausea, vomiting, yellow eyes, brown urine, and pain in right upper quadrant).
  - Instruct patient to present early if any of these symptoms arise.
  - Patients should be followed up monthly for the first 3 months.

In pregnant women, starting ART:

» If CD4 >350 cells/mm^3. • Defer TPT until after delivery.	» If CD4 ≤350 cells/mm^3. • Exclude active TB with symptom screen and TB Xpert MTB/RIF Ultra ®, then give TPT. *LoE:IIIa*[xxxiv]

10.2.2 OPPURTUNISTIC INFECTION PROPHYLAXIS, WITH COTRIMOXAZOLE

Z29.2 + (B24)

DESCRIPTION

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

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

Indications for primary prophylaxis: *LoE:IIa*[xxxv]

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

MEDICINE TREATMENT

Prophylaxis

- Cotrimoxazole, oral, 160/800 daily. *LoE:IIa*[xxxvi]

Note:

Once the CD4 >200 cells/mm^3 (as measured at the routine CD4 count done at 1 year on ART), discontinue prophylaxis. 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

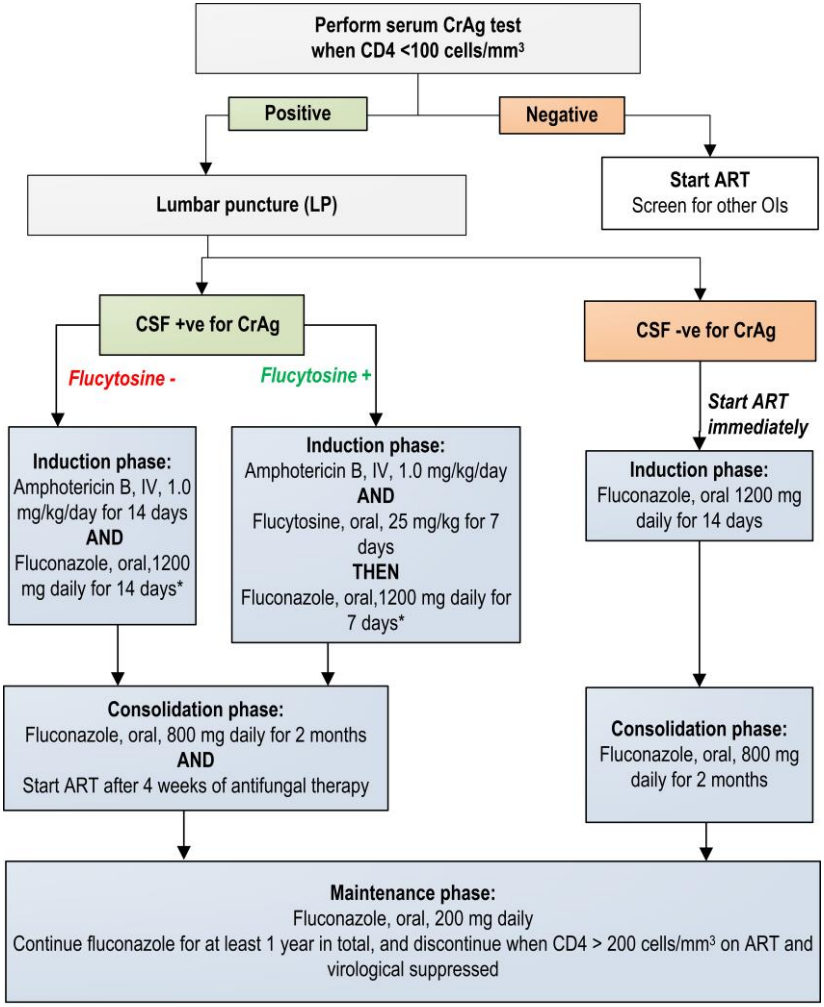
Maintain adequate hydration.

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 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



Note: If there is a delay in performing LP, obtaining LP results or in starting amphotericin B therapy, start fluconazole 1200 mg immediately.

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

10.2.4.1 CRYPTOCOCCOSIS, CSF CRAG NEGATIVE

B20.5

DESCRIPTION

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

LoE:IIa[xxxviii]

MEDICINE TREATMENT

If cryptococcal meningitis is excluded by negative CSF CrAg:

Induction phase

- Fluconazole, oral 1200 mg daily for 14 days.

Consolidation phase

Follow with:

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

Maintenance phase

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

LoE:IIIb[xxxix]

- Commence ART after completion of the induction phase (at 2 weeks after starting antifungal therapy). See section 10.1: Antiretroviral therapy.

LoE:IIIa[xl]

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. Even for higher doses, the benefits will likely outweigh the risks, 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.

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

MEDICINE TREATMENT

Induction phase

If flucytosine is available:

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

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

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

LoE:IIa[xliii]

AND

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

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

- Fluconazole, oral 1200mg daily for 7 days.

LoE:IVb[xliv]

If flucytosine is not available:

- Fluconazole, oral 1200 mg daily for 14 days.

AND

LoE:IIa[xlv]

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

Consolidation phase
Follow with:
- Fluconazole, oral, 800 mg daily for 8 weeks.

LoE:IIIa[xlvi]

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

LoE:Ia[xlvii]

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

LoE:IIIa[xlviii]

Note: Adjunctive corticosteroids have been shown to be detrimental.

LoE:Ia[xlix]

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
B20.8 + (A07.2)

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.

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

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.

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.

OR

If allergic to cotrimoxazole:

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

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.

AND *LoE:IIIa*[I]

- 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

All patients:

- Cotrimoxazole 80/400 mg, oral, 6 hourly for 21 days.
  - <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.
  - <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 this 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/5ml. 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 10.8: 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.

OR

If primaquine is not available, consider:

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

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.

Alternatively, in case of intolerance to cotrimoxazole:

- Dapsone, oral, 100 mg daily.

REFERRAL/CONSULTATION

Specialist or tertiary

Intolerance to second line regimen.

10.2.10 CEREBRAL TOXOPLASMOSIS

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, oral, 2 tablets 12 hourly for 28 days, followed by 1 tablet 12 hourly for 3 months.

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.

See cotrimoxazole desensitisation: Page 10.23.

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

B23.8 + (N28.9)

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; if this is >0.15 g/mmol discuss with a specialist).
- Serum creatinine and eGFR.

Dose adjustment of ART in renal impairment: Refer to table: Dosing of ART for renal adjusted doses 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 if chemotherapy is considered. 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, oral, 300 mg daily for 4 weeks (provided baseline eGFR is >50 mL/minute).

and

- Lamivudine, oral, 300 mg daily for 4 weeks

and

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

If DTG is not tolerated:

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

and

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

and *LoE:IIIb[ii]*

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

Or

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

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

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

and

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

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

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.

Table 10.9: PEP for healthcare worker following occupational HIV exposure:

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** • 3-drug regimen

When the source patient is known to be failing ART, modify the PEP regimen:
» If the patient is on zidovudine, use tenofovir.
» If the patient is on tenofovir, use zidovudine.

Table 10.10: PEP for healthcare workers following hepatitis B exposure

	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)

* 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[iii]

Table 10.11: Investigations and monitoring in occupational exposures

	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		

*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

LoE:IVb[iv]

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 10.4.1 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, counseling 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[iv]

OR

- Levonorgestrel 1.5 mg, oral, as a single dose as soon as possible after

- unprotected intercourse, and not later than 5 days. *LoE:Ia*[lvi]
  - 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.

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[lvii]

An anti-emetic:

- Metoclopramide oral, 10 mg 8 hourly as needed.

LoE:IVb[lviii]

STI prophylaxis

- Ceftriaxone, IM, 250 mg as a single dose.
  - 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.

AND

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

LoE:IIIb[lix]

HIV PrEP

If patient is at ongoing high risk of HIV acquisition, commence PrEP after PEP has been completed.
Perfom HIV test 4-weeks after initiating PrEP.
See PHC STGs and EML, section 11.11: Pre-exposure prophylaxis (PrEP).

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[lx]

10.5.3 NON OCCUPATIONAL POST EXPOSURE PROPHYLAXIS, INADVERTENT NON-OCCUPATIONAL

Z29.8

Management of inadvertent (non-occupational) HIV exposure is the same as for occupational HIV exposure. See section 10.4.1 Post-exposure prophylaxis, occupational.

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SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 10: HIV AND AIDS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2020 -2023 REVIEW CYCLE)

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG).
All reviews may be accessed at: https://www.knowledgehub.org.za/elibrary/hospital-level-adult-medicine-reviews-2020-2023
All costing reports may be accessed at: https://www.knowledgehub.org.za/elibrary/hospital-level-adult-costing-reports-2020-2023

MEDICINE AMENDMENTS:

SECTION	MEDICINE	ADDED/DELETED/AMENDED/NOT ADDED/RETAINED
10.1 Antiretroviral therapy, adults - *Clinical indications for deferring ART initiation* *- Asymptomatic cryptococcal infection*	ART	Directions amended
10.1 Antiretroviral therapy, adults (1st line) *- Treatment-naïve patients without TB*	TDF+3TC+DTG	Amended indication - expanded to ALL women
	TAF	Not added
10.1 Antiretroviral therapy, adults (1st line) *- Treatment-naïve patients with TB*	Double-dosed DTG (TLD + DTG 50 mg)	Indication expanded to DTG-naïve patients initiating ART with concomitant rifampicin-containing TB therapy
	TDF +EFV+FTC	Retained
10.1 Antiretroviral therapy, adults (1st line) *- Contraindication to TDF*	ABC + 3TC	Amended as preferred treatment
10.1 Antiretroviral therapy, adults (2nd line) *- Recycling TDF in 2nd-line regimens*	TDF	Added
	AZT	Deleted
10.1 Antiretroviral therapy, adults (2nd line) *- Protease inhibitors (PI)*	LPV/r	Retained
	ATV/r	Indication expanded to preferred 2nd line PI
	DRV/r	Not added to the STG, but included in therapeutic interchange database (patients not on TB-rifampicin therapy)
10.1 Antiretroviral therapy, adults (3rd line)	Resistance testing	Retained, and emphasised
10.1 Antiretroviral therapy, adults (2nd line) *- Failing a NNRTI-based 1st line regimen + HbsAg positive*	AZT + 3TC + DTG plus TDF	Deleted
10.1 Antiretroviral therapy, adults (2nd line) *- DTG contraindicated/not tolerated, not on rifampicin*	TDF + 3TC/FTC + ATV/r	Added
10.1 Antiretroviral therapy, adults (2nd line) *- TDF contraindicated/not tolerated, not on rifampicin*	AZT + 3TC + DTG	Added
10.1 Antiretroviral therapy, adults (2nd line) *- AZT and TDF contraindicated/not tolerated, not on rifampicin*	ABC + 3TC + DTG	Added
10.1 Antiretroviral therapy, adults (2nd line) *- Failing a DTG- based 1st line regimen for >2 years (TDF+3TC+DTG)*	AZT + 3TC/FTC + ATV/r	Deleted
	TDF + 3TC/FTC +ATV/r	Added
10.1 Antiretroviral therapy, adults (2nd line) *- Rifampicin-based TB treatment (on DTG-regimen)*	DTG	Added
10.1 Antiretroviral therapy, adults *- Currently available ARV FDC preparations on contract*	ATV/r	Added
	ABC + 3TC + DTG	Added
ART: Dosing and important adverse effects	Tenofovir, abacavir, lamivudine, emtricitabine, oral	Amended - very low risk, "Hyperlactataemia/ steatohepatitis" was deleted
	Dolutegravir, oral	Amended - weight-gain deleted
	Nevirapine, oral	Adverse effects and dosing information deleted
	Raltegravir, oral	Adverse effects and dosing information deleted
Monitoring on ART *- At HIV diagnosis: CrAg screening*	CrAg screening	Not amended
10.1.1 Management of selected antiretroviral adverse drug reactions *- drug-induced liver injury (DILI)*	Algorithm to manage DILI	Amended
10.2.1 Tuberculosis preventive therapy (TPT) *-Adult PLHIV initiated on ARVs*	TPT	Added as a therapeutic group
	Isoniazid (12H)	Retained as an example of class in the STG

	Rifapentine + isoniazid (3HP)	Added as a therapeutic alternative in the therapeutic interchange database
10.2.3 Candidiasis of oesophagus/trachea/bronchi	Fluconazole, oral	Directions for use amended
10.2.4 Cryptococcosis	Algorithm for the prevention, diagnosis and management of cryptococcosis among PLHIV	Amended
	ART (if CSF CrAg negative)	Directions for use amended (timing of initiation)
10.2.4.1 Cryptococcosis, CSF CrAg negative	ART	Directions amended
10.2.4.2 Cryptococcal meningitis	Flucytosine, oral	Added
	Amphotericin B	Retained
	Fluconazole, oral	Retained
	Liposomal amphotericin B	Not added
10.2.4.2 Symptomatic, non-meningeal cryptococcosis	Fluconazole, oral	Deleted
	Amphotericin B	Deleted
	ART	Deleted
10.2.6 Cytomegalovirus (CMV)	Ganciclovir, parenteral	Deleted
- maintenance treatment	Valganciclovir, oral	Retained
10.2.9 Pneumocystis pneumonia	Primaquine, oral	Directions for access, added
10.5.1 Post-exposure prophylaxis, occupational, *and*	LPV/r	Retain
	ATV/r	Expanded to include all patients - preferred 2nd line PI
	DRV/r	Not added to the STG, but included in therapeutic interchange database (not on TB-rifampicin therapy)
- PEP for healthcare workers following hepatitis B exposure	Hepatitis B Immunoglobulin	Amended
- Delay in obtaining HBsAb results	Time period of delay	Amended
10.5.2 Non occupational post exposure prophylaxis, sexual assault	LPV/r	Retain
	ATV/r	Expanded to include all patients - preferred 2nd line PI
	DRV/r	Not added to the STG, but included in therapeutic interchange database (not on TB-rifampicin therapy)
	HIV PrEP	Added as a cross reference to the PHC STGs and EML (PrEP section)
- Emergency contraception after pregnancy is excluded	Copper IUCD	Added (as first line option)
	Levonorgestrel, oral	Retained (as 2nd line option)
- Obese women	Levonorgestrel, oral	Dose not amended
10.5.3 Non occupational post exposure prophylaxis, inadvertent non-occupational	LPV/r	Retain
	ATV/r	Expanded to include all patients - preferred 2nd line PI
	DRV/r	Not added to the STG, but included in therapeutic interchange database (not on TB-rifampicin therapy)
- Emergency contraception after pregnancy is excluded	Copper IUCD	Added (as first line option)
	Levonorgestrel, oral	Retained (as 2nd line option)
- Obese women	Levonorgestrel, oral	Dose not amended

ABC= Abacavir, ART=antiretroviral therapy, ATV/r=Atazanavir/ritonavir, AZT=Zidovudine, 3TC= Lamivudine, CSF=cerebrospinal fluid; CrAg=cryptococcal antigen, DRV/r=Darunavir/ritonavir, DTG= Dolutegravir, EFV= Efavirenz FTC = Emtricitabine, IUCD=intrauterine copper device, LPV/r=Lopinavir/ritonavir, PrEP=pre-exposure prophylaxis, TAF=tenofovir alafenamide, TDF = Tenofovir disoproxil fumarate

10.1 ANTIRETROVIRAL THERAPY, ADULTS - CLINICAL INDICATIONS FOR DEFERRING ART INITIATION

- ***ASYMPTOMATIC CRYPTOCOCCAL INFECTION***

ART: *directions added*

In patients with positive cryptococcal antigen and no evidence for meningitis on LP, guidance provided in the STG to defer ART until 2 weeks after initiating fluconazole. Immediate ART initiation is not recommended among PLHIV who have cryptococcal meningitis because of the risk of increased mortality presumed to be caused by immune

reconstitution inflammatory syndrome in the central nervous system.[1] Thus, the STG recommends that ART be deferred 4–6 weeks from the initiation of antifungal treatment. The South African HIV Clinicians Society guideline[2] recommends that asymptomatic CrAg-positive patients who decline consent for a lumbar puncture or where lumbar punctures are contra-indicated to initiate ART after at least 2 weeks of antifungal treatment. For pragmatic purposes, deferral of ART for 2 weeks was retained for asymptomatic CrAg-positive patients with no evidence of meningitis on lumbar puncture.

The STG text was amended as follows:

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

Level of Evidence: Very low certainty, conditional recommendation

- ***TREATMENT-NAÏVE PATIENTS WITHOUT TB***

Tenofovir + lamivudine + dolutegravir, oral: *amended indication to include all women*
Indication expanded from "≥6 weeks gestation" to "ALL women".
Refer to the medicine review: Dolutegravir in pregnancy, 17 June 2021 v2:

DTG in pregnancy_PHC-Adult

Recommendation: The PHC/Adult Hospital Level Committee recommends that dolutegravir should be part of the preferred first line ART regimen for all adults and adolescents living with HIV, including pregnant women and women of child-bearing potential. The existing contra-indication in pregnancy should be removed from the STG *(strong recommendation)*

Rationale: The estimated risk of neural tube defects in infants exposed to dolutegravir in early pregnancy that was first identified in the Tsepamo observational study in Botswana has diminished over time, with the accumulation of further data. The risk difference between dolutegravir and efavirenz is no longer significant.

Dolutegravir (especially when combined with tenofovir alafenamide) is associated with more weight gain during pregnancy than efavirenz, but the difference is of uncertain clinical relevance.

Randomised controlled trials have shown non-inferiority in terms of maternal viral suppression rates at 48 weeks. Dolutegravir causes more rapid viral suppression than efavirenz, resulting in increased viral suppression rates by time of delivery in randomised controlled trials of ART initiation in the second and third trimester of pregnancy. This has not yet translated into a demonstrable difference in mother-to-child transmission risk, but event rates are very low with both regimens.

A standardised regimen for all adults and adolescents living with HIV is likely to be easier to provide.

Based on those findings and observations, the PHC/Adult Hospital Level Committee feel that the potential long-term benefits to pregnant women and WOCP (Women of Child Bearing Potential), as well as potential short-term benefits to their infants, outweigh the risks.

Level of Evidence: Moderate certainty of evidence
Review indicator: New evidence of harms

NEMLC MEETING OF 24 JUNE 2021:
NEMLC Recommendation: The NEMLC accepted the recommendation as proposed by the PHC/Adult Hospital Level Committee, which would support the universal test-and-treat (UTT) strategy of the National HIV Programme.
It was also duly noted that the South African Health Products Regulatory Authority were currently reviewing the label of dolutegravir products registered on the South African market.

Tenofovir alafenamide (TAF): *not added*
Refer to the updated medicine review, May 2022 (update of initial February 2020 review), noting that no new evidence was identified:

[1] 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.
[2] 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.


Tenofovir alafenamide for HIV_A

Recommendation: TAF not be considered for inclusion in the national Adult Hospital Level EML, currently *(strong recommendation).*

Note:

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

Rationale:

- The efficacy and safety of TAF-containing regimens vs. TDF-containing regimens have been mostly evaluated in the context of the coformulation of elvitegravir, cobicistat, emtricitabine and darunavir. There is insufficient data where it has been evaluated in standard formulations used in low-middle income countries (LMICs).
- The synthesis shows that TAF is no more effective than TDF. TAF overall, shows slightly lower toxicity in these studies especially with regard to renal and bone health markers – the clinical significance of these differences in markers is not clear. However, these findings should be interpreted cautiously as in most studies TAF was co-formulated with cobicistat, where the TAF dose is reduced from 25mg to 10mg. There is a need for trials comparing or evaluating efficacy and especially safety of TAF head for head in standard coformulations used in low middle-income countries.
- Emerging observational data suggests switching from TDF to TAF and may cause a statistically significant worsening of the lipid profile that may have clinical relevance. This is likely seen in patients with cardiovascular risk factors such as older age and high body mass index (BMI). The lower concentrations of TDF in plasma from TAF as compared with TDF, and the lipid-lowering effect of TDF may explain the increases in total cholesterol in the TAF group compared with the TDF group. It may be important to weigh the possible benefit of lipid changes associated with TDF against the possible benefit of TAF for bone and kidney.

Level of Evidence: Systematic Reviews and Meta-Analysis of Randomized Clinical Trials

Review indicator: New high quality evidence of a clinically relevant benefit

NEMLC MEETING OF 19 MARCH 2019:

NEMLC accepted this evidence review and the proposal as recommended by the Adult Hospital Level Expert Review Committee, above. NEMLC also acknowledged that TAF-containing fixed-dose combination formulations are currently not SAHPRA registered and thus not currently available on the South African market. The current antiretroviral recommendations, as recommended in the Standard Treatment Guidelines (Adult Hospital Level, 2019 edition) and National HIV Guidelines, 2019 edition are sufficient.

NEMLC MEETING OF 23 JUNE 2022:

NEMLC Discussion

- *Renal impairment:* It was noted that patients with renal impairment are generally referred to the tertiary level of care and TAF may be potentially advantageous for this cohort so there may be some consideration to limit access to tertiary centres
- *SAHPRA registration:* TAF is currently not registered locally.

NEMLC Recommendation: The NEMLC upheld the previous decision from 2019 which was not to recommend TAF for the inclusion on the national EML. However, TAF could be accessed by Provinces for individual patients on a named-patient basis. NEMLC also acknowledged that TAF-containing fixed-dose combination formulations are currently not SAHPRA registered.

- ***ART- TREATMENT-NAÏVE PATIENTS WITH TB***

Double-dosed dolutegravir (TLD + DTG 50 mg): *indication expanded to DTG-naïve patients initiating ART with concomitant rifampicin-containing TB therapy*

Tenofovir + Efavirenz + Emtricitabine (TEE): *retained*

Refer to the updated DTG in HIV-infected patients review with addendum, 21 July 2021 (second update of initial 26

January 2017 review):

DTG for HIV-infected patients commencing

Recommendation: Based on this evidence summary, the PHC/Adult Hospital Level Committee recommends that dolutegravir 50mg 12 hourly be included as an option in the standard treatment guidelines for adult patients initiating antiretroviral therapy while taking rifampicin-containing TB treatment, as an alternative to using efavirenz for the duration of TB treatment *(conditional recommendation).*

Rationale: Randomised open-label INSPIRING study[3] [4] showed that initiation of DTG-containing ART with DTG double dosing is well tolerated; and that virological suppression for efavirenz-containing ART regimen and double-dosed DTG-containing ART regimen were similar amongst ART-naive adults initiating ART, whilst on rifampicin-based tuberculosis treatment.

Level of evidence: Low certainty evidence

NEMLC MEETING OF 21 JULY 2021:
NEMLC accepted the proposed recommendation made by the PHC/Adult Hospital Level Committee.

- ***CONTRAINDICATION TO TDF***

Abacavir + lamivudine, oral: *amended as preferred treatment*

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

The following STG text was deleted:

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

Aminoglycosides are no longer recommended for management of drug-resistant TB. However, available evidence did not show a significant increased risk of nephrotoxicity with TDF in DR-TB patients on kanamycin.[5] [6]

10.1 ANTIRETROVIRAL THERAPY, ADULTS (2nd LINE ART REGIMENS)

- ***RECYCLING TDF IN 2ND-LINE REGIMENS***

Tenofovir: *added*

Zidovudine: *deleted*

As the 96-weeks follow up data of the NADIA RCT[7] has been published in peer-review format, and an updated evidence summary was updated (TDF-backbone as 2nd line in HIV, Adult review, 19 May 2022, update2022, update of the initial review of 30 November 2021):

TDF-backbone as 2nd line in HIV_Adults

Recommendation: Based on this evidence review, the PHC/Adult Hospital Level Committee suggest that tenofovir should be recycled in 2nd line dolutegravir-based antiretroviral therapy *(conditional recommendation).*

Rationale: For patients in whom neither agent is contraindicated, recycled TDF is non-inferior to AZT in 2nd line therapy (assuming TDF use in 1st line), and adverse events rates are similar. In addition, compared to AZT, it is cheaper, can be given once daily, is available as a single fixed dose combination tablet (TLD), and requires less intense initial monitoring.

Level of Evidence: RCTs of moderate certainty evidence

Review indicator: Evidence of harm or inferior viral suppression rates

[3] 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.

[4] 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.

[5] Perumal R, Abdelghani N, Naidu N, Yende-Zuma N, Dawood H, Naidoo K, et al. Risk of nephrotoxicity in patients with drug-resistant tuberculosis treated With kanamycin/capreomycin with or without concomitant use of tenofovir-containing antiretroviral therapy. J Acquir Immune Defic Syndr. 2018;78: 536–542. https://pubmed.ncbi.nlm.nih.gov/29683992/

[6] Sagwa EL, Ruswa N, Mavhunga F, Rennie T, Mengistu A, Mekonen TT, et al.. Renal function of MDR-TB patients treated with kanamycin regimens or concomitantly with antiretroviral agents. Int J Tuberc Lung Dis. 2017;21: 1245–1250. https://pubmed.ncbi.nlm.nih.gov/29297444/

[7] Paton NI, Musaazi J, Kityo C, Walimbwa S, Hoppe A, Balyegisawa A, et al. Efficacy and safety of dolutegravir or darunavir in combination with lamivudine plus either zidovudine or tenofovir for second-line treatment of HIV infection (NADIA): week 96 results from a prospective, multicentre, open-label, factorial, randomised, non-inferiority trial. Lancet HIV. 2022. https://pubmed.ncbi.nlm.nih.gov/35460601/

NEMLC RECOMMENDATION (MEETING OF 23 JUNE 2022):
NEMLC accepted the proposed recommendation, as mentioned above.

- ***DTG CONTRAINDICATED/ NOT TOLERATED/FAILING***

Atazanavir/ritonavir: *expanded to include all patients - preferred 2nd line PI*
Lopinavir/ritonavir: *retained*
Refer to the medicine review (Atazanavir/ritonavir vs lopinavir/ritonavir as 2nd line adult HIV therapy, 18 November 2021), below:


Atazanavir-ritonavir vs lopinavir-ritonavir a

Recommendation: The PHC/Adult Hospital Level Committee suggests that ritonavir-boosted atazanavir be the preferred protease inhibitor for second-line therapy in all adult patients without concomitant TB. Ritonavir-boosted lopinavir must still be available for use with rifampicin-containing TB therapy *(conditional recommendation).*
Rationale: Ritonavir-boosted atazanavir is at least non-inferior to ritonavir-boosted lopinavir in terms of viral suppression, is associated with fewer gastrointestinal side-effects and lipid profile abnormalities than ritonavir-boosted lopinavir and is dosed once-daily.
Level of Evidence: Low to moderate certainty evidence

NEMLC MEETING 9 DECEMBER 2021:
NEMLC Recommendation: The NEMLC accepted the proposed recommendation. It was furthermore noted that the global market is shifting from LPV/r to other protease inhibitors (i.e. DRV/r and ATV/r) and competition will likely push down the price of other protease inhibitors.

Darunavir/ritonavir: *not added to the STG, but proposed for inclusion in therapeutic interchange database for patients not on TB-rifampicin therapy*
Refer to the medicine review (Darunavir-ritonavir vs lopinavir-ritonavir as 2nd line adult HIV therapy review, 27 July 2021), below:


Darunavir-ritonavir vs lopinavir-ritonavir_2nc

Recommendation: The Committee suggests that DRV/r not be used in preference to LPV/r *(conditional recommendation).*
Rationale: Despite DRV/r-containing ART regimens being associated with higher viral suppression rates and being better tolerated than LPV/r, at the current cost it is considered unaffordable, and there are concerns regarding the supply. It would also not be suitable for the minority of patients on a PI-based regimen who require rifampicin-based tuberculosis treatment. DRV/r is recommended for inclusion on the therapeutic interchange database as an alternative to LPV/r and ATV/r, for patients not on TB-rifampicin therapy.
Level of Evidence: Moderate certainty evidence
Review indicators: Reduction in DRV/r price

NEMLC MEETING 9 DECEMBER 2021:
NEMLC Recommendation: The NEMLC accepted the proposed recommendation made by the PHC/Adult Hospital Level Committee above.

The therapeutic interchange database update as follows:

Indication	Medicine (INN)	Daily dosing	Therapeutic class	Therapeutic ATC
Adult 2nd line HIV management (patients not on rifampicin TB therapy)	Darunavir and ritonavir	800/100 mg	Protease inhibitors for HIV (combinations)	J05AR
	Lopinavir and ritonavir	800/200 mg	Protease inhibitors for HIV (combinations)	J05AR

As the proposed second line ART regimen is now a TDF-containing regimen, the following was updated, accordingly – aligned with guideline recommendations:

a. Failing a NNRTI-based 1st line regimen + HbsAg positive
AZT + 3TC + DTG plus TDF: *deleted*

b. DTG contraindicated/not tolerated, not on rifampicin
TDF + 3TC/FTC + ATV/r: *added*

c. TDF contraindicated/not tolerated, not on rifampicin
AZT + 3TC + DTG: *added*

d. Failing a DTG- based 1st line regimen for >2 years (TDF+3TC+DTG)
AZT + 3TC/FTC + ATV/r: *deleted*
TDF + 3TC/FTC +ATV/r: *added*

Rifampicin-based TB treatment (on DTG-regimen)
DTG: *added*
STG text was amended to align with the previously reviewed addendum to the DTG review (see details above):

If on DTG: DTG needs to be given at a dose of 50 mg 12-hourly (add DTG 50mg)

10.1 ANTIRETROVIRAL THERAPY, ADULTS (3rd LINE ART REGIMENS)

Resistance testing: *emphasised*
The PHC/Adult Hospital Level Committee raised concerns regarding the emergence of DTG resistance in 4 NADIA participants, especially as DTG is used in second-line antiretroviral therapy in South Africa. Therefore, the statement in the STG, prompting consideration of resistance testing for patients failing DTG-containing 2nd line antiretroviral therapy, was emphasised.

10.1 ANTIRETROVIRAL THERAPY, ADULTS – ADDITIONAL INFORMATION

- ***ART: DOSING AND IMPORTANT ADVERSE EFFECTS***

Tenofovir, abacavir, lamivudine, emtricitabine, oral: *amended - very low risk, "Hyperlactataemia/ steatohepatitis" deleted*
Dolutegravir, oral: *amended - weight-gain deleted*
Nevirapine, oral: *adverse effects and dosing information deleted*
Raltegravir, oral: *adverse effects and dosing information deleted*

Dolutegravir (weight gain):
Refer to the NEMLC-approved medicine review: Dolutegravir in pregnancy, June 2021 – see page 2:
"Dolutegravir (especially when combined with tenofovir alafenamide) is associated with more weight gain during pregnancy than efavirenz, but the difference is unlikely to be clinically relevant".

NEMLC MEETING OF 24 JUNE 2021: **NEMLC Recommendation:** The NEMLC accepted the recommendation as proposed by the PHC/Adult Hospital Level Committee, which would support the universal test-and-treat (UTT) strategy of the National HIV Programme. It was also duly noted that the South African Health Products Regulatory Authority were currently reviewing the label of dolutegravir products registered on the South African market.

Nevirapine, oral: The Information on the dosing and adverse effects of nevirapine was removed as long-term use of has been removed from the National Guidelines.

Raltegravir, oral: Dosing and adverse effects information was deleted, as raltegravir has been removed from the 3rd line National ARV protocols.

- ***CURRENTLY AVAILABLE ARV FDC PREPARATIONS ON CONTRACT***

ATV/r: *added*
ABC + 3TC + DTG: *added*
STG text was updated to reflect currently available fixed-dose combination antiretrovirals that are accessible on the current public sector tender.[8]

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

- ***MONITORING ON ART: CRAG SCREENING AT HIV DIAGNOSIS***

CrAg screening*: not amended (threshold not amended to CD4<200 cells/mm^3, but maintained at CD4<100 cells/mm^3)*

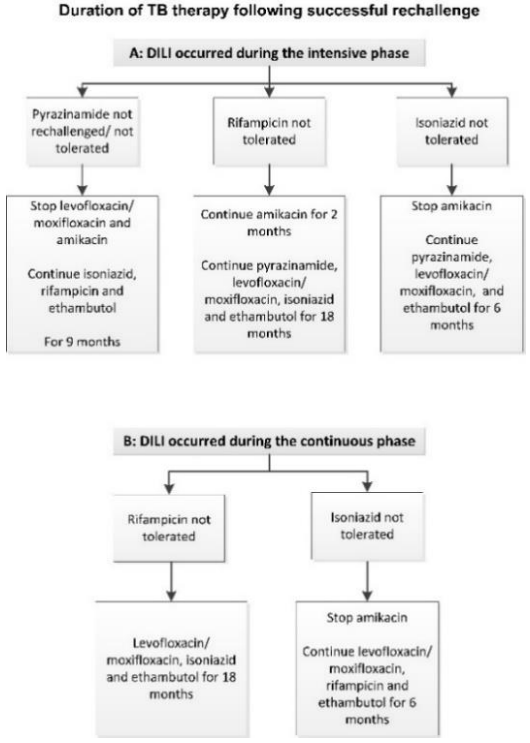
Reflex screening of Cryptococcal Antigen (CrAg) in PLHIV was maintained at CD4<100 cells/mm^3. This is aligned with the WHO guidelines that recommends "Screening for cryptococcal antigen followed by pre-emptive antifungal therapy among cryptococcal antigen–positive people to prevent the development of invasive cryptococcal disease are recommended before initiating or reinitiating ART for PLHIV who have a CD4 count <100 cells/mm^3 (*strong recommendation, moderate certainty evidence*).[9] The cost per disability-adjusted life year saved was estimated as $21 (95% CI, $15-$32) for CrAg screening of PLHIV at CD4<100 cells/mm^3 with pre-emptive fluconazole treatment.[10] Ford et al's systematic review showed that Africa had the highest prevalence of CD4<100 cells/mm^3 and the authors suggest that "consideration should be given to screening at a higher CD4 count of ≤200 cells/mm^3 in settings where there are sufficient resources to implement such an approach, or where a simplified package of care for advanced disease is required based on a unified CD4 threshold" (*conditional recommendation, moderate certainty evidence*). [11] However, the NDoH HIV Programme recommends the lower threshold of CD4<100 cells/mm^3,[12] and have not recommended a higher CD4 threshold as it is currently unaffordable. It is noted that NHLS recommends reflex monitoring of CrAg at a CD4 ≤200 cells/mm^3, aligned with the South African HIV Clinician Society Guidelines[13], which probably needs to be addressed.

10.1.1 MANAGEMENT OF SELECTED ANTIRETROVIRAL ADVERSE DRUG REACTIONS

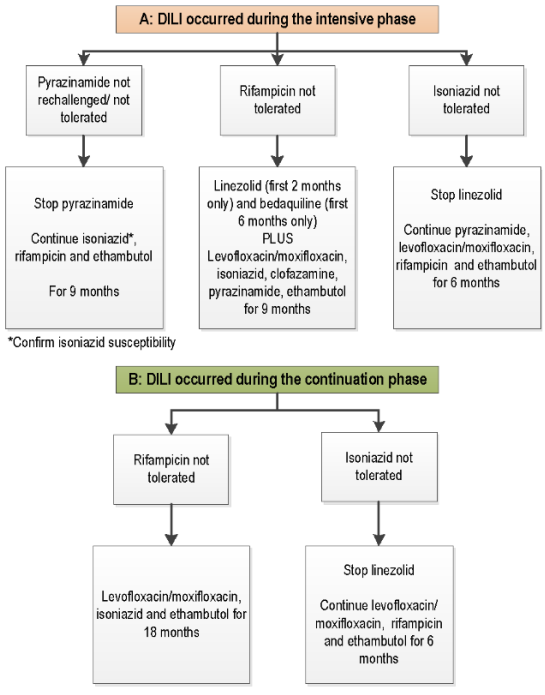
Hepatotoxicity

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

From:



To:



[9] WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021.
[10] Meya DB, Manabe YC, Castelnuovo B, Cook BA, Elbireer AM, Kambugu A, Kamya MR, Bohjanen PR, Boulware DR. Cost-effectiveness of serum cryptococcal antigen screening to prevent deaths among HIV-infected persons with a CD4+ cell count < or = 100 cells/microL who start HIV therapy in resource-limited settings. Clin Infect Dis. 2010 Aug 15;51(4):448-55.
[11] 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.
[12] 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.
[13] 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.

10.2.1 TUBERCULOSIS PREVENTIVE THERAPY (TPT)

Adult PLHIV initiated on ARVs

TB preventive therapy: *added as a therapeutic group*
Isoniazid (12H): *retained as an example of class in the STG*
Rifapentine + isoniazid (3HP): *added as a therapeutic alternative in the therapeutic interchange database*

Background: During the previous review cycles, the NEMLC approved 12 months of daily isoniazid (12H) for PLHIV and not 3HP. Non-inferiority trials suggested that 3HP prophylaxis was not inferior to 12H in PLHIV. However, 3HP is more expensive than 12H. Refer to the previous NEMLC-approved reviews for rifapentine in PLHIV (14 November 2019) and rifapentine in PLHIV on DTG-containing antiretroviral therapy (11 November 2019), and the historic NEMLC minutes (meeting of 21 February 2019):

Rifapentine (3HP) as TPT in PLHIV -Adult re

Rifapentine (3HP) as TPT in PLHIV on DTG-

BACKGROUND

NEMLC MEETING OF 21 FEBRUARY 2019:

Available evidence for IPT in PLHIV: *Most of the evidence for isoniazid prevention therapy (IPT) in people living with HIV (PLHIV) was from the pre-ART era. Two RCTs done in PLHIV: i)RCT in Khayelitsha by Rangaka et al, 20146 of PLHIV either starting or established on ART comparing 12 months of isoniazid vs placebo; ii) Temprano RCT by Danel et al, 20157, where IPT; ART and IPT+ART were evaluated either starting early or late.*

Previous NEMLC recommendation: *In the PHC STGs and EML, 2018 IPT was simplified to 12 months, from the previous complex algorithm requiring TST, based on the Khayelitsha RCT.*

Evidence for 6 months IPT: *The Adult Hospital Level Committee's recommendation to change duration of IPT to 6 months based on a mortality benefit from the Temprano RCT, raised a concern. The Temprano RCT was done in West Africa, where the incidence of TB is lower compared to South Africa. It was stated that greater mortality benefit of 6 months IPT compared to 12 months IPT was biologically implausible, unless IPT is very toxic, however this is not the case.*

Network meta-analysis *of individual patient data (including South African data) is currently underway in the USA which should further inform decision-making on duration of IPT in PLHIV.*

WHO recommendation *of 36 months was discussed, noting that the evidence base was from the pre-ART era. IPT with ART was reported to be more durable than IPT without ART.*

Recommendation: *Previous NEMLC recommendation of IPT in PLHIV be retained as 12 months duration, until further evidence is forthcoming.*

Rationale: Biologically plausible that 12 months rather than six months IPT would have greater benefit.

Despite the lack of data comparing duration of IPT therapy, available evidence in the local South African setting suggests that 12 months IPT would be reasonable.

Level of Evidence: I RCT

Current 2020-3 review cycle: In the current review cycle, 3HP was recommended for inclusion to the therapeutic interchange database:

- 12H: Isoniazid, oral, 300 mg daily for 12 months
- 3HP: Isoniazid, oral 900 mg + Rifapentine, oral 900 mg weekly for 3 months (preferably as an FDC).

NEMLC MEETING OF 23 JUNE 2022:

NEMLC recommended that 3HP be included as a therapeutic alternative to 12H in PLHIV initiated on ART – however, for DTG-containing regimens, patients to be virally suppressed (this would promote competitive pricing).

However, as there is currently no available RCT evidence for concomitant use of rifapentine with viraemic patients on DTG, the following text was added to the STG:

Ideally start TPT together with ARVs. However, if a rifapentine-containing TPT regimen is available, it should only be initiated together with an EFV-based ART regimen. A rifapentine-containing TPT regimen can be used with a DTG-based ART regimen in patients who are already virally suppressed. Do not use in patients on protease inhibitor-based ART, or in women on oral or hormonal contraceptives. *[See the therapeutic interchange database for details regarding the rifapentine-containing TPT regimen].*

The therapeutic interchange database update as follows:

Indication	Criteria	Medicine (INN)	Treatment course	Therapeutic class	Therapeutic ATC
TPT for ART-naïve HIV adult patients	n/a	Isoniazid	300 mg daily x 12 months	TPT	J04A
	• Initiated on TEE • Initiated on TLD BUT virally suppressed • NOT on a PI • Not on oral hormonal contraceptives	Isoniazid and rifapentine (FDC)	900/900 mg weekly x 3 months	TPT	J04A

FDC=fixed dose combination; TEE= TDF+EFV+FTC; TLD= TDF+3TC+DTG; TPT=TB preventive therapy; PI=protease inhibitor

10.2.3 CANDIDIASIS OF OESOPHAGUS/TRACHEA/BRONCHI

Fluconazole, oral: *directions for use amended*

The STG was editorially amended as follows:

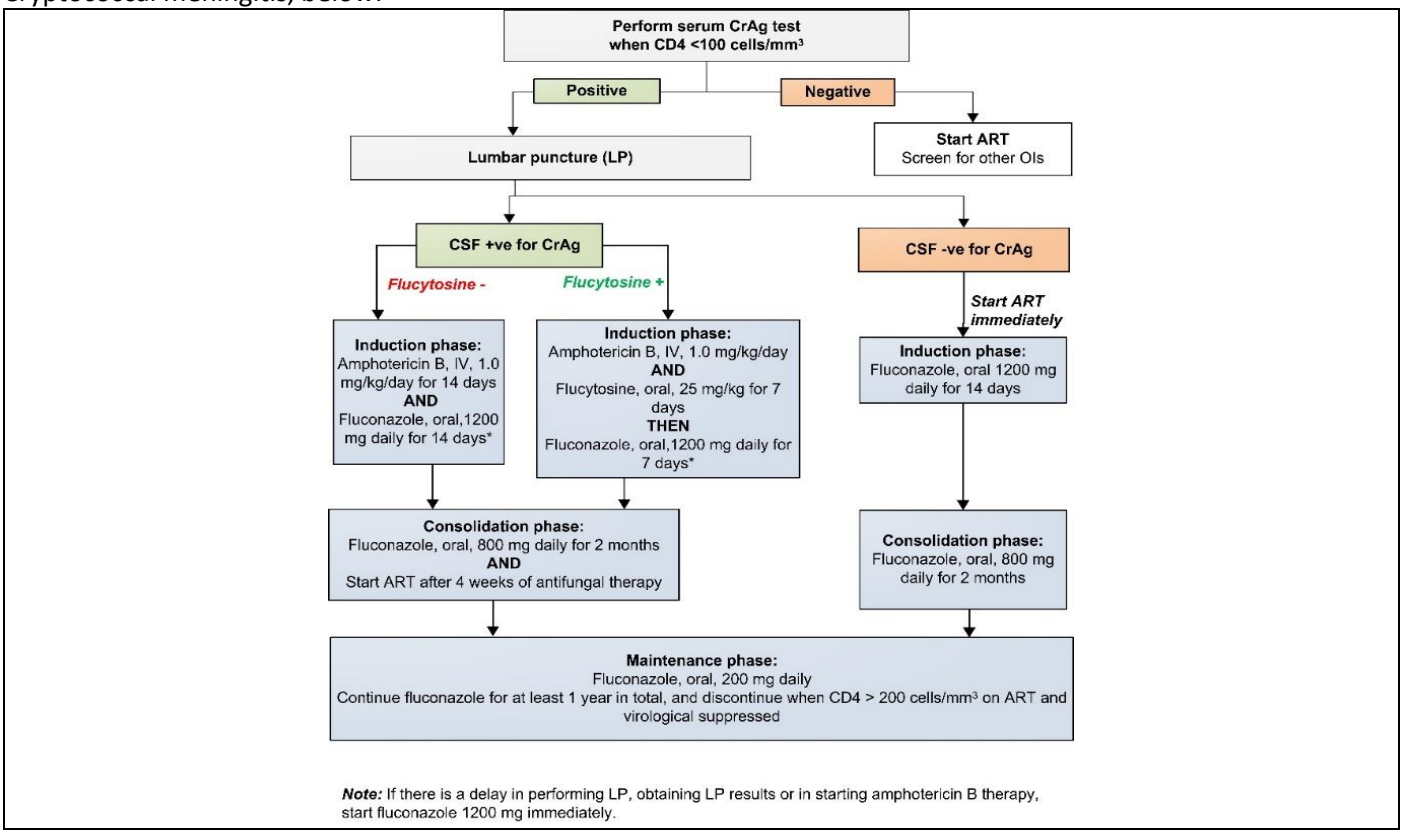
- Fluconazole, IV/oral, 200 mg daily for 14 days.
  - The usual route is oral but give IV if patient unable to swallow or is vomiting.
  - An early relapse should be treated with a 4-week course of fluconazole as above.
  - If no response to fluconazole, collect sample to confirm diagnosis of candidiasis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

10.2.4 CRYPTOCOCCOSIS

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

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

Treatment algorithm was amended for clarity purposes and correctness. It was noted that NEMLC had previously recommended that the SA HIV Clinicians Society algorithm be adapted, and the option to refuse a lumbar puncture be removed from the algorithm. Therefore, this section was delineated into management for i) CSF CrAg negative and ii) Cryptococcal meningitis, aligned with the most recent SA HIV Clinician Society algorithm[14], and section 10.2.4.2: Cryptococcal meningitis, below.



CrAg screening: *not amended*

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

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

10.2.4.1 CRYPTOCOCCOSIS, CSF CRAG NEGATIVE

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

10.2.4.2 CRYPTOCOCCAL MENINGITIS

Flucytosine, oral: *added*
Amphotericin B, IV*: retained*
Fluconazole, oral: *retained*

Previously NEMLC had recommended that flucytosine be considered for inclusion in the EML, once SAHPRA registered and if the price for the oral regimen was reduced by 42% (R2195 per pack of 500mg, 100 tablets). See the medicine review (November 2018), economic analysis (June 2019) and extracts from the respective NEMLC minutes of the meeting, below.

Flucytosine for cryptococcal meningit

Flucytosine health economics and budge

NEMLC MEETING 6 DECEMBER 2018:
The NEMLC accepted the Adult Hospital Level Recommendations for flucytosine.
Flucytosine has been shown to be efficacious, but is currently not registered and is only available through section 21 application but inequitable access is a concern. Concerns of blanket S21 approvals were raised – these should essentially be reserved for emergency situations and not used by suppliers to circumvent registration processes. Donations through non-governmental organisations should also be considered with caution as SAHPRA regulatory oversight would be amiss.
Recommendations: Economic evaluation be undertaken through the Adult Hospital level Committee.

NEMLC MEETING OF 11 JULY 2019:
NEMLC Recommendation: Flucytosine be considered for inclusion to the EML, pending SAHPRA registration *with* a reduction in price.
Rationale: Simulation confirms that flucytosine is cost-effective as induction therapy for treatment of cryptococcal meningitis amongst HIV-infected. Incremental budget impact of flucytosine compared to current standard of care is an estimated R8 million per annum, but savings could be achieved with early discharge of patients (i.e. LOS 10 days or less). A 60% reduction in price would result in a cost-neutral budget impact (R1500.00 per 100 flucytosine tablets) for the 1 week AmBd/5FC course and cost neutrality would be achieved at a price of R2195 per pack (42% price reduction) for the oral regimen. However, this is subject to uncertainty in the model, including the impact of reduction in LOS, uptake of flucytosine and use of different regimens and so a price reduction of around 40% is likely to be reasonable.
Level of Evidence: I RCT, Costing analyses, Expert opinion
Review indicators: SAHPRA registration; price reduction

Flucytosine has been recently registered with SAHPRA in December 2021, and the following has been proposed for inclusion to the STG:

If flucytosine is available:

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

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

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

AND

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

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

- Fluconazole, oral 1200mg daily for 7 days.

It was further recommended that flucytosine be advertised on the antimicrobial tender for the next cycle, with a reference price as stipulated above.

Dosing in renal impairment has also been included in Appendix II for preventing, monitoring and management of toxicity, aligned with Guidelines *(note: to be published with the final Adult Hospital Level STGs and EML, 2023 edition):*

FLUCYTOSINE, ORAL

- Flucytosine, oral, 25mg/kg 6 hourly.
  - If on digoxin trough plasma levels of digoxin (before the morning dose) should be maintained between 0.6-1 nmol/L. Monitor after 7 days and periodically thereafter.
  - Renal impairment: adjust interval:
    - eGFR 10-50 ml/min: 25mg/kg 12 hourly
    - eGFR <10 ml/min: 25mg/kg daily
  - **Monitoring**
    - Baseline and day 7 full blood count + differential.

(Adapted from: Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. South Afr J HIV Med. 2019 Nov 8;20(1):1030. https://pubmed.ncbi.nlm.nih.gov/32201629/ Source: The Sanford guide to antimicrobial therapy 2019 / editors, David N, Gilbert MD, George M, Eliopoulos MD, Henry F, Chambers MD et al. Sperryville, VA, USA: Antimicrobial Therapy, Inc., [2019])

10.2.4.2 SYMPTOMATIC, NON-MENINGEAL CRYPTOCOCCOSIS

Fluconazole, oral: *deleted*

Amphotericin B, parenteral: *deleted*

ART: *deleted*

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

~~**DESCRIPTION**~~

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

~~**MEDICINE TREATMENT**~~

~~**Induction phase**~~

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

~~**AND**~~

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

~~**Consolidation phase**~~

~~Follow with:~~

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

~~**Maintenance phase**~~

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

10.2.4.2 CRYPTOCOCCAL MENINGITIS

Liposomal amphotericin B: *not added*

Amphotericin B: *retained*

Refer to the updated liposomal amphotericin B review, 29 May 2022:

Liposomal Amphotericin B for cry

Recommendation: Based on the updated evidence review, the PHC/Adult Hospital Level Committee would recommend the use of liposomal amphotericin B for treating patients with cryptococcal meningitis where there are severe intractable complications of either nephrotoxicity, hypokalaemia, or anaemia when using amphotericin B deoxycholate (that does not respond to corrective medical therapy). It is important that all necessary precautions be taken prior to prevent these complications and during treatment with amphotericin B deoxycholate. However, liposamal amphotericin B is cost-prohibitive, compared to current standard of care, amphotericin B deoxycholate; and a threshold price of $16.25 per 50mg vial is proposed; *(conditional recommendation).*

Rationale: The current evidence, of moderate risk of bias, shows that liposomal amphoteracin B is as efficacious as amphoteracin B deoxycholate in the management of cryptococcal meningitis. Safety outcomes reflect the superiority of liposomal amphotericin B regarding infusion related reactions, nephrotoxicity, hypokalaemia, and anaemia versus amphoteracin B deoxycholate. However, liposomal amphotericin B is not affordable for inclusion on the Adult Hospital Level EML.

Level of Evidence: Low to moderate certainty evidence

Review indicators: Price reduction

NEMLC MEETING OF 21 FEBRUARY 2019: NEMLC ratified the medicine review and accepted the recommendation not to include liposomal amphotericin B in the Adult Hospital Level EML, as although small and of moderate risk of bias, shows that liposomal amphoteracin B is as efficacious as amphoteracin B deoxycholate in the management of cryptococcal meningitis, it is currently not affordable.
NEMLC MEETING OF 23 JUNE 2022: NEMLC upheld the previous recommendation not to include liposomal amphotericin B on the national EML, but amended the strength of recommendation from "strong" to "conditional", with a review indicator of "price reduction". The NEMLC further recommended that the proposed Gilead price of $16.25 per 50 mg vial be added as a threshold price.

10.2.6 CYTOMEGALOVIRUS (CMV)

Maintenance treatment

Ganciclovir, parenteral: *deleted*

Valganciclovir, oral: *retained*

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

Level of Evidence: IV Expert opinion

NEMLC MEETING OF 24 FEBRUARY 2022:

DISCUSSION:

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

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

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

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

10.2.9 PNEUMOCYSTIS PNEUMONIA

Primaquine, oral: *directions for access added*

The STG text was amended to include S21 access of primaquine (with more guidance to be added to the preface of the guidelines).

10.5.1 POST-EXPOSURE PROPHYLAXIS, OCCUPATIONAL

Darunavir/ritonavir: *not added*

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

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

PEP for healthcare workers following hepatitis B exposure

Hepatitis B Immunoglobulin: *amended*

Aligned with the National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020[15] - STG text was updated as follows:

	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)

Delay in obtaining HBsAb results

Time period of delay: *amended*

Aligned with the National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020[16]- STG text was updated as follows:

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

10.5.2 NON OCCUPATIONAL POST EXPOSURE PROPHYLAXIS, SEXUAL ASSAULT

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

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

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

Emergency contraception

Copper IUCD: *added (as first line option)*

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

[15] 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

[16] 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

Copper IUCD placed as the first line option as this agent has less drug-drug interactions compared to oral levonorgestrel 1.5mg and is the agent of choice for obese women. Copper IUCD can also be used as a long-acting reversible contraceptive.[17] [18]

Emergency contraception for obese women

Levonorgestrel, oral: *dose not amended*

An external comment was received that there is no need to double the dose of levonorgestrel for obese women for emergency contraception. Limited data suggests that obese women have an increased risk of pregnancy after use of levonorgestrel and ulipristal acetate emergency contraception compared to those who are not obese.[19] In a pharmacokinetic study with 10 participants, levonorgestrol Cmax in obese participants was half that achieved in participants with normal BMI, and doubling the levonorgestrol dose in obese participants resulted in a similar Cmax to that seen in those with normal BMI[20]. Faculty of Sexual & Reproductive Healthcare (FSRH) Overweight, Obesity and Contraception Guidelines of April 2019, therefore recommends "double-dose (3 mg) of levonorgestrel emergency contraception, if BMI >26 kg/m2 or weight >70 kg". However, the effectiveness of double-dosing in preventing pregnancy is unknown.[21] In an randomised pharmacodynamic study with 70 obese participants, doubling the levonorgestrol dose did not result in improved inhibition of ovulation: proportion of women with no follicle rupture within 5 days of levonorgestrol administration was similar with standard and double dosing [22]. This suggests that doubling dose may not be sufficient to improve efficacy of oral levonorgestrol in obese women, although this study did not directly explore effect of double dosing on subsequent rates of pregnancy. Therefore, until new evidence emerges the recommendation of double-dosing of levonorgestrel amongst obese/overweight women will be retained, aligned with Guidelines.[5] Available evidence also suggests that the effectiveness of the copper IUCD is not affected by body weight or BMI. The copper IUCD is therefore the preferred method for emergency contraception in the obese.[23]

Level of Evidence: Guidelines

The caution box in the STG was amended as follows:

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

[17] 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/

[18] 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/

[19] 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

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

[21] 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/

[22] Edelman, Alison B. MD, MPH; Hennebold, Jon D. PhD; Bond, Kise PSM; Lim, Jeong Y. PhD; Cherala, Ganesh PhD; Archer, David F. MD; Jensen, Jeffrey T. MD, MPH Double Dosing Levonorgestrel-Based Emergency Contraception for Individuals With Obesity, Obstetrics & Gynecology: June 9, 2022 - Volume - Issue - 10.1097/AOG.0000000000004717 doi: 10.1097/AOG.0000000000004717

[23] 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/