

CHAPTER 27

TUBERCULOSIS

TB guidelines are updated regularly. This STG should be read in conjunction with the most recent National Tuberculosis Control Programme Guidelines.

27.1 DRUG-SUSCEPTIBLE TUBERCULOSIS

* Notifiable medical condition.

DESCRIPTION

Tuberculosis (TB) is a serious health problem in South Africa. TB is an infection caused by *Mycobacterium tuberculosis*. TB can affect the lungs (pulmonary TB) or the lymph nodes, abdomen, central nervous system, and many other extrapulmonary sites. The signs and symptoms of TB depend on the site of infection, and include loss of weight, night sweats and fever. The risk of developing TB disease is higher among people living with HIV (PLWH). All people diagnosed with TB must be screened for HIV.

DIAGNOSIS

Molecular tests (e.g. TB nucleic acid amplification tests, TB-NAAT), smear microscopy and TB culture are used to diagnose TB by identifying *M. tuberculosis* in sputum and other samples (e.g. urine, cerebrospinal fluid, pleural fluid, ascitic fluid, lymph node aspirate). TB-NAAT testing is also used to rapidly determine drug susceptibility. Some TB-NAAT assays, such as BD MAX™ MDR-TB, test for both rifampicin and isoniazid resistance. Other types of TB-NAAT assays include Xpert® MTB/RIF Ultra which tests for rifampicin resistance only, and Xpert® MTB/XDR which detects a wider range of drug resistance including fluoroquinolone resistance.

In PLWH, TB-NAAT is not an adequate 'rule out' test. PLWH who have features of TB but are TB-NAAT negative require further investigation (e.g. chest X-ray, TB culture, urine lipoarabinomannan (U-LAM)) and may need empiric anti-tuberculosis therapy. Perform a U-LAM in the following people being investigated for TB:

- All PLWH admitted to hospital
- All symptomatic PLWH seen in an outpatient setting with:
 - CD4 ≤ 200 within the last 6 months **OR**
 - Advanced HIV disease **OR**
 - Current serious illness warranting admission.

27.1.1 TUBERCULOSIS, PULMONARY

A15.0-3/A15.7-8/A16.0-2/A16.4/A16.7-9 + (B20.0)

* Notifiable medical condition.

DESCRIPTION

Pulmonary tuberculosis (PTB) refers to infection of the lung tissue or airways caused by *M. tuberculosis*.

DIAGNOSIS

PTB is diagnosed on sputum by TB-NAAT, smear microscopy, or TB culture. Sputum induction with nebulised sodium chloride 5% should be attempted for patients unable to spontaneously produce sputum.

In people with suspected PTB:

- » Send one sputum specimen for TB-NAAT.
- » Manage results of TB-NAAT, based on the patient’s previous history of TB, as outlined in Figures 27.1, 27.2 and 27.3 below.
- » All patients with MTB detected on TB-NAAT require additional sputum to be sent at baseline for acid-fast bacilli (AFB) smear microscopy to establish a baseline for treatment monitoring.
- » Patients who are at risk of drug-resistant TB (e.g. previous episode of TB treatment, prisoners, healthcare workers) should have sputum sent to exclude isoniazid mono-resistance if the specific TB-NAAT test used for diagnosis of PTB did not already test for this.

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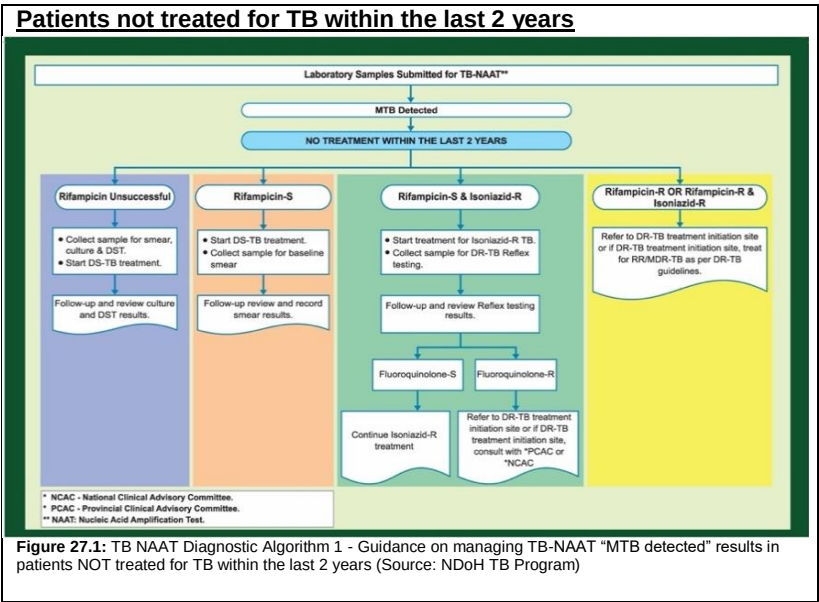
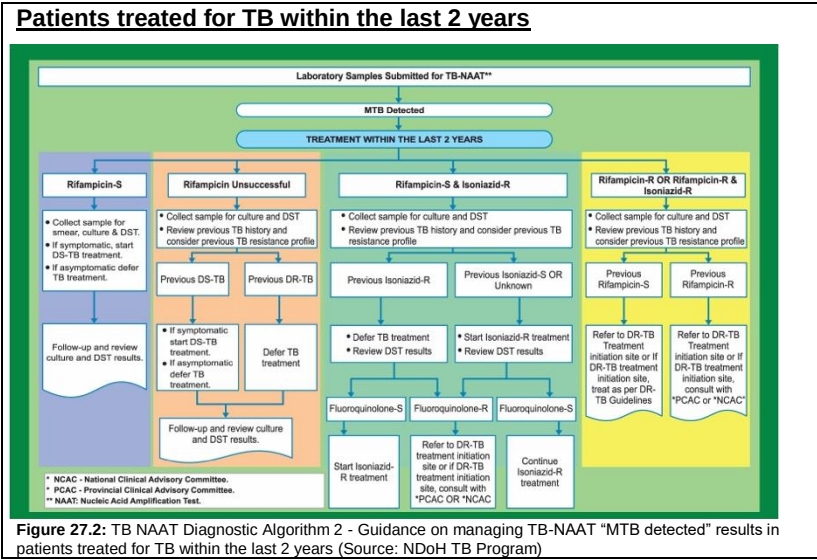
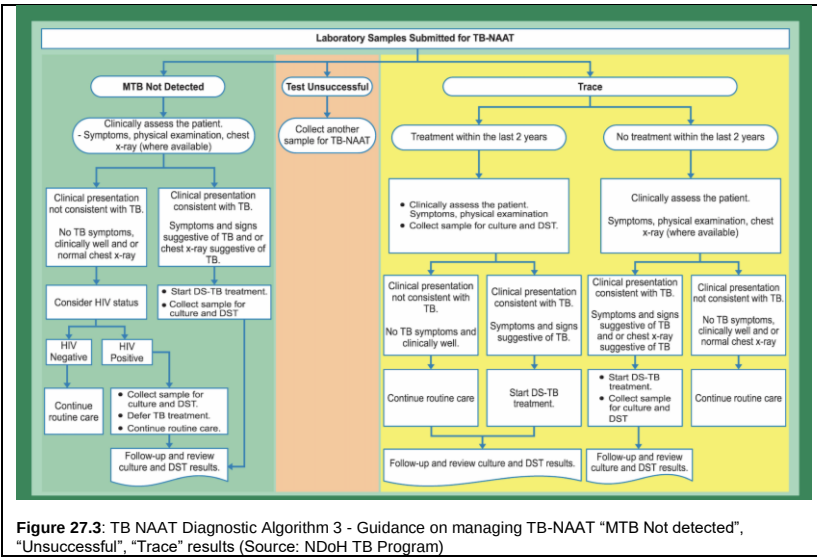


Figure 27.1: TB NAAT Diagnostic Algorithm 1 - Guidance on managing TB-NAAT “MTB detected” results in patients NOT treated for TB within the last 2 years (Source: NDoH TB Program)



Patients who have previously completed TB treatment (especially within the last 2 years) may still test TB-NAAT positive in the absence of active disease. In these patients, new TB disease should be confirmed with TB culture.



NOTE: In PLWH, TB-NAAT is not an adequate 'rule out' test. PLWH who have features of TB but are TB-NAAT negative require further investigation (e.g. chest X-ray, TB culture, urine lipoarabinomannan (U-LAM)) and may require empiric anti-tuberculosis therapy.

Perform a U-LAM in the following people being investigated for TB:

- All PLWH admitted to hospital
- All symptomatic PLWH seen in an outpatient setting with:
 - CD4 $\leq$ 200 within the last 6 months **OR**
 - Advanced HIV disease **OR**
 - Current serious illness warranting admission.

GENERAL MEASURES

- » Ensure that appropriate infection prevention and control measures are implemented at the facility, including:
 - Adequate ventilation.
 - Isolation of patients with confirmed or suspected infectious pulmonary TB.
 - Use of personal respiratory protection by healthcare workers (e.g. respirator masks).
- » Counsel patients about the disease and infection control in the home.
- » Contacts of people diagnosed with PTB should be screened for TB disease. A contact is any person that has shared the same enclosed space with a person with pulmonary TB (e.g. the TB source patient), for one or more nights, or for frequent or extended daytime periods, during the three months before the source patient started TB treatment.
- » Explain the importance of completing treatment.
- » Advise against the use of tobacco and excessive alcohol.
- » If more than two doses of treatment are missed, make extra effort to identify and manage any problems affecting adherence.
- » Patients with PTB must have a baseline smear microscopy result. Treatment response is monitored by repeat sputum smear microscopy at 7 and 23 weeks of treatment. TB-NAAT should **NOT** be used for monitoring on treatment. Refer to Table 27.1 below for the timing of sputum examinations and the recommended actions based on results.
- » If there is a poor response to treatment, alternative diagnoses and drug resistance must be considered.

Table 27.1. Sputum smear microscopy monitoring in patients with drug-susceptible pulmonary TB

End of Intensive Phase	
Timing of sputum examination	Action
One week before the end of the 2 months intensive phase of treatment (i.e. at 7 weeks).	If sputum smear microscopy negative: » Change to the continuation phase of treatment at the end of the 8th week of intensive phase treatment. » Repeat smear microscopy at 23 weeks of treatment.
	If sputum smear microscopy positive: » Reassess the patient clinically. » Address treatment compliance by counselling the patient and identifying a treatment supporter where necessary. » Repeat drug susceptibility testing including TB-NAAT, culture and DST. » Continue intensive phase treatment (e.g. RHZE) for one month but review the drug susceptibility results as soon as available. » If drug susceptible, repeat smear microscopy one week before the end of the third month of treatment (i.e. at 11 weeks). » If the repeat smear microscopy at week 11 is negative, change to the continuation phase of treatment at the end of the 12th week. » If drug resistance is detected, refer to Section 23.3. Drug-Resistant Tuberculosis for initiation of treatment.
End of Continuation Phase	
Timing of sputum examination	Action
One week before the end of the 4 months continuation phase (i.e. at 23 weeks).	If sputum smear microscopy negative: » Stop treatment at the end of the 24th week of treatment. » Register the patient as “Cured”.
	If sputum smear microscopy positive: » Reassess the patient clinically. » Stop TB treatment and register the patient as “Treatment failure”. » Repeat drug susceptibility testing including TB-NAAT, culture and DST. » Review the drug susceptibility results as soon as available. » If drug resistance is detected, refer to Section 23.3. Drug-Resistant Tuberculosis for initiation of treatment. » If drug susceptible, re-start TB treatment, counsel the patient and provide treatment support.

Adapted from National Tuberculosis Management Guideline, 2014.

MEDICINE TREATMENT

Administer the total daily amount of each medicine as a single daily dose, not as divided doses.

Adolescents aged 12 to < 15 years

Adolescents aged 12 to < 15 years with non-severe drug-susceptible PTB and/or TB lymphadenitis are eligible for a shortened 4-month treatment regimen. Severity of disease and eligibility for treatment shortening in adolescents is based on clinical, radiological and microbiological features at the time of TB diagnosis, at month 1 of treatment, and at month 4 of treatment (see Figure 27.4 below).

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At Diagnosis	Clinical Criteria	Eligible for treatment shortening if <u>ALL</u> of the below criteria are met: • Age 3 months to < 15 years at start of TB treatment • Non-severe drug-susceptible pulmonary TB (including simple TB pleural effusion or cervical TB lymphadenitis) presumed or confirmed with no evidence of extrapulmonary TB other than lymphadenitis • First episode of TB (no previous TB treatment) • No danger signs indicating severe illness at presentation¹ • No severe acute malnutrition • No asymmetric or persistent wheezing • If living with HIV: viral load < 1000 in the preceding 3 months AND on ART for >3 months • No respiratory sample that is AFB smear positive
	Radiological Criteria	Eligible for treatment shortening if <u>NONE</u> of the following are present: • Complicated intra-thoracic lymph node TB (i.e., airway compression or deviation and/or hyperinflation or collapse) • Consolidation ≥ 1 lobe • Complicated pleural effusion (loculated effusion, empyema or pneumothorax) • Miliary pattern • Cavities
At Follow-up	Clinical Criteria	Eligible for shorter treatment if <u>ALL</u> below criteria are met: • Adherent to treatment • MONTH 1: All TB signs and symptoms improved • MONTH 4: All TB signs and symptoms resolved and appropriate/improving weight trend

¹General danger signs include being unable to drink, vomiting everything, convulsions, unconsciousness, signs of shock. In addition, any signs of severe respiratory illness, signs of severe dehydration, signs of meningitis, or severe anaemia (HB < 7 g/dL).

Figure 27.4: Eligibility for TB treatment shortening in adolescents 12 to <15 years of age. (Adapted from Box 1 and Figure 10 from the National Department of Health “A Clinical Guideline for the Diagnosis and Treatment of Drug-susceptible TB in Children and Adolescents in South Africa. 2015.”)

NOTE:

- » If no chest X-ray (CXR) is available to confirm that the radiological criteria outlined in Figure 27.4 for non-severe pulmonary TB are met, adolescents aged 12 to < 15 years are **NOT** eligible for the shorter 4-month treatment regimen.
- » Adolescents 12 to < 15 years with a sputum sample that is AFB smear-positive are **NOT** eligible for the shorter 4-month treatment regimen. Lymph node fine needle aspiration smear positivity is not an exclusion.
- » Adolescents who are not eligible for the shortened treatment regimen and adolescents ≥ 15 years should receive the standard six-month drug-susceptible TB treatment regimen outlined below, or the recommended regimens for other forms of extrapulmonary TB.
- » If there is any uncertainty about whether an adolescent aged 12 to < 15 years is eligible for treatment shortening or not, rather treat for the full 6 months.
- » In adolescents with TB lymphadenitis, if cervical lymph nodes did not decrease in size by month 4 of treatment, continue to 6 months of treatment. If there is not a significant reduction in size of the lymph nodes, or if there is enlargement in lymph nodes, especially if TB was not bacteriologically confirmed, refer for further investigation.

The shortened 4-month treatment regimen consists of 2 months of intensive phase treatment and 2 months of continuation phase treatment.

Dosing for adolescents 12 to < 15yrs with drug-susceptible TB eligible for treatment shortening:

- » Adjust treatment dosages to current body weight.

Table 27.2: Weight-based dosing guidance for adolescents 12 to < 15yrs with drug-susceptible TB.

Pre-treatment body weight	2 months intensive phase given daily		2 months continuation phase given daily	
	RHZ	E	RH	
	75/50/150 mg dispersible tablet (scored)	400 mg tablet (not scored) OR 400 mg/8ml suspension [#]	75/50 mg dispersible tablet (scored)	
12–15.9 kg	3 tablets	$\frac{3}{4}$ tab or 6 mL	3 tablets	
16–24.9 kg	4 tablets	1 tab or 8 mL	4 tablets	
	RHZE 150, 75, 400, 275 mg tablet		RH RH 150,75 tablet OR RH 300,150 tablet	
			RH (150,75)	RH (300,150)
25–29.9 kg	2 tablets		2 tablets	1 tablet

30–34.9 kg	3 tablets	3 tablets	-
35–64.9 kg	4 tablets	4 tablets	2 tablets
≥65 kg	5 tablets	5 tablets	-
R-rifampicin, H-isoniazid, E-ethambutol, Z-pyrazinamide An oral suspension can be made by dispersing the required number of tablets & in a small amount of water (5-10 ml) and administering all the suspension to the adolescent orally or via nasogastric tube. # If oral suspension required, for each dose, crush 1 x ethambutol 400 mg tablet to a fine powder, disperse in 8 ml of water to prepare a concentration of 400 mg/8 ml (50 mg/ml), administer required dose as indicated in above chart, discard unused suspension.			

Should there be insufficient clinical improvement after completion of four-months of treatment, treatment may be extended to six months while considering alternative diagnoses, including drug-resistant TB.

AND

- Pyridoxine 25 mg, oral, daily for duration of INH-containing TB therapy.
 - Isoniazid may cause peripheral neuropathy due to drug-induced pyridoxine deficiency.

Adults and adolescents ≥ 15 years

All adults and adolescents ≥ 15 years diagnosed with drug-susceptible pulmonary TB should receive 6 months of treatment (intensive phase treatment for 2 months and continuation phase treatment for 4 months - see Table 27.3 below).

Treatment for known or presumed drug-susceptible TB:

- Rifampicin/isoniazid/pyrazinamide/ethambutol, oral, daily for 2 months, followed by rifampicin/isoniazid, oral, daily for 4 months.
 - Weigh patient frequently and adjust the dose according to current weight.

Table 27.3: Weight-based dosing guidance for adults and adolescents ≥ 15 years with drug-susceptible TB

Body weight	Two months intensive phase	Four months continuation phase	
	RHZE (150/75/400/275)	RH (150/75)	RH (300/150)
30–37 kg	2 tablets	2 tablets	
38–54 kg	3 tablets	3 tablets	
55–70 kg	4 tablets		2 tablets
71 kg and over	5 tablets		2 tablets
R-rifampicin, H-isoniazid, Z-pyrazinamide, E-ethambutol			

AND

Pyridoxine supplementation is recommended in patients on isoniazid that are at high risk of peripheral neuropathy (e.g. HIV, diabetes, alcohol use disorder).

- Pyridoxine 25 mg, oral, daily for duration of isoniazid-containing TB therapy.

Important medicine interactions

Rifampicin may reduce the efficacy of low dose combined oral contraceptives and progestin-only implants, resulting in possible unplanned pregnancies (See PHC Chapter 7: Family planning).

- » Advise the use of alternative contraceptive methods, such as IUD or DMPA.
- » Women that choose to use a progestin-only subdermal implant should be advised to use additional contraception for the duration of rifampicin-containing TB treatment and for 2 weeks after stopping rifampicin.

CAUTION

Antiretroviral medicines frequently interact with TB medicines. In PLWH on dolutegravir-based ART and rifampicin-containing TB treatment, dolutegravir is dosed twice daily (12 hourly). Continue twice daily dosing of dolutegravir until 2 weeks after stopping rifampicin.

Refer to Section 10.1: Antiretroviral treatment or consult the National Department of Health antiretroviral treatment guidelines.

Dose adjustment of TB treatment in renal impairment (eGFR < 30 mL/min)

- Ethambutol 15 – 25 mg/kg three times weekly.
- Pyrazinamide 20 – 30 mg/kg three times weekly.
- Rifampicin and isoniazid do not require dose adjustment.

Example of dose adjusted regimen using alternate day dosing of RH and RHZE:

Intensive phase of treatment:

- RHZE: Administer standard weight-based dosing with RHZE on Monday, Wednesday, Friday.
- RH: Administer standard weight-based dosing of RH on Tuesday, Thursday, Saturday, Sunday.

	Sun	Mon	Tues	Wed	Thu	Fri	Sat
RHZE	Skip	Take	Skip	Take	Skip	Take	Skip
RH	Take	Skip	Take	Skip	Take	Skip	Take

Continuation phase of treatment:

- RH: No dose adjustment required. Continue daily weight-based dosing of RH.

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Common adverse drug reactions associated with DS-TB medicines

Table 27.4: Common adverse drug reactions associated with DS-TB medicines in adults

Adverse effect	Most likely responsible drug	Management
Hepatotoxicity (e.g. jaundice, nausea, malaise, abdominal pain)	Rifampicin, isoniazid, pyrazinamide	Exclude drug-induced liver injury/hepatitis – perform urgent (same day) ALT and manage further as appropriate.
Gastrointestinal intolerance (nausea, vomiting, anorexia)	Most DS-TB medicines	Exclude drug-induced liver injury/hepatitis – perform urgent (same day) ALT. Exclude other causes such as alcohol use, non-steroidal anti-inflammatory drugs. If drug-induced liver injury and other causes excluded, manage symptomatically. Change the timing of medication administration to just before or after a light snack or at bedtime.
Joint pain	Pyrazinamide	Exclude gout. Treat symptomatically with analgesia (See Chapter 25: Pain, for treatment options).
Peripheral neuropathy (e.g. tingling pain or burning or numbness in hands and feet)	Isoniazid	Initiate or increase pyridoxine to 50 mg daily. Note: Doses of pyridoxine > 100 mg daily may cause or worsen peripheral neuropathy and should be avoided (See Section 25.1.4: Peripheral neuropathy). Discuss with expert and consider withdrawal of offending drug if worsening symptoms. Note: Drug-induced peripheral neuropathy can be irreversible if the offending drug is not stopped promptly.
Orange coloured urine	Rifampicin	Reassure the patient that this is normal and to be expected while taking rifampicin. No intervention required.
Rash	Rifampicin, isoniazid,	For mild, itching rash, with no blistering, mucosal involvement or

	pyrazinamide, ethambutol	systemic involvement, treat symptomatically. If erythematous rash with fever, blistering, mucosal involvement, hepatitis, stop all medicines urgently.
Thrombocytopenia and/or purpura or petechial rash	Rifampicin	If petechial rash, assess platelet count. If thrombocytopenia, stop rifampicin.
For additional guidance on the management of adverse drug reactions refer to: https://mic.uct.ac.za/sites/default/files/media/documents/mic_uct_ac_za/2157/ade-booklet.pdf		

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27.2 TUBERCULOSIS, EXTRAPULMONARY

A15.6/A16/A18/A19/B90.0/B90.9

DESCRIPTION

Extrapulmonary TB (EPTB) refers to *M. tuberculosis* infection occurring outside the lungs. EPTB is more common in PLWH. Commonly affected sites include the lymph nodes, pleura, pericardium, central nervous system and bones and joints. EPTB may present with non-specific symptoms such as unintentional weight loss (> 1.5 kg in a month), night sweats, and fever. Other symptoms depend on the specific organ affected. Extrapulmonary TB can occur with or without active pulmonary TB. Disseminated TB refers to TB that has spread, usually via the bloodstream, to involve multiple organs or sites, and includes miliary TB.

The most common sites of extrapulmonary TB are listed below along with commonly associated signs and symptoms:

Table 27.5: Common presenting signs and symptoms of extrapulmonary tuberculosis

Extrapulmonary TB type	Common presenting signs/symptoms
TB lymphadenitis	» Peripheral TB lymphadenopathy occurs in neck and armpits. Typically, nodes are large (> 2 cm), non-tender, non-symmetrical, matted, firm to fluctuant and rapidly growing. » Audible wheeze or typical brassy cough caused by large mediastinal lymph nodes. (See Section 27.5: Extrapulmonary tuberculosis, lymphadenitis, for further guidance)
TB pleural effusion (usually unilateral)	» Non-productive cough. » Chest pain. » Shortness of breath. » Tracheal and mediastinal shift away from the side of the effusion.

	» Decreased chest movement. » Stony dullness on percussion on the side of the effusion. (See Section 27.3: Extrapulmonary Tuberculosis, pleural, for further guidance)
TB empyema	» Similar to pleural effusion, but aspiration reveals thick pus. (See Section 27.4: Extrapulmonary Tuberculosis, empyema, for further guidance)
TB of spine, bones and joints	» Decreased movement in the joints. » Joint swelling with warm, tender joints. » Muscle atrophy and/or spasms. » Numbness, tingling, or weakness below the infection (if the spine is involved). (See Section 27.8: Tuberculosis, osteoarticular for further guidance)
TB pericarditis/pericardial effusion	» Chest pain. » Shortness of breath. » Dizziness and weakness from low cardiac output » Signs and symptoms of right-sided heart failure (tachycardia, low BP, peripheral oedema, liver congestion, ascites). (See Section 27.7: Tuberculous pericarditis for further guidance)
TB meningitis	» During the early phase of TB meningitis, malaise, headache and personality change may be present. » With suspected established infection assess for: - gradual onset of headache, - malaise - confusion - decreased consciousness - vomiting - neck stiffness (See Section 27.9: Tuberculosis, Meningitis for further guidance)
Disseminated/miliary TB	» Fever. » Cough. » Generalised lymphadenopathy. » Hepatomegaly. » Consider in febrile patients presenting with HIV wasting syndrome (See Sections 27.3 to 27.9 for further guidance)
TB abdomen/peritoneum	» Ascites with no signs of portal hypertension. » Possible palpable abdominal masses. » Possible bowel obstruction. (See Section 27.6: Tuberculosis, Abdominal for further guidance)
Urogenital TB	» Dysuria, urinary frequency or urgency » Haematuria » Sterile pyuria » Pelvic, flank, or perineal pain » Infertility in men and women (Discuss patients with high suspicion of urogenital TB with specialist)

DIAGNOSIS

Special investigations to diagnose EPTB are guided by the clinical examination and site involved, and may include:

- » abdominal ultrasound;
- » cardiac point-of-care ultrasound or echocardiography;
- » lumbar puncture;
- » computed tomography (CT) scan;
- » TB-NAAT, smear microscopy, and TB culture of tissue or fluid from any biopsy or aspirate;
- » histologic examination of tissue (necrotizing granulomas may be suggestive of TB);
- » or cytological examination of fine needle aspirate.
- » In PLWH, specifically:
 - TB blood culture: consider in PLWH with CD4 counts < 100
 - Urine lipoarabinomannan (U-LAM). A positive U-LAM suggests disseminated TB in PLWH. U-LAM is indicated in the following people being investigated for TB:
 - o All PLWH admitted to hospital
 - o All symptomatic PLWH seen in an outpatient LoE: I^{iv}
 - setting with:
 - CD4 ≤ 200 within the last 6 months **OR**
 - Advanced HIV disease **OR**
 - Current serious illness warranting admission.

GENERAL MEASURES

- » Patients with extrapulmonary TB, or clinically diagnosed TB without bacteriological confirmation, are monitored clinically throughout treatment. Weight is a useful indicator of clinical response and should be monitored monthly.
- » If there is a poor response to treatment, alternative diagnoses and drug resistance must be considered.

27.3 EXTRAPULMONARY TUBERCULOSIS, PLEURAL (TB PLEURISY)

A15.6/A16.5/B90.9

DESCRIPTION

TB pleurisy is a form of extrapulmonary TB characterised by inflammation of the pleura due to infection with *M. tuberculosis*. TB pleurisy may present with a few weeks of pleuritic pain; often associated with a dry cough, fever, night sweats, weight loss, and, with large effusions, progressive shortness of breath.

DIAGNOSIS

Suspected pleural effusions should be confirmed on chest X-ray (CXR).

It is essential to perform a diagnostic tap of pleural effusions confirmed on CXR.

Pleural fluid findings suggestive of TB:

- » Straw-coloured exudate
- » Elevated protein (>30 g/L)
- » Elevated white cell count (predominantly lymphocytes)
- » Raised adenosine deaminase (ADA) (>30 IU/L)

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LoE:IVb^{vi}

Pleural fluid should be sent for TB-NAAT and TB culture. Due to the low bacterial load in TB pleural effusion, TB-NAAT has a low sensitivity on pleural fluid, and a negative test result cannot be used to rule out TB. A definite diagnosis of pleural TB is made by positive TB-NAAT, smear microscopy or TB culture, or on histology of a pleural biopsy. However, the presence of a lymphocytic exudate on pleural fluid analysis is adequate to start empiric TB therapy in areas with a high TB burden, particularly in PLWH.

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A pleural biopsy at initial presentation is strongly recommended for the following patients: >50 years of age, suspected malignancy, or those with symptoms atypical for TB.

All patients started on empiric TB therapy for pleural TB must be followed up closely. Failure to respond as expected must prompt investigations to exclude other causes. On TB treatment, signs and symptoms should resolve within 2 weeks. Radiographic improvement is usually evident by 6 weeks, but complete resorption can take up to 4 months. Pleural thickening may persist.

MEDICINE TREATMENT

Treatment of pleural TB is as for pulmonary TB (see Section 27.1.1: Tuberculosis, pulmonary).

Adolescents 12 to < 15 years with a simple TB pleural effusion may be eligible for a shorter 4-month treatment regimen (see Figure 27.4: “Eligibility for TB treatment shortening in adolescents 12 to <15 years of age” above).

Note:

- » Total drainage of TB pleural effusion by aspiration or intercostal tube is not needed. For large effusions that cause dyspnoea, drain a maximum of 1 litre at a time.

REFERRAL

- » Non-resolving effusions: Suspect an incorrect diagnosis of TB pleurisy if the effusion does not improve on CXR after 3 months of treatment, or if the patient deteriorates.
- » Bronchopleural fistula, not resolving after 6 weeks.

27.4 EXTRAPULMONARY TUBERCULOSIS, EMPYEMA

A15.6/A16.1/B90.0/B90.9

DESCRIPTION

Pus in the pleural cavity caused by chronic *M. tuberculosis* infection.

The clinical presentation may be similar to TB pleural effusion but on diagnostic tap pus is aspirated. TB empyema may be loculated, and lead to extensive thickening and calcification of the pleura. TB empyema may be associated with bronchopleural fistula and complicated by co-infection with other bacteria.

DIAGNOSIS

Aspirate and analyse all pleural effusions.

A TB pleural effusion should be distinguished from TB empyema by macroscopic appearance and biochemical analysis of the fluid.

Pleural fluid findings suggestive of TB empyema include:

- » Purulent fluid
- » Elevated white cell count (predominantly neutrophils)
- » Low fluid pH (< 7.2) and low glucose concentrations

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TB-NAAT, microscopy and TB culture of the purulent pleural fluid should be requested to confirm the diagnosis.

GENERAL MEASURES

The primary management of TB empyema is early and complete drainage by insertion of an intercostal tube and anti-tuberculosis treatment.

Further surgical intervention may be required – discuss with cardiothoracic surgery.

MEDICINE TREATMENT

Treatment of TB empyema is as for pulmonary TB (see Section 27.1.1: Tuberculosis, pulmonary).

Adolescents 12 to < 15 years with TB empyema are **NOT** eligible for a shorter 4-month treatment regimen (see Figure 27.4 above).

REFERRAL

- » Loculated TB empyema, not resolving after intercostal underwater tube drainage and needing assessment for surgical drainage.
- » Chronic empyema with pleural thickening and restrictive lung disease for consideration of surgical decortication.

27.5 EXTRAPULMONARY TUBERCULOSIS, LYMPHADENITIS

A15.4/A16.3/A18.2/B90.0/B90.9

DESCRIPTION

Infection of lymph nodes with *M. tuberculosis*. TB lymphadenitis typically presents with swollen, often visibly enlarged nodes that are firm, painless and may be matted. Lymph node enlargement persists for more than 2 weeks and does not respond to antibiotic treatment. TB lymphadenitis may be associated with a discharging skin sinus.

DIAGNOSIS

Fine needle aspirate for TB-NAAT, culture, and cytology.

Investigate for TB at other sites (e.g. send sputum for TB-NAAT, U-LAM in eligible PLWH).

MEDICINE TREATMENT

Treatment of TB lymphadenitis is as for pulmonary TB (see Section 27.1.1 Tuberculosis, pulmonary).

Adolescents 12 to < 15 years with isolated TB lymphadenitis may be eligible for a shorter 4-month treatment regimen (see Figure 27.4 above).

REFERRAL

- » Discuss patients with results not suggestive of TB (i.e. negative FNA TB-NAAT and no evidence of TB elsewhere) for lymph node biopsy.
- » Refer for further investigation or discuss with an expert if there is no significant reduction in size of the lymph nodes, or if there is enlargement in lymph nodes on treatment, especially if TB was not bacteriologically confirmed.

27.6 TUBERCULOSIS, ABDOMINAL

A18.3/B90

DESCRIPTION

Abdominal tuberculosis refers to extrapulmonary TB involving the gastrointestinal tract, peritoneum, intra-abdominal lymph nodes or abdominal organs. Presenting symptoms may include fever, weight loss, vomiting, abdominal distension and pain, diarrhoea, constipation, and jaundice. Clinical examination may reveal hepatosplenomegaly, ascites, or palpable abdominal masses due to mesenteric lymph nodes.

DIAGNOSIS

- » Abdominal ultrasound: lymphadenopathy, ascites, and splenic hypodensities are suggestive of abdominal TB
- » If ascites is present, perform diagnostic paracentesis (ascitic tap).

- » Ascitic fluid features suggestive of TB:

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 - Exudate
 - Elevated protein (>30 g/L)
 - Elevated white cells with lymphocytes predominantly
 - Elevated adenosine deaminase (ADA)
 - Serum-ascites albumin gradient < 1.1 g/dL
 - Positive TB-NAAT, smear microscopy or TB culture
- » Histologic examination of tissue (intestinal, peritoneal) biopsy
- » Investigate for TB at other sites (e.g. CXR, send sputum for TB-NAAT, U-LAM in eligible PLWH).

MEDICINE TREATMENT

Treatment of abdominal TB is as for pulmonary TB (see Section 27.1.1: Tuberculosis, pulmonary and lymphadenitis).

Adolescents 12 to < 15 years with abdominal TB are **NOT** eligible for a shorter 4-month treatment regimen (see Figure 27.4 above).

REFERRAL

- » Acute abdomen – refer urgently.
- » Suspected bowel obstruction or perforation – refer urgently.
- » Diagnostic uncertainty (e.g. terminal ileal disease: TB vs Crohn's disease).
- » Abdominal TB without microbiological confirmation, and without improvement despite ≥ 1 month of appropriate TB treatment.

27.7 TUBERCULOUS PERICARDITIS

I30.1

DESCRIPTION

TB pericarditis is defined as pericardial infection with *Mycobacterium tuberculosis*, and is characterised by various stages. The most common initial presentation is a pericardial effusion. Pericardial effusion may be followed by partial or complete resorption of the fluid and development of pericardial thickening, fibrosis and calcification. This progressive pericardial thickening and fibrosis may impede filling of the heart and is referred to as constrictive pericarditis.

TB accounts for > 90% of pericardial effusions in PLWH, and 50% of pericardial effusions in people without HIV. Symptoms of TB pericarditis may include fever, weight loss, night sweats, chest pain, shortness of breath, cough, dizziness and weakness. Clinical cardiovascular examination findings that may suggest TB pericarditis include tachycardia, hypotension, raised jugular venous pressure, pulsus paradoxus, soft or muffled heart sounds and

a pericardial friction rub. Hepatomegaly, abdominal distension with ascites, and lower limb oedema may also be present.

TB pericardial effusion may be complicated by cardiac tamponade, a medical emergency, which requires urgent pericardiocentesis.

LoE:IIIb^x

DIAGNOSIS

- » CXR may show a large globular heart and features of pulmonary TB or pleural effusion.
- » ECG findings that suggest pericardial effusion include tachycardia, low voltage QRS complexes, and electrical alternans.
- » Cardiac point-of-care ultrasound or echocardiography confirms the presence of a pericardial effusion and can evaluate for tamponade. Fibrinous strands in the pericardial space and pericardial thickening suggest TB pericarditis.
- » Features of TB pericarditis on diagnostic pericardiocentesis:
 - Exudate
 - Elevated ADA (≥ 30 IU/L)
 - Elevated white cells with lymphocytes predominantly, pericardial fluid lymphocyte: neutrophil ratio ≥ 1
 - Positive TB-NAAT, microscopy and TB culture
- » Histologic examination of pericardial biopsy
- » Investigate for TB at other sites (e.g. send sputum for TB-NAAT, U-LAM in eligible PLWH).

LoE:IIIb^{xi}

The diagnosis of TB pericarditis is “definite” when TB bacilli are present in a smear or culture of pericardial fluid, and/or TB bacilli or caseating granulomata are found on histological examination of pericardium. A diagnosis of “probable” TB pericarditis is made when there is evidence of pericarditis in a patient with TB elsewhere and/or a lymphocytic pericardial exudate with elevated ADA and/or a good response to anti-tuberculosis treatment.

LoE:IVb^{xii}

NOTE: In areas with a high burden of HIV and TB, it may be safer for the patient to start empiric TB treatment before establishing a definitive diagnosis, than to undergo diagnostic pericardiocentesis.

LoE:IVb^{xiii}

MEDICINE TREATMENT

Treatment of TB pericarditis is as for pulmonary TB (see Section 27.1.1: Tuberculosis, pulmonary and lymphadenitis).

Note: Adolescents 12 to < 15 years with TB pericarditis are **NOT** eligible for a shorter 4-month treatment regimen (see Figure 27.4 above).

LoE:IIIb^{xiv}

If definite or probable TB pericarditis, ADD:

- Corticosteroids (intermediate-acting), e.g.:
- Prednisone, oral, 120 mg daily for 1 week. Then taper gradually over the next 6 weeks (refer to dosing regimen tabulated below).

LoE:IIIb^{xv}

Weeks	Dosing Regimen
Week 1	120 mg/day
Week 2	90 mg/day
Week 3	60 mg/day
Week 4	30 mg/day
Week 5	15 mg/day
Week 6	5 mg/day

CAUTION

In PLWH, perform a thorough clinical examination before starting corticosteroids to exclude Kaposi's sarcoma and other HIV-related cancers. In PLWH started on corticosteroids, antiretroviral therapy should be initiated promptly in accordance with Section 10.1: Antiretroviral treatment.

REFERRAL

- » Suspected pericardial tamponade
- » Constrictive pericarditis

27.8 TUBERCULOSIS, OSTEOARTICULAR

A18.0/B90.0/B90.2

DESCRIPTION

Osteoarticular TB is extrapulmonary *M. tuberculosis* infection of the bone and/or joints. TB infection can involve any joint and is usually limited to one joint, such as the hip or knee, at a point in time. TB infection of the bone is called TB osteomyelitis, and any bone may be affected. Symptoms of TB joint or bone infection include swelling, pain and loss of function. The affected joint or bone is usually not red or warm, thus differentiating it from septic arthritis. There may be associated constitutional symptoms of fever and weight loss. In people with delayed presentation of TB bone or joint infection, there may be significant deformity.

TB osteomyelitis that involves the vertebral column is referred to as spinal TB. Spinal TB may present with pain, muscle spasm, rigidity, neurological signs, fever and loss of weight. Spinal TB may lead to severe neurological complications such as paraplegia from spinal cord compression. Spinal TB is characterised by loss of vertebral body bone density and slow bone erosion, with the disc space preserved for a long time, which differentiates it from pyogenic infection. Collapse of adjacent vertebral bodies may lead to

angulated kyphosis (also known as gibbus deformity). Local spread of TB infection may occur into the soft paravertebral tissue to form a cold “psoas abscess”.

DIAGNOSIS

- » Imaging (e.g. X-ray, CT scan) may be suggestive of TB.
- » Tissue biopsy and/or aspiration of pus may be performed.
- » TB-NAAT, smear microscopy, or TB culture of tissue biopsy or aspirated material are confirmatory.
- » Investigate for TB at other sites (e.g. CXR, send sputum for TB-NAAT, U-LAM in eligible PLWH).

MEDICINE TREATMENT

Treatment of TB of the bone and/or joints is as for pulmonary TB (see Section 27.1.1: Tuberculosis, pulmonary and lymphadenitis). Treat with standard combination tuberculosis therapy and extend the duration of therapy to 9 months (2 months intensive phase, 7 months continuation phase).

Adolescents 12 to < 15 years with TB of the bone and/or joints are **NOT** eligible for a shorter 4-month treatment regimen (see Figure 27.4 above).

27.9 TUBERCULOSIS, MENINGITIS

A17.0/G00.8/G00.9/G02.8/G03.9

DESCRIPTION

TB meningitis is infection of the meninges by *M. tuberculosis*. TB meningitis is associated with high morbidity and mortality. Patients may present with headache, confusion and decreased consciousness. On examination, they may have meningism. Patients with suspected TB meningitis should be referred to hospital urgently.

DIAGNOSIS

- » Diagnosis of TB meningitis is based on clinical presentation and cerebrospinal fluid (CSF) analysis following lumbar puncture, with or without evidence of TB disease elsewhere.
- » If TB meningitis is suspected, treatment should be initiated without awaiting bacteriological proof of diagnosis.
- » Imaging (e.g. CT brain) should be performed prior to lumbar puncture if there is concern for raised intracranial pressure.
- » CSF findings are variable, but findings suggestive of TB meningitis include:
 - Elevated lymphocytes (30 – 300/mm³). Note that polymorphs predominate initially in about a third of patients.
 - Elevated protein (usually > 1 g/L).

- Low glucose.
- Negative cryptococcal antigen test.
- Positive TB-NAAT and/or TB culture on CSF.
- » In cases where the differential diagnosis between bacterial and tuberculous meningitis is in doubt, lumbar puncture should be repeated 2–3 days later while still on ceftriaxone. If the aetiology is bacterial, considerable improvement in CSF findings is expected. With untreated tuberculous meningitis, the cell counts and protein levels will be the same as, or higher than, the original CSF findings; and the glucose level will be the same or lower.
- » TB meningitis severity can be graded as follows:
 - Grade I: Alert, orientated, without focal neurological deficit
 - Grade II: Glasgow Coma score 10 to 14 with or without focal neurological deficit, or Glasgow Coma score of 15 with focal neurological deficit.
 - Grade III: Glasgow Coma score less than 10 with or without focal neurological deficit.

 LoE:IIb^{xvi}

GENERAL MEASURES

- » Hospitalise all patients with presumed TBM.
- » Monitor respiratory rate and pattern, pulse rate, blood pressure and oxygen saturation.
- » Monitor fluid and electrolyte status, particularly serum sodium, and manage hyponatraemia appropriately (Refer Chapter 7, Section 7.2.4 Hyponatraemia).
- » Monitor neurological status regularly, including level of consciousness, pupil responses and focal neurological signs.
- » A rapid deterioration in level of consciousness may indicate worsening hydrocephalus, hyponatraemia or cerebral infarction. Review serum sodium urgently and consider repeat neuroimaging.
- » Seizures may occur acutely and survivors of TBM may develop epilepsy. Monitor for seizures. To manage status epilepticus and seizures, refer to Chapter 14, sections 14.4. Epileptic seizures, 14.5 Status epilepticus and 14.6 Epilepsy. Choice of antiseizure medication should include consideration of the drug interactions with rifampicin and other anti-TB medicines.
- » Ensure adequate nutrition and refer for nutritional support. Enteral feeding may be required in patients with impaired consciousness or swallowing.
- » Refer for rehabilitative support, including physiotherapy, occupational therapy and speech therapy.

MEDICINE TREATMENT

Treatment of TB meningitis is as for pulmonary TB (see Section 27.1.1: Tuberculosis, pulmonary and lymphadenitis). Treat with standard combination

tuberculosis therapy and extend the duration of therapy to 9 months (2 months intensive phase, 7 months continuation phase).

Adolescents 12 to < 15 years with TB meningitis are **NOT** eligible for a shorter 4-month treatment regimen (see Figure 27.4 above)

In adults without HIV and PLWH with CD4 count > 200 cells/mm³ with TB meningitis of any grade, ADD:

- Dexamethasone, IV, dosing as follows:

Weeks	Dosing Regimen
Initial Dose	0.3 – 0.4 mg/kg/day for 2 weeks
Week 3	0.2 mg/kg daily
Week 4	0.1 mg/kg daily
Week 5 to 8	4 mg/day, tapering daily dose by 1 mg each week

OR

- Oral corticosteroids (intermediate-acting), e.g.:
 - Prednisone, oral, 60 mg daily for 2 weeks.
 - Then taper gradually over the next 6 weeks. See Appendix II for an example of a dose reduction regimen.

In PLWH with CD4 count ≤ 200 cells/mm³ and TB meningitis of any grade:

Adjunctive corticosteroids should not be routinely used in PLWH with CD4 counts ≤ 200 cells/mm³ and TB meningitis, as current evidence does not demonstrate clinical benefit.

27.10 DRUG-RESISTANT TB

U50, U50.9, U50.91

See the National Department of Health Updated Clinical Reference Guide: Clinical Management of **Rifampicin-Resistant Tuberculosis**, September 2023.

DESCRIPTION

Table 27.6 below presents key definitions and terminology for drug-resistant tuberculosis.

Table 27.6: Terminology and definitions associated with DR-TB

Drug Resistance Terminology	
Monoresistant TB	Resistant to only one anti-TB medicine, without resistance to other drugs.
Rifampicin-resistant TB (RR-TB)	Resistant to rifampicin ± resistance to another anti-TB medicine.

Multidrug resistant TB (MDR-TB)	Resistant to rifampicin AND isoniazid ($\pm$ resistance to other anti-TB medicines)
Pre-extensively drug-resistant TB (Pre-XDR-TB)	Resistant to rifampicin ($\pm$ resistant to isoniazid) AND resistant to fluoroquinolones
Extensively drug-resistant TB (XDR)	Resistant to: • Rifampicin ($\pm$ resistant to isoniazid), AND • At least one fluoroquinolone (levofloxacin or moxifloxacin) AND • Bedaquiline OR linezolid

LoE:IVb^{xx}

GENERAL MEASURES

- » Ensure that appropriate infection prevention and control measures are implemented at the facility, including:
 - adequate ventilation,
 - isolation of patients with confirmed or suspected infectious pulmonary TB, and
 - use of personal respiratory protection by healthcare workers (e.g. respirator **masks**).
- » Counsel and educate patients about the disease and its treatment, including treatment duration.
- » Explain the importance of completing treatment.
- » Advise against the use of tobacco and excessive alcohol.
- » Institute measures to prevent TB transmission in homes, including:
 - Instruct patients to cover their mouth and nose with their sleeve or a tissue when coughing or sneezing. After that, they should wash their hands and throw their tissue in the bin.
 - Windows and doors must be kept open (weather permitting) to increase the ventilation.
 - Where possible, sleep alone and not in a room with other household members.
 - While the patient is still considered infectious, provide them with surgical masks to wear at home, during transportation and medical consultations.
 - Refrain from having visitors in the home.
- » Screen all contacts for signs and symptoms of TB, and collect sputum for TB-NAAT to detect TB disease and determine susceptibility. A contact is any person who has shared the same enclosed space with a person with pulmonary TB (e.g. the TB source patient), for one or more nights **OR** for frequent or extended daytime periods. The exposure must have occurred while the source patient was not on TB treatment **OR** if the source patient is on treatment the exposure must have occurred during the three months before the source patient started TB treatment

- » Women and girls of childbearing potential should be encouraged to use effective contraception for the duration of DR-TB treatment to avoid becoming pregnant.

27.10.1 ISONIAZID MONORESISTANT TB

U50.00, U50.1, U50.10, U50.11

DESCRIPTION

Isoniazid monoresistant TB is TB disease caused by *M. tuberculosis* that is resistant to isoniazid but susceptible to rifampicin. If isoniazid monoresistant TB is detected by TB-NAAT, collect another sample to determine fluoroquinolone susceptibility (see Figure 27.1 and Figure 27.2). If isoniazid monoresistance is detected > 28 days after starting treatment with RHZE for drug-susceptible TB, repeat TB-NAAT testing to rapidly assess for rifampicin resistance.

MEDICINE TREATMENT

- » Treatment should be given for at least 6 months.

Confirmed isoniazid monoresistant TB and fluoroquinolone susceptible:

- RHZE, oral, daily at standard weight-based dosing for 6 months.

AND

- Levofloxacin, oral, daily for 6 months:
 - Body weight 30 to < 46 kg: 750 mg.
 - Body weight ≥ 46 kg: 1000 mg.

Confirmed isoniazid monoresistant AND fluoroquinolone susceptible with isoniazid contraindication:

- Rifampicin, oral, 10 mg/kg daily for 6 months.

AND

- Ethambutol, oral, 15 mg/kg daily for 6 months.

AND

- Pyrazinamide, oral, 25 mg/kg daily for 6 months.

AND

- Levofloxacin, oral, daily for 6 months:
 - Body weight 30 to <46 kg: 750 mg.
 - Body weight ≥ 46 kg: 1000 mg.

REFERRAL

- » If isoniazid AND fluoroquinolone resistance is detected, discuss with an expert.
- » If isoniazid resistance is detected late in a patient not responding to drug-susceptible TB treatment, discuss with an expert.

27.10.2 RIFAMPICIN RESISTANT, PRE-XDR AND XDR TB

U50.0, U50.2, U50.20, U50.21, U50.5

DESCRIPTION

Rifampicin resistant tuberculosis (RR-TB) is TB disease caused *M. tuberculosis* that is resistant to rifampicin, with or without resistance to other anti-TB drugs. Pre-XDR-TB is TB disease caused by *M. tuberculosis* that is resistant to rifampicin (with or without resistance to isoniazid) and to at least one fluoroquinolone (either levofloxacin or moxifloxacin). Extensively drug-resistant TB (XDR-TB) is TB disease caused by *M. tuberculosis* that is resistant to rifampicin AND at least one fluoroquinolone (levofloxacin or moxifloxacin) AND either bedaquiline or linezolid.

DIAGNOSIS

All people with signs and symptoms of TB should have a specimen sent for TB-NAAT testing. Some TB-NAAT assays test for both rifampicin and isoniazid resistance (e.g. BD MAX™ MDR-TB). Xpert® MTB/RIF Ultra, a type of TB-NAAT, only tests for rifampicin resistance. A rifampicin resistant result detected by Xpert® MTB/RIF Ultra, or other TB-NAAT, is sufficient to start a patient on RR-TB treatment. However, all people who test positive for *M. tuberculosis* with rifampicin resistance must have an additional specimen sent for DR-TB reflex testing which may include Xpert® MTB/XDR testing for fluoroquinolone resistance, targeted next generation sequencing (tNGS), TB microscopy and culture, and phenotypic drug susceptibility testing for bedaquiline and linezolid if culture positive.

MEDICINE TREATMENT**RR-TB and Pre-XDR-TB treatment**

Consult the most recent national drug-resistant TB programme guidelines. Most people with RR- or Pre-XDR-TB will be eligible to receive the 6-month BPaL-L regimen.

Non-pregnant adults and adolescents (≥ 15 years) with pulmonary or non-severe extrapulmonary RR- or Pre-XDR-TB:**BPaL-L regimen**

- Bedaquiline, oral, 400 mg daily for 2 weeks.
Followed by bedaquiline, oral, 100 mg, daily from week 3 to week 24
AND
- Pretomanid, oral, 200 mg daily for 24 weeks.
AND
- Linezolid, oral, daily for 24 weeks:
 - 30 – 35.9 kg: 300 mg.
 - ≥ 36 kg: 600 mg.**AND**

LoE:IVb ^{xxi}

- Levofloxacin, oral, daily for 24 weeks:
 - 30 to < 46 kg: 750 mg.
 - ≥ 46 kg: 1000 mg.
 - NOTE: If fluoroquinolone resistance is detected (e.g. Pre-XDR-TB), stop levofloxacin and continue treatment with bedaquiline, pretomanid and linezolid for the remaining duration of the 24 week course.

CAUTION

The following patient groups are ineligible for the BPAL-L regimen:

- » People with severe extrapulmonary RR- or Pre-XDR-TB (e.g. TB meningitis, osteoarticular TB, or disseminated or miliary TB).
- » People with an RR-TB strain that is resistant to bedaquiline, linezolid, pretomanid or delamanid.
- » Pregnant women and children or adolescents < 15 years.

Refer to the most recent National Department of Health programmatic guidelines and circulars for further management guidance.

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Common adverse drug reactions associated with medicines included in the BPAL-L regimen

Table 27.7: Adverse drug reactions associated with BPAL-L

Adverse drug reaction	Most likely drug responsible	Management
Anaemia	Linezolid	If Hb < 8 g/dL in first 8 weeks of BPAL-L treatment: Interrupt linezolid treatment, monitor and consider blood transfusion if clinically appropriate. Linezolid must be used for at least 2 months for the BPAL-L regimen to be considered effective. If linezolid must be interrupted, discuss with NCAC/expert. If Hb < 8 g/dL after 8 weeks of BPAL-L: linezolid can be stopped provided there has been a clinical response (e.g. reduction in symptoms, weight gain, or culture conversion). If clinical response inadequate, discuss with NCAC/expert.
Thrombocytopenia	Linezolid	If platelets < 50 x 10⁹/L: Stop linezolid until thrombocytopenia improves, exclude other causes, and discuss further management with NCAC/expert.
Neutropenia	Linezolid	If neutrophils < 0.75 x 10⁹/L:

		Stop linezolid until neutropenia improves, exclude other causes, and discuss further management with NCAC/expert.
Peripheral neuropathy	Linezolid	Drug-induced peripheral neuropathy can be irreversible if the offending drug is not stopped promptly. If neuropathy interferes with daily activities, stop linezolid. If this occurs before 8 weeks of therapy, discuss with an expert. For milder forms of neuropathy treat symptomatically and try to continue linezolid until at least 8 weeks of therapy with close monitoring for deterioration in symptoms. Reduce the dose or discontinue linezolid if symptomatic neuropathy occurs after 8 weeks. For symptomatic management of neuropathy avoid amitriptyline, which may prolong the QT interval in association with other DRTB medicines, and carbamazepine, which may interact with other TB medicines. Special access to pregabalin or gabapentin may be granted on recommendation by local pharmacy and therapeutics committees (PTCs) for these patients.
Visual impairment	Linezolid	If there is a decline in visual acuity, withhold linezolid and refer patient to ophthalmologist for further evaluation.
QTcF prolongation (QTcF = Fridericia corrected QT interval)	Bedaquiline, moxifloxacin, pretomanid, delamanid, levofloxacin	• If QTcF ≥ 450 ms and symptomatic (e.g. syncope, fainting, chest pain, palpitations, dizziness or loss of consciousness), hospitalise patient and withhold all medicines that may prolong QT until cause of symptoms has been assessed. • If QTcF ≥ 450 ms but < 470 ms with no symptoms: continue routine monthly QT monitoring. Discontinue other QT-prolonging medications where possible. • If QTcF ≥ 470 ms but < 500 ms with no symptoms: repeat ECG at rest on the same day. If still ≥ 470 ms but < 500 ms and asymptomatic, repeat ECG weekly until stable. Check TSH and check and correct electrolytes. Discontinue other QT-prolonging medications where possible.

		If QTcF ≥ 500 ms with no symptoms repeat ECG at rest on the same day. If still ≥ 500 ms, withhold all QT-prolonging medicines and all TB medicines. Check TSH and check and correct electrolytes. Discuss patient with expert.
Arthralgia, arthritis	Fluoroquinolones, bedaquiline	Manage symptomatically with non-pharmacological measures (e.g. physical therapy, massage) and analgesia.
Hyperlactataemia, lactic acidosis	Linezolid	Hospitalise patient with hyperlactataemia or lactic acidosis and stop linezolid immediately.
Hepatotoxicity (e.g. nausea, vomiting, right upper quadrant pain, jaundice)	Bedaquiline, fluoroquinolones, pretomanid	- Monitor LFTs. - If elevated ALT, do full LFTs and INR and rule out other potential causes of hepatitis. - Stop BPaL-L and all potentially hepatotoxic medicines if ALT > 5 times the upper limit of normal (ULN) irrespective of symptoms, or if > 3 times the ULN and patient has symptoms of DILI. - Start background regimen of linezolid, clofazimine, terizidone and delamanid. - Wait for ALT to decrease to < 100 IU/L before considering re-challenge. - Re-challenge sequentially with treatment dosages of levofloxacin, followed by pretomanid, followed by bedaquiline, every 5 to 7 days, with monitoring of liver function before introducing the next medicine. - Once successfully re-challenged, stop clofazimine, terizidone and delamanid and continue BPaL-(L). If re-challenge is unsuccessful, discuss with an expert.
Skin reactions	All agents	Treatment can be continued if rash is mild. Stop treatment if rash is severe e.g. blistering, mucosal involvement, fever, feeling unwell or hepatitis. Patients with a severe rash must be hospitalised. Patients with a severe rash should be discussed with NCAC/expert.

LoE: IVb^{xxiii}

Patients who are not eligible for the BPAL-L regimen or in whom bedaquiline, linezolid or pretomanid are prematurely and permanently discontinued due to toxicity may require an individualised regimen. Discuss these patients with a TB expert.

Examples of anti-tuberculosis medicines used in RR- and Pre-XDR-TB individualised regimens include:

- Levofloxacin
- Bedaquiline
- Linezolid
- Clofazimine
- Terizidone
- Ethambutol
- Delamanid
- Pyrazinamide
- Ethionamide
- Para aminosalicylic acid
- High-dose isoniazid

LoE:IVb^{xxiv}

XDR-TB treatment

There is no standardised treatment for XDR-TB. Patients with XDR-TB should be discussed with the National Clinical Advisory Committee (Email: NCAC@witshealth.co.za) and referred to a TB hospital. These patients require an individualised regimen of at least 4 effective medicines, selected from the list above, based on susceptibility tests and treatment history, and potentially including amikacin and a carbapenem. Infection control to prevent airborne transmission is essential to prevent nosocomial transmission.

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^{xx} Terminology: NDoH. Clinical management of rifampicin- resistant tuberculosis. September 2023 accessible online: <https://www.health.gov.za/wp-content/uploads/2023/10/Updated-RR-TB-Clinical-Guidelines-September-2023.pdf>

^{xxi} Linezolid (dose rounding): Shorter RR-TB regimen (BPAL-L) in patients ≥ 15 yrs October 2024. Version 3, updated February 2026 based on Clinical Management of Rifampicin-Resistant Tuberculosis: Updated Clinical Reference Guide, September 2023, Circular 2/23: Implementation of BPAL-L regimen and Circular 1/2026: Clinical Management of Rifampicin-resistant Tuberculosis in Pregnancy and Breastfeeding, South African National Department of Health. Accessible online:

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^{xxii} BPAL-M regimen: NDoH. Review - Adolopment_WHO_DRTB_Guidelines_4May2023_Final.

^{xxiii} BPAL-L (ADRs): 2023 RR Guidelines, 2019 RR Guidelines.

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SOUTH AFRICAN NATIONAL DEPARTMENT OF HEALTH
NEMLC SUMMARY REPORT ON UPDATES MADE TO THE
THE STANDARD TREATMENT GUIDELINES AND ESSENTIAL MEDICINE LIST GUIDANCE
PRODUCTS
AH Chp 27 TUBERCULOSIS

Document Version Control

Report Version	Date	Detail
V1.0	30/07/2026	The AH Chp 27 is a newly developed chapter detailing the management of tuberculosis and related complications. It includes updates to STGs that were previously included across different chapters of the AH publication as well as some newly developed STGs.
V1.1	28/09/2026	Ratified for publication

Summary Tables

New STGs

Newly developed STGs added to the AH publication include:

STG/SECTION	GUIDANCE PRODUCTS (Tick relevant)				MEDICINE / MANAGEMENT	ADDED / DELETED / AMENDED	TI* CONSIDERATIONS (if applicable)
	PHC STGs & EML	AH STG & EML	PaedH STG & EML	TQ EML			
Report Version 1.0							
27.1 Drug-susceptible TB	✓	✓	✓				
27.2 Tuberculosis, extrapulmonary	✓	✓	✓				
27.4 Extrapulmonary tuberculosis, empyema	✓	✓	✓				
27.5 Extrapulmonary tuberculosis, lymphadenitis	✓	✓	✓				
27.6 Tuberculosis, abdominal	✓	✓	✓				
27.7 Tuberculous pericarditis	✓	✓	✓		Corticosteroids, oral prednisolone	Added	Yes Prednisolone or prednisone
27.8 Tuberculous, osteoarticular	✓	✓	✓				
27.10 Drug-resistant TB	✓	✓	✓				

Medicine Amendments

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

STG/SECTION	GUIDANCE PRODUCTS (Tick relevant)				MEDICINE / MANAGEMENT	ADDED / DELETED / AMENDED	TI* CONSIDERATIONS (if applicable)
	PHC STGs & EML	AH STG & EML	PaedH STG & EML	TQ EML			
Report Version 1.0							
27.1.1 Tuberculosis, pulmonary	✓	✓	✓		Pyridoxine - Isoniazid-containing TB regimens (standard dose isoniazid)	Retained	N
27.9 Tuberculosis, meningitis		✓			Corticosteroids, IV dexamethasone - HIV-negative adults with TB meningitis (any grade)	Added	N
		✓			Corticosteroids, oral prednisolone - HIV-negative adults with TB meningitis (any grade)	Added	Yes Prednisolone or prednisone
		✓			Corticosteroids, IV dexamethasone - adults with HIV and TB meningitis of any grade, with CD4 count ≤ 200 cells/mm ³	Not added	
		✓			Corticosteroids, oral prednisolone - adults with HIV and TB meningitis of any grade, with CD4 count ≤ 200 cells/mm ³	Not added	
		✓			Corticosteroids, IV dexamethasone - adults with HIV and TB meningitis of any grade, with CD4 count > 200 cells/mm ³ :	Added	N
		✓			Corticosteroids, oral prednisolone - adults with HIV and TB meningitis of any grade, with CD4 count > 200 cells/mm ³	Added	Yes Prednisolone or prednisone
27.10.2 Rifampicin resistant, Pre-XDR & XDR TB		✓			Gabapentin - Linezolid-induced peripheral neuropathy	Not added	

		✓		✓	Pregabalin - Linezolid-induced peripheral neuropathy	Not added (on T&Q EML)	
	✓	✓	✓		Delamanid- anti- tuberculosis medicines used in RR- and Pre-XDR-TB individualised regimens	Added	N
	✓	✓	✓		Para-aminosalicylic acid (PAS) - anti- tuberculosis medicines used in RR- and Pre-XDR-TB individualised regimens	Added	N
	✓	✓			High-dose isoniazid	Added	N

*Therapeutic Interchange

AH Tuberculosis Chapter 27

Alignment with national TB programme guidelines: The intended focus of the Standard Treatment Guidelines (STGs) is on medicine treatment. Updates to the STGs on the management of TB has been done in close collaboration with the national TB programme and relevant cross-references to the various TB programme guidelines have been included in the STG, where appropriate and supported by the NEMLC. Cross references to operational guides on the management of TB are not included in the STGs as review of these guides/manuals remain outside the scope of the NEMLC.

Terminology

- Following external stakeholder comment, the term ‘drug-sensitive’ was amended to ‘drug-susceptible’ throughout the chapter.
- The acronym for rifampicin, isoniazid, pyrazinamide and ethambutol fixed-dose combinations were standardised as follows “RHZE; RHZ; RH”.

Section 27.1 Drug-susceptible tuberculosis

STG – New addition

New STG guidance on the management of drug-sensitive TB has been added as tabulated below.

27.1 DRUG-SUSCEPTIBLE TUBERCULOSIS

* Notifiable medical condition.

DESCRIPTION

Tuberculosis (TB) is a serious health problem in South Africa. TB is an infection caused by *Mycobacterium tuberculosis*. TB can affect the lungs (pulmonary TB) or the lymph nodes, abdomen, central nervous system, and many other extrapulmonary sites. The signs and symptoms of TB depend on the site of infection, and include loss of weight, night sweats and fever. The risk of developing TB disease is higher among people living with HIV (PLWH). All people diagnosed with TB must be screened for HIV.

DIAGNOSIS

Molecular tests (e.g. TB nucleic acid amplification tests, TB-NAAT), smear microscopy and TB culture are used to diagnose TB by identifying *M. tuberculosis* in sputum and other samples (e.g. urine, cerebrospinal fluid, pleural fluid, ascitic fluid, lymph node aspirate). TB-NAAT testing is also used to rapidly determine drug susceptibility. Some TB-NAAT assays, such as BD MAX™

MDR-TB, test for both rifampicin and isoniazid resistance. Other types of TB-NAAT assays include Xpert® MTB/RIF Ultra which tests for rifampicin resistance only, and Xpert® MTB/XDR which detects a wider range of drug resistance including fluoroquinolone resistance.

In PLWH, TB-NAAT is not an adequate 'rule out' test. PLWH who have features of TB but are TB-NAAT negative require further investigation (e.g. chest X-ray, TB culture, urine lipoarabinomannan (U-LAM)) and may need empiric anti-tuberculosis therapy. Perform a U-LAM in the following people being investigated for TB:

- All PLWH admitted to hospital
- All symptomatic PLWH seen in an outpatient setting with:
 - CD4 ≤ 200 within the last 6 months **OR**
 - Advanced HIV disease **OR**
 - Current serious illness warranting admission.

Section 27.1.1 Tuberculosis, pulmonary

Pyridoxine - Isoniazid-containing TB regimens (standard dose isoniazid): Retained

The recommendation for daily oral supplementation of pyridoxine 25mg for the duration of isoniazid-containing TB therapy has been retained as it is aligned with the NDoH South African National TB Guidelines – Adults¹ and WHO TB guidelines² i.e. to include supplementation for high-risk individuals. According to the WHO, "Routine administration of pyridoxine supplements to otherwise healthy individuals on a standard dose of isoniazid is not usually required."

DS-TB – age thresholds

NEMLC has applied an age threshold of < 15 years for eligibility for the shortened TB treatment regimen in children with DS-TB. NEMLC acknowledges that this is discordant with the results from the SHINE trial³. NEMLC, in consultation with the national TB programme, has agreed to align the age threshold with national TB guideline recommendations, to facilitate ease of implementation.

Infection prevention and control measures

Guidance on basic infection prevention and control measures has been added under the section on general measures as detailed below, in response to external comments received.

Specimens for TB-NAAT

The recommendation to send two sputum samples up front for TB-NAAT in people with suspected pulmonary TB, was not supported as the TB programme diagnostic algorithm recommends that one sputum sample be sent for testing initially. As testing two sputum samples for all suspected cases will have cost implications, the TB programme would need to assess cost effectiveness and affordability before such a change to the diagnostic guidance can be supported.

TB-NAAT diagnostic algorithms

¹ NDoH South African National TB Guidelines – Adults https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-04/TB%2520Adult_2017.pdf

² WHO Operational Handbook Module 1: Prevention (TB Preventive therapy) <https://tbksp.who.int/en/node/1271>

³ Turkova A, Wills Genevieve H, Wobudeya E, et al. Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children. New England Journal of Medicine. 2022;386(10):911-922. Treated for Nonsevere Tuberculosis in the SHINE Trial. Clin Infect Dis. 2024 Jul 19;79(1):70-77. doi: 10.1093/cid/ciae193. PMID: 38592950; PMCID: PMC11259218.

The three TB NAAT diagnostic algorithms as included in the STGs (detailed below) were provided by the TB programme. External comment regarding the appropriateness of collecting of additional sputum samples for culture in people living with HIV with negative TB-NAAT who are asymptomatic, has been referred to the TB program for review. External comment suggested that the low yield in this population may not be cost effective.

Urine lipoarabinomannan (U-LAM) test

Guidance for U-LAM testing in PLWH is aligned to guidance in the National consolidated guidelines for the management of advanced HIV disease⁴.

Contacts of people diagnosed with TB

In response to an external comment received, the following definition has been added for contacts of people diagnosed with TB: *“A contact is any person that has shared the same enclosed space with a person with pulmonary TB (e.g. the TB source patient), for one or more nights, or for frequent or extended daytime periods, during the three months before the source patient started TB treatment.”*

Monitoring of patients with pulmonary TB

Guidance on baseline and follow-up sputum smear microscopy has been added in response to external comment received, as detailed in the STG text below.

Non-severe DS-TB in adolescents – radiological criteria

STG guidance on the radiological criteria that excludes adolescents from treatment shortening for non-severe DS-TB has been retained as lung consolidation ≥ 1 lobe. This aligns with the national TB programme guideline and is informed by the radiological definition included in the SHINE trial⁵. This is in contrast to the WHO guideline⁶ which defines non-severe DS-TB as PTB confined to one lobe.

Treatment: Weight-based dosing guidance for RHZE

The NEMLC acknowledges that the dose guidance included in the STGs is not aligned to the most recent WHO guideline recommendations dosing table.⁷ The WHO adult weight-band dosing table first appeared in the 2022 iteration of WHO guidelines. However, no specific reference to guideline development group discussions or the evidence underpinning these revised dosing recommendations is provided. The same dosing table is retained in 2025 WHO guidelines. There is some concern with the current WHO weight-bands, specifically relating to the broad 35 – 65kg weight band versus the comparatively narrow 25 – 30 kg and 30 – 35 kg bands. Given the lack of supporting evidence for these weight bands, and anticipated revisions in the weight-banded dosing recommended by WHO over the coming months, the NEMLC recommends that the existing STG dose recommendations, which are aligned with 2014 programmatic guidance, be retained.

Management of adverse drug reactions

⁴ National Department of Health. National Consolidated Guidelines for the prevention and management of HIV in adults, adolescents, children, infants and pregnant and breastfeeding women. May 2026 v2. Last accessed online on 16 Sep 2026: <https://knowledgehub.health.gov.za/system/files/elibdownloads/2026-06/National%20Consolidated%20Guidelines%2014-05-2026%20version%20web%20FFF.pdf>

⁵ Turkova A, Wills Genevieve H, Wobudeya E, et al. Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children. New England Journal of Medicine. 2022;386(10):911-922. Treated for Nonsevere Tuberculosis in the SHINE Trial. Clin Infect Dis. 2024 Jul 19;79(1):70-77. doi: 10.1093/cid/ciae193. PMID: 38592950; PMCID: PMC11259218.

⁶ WHO operational handbook on tuberculosis. Module 4: treatment and care. Geneva: World Health Organization; 2025. Licence: CC BY-NC-SA

⁷ WHO operational handbook on tuberculosis. Module 4: treatment and care. Geneva: World Health Organization; 2025. Licence: CC BY-NC-SA

A link to the University of Cape Town Medicines Information Centre (UCT MIC) booklet, for managing adverse drug reactions associated with TB medicines has been added to the STG. The National HIV & TB Health Care Worker Hotline on 0800 212 506, has recently been discontinued. It is anticipated that going forward, healthcare worker queries are likely to be directed to the UCT MIC. Referencing the source booklet in the STGs may be beneficial to clinical staff.

STG –Update

STG guidance on the management of pulmonary TB has been subject to editorial updates as detailed below and transferred from AH Chp 16 Respiratory conditions to Chp 27 Tuberculosis.

AMENDED FROM	AMENDED TO
16.9 TUBERCULOSIS, PULMONARY A15.0-3/A15.7-8/A16.0-2/A16.4/A16.7-9 + (B20.0) * Notifiable medical condition. Tuberculosis (TB) treatment guidelines are updated regularly. This STG should be read in conjunction with the most recent National Tuberculosis Control Programme guidelines. DESCRIPTION A chronic, granulomatous infection of the lungs caused by <i>M. tuberculosis</i>. Pulmonary tuberculosis is a serious health problem in South Africa and is exacerbated by HIV and multidrug resistant tuberculosis (MDR-TB). <i>Note: All patients with TB disease should be notified.</i> Diagnosis Molecular tests (TB nucleic acid amplification tests, TB-NAAT) are used for the diagnosis of <i>M. tuberculosis</i> and the identification of drug-resistant organisms. While some TB-NAAT assays test for both rifampicin and isoniazid resistance, Xpert® MTB/RIF Ultra, a type of TB-NAAT, only tests for rifampicin resistance. Refer to PHC EML Section 17.4.1 Pulmonary TB in adults for guidance on sputum sampling and interpretation of results relating to TB-NAAT assays. The diagnosis of pulmonary TB in adults is made on a positive TB-NAAT on sputum. In some patients, especially HIV-infected patients, TB-NAAT is not an adequate 'rule out' test. PLHIV who have features of TB but are TB-NAAT negative require further investigation and may	27.1.1 TUBERCULOSIS, PULMONARY A15.0-3/A15.7-8/A16.0-2/A16.4/A16.7-9 + (B20.0) * Notifiable medical condition. DESCRIPTION Pulmonary tuberculosis (PTB) refers to infection of the lung tissue or airways caused by <i>M. tuberculosis</i>. DIAGNOSIS PTB is diagnosed on sputum by TB-NAAT, smear microscopy, or TB culture. Sputum induction with nebulised sodium chloride 5% should be attempted for patients unable to spontaneously produce sputum. In people with suspected PTB: » Send 1 sputum specimen for TB-NAAT » Manage results of TB-NAAT, based on the patient's previous history of TB, as outlined in Figures 27.1, 27.2 and 27.3 below. » All patients with MTB detected on TB-NAAT require additional sputum to be sent at baseline for acid-fast bacilli (AFB) smear microscopy to establish a baseline for treatment monitoring. » Patients who are at risk of drug-resistant TB (e.g. previous episode of TB treatment, prisoners, healthcare workers) should have sputum sent to exclude isoniazid monoresistance if the specific TB-NAAT test used for diagnosis of PTB did not already test for this. Patients not treated for TB within the last 2 years

need empiric anti-tuberculosis therapy while awaiting TB cultures.

Patients who have previously completed TB treatment (especially within the last 2 years) may still test TB-NAAT positive in the absence of active disease. TB should be confirmed on culture in this setting.

All patients who are TB-NAAT positive require further sputum to be sent for AFB to allow for monitoring of treatment. TB-NAAT should not be used for monitoring.

All TB patients must be screened for HIV. PLHIV with concomitant TB are eligible for cotrimoxazole prophylaxis, regardless of CD4 count.

Sputum induction with nebulised sodium chloride 5% should be attempted for patients unable to spontaneously produce sputum. A wide bore needle (e.g. 18G) aspiration for TB-NAAT should be done in patients with suspected TB lymphadenitis.

Urine lipoarabinomannan (LAM) is a good “rule-in” diagnostic test for:

- 1) PLHIV with CD4 ≤ 200 cells/ μ L who have signs and symptoms of pulmonary and/or extrapulmonary TB, and
- 2) PLHIV who are seriously ill.

MEDICINE TREATMENT

All patients with active TB who are TB-NAAT positive and rifampicin sensitive should receive intensive phase therapy for 2 months and 4 months of continuation phase treatment (see table below). Patients who are at risk of having resistant TB (e.g. previous episode of TB treatment, prisoners, and health care workers) should have sputum sent to exclude INH mono resistance if the particular TB-NAAT test in use for pulmonary specimens does not already test for this.

National tuberculosis control programme guidelines

Figure 27.1: TB NAAT Diagnostic Algorithm 1 - Guidance on managing TB-NAAT “MTB detected” results in patients NOT treated for TB within the last 2 years (Source: NDoH TB Program)

Patients treated for TB within the last 2 years

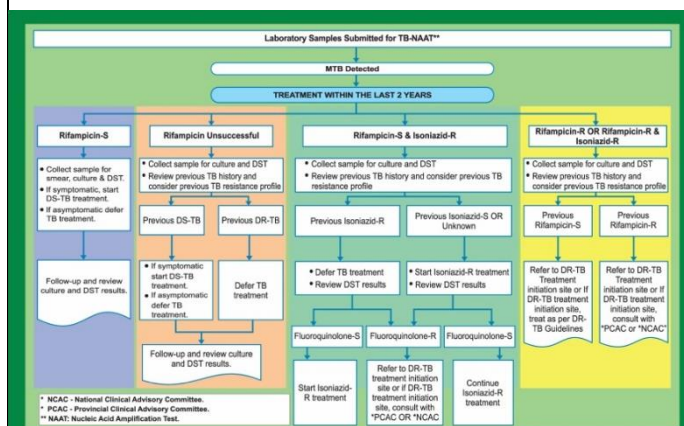


Figure 27.2: TB NAAT Diagnostic Algorithm 2 - Guidance on managing TB-NAAT “MTB detected” results in patients treated for TB within the last 2 years (Source: NDoH TB Program)

Patients who have previously completed TB treatment (especially within the last 2 years) may still test TB-NAAT positive in the absence of active disease. In these patients, new TB disease should be confirmed with TB culture.

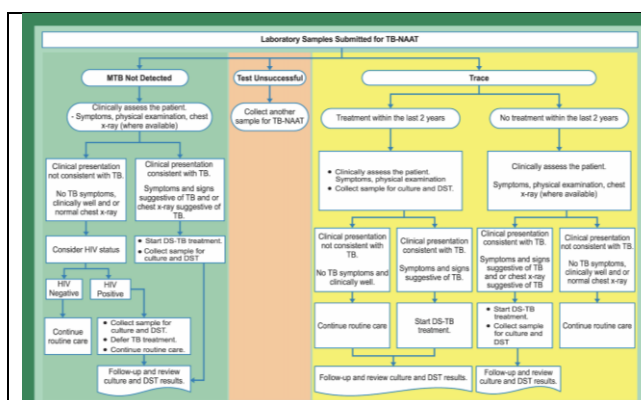


Figure 27.3: TB NAAT Diagnostic Algorithm 3 - Guidance on managing TB-NAAT “MTB Not detected”, “Unsuccessful”, “Trace” results (Source: NDoH TB Program)

NOTE: In PLWH, TB-NAAT is not an adequate ‘rule out’ test. PLWH who have features of TB but are TB-NAAT negative require further investigation (e.g. chest X-ray, TB culture, urine lipoarabinomannan (U-LAM)) and may require empiric anti-tuberculosis therapy.

Perform a U-LAM in the following people being investigated for TB:

- All PLWH admitted to hospital
- All symptomatic PLWH seen in an outpatient setting with:
 - CD4 ≤ 200 within the last 6 months **OR**
 - Advanced HIV disease **OR**
 - Current serious illness warranting admission.

GENERAL MEASURES

Fixed dose drug combinations available:			
RH – 150/75 mg		RH – 300/150 mg	
RHZE – 150/75/400/275 mg			
R – Rifampicin		H – Isoniazid (INH)	
Z – Pyrazinamide		E – Ethambutol	

Treatment for known or presumed drug sensitive TB:

Pre-treatment body weight	Two months initial phase	Four months continuation phase	
	RHZE (150/75/400/275)	RH (150/75)	RH (300/150)
30–37 kg	2 tablets	2 tablets	
38–54 kg	3 tablets	3 tablets	
55–70 kg	4 tablets		2 tablets
71 kg and over	5 tablets		2 tablets

INH may result in the development of a peripheral neuropathy due to drug-induced pyridoxine deficiency. Prophylactic pyridoxine supplementation is recommended in patients on INH that are at high risk of peripheral neuropathy (e.g. HIV, diabetes, alcoholics).

- Pyridoxine 25 mg, oral, daily for duration of INH-containing TB therapy.

Close contacts of TB patients (particularly children <5 years of age) should be screened and managed as per National TB Guidelines.

- » Ensure that appropriate infection prevention and control measures are implemented at the facility, including:
 - Adequate ventilation.
 - Isolation of patients with confirmed or suspected infectious pulmonary TB.
 - Use of personal respiratory protection by healthcare workers (e.g. respirator masks).
- » Counsel patients about the disease and infection control in the home.
- » Contacts of people diagnosed with PTB should be screened for TB disease. A contact is any person that has shared the same enclosed space with a person with pulmonary TB (e.g. the TB source patient), for one or more nights, or for frequent or extended daytime periods, during the three months before the source patient started TB treatment.
- » Explain the importance of completing treatment.
- » Advise against the use of tobacco and excessive alcohol.
- » If more than two doses of treatment are missed, make extra effort to identify and manage any problems affecting adherence.
- » Patients with PTB must have a baseline smear microscopy result. Treatment response is monitored by repeat sputum smear microscopy at 7 and 23 weeks of treatment. TB-NAAT should **NOT** be used for monitoring on treatment. Refer to Table 27.1 below for the timing of sputum examinations and the recommended actions based on results.
- » If there is a poor response to treatment, alternative diagnoses and drug resistance must be considered.

MEDICINE TREATMENT

Administer total daily amount of each medicine in one dose and not as divided doses.

Adolescents aged 12 to < 15 years

Adolescents aged 12 to < 15 years with non-severe drug-sensitive PTB and/or TB lymphadenitis are eligible for a shortened 4-month treatment regimen. Severity of disease and eligibility for treatment shortening in adolescents is based on clinical, radiological and microbiological features at the time of TB diagnosis, at month 1 of treatment, and at month 4 of treatment (see Figure 26.4 below).

Table 27.1. Sputum smear microscopy monitoring in patients with drug-susceptible pulmonary TB

End of Intensive Phase	
Timing of sputum examination	Action
	If sputum smear microscopy negative: » Change to the continuation phase of treatment at the end of the 8th week of intensive phase treatment. » Repeat smear microscopy at 23 weeks of treatment.

	One week before the end of the 2 months intensive phase of treatment (i.e. at 7 weeks).	If sputum smear microscopy positive: » Reassess the patient clinically. » Address treatment compliance by counselling the patient and identifying a treatment supporter where necessary. » Repeat drug susceptibility testing including TB-NAAT, culture and DST. » Continue intensive phase treatment (e.g. RHZE) for one month but review the drug susceptibility results as soon as available. » If drug susceptible, repeat smear microscopy one week before the end of the third month of treatment (i.e. at 11 weeks). » If the repeat smear microscopy at week 11 is negative, change to the continuation phase of treatment at the end of the 12th week. » If drug resistance is detected, refer to Section 23.3. Drug-Resistant Tuberculosis for initiation of treatment.
	End of Continuation Phase	
	Timing of sputum examination	Action
	One week before the end of the 4 months continuation phase (i.e. at 23 weeks).	If sputum smear microscopy negative: » Stop treatment at the end of the 24th week of treatment. » Register the patient as “Cured”. If sputum smear microscopy positive: » Reassess the patient clinically. » Stop TB treatment and register the patient as “Treatment failure”. » Repeat drug susceptibility testing including TB-NAAT, culture and DST. » Review the drug susceptibility results as soon as available. » If drug resistance is detected, refer to Section 23.3. Drug-Resistant Tuberculosis for initiation of treatment. » If drug susceptible, re-start TB treatment, counsel the patient and provide treatment support.
Adapted from National Tuberculosis Management Guideline, 2014.		
MEDICINE TREATMENT Administer the total daily amount of each medicine as a single daily dose, not as divided doses.		
Adolescents aged 12 to < 15 years Adolescents aged 12 to < 15 years with non-severe drug-susceptible PTB and/or TB lymphadenitis are eligible for a shortened 4-month treatment regimen. Severity of disease and eligibility for treatment shortening in adolescents is based on clinical, radiological and microbiological features at the time of TB diagnosis, at month 1 of treatment, and at month 4 of treatment (see Figure 27.4 below).		
Figure 27.4: Eligibility for TB treatment shortening in adolescents 12 to <16 years of age. (Adapted from Box 1 and Figure 10 from the National Department of Health “A Clinical Guideline for the Diagnosis and Treatment of Drug-susceptible TB in Children and Adolescents in South Africa. 2015.”)		
NOTE:		

	At Diagnosis	Clinical Criteria	Eligible for treatment shortening if ALL of the below criteria are met: • Age 3 months to < 15 years at start of TB treatment • Non-severe drug-sensitive pulmonary TB (including simple TB pleural effusion or cervical TB lymphadenitis)presumed or confirmed with no evidence of extrapulmonary TB other than lymphadenitis • First episode of TB (no previous TB treatment) • No danger signs indicating severe illness at presentation¹ • No severe acute malnutrition • No asymmetric or persistent wheezing • If living with HIV: viral load < 1000 in the preceding 3/12 AND on ART for >3/12 • No respiratory sample that is AFB smear positive
		Radiological Criteria	Eligible for treatment shortening if NONE of the following are present: • Complicated intra-thoracic lymph node TB (i.e., airway compression or deviation and/or hyperinflation or collapse) • Consolidation ≥ 1 lobe • Complicated pleural effusion (loculated effusion, empyema or pneumothorax) • Miliary pattern • Cavities
	At Follow-up	Clinical Criteria	Eligible for shorter treatment if ALL below criteria are met: • Adherent to treatment • MONTH 1: All TB signs and symptoms improved • MONTH 4: All TB signs and symptoms resolved and appropriate/improving weight trend
	¹ General danger signs include being unable to drink, vomiting everything, convulsions, unconsciousness, signs of shock. In addition, any signs of severe respiratory illness, signs of severe dehydration, signs of meningitis, or severe anaemia (HB < 7 g/dL). » If no chest X-ray (CXR) is available to confirm that the radiological criteria outlined in Figure 27.4 for non-severe pulmonary TB are met, adolescents aged 12 to < 15 years are NOT eligible for the shorter 4-month treatment regimen. » Adolescents 12 to < 15 years with a sputum sample that is AFB smear-positive are NOT eligible for the shorter 4-month treatment regimen. Lymph node fine needle aspiration smear positivity is not an exclusion. » Adolescents who are not eligible for the shortened treatment regimen and adolescents ≥ 15 years should receive the standard six-month drug-susceptible TB treatment regimen outlined below, or the recommended regimens for other forms of extrapulmonary TB. » If there is any uncertainty about whether an adolescent aged 12 to < 15 years is eligible for treatment shortening or not, rather treat for the full 6 months. » In adolescents with TB lymphadenitis, if cervical lymph nodes did not decrease in size by month 4 of treatment, continue to 6		

months of treatment. If there is not a significant reduction in size of the lymph nodes, or if there is enlargement in lymph nodes, especially if TB was not bacteriologically confirmed, refer for further investigation.

The shortened 4-month treatment regimen consists of 2 months of intensive phase treatment and 2 months of continuation phase treatment.

Dosing for adolescents 12 to < 15yrs with drug-susceptible TB eligible for treatment shortening:

» Adjust treatment dosages to current body weight.

Table 27.2: Weight-based dosing guidance for adolescents 12 to < 15yrs with drug-susceptible TB.

Pre-treatment body weight	2 months intensive phase given daily		2 months continuation phase given daily	
	RHZ	E	RH	
	75/50/150 mg dispersible tablet (scored)	400mg tablet (not scored) OR 400mg/8ml suspension [#]	75/50 mg dispersible tablet (scored)	
12–15.9 kg	3 tablets	¾ tab or 6 mL	3 tablets	
16–24.9 kg	4 tablets	1 tab or 8 mL	4 tablets	
	RHZE 150, 75, 400, 275mg tablet		RH 150,75 tablet OR RH 300,150 tablet	
			RH (150,75)	RH (300,150)
25–29.9 kg	2 tablets		2 tablets	1 tablet
30–34.9 kg	3 tablets		3 tablets	-
35–64.9 kg	4 tablets		4 tablets	2 tablets
≥65 kg	5 tablets		5 tablets	-

R-rifampicin, H-isoniazid, E-ethambutol, Z-pyrazinamide
 An oral suspension can be made by dispersing the required number of tablets & in a small amount of water (5-10 ml) and administering all the suspension to the adolescent orally or via nasogastric tube.
[#] If oral suspension required, for each dose, crush 1 x ethambutol 400 mg tablet to a fine powder, disperse in 8 ml of water to prepare a concentration of 400 mg/8 ml (50 mg/ml), administer required dose as indicated in above chart, discard unused suspension.

Table 26.1: Dosing table for adolescents 12 to <16yrs with drug-sensitive TB.

Should there be insufficient clinical improvement after completion of four-months of treatment, treatment may be extended to six months while considering alternative diagnoses, including drug-resistant TB.

AND

- Pyridoxine 25 mg, oral, daily for duration of INH-containing TB therapy.
 - Isoniazid may cause peripheral neuropathy due to drug-induced pyridoxine deficiency.

Adults and adolescents ≥ 15 years

All adults and adolescents ≥ 15 years diagnosed with drug-sensitive pulmonary TB should receive 6 months of treatment (intensive phase treatment for 2 months and continuation phase treatment for 4 months - see table 27.3 below).

Treatment for known or presumed drug-sensitive TB:

- Rifampicin/isoniazid/pyrazinamide/ethambutol, oral, daily for 2 months, followed by rifampicin/isoniazid, oral, daily for 4 months.
 - Weigh patient frequently and adjust the dose according to current weight.

Table 27.3: Weight-based dosing guidance for adults and adolescents ≥ 15 years with drug-susceptible TB

Body weight	Two months intensive phase	Four months continuation phase	
	RHZE (150/75/400/275)	RH (150/75)	RH (300/150)
30–37 kg	2 tablets	2 tablets	
38–54 kg	3 tablets	3 tablets	
55–70 kg	4 tablets		2 tablets
71 kg and over	5 tablets		2 tablets
R-rifampicin, H-isoniazid, Z-pyrazinamide, E-ethambutol			

Table 26.2: Weight-based dosing guidance for adults and adolescents ≥ 16 years with drug-sensitive TB

AND

Pyridoxine supplementation is recommended in patients on isoniazid that are at high risk of peripheral neuropathy (e.g. HIV, diabetes, alcohol use disorder).

- Pyridoxine 25 mg, oral, daily for duration of isoniazid-containing TB therapy

Important medicine interactions

Rifampicin may reduce the efficacy of low dose combined oral contraceptives and progestin-only implants, resulting in possible unplanned pregnancies (See PHC Chapter 7: Family planning).

- » Advise the use of alternative contraceptive methods, such as IUD or DMPA.
- » Women that choose to use a progestin-only subdermal implant should be advised to use additional contraception for the duration of rifampicin-containing TB treatment and for 2 weeks after stopping rifampicin.

CAUTION

Antiretroviral medicines frequently interact with TB medicines. In PLWH on dolutegravir-based ART and rifampicin-containing TB treatment, dolutegravir is dosed twice daily (12 hourly). Continue twice daily dosing of dolutegravir until 2 weeks after stopping rifampicin.

Refer to Section 10.1: Antiretroviral treatment or consult the National Department of Health antiretroviral treatment guidelines.

Dose adjustment of TB treatment in renal impairment (eGFR < 30 mL/min)

- Ethambutol 15 – 25mg/kg three times weekly.
- Pyrazinamide 20 – 30 mg/kg three times weekly.

- Rifampicin and isoniazid do not require dose adjustment.

Example of dose adjusted regimen using alternate day dosing of RH and RHZE

Intensive phase of treatment:

- RHZE: Administer standard weight-based dosing with RHZE on Monday, Wednesday, Friday.
- RH: Administer standard weight-based dosing of RH on Tuesday, Thursday, Saturday, Sunday.

	Sun	Mo	Tue	We	Thu	Fri	Sat
		n	s	d			
RHZE	Skip	Tak	Skip	Tak	Skip	Tak	Skip
RH	Tak	Skip	Tak	Skip	Tak	Skip	Tak

Continuation phase of treatment:

- RH: No dose adjustment required. Continue daily weight-based dosing of RH.

Common adverse drug reactions associated with DS TB medicines

Table 27.4: Common adverse drug reactions associated with DS-TB medicines in adults

Adverse effect	Most likely responsible drug	Management
Hepatotoxicity (e.g. jaundice, nausea, malaise, abdominal pain)	Rifampicin, isoniazid, pyrazinamide	Exclude drug-induced liver injury/hepatitis – perform urgent (same day) ALT and manage further as appropriate.
Gastrointestinal intolerance (nausea, vomiting, anorexia)	Most DS-TB medicines	Exclude drug-induced liver injury/hepatitis – perform urgent (same day) ALT.. Exclude other causes such as alcohol use, non-steroidal anti-inflammatory drugs. If drug-induced liver injury and other causes excluded, manage symptomatically. Change the timing of medication administration to just before or after a light snack or at bedtime.
Joint pain	Pyrazinamide	Exclude gout. Treat symptomatically with analgesia (See Chapter 25: Pain, for treatment options).

	Peripheral neuropathy (e.g. tingling pain or burning or numbness in hands and feet)	Isoniazid	Initiate or increase pyridoxine to 50 mg daily. Note: Doses of pyridoxine > 100 mg daily may cause or worsen peripheral neuropathy and should be avoided (See Section 25.1.4: Peripheral neuropathy). Discuss with expert and consider withdrawal of offending drug if worsening symptoms. Note: Drug-induced peripheral neuropathy can be irreversible if the offending drug is not stopped promptly.
	Orange coloured urine	Rifampicin	Reassure the patient that this is normal and to be expected while taking rifampicin. No intervention required.
	Rash	Rifampicin, isoniazid, pyrazinamide, ethambutol	For mild, itching rash, with no blistering, mucosal involvement or systemic involvement treat symptomatically. If erythematous rash with fever, blistering, mucosal involvement, hepatitis, stop all medicinesurgently.
	Thrombocytopenia and/or purpura or petechial rash	Rifampicin	If petechial rash, assess platelet count. If thrombocytopenia, stop rifampicin.
	For additional guidance on the management of adverse drug reactions refer to: https://mic.uct.ac.za/sites/default/files/media/documents/mic_uct_ac_za/2157/ade-booklet.pdf		

Section 27.2 Tuberculosis, extrapulmonary

STG – New addition

New STG guidance on the management of extrapulmonary TB has been added as tabulated below.

Extrapulmonary TB – uro-genital manifestation

In response to an external comment received, guidance on the common presenting signs and symptoms of urogenital TB has been added.

27.2 TUBERCULOSIS, EXTRAPULMONARY

A15.6/A16/A18/A19/B90.0/B90.9

DESCRIPTION

Extrapulmonary TB (EPTB) refers to *M. tuberculosis* infection occurring outside the lungs. EPTB is more common in PLWH. Commonly affected sites include the lymph nodes, pleura, pericardium, central nervous system and bones and joints. EPTB may present with non-specific symptoms such as unintentional weight loss (> 1.5 kg in a month), night sweats, and fever. Other symptoms depend on the specific organ affected. Extrapulmonary TB can occur with or without active pulmonary TB. Disseminated TB refers to TB that has spread, usually via the bloodstream, to involve multiple organs or sites, and includes miliary TB.

The most common sites of extrapulmonary TB are listed below along with commonly associated signs and symptoms:

Table 27.5: Common presenting signs and symptoms of extra-pulmonary tuberculosis

Extrapulmonary TB type	Common presenting signs/symptoms
TB lymphadenitis	» Peripheral TB lymphadenopathy occurs in neck and armpits. Typically, nodes are large (> 2 cm), non-tender, non-symmetrical, matted, firm to fluctuant and rapidly growing. » Audible wheeze or typical brassy cough caused by large mediastinal lymph nodes. (See Section 27.5: Extrapulmonary tuberculosis, lymphadenitis, for further guidance)
TB pleural effusion (usually unilateral)	» Non-productive cough. » Chest pain. » Shortness of breath. » Tracheal and mediastinal shift away from the side of the effusion. » Decreased chest movement. » Stony dullness on percussion on the side of the effusion. (See Section 27.3: Extrapulmonary Tuberculosis, pleural, for further guidance)
TB empyema	» Similar to pleural effusion, but aspiration reveals thick pus. (See Section 27.4: Extrapulmonary Tuberculosis, empyema, for further guidance)
TB of spine, bones and joints	» Decreased movement in the joints. » Joint swelling with warm, tender joints. » Muscle atrophy and/or spasms. » Numbness, tingling, or weakness below the infection (if the spine is involved). (See Section 27.8: Tuberculosis, osteoarticular for further guidance)
TB pericarditis/pericardial effusion	» Chest pain. » Shortness of breath. » Dizziness and weakness from low cardiac output » Signs and symptoms of right-sided heart failure (tachycardia, low BP, peripheral oedema, liver congestion, ascites). (See Section 27.7: Tuberculosis pericarditis for further guidance)
TB meningitis	» During the early phase of TB meningitis, malaise, headache and personality change may be present. » With suspected established infection assess for: - gradual onset of headache, - malaise - confusion - decreased consciousness - vomiting - neck stiffness (See Section 27.9: Tuberculosis, Meningitis for further guidance)
Disseminated/miliary TB	» Fever. » Cough. » Generalised lymphadenopathy. » Hepatomegaly. » Consider in febrile patients presenting with HIV wasting syndrome (See Sections 27.3 to 27.9 for further guidance)
TB abdomen/peritoneum	» Ascites with no signs of portal hypertension. » Possible palpable abdominal masses. » Possible bowel obstruction. (See Section 27.6: Tuberculosis, Abdominal for further guidance)
Urogenital TB	» Dysuria, urinary frequency or urgency » Haematuria » Sterile pyuria » Pelvic, flank, or perineal pain » Infertility in men and women (Discuss patients with high suspicion of urogenital TB with specialist)

DIAGNOSIS

Special investigations to diagnose EPTB are guided by the clinical examination and site involved, and may include:

- » abdominal ultrasound;
- » cardiac point-of-care ultrasound or echocardiography;
- » lumbar puncture;
- » computed tomography (CT) scan;
- » TB-NAAT, smear microscopy, and TB culture of tissue or fluid from any biopsy or aspirate;
- » histologic examination of tissue (necrotizing granulomas may be suggestive of TB);
- » or cytological examination of fine needle aspirate.
- » In PLWH, specifically:
 - TB blood culture: consider in PLWH with CD4 counts < 100
 - Urine lipoarabinomannan (U-LAM). A positive U-LAM suggests disseminated TB in PLWH. U-LAM is indicated in the following people being investigated for TB:
 - o All PLWH admitted to hospital
 - o All symptomatic PLWH seen in an outpatient setting with:
 - CD4 ≤ 200 within the last 6 months **OR**
 - Advanced HIV disease **OR**
 - Current serious illness warranting admission

GENERAL MEASURES

- » Patients with extrapulmonary TB, or clinically diagnosed TB without bacteriological confirmation, are monitored clinically throughout treatment. Weight is a useful indicator of clinical response and should be monitored monthly.
- » If there is a poor response to treatment, alternative diagnoses and drug resistance must be considered.

Section 27.3 Extrapulmonary tuberculosis, pleural (TB pleurisy)

STG Update

STG guidance on the management of TB pleurisy has been subject to editorial updates as detailed below and transferred from AH Chp 16 Respiratory conditions to Chp 27 Tuberculosis.

Diagnosis - adenosine deaminase (ADA): Not amended

External comment received to include a fluid adenosine deaminase (ADA) value of > 40 U/L as supportive for the diagnosis of pleural tuberculosis in a high TB burden area. The National Health Laboratory Services (NHLS) handbook lists an (ADA) value of > 30 U/L as suggestive of TB which was verified via email correspondence with supporting references from the NHLS⁸. An (ADA) value of > 30 U/L is also concordant with the National TB management guidelines 2014⁹.

AMENDED FROM	AMENDED TO
16.10 TUBERCULOSIS, PLEURAL (TB PLEURISY) A16.5 + (B20.0)	27.3 EXTRAPULMONARY TUBERCULOSIS, PLEURAL (TB PLEURISY) A15.6/A16.5/B90.9
DESCRIPTION TB pleurisy may present with a few weeks of pleuritic pain; often associated with a dry cough, fever, night sweats, weight loss, and, with large effusions, progressive shortness of breath.	DESCRIPTION TB pleurisy is a form of extrapulmonary TB characterised by inflammation of the pleura due to infection with <i>M. tuberculosis</i> . TB pleurisy may present with a few weeks of pleuritic pain; often associated with a dry cough, fever, night sweats, weight loss, and, with large effusions, progressive shortness of breath.

⁸ Personal email correspondence dated 17 July 2026.

Blakiston M, Chiu W, Wong C, Morpeth S, Taylor S. Diagnostic Performance of Pleural Fluid Adenosine Deaminase for Tuberculous Pleural Effusion in a Low-Incidence Setting. J Clin Microbiol. 2018 Jul 26;56(8):e00258-18. doi: 10.1128/JCM.00258-18 J Thorac Dis 2023;15(5):2627-2635 | <https://dx.doi.org/10.21037/jtd-2> Aggarwal AN, Agarwal R, Sehgal IS, Dhooria S (2019) Adenosine deaminase for diagnosis of tuberculous pleural effusion: A systematic review and meta-analysis. PLoS ONE 14(3): e0213728. <https://doi.org/10.1371/journal.pone.0213728> PLoS One. 2019 Mar 26;14(3):e0213728. doi: [10.1371/journal.pone.0213728](https://doi.org/10.1371/journal.pone.0213728) Blake J, Berman P. The use of adenosine deaminase assays in the diagnosis of tuberculosis. S Afr Med J. 1982 Jul 3;62(1):19-21. PMID: 7089774.

⁹ National Department of Health. National Tuberculosis Management Guidelines 2014

Diagnosis It is essential to perform a diagnostic tap of pleural effusions confirmed on CXR. Although a definite diagnosis can only be made by demonstrating the organisms on smear or culture, or on histology of a pleural biopsy, the presence of a lymphocytic exudate on pleural fluid analysis is adequate to start empiric TB therapy in areas with a high TB burden, particularly if the patient has HIV infection. All patients started on empiric TB therapy for pleural TB must be followed up closely; failure to respond as expected must prompt investigations to exclude other causes. Once TB therapy is started, signs and symptoms should resolve within 2 weeks. Radiographic improvement is usually evident by 6 weeks, but complete resorption can take up to 4 months. However, pleural thickening may persist. A pleural biopsy at initial presentation is strongly recommended for the following patients: >50 years of age, suspected malignancy, or those with atypical TB symptoms. Treatment is as for pulmonary TB (see Section 16.9: Tuberculosis, pulmonary). <i>Note: Total drainage by aspiration or under-water tube is not needed. For large effusions that cause dyspnoea, drain a maximum of 1 litre at a time. However, note that a TB pleural empyema must be drained by intercostal tube.</i> Referral » Non-resolving effusions. Suspect an incorrect diagnosis of TB pleurisy if the effusion does not improve on the CXR after 3 months of treatment, or if the patient deteriorates. » Loculated TB empyema, not resolving after intercostal underwater tube drainage and needing assessment for surgical drainage. » Bronchopleural fistula, not resolving after 6 weeks.	Diagnosis Suspected pleural effusions should be confirmed on chest X-ray (CXR). It is essential to perform a diagnostic tap of pleural effusions confirmed on CXR. Pleural fluid findings suggestive of TB include: ➤ Straw-coloured exudate ➤ Elevated protein (>30g/L) ➤ Elevated white cell count (predominantly lymphocytes) ➤ Raised adenosine deaminase (ADA) (>30 IU) Pleural fluid should be sent for TB-NAAT and TB culture. Due to the low bacterial load in TB pleural effusion, TB-NAAT has a low sensitivity on pleural fluid, and a negative test result cannot be used to rule out TB. A definite diagnosis of pleural TB is made by positive TB-NAAT, smear microscopy or TB culture, or on histology of a pleural biopsy. However, the presence of a lymphocytic exudate on pleural fluid analysis is adequate to start empiric TB therapy in areas with a high TB burden, particularly in PLWH. A pleural biopsy at initial presentation is strongly recommended for the following patients: >50 years of age, suspected malignancy, or those with symptoms atypical for TB. All patients started on empiric TB therapy for pleural TB must be followed up closely. Failure to respond as expected must prompt investigations to exclude other causes. On TB treatment, signs and symptoms should resolve within 2 weeks. Radiographic improvement is usually evident by 6 weeks, but complete resorption can take up to 4 months. Pleural thickening may persist. MEDICINE TREATMENT Treatment of pleural TB is as for pulmonary TB (see Section 27.1.1: Tuberculosis, pulmonary). Adolescents 12 to < 15 years with a simple TB pleural effusion may be eligible for a shorter 4-month treatment regimen (see Figure 27.4: “Eligibility for TB treatment shortening in adolescents 12 to <15 years of age” above). Note: » Total drainage of TB pleural effusion by aspiration or intercostal tube is not needed. For large effusions that cause dyspnoea, drain a maximum of 1 litre at a time. Referral » Non-resolving effusions: Suspect an incorrect diagnosis of TB pleurisy if the effusion does not improve on CXR after 3 months of treatment, or if the patient deteriorates. » Bronchopleural fistula, not resolving after 6 weeks.
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Section 27.4 Extrapulmonary tuberculosis, empyema

STG – New addition

New STG guidance on the management of extrapulmonary TB empyema has been added as tabulated below.

27.4 EXTRAPULMONARY TUBERCULOSIS, EMPYEMA

A15.6/A16.1/B90.0/B90.9

DESCRIPTION

Pus in the pleural cavity caused by chronic *M. tuberculosis* infection.

The clinical presentation may be similar to TB pleural effusion but on diagnostic tap pus is aspirated. TB empyema may be loculated, and lead to extensive thickening and calcification of the pleura. TB empyema may be associated with bronchopleural fistula and complicated by co-infection with other bacteria.

Diagnosis

Aspirate and analyse all pleural effusions.

A TB pleural effusion should be distinguished from TB empyema by macroscopic appearance and biochemical analysis of the fluid.

Pleural fluid findings suggestive of TB empyema include:

- Purulent fluid
- Elevated white cell count (predominantly neutrophils)
- Low fluid pH (< 7.2) and glucose concentrations

TB-NAAT, microscopy and TB culture of the purulent pleural fluid should be requested to confirm the diagnosis.

GENERAL MEASURES

The primary management of TB empyema is early and complete drainage by insertion of an intercostal tube and anti-tuberculosis treatment.

Further surgical intervention may be required – discuss with cardiothoracic surgery.

MEDICINE TREATMENT

Treatment of TB empyema is as for pulmonary TB (see Section 27.1.1: Tuberculosis, pulmonary).

Adolescents 12 to < 15 years with TB empyema are **NOT** eligible for a shorter 4-month treatment regimen (see Figure 27.4 above).

REFERRAL

- » Loculated TB empyema, not resolving after intercostal underwater tube drainage and needing assessment for surgical drainage.
- » Chronic empyema with pleural thickening and restrictive lung disease for consideration of surgical decortication.

Section 27.5 Extrapulmonary tuberculosis, lymphadenitis

STG – New addition

New STG guidance on the management of extrapulmonary TB lymphadenitis has been added as tabulated below.

Referral

For patients presenting with lymphadenitis and special investigations not suggestive of TB, a recommendation to consider referral for lymph node biopsy has been added to the STG, in response to an external comment.

27.5 EXTRAPULMONARY TUBERCULOSIS, LYMPHADENITIS

B90.0, B90.9

DESCRIPTION

Infection of lymph nodes with *M. tuberculosis*. TB lymphadenitis typically presents with swollen, often visibly enlarged nodes that are firm, painless and may be matted. Lymph node enlargement persists for more than 2 weeks and does not respond to antibiotic treatment. TB lymphadenitis may be associated with a discharging skin sinus.

Diagnosis

Fine needle aspirate for TB-NAAT, culture, and cytology.

Investigate for TB at other sites (e.g. send sputum for TB-NAAT, U-LAM in eligible PLWH).

MEDICINE TREATMENT

Treatment of TB lymphadenitis is as for pulmonary TB (see Section 27.1.1 Tuberculosis, pulmonary).

Adolescents 12 to < 15 years with isolated TB lymphadenitis may be eligible for a shorter 4-month treatment regimen (see Figure 27.4 above).

REFERRAL

- » Discuss patients with results not suggestive of TB (i.e. negative FNA TB-NAAT and no evidence of TB elsewhere) for lymph node biopsy.
- » Refer for further investigation or discuss with an expert if there is no significant reduction in size of the lymph nodes, or if there is enlargement in lymph nodes on treatment, especially if TB was not bacteriologically confirmed.

Section 27.6 Tuberculosis, abdominal

STG – New addition

New STG guidance on the management of abdominal TB has been added as tabulated below.

27.6 TUBERCULOSIS, ABDOMINAL

B90, B90.8

DESCRIPTION

Abdominal tuberculosis refers to extrapulmonary TB involving the gastrointestinal tract, peritoneum, intra-abdominal lymph nodes or abdominal organs. Presenting symptoms may include fever, weight loss, vomiting, abdominal distension and pain, diarrhoea, constipation, and jaundice. Clinical examination may reveal hepatosplenomegaly, ascites, or palpable abdominal masses due to mesenteric lymph nodes.

Diagnosis

- » Abdominal ultrasound: lymphadenopathy, ascites, and splenic hypodensities are suggestive of abdominal TB
- » If ascites is present, perform diagnostic paracentesis (ascitic tap).
- » Ascitic fluid features suggestive of TB:
 - Exudate
 - Elevated protein (>30 g/L)
 - Elevated white cells with lymphocytes predominantly
 - Elevated adenosine deaminase (ADA)
 - Serum-ascites albumin gradient < 1.1 g/dL
 - Positive TB-NAAT, smear microscopy or TB culture
- » Histologic examination of tissue (intestinal, peritoneal) biopsy
- » Investigate for TB at other sites (e.g. CXR, send sputum for TB-NAAT, U-LAM in eligible PLWH).

MEDICINE TREATMENT

Treatment of abdominal TB is as for pulmonary TB (see Section 27.1.1: Tuberculosis, pulmonary and lymphadenitis).

Adolescents 12 to < 15 years with abdominal TB are **NOT** eligible for a shorter 4-month treatment regimen (see Figure 27.4 above).

REFERRAL

- » Acute abdomen – refer urgently
- » S Acute abdomen – refer urgently.
- » Suspected bowel obstruction or perforation – refer urgently.
- » Diagnostic uncertainty (e.g. terminal ileal disease: TB vs Crohn's disease).
- » Abdominal TB without microbiological confirmation, and without improvement despite ≥ 1 month of appropriate TB treatment.

Section 27.7 Tuberculous pericarditis

Corticosteroids, oral prednisolone - Adults with or without HIV : Added

The use of oral corticosteroids for the management of TB pericarditis was approved for addition to the EML in accordance with the NEMLC recommendation from the evidence review detailed below. A copy of the complete evidence review may be accessed at the end of this report or on the NHI webpage. The dose regimen as included in the STG below, is based on the largest RCT by Mayosi¹⁰ that was included in the NEMLC evidence review.

Key Recommendations

Type of ERC recommendation	We recommend against the option and for the alternative (strong)		We suggest not to use the option or to use the alternative (conditional)		We suggest using the option (conditional)		We recommend the option (strong)	
	☐		☐		☒ See recommendation 2		☒ See recommendation 1	
High level summary of conclusions	1. In adults with or without HIV, and with tuberculous pericarditis, we recommend using corticosteroids. 2. In children with or without HIV, and with tuberculous pericarditis, we suggest using corticosteroids.							
NEMLC Ratification	Date		Comments/Recommendation					
	4 June 2026		NEMLC ratified the ERC recommendation as above.					
Therapeutic Interchange Considerations (if applicable)*	If YES:	Alternative medicine/s name (INN)	Alternative/s SAHPRA registered?	Formulation/s	Equipotent dose/ Dose range and dosing interval		If NO, tick box	
								✓
Trigger for review	Additional clinical trial data or safety signals.							

*Depending on the review and number of products, an annexure may need to be included

STG – New addition

New STG guidance on the management of TB pericarditis has been added as tabulated below.

27.7 TUBERCULOUS PERICARDITIS

¹⁰ Mayosi BM, Ntsekhe M, Bosch J, et al. Prednisolone and Mycobacterium indicus pranii in tuberculous pericarditis. N Engl J Med. 2014;371(12):1121–30.

DESCRIPTION

TB pericarditis is defined as pericardial infection with *Mycobacterium tuberculosis*, and is characterised by various stages. The most common initial presentation is a pericardial effusion. Pericardial effusion may be followed by partial or complete resorption of the fluid and development of pericardial thickening, fibrosis and calcification. This progressive pericardial thickening and fibrosis may impede filling of the heart and is referred to as constrictive pericarditis.

TB accounts for > 90% of pericardial effusions in PLWH, and 50% of pericardial effusions in people without HIV. Symptoms of TB pericarditis may include fever, weight loss, night sweats, chest pain, shortness of breath, cough, dizziness and weakness. Clinical cardiovascular examination findings that may suggest TB pericarditis include tachycardia, hypotension, raised jugular venous pressure, pulsus paradoxus, soft or muffled heart sounds and a pericardial friction rub. Hepatomegaly, abdominal distension with ascites, and lower limb oedema may also be present.

TB pericardial effusion may be complicated by cardiac tamponade, a medical emergency, which requires urgent pericardiocentesis

DIAGNOSIS

- CXR may show a large globular heart and features of pulmonary TB or pleural effusion.
- ECG findings that suggest pericardial effusion include tachycardia, low voltage QRS complexes, and electrical alternans.
- Cardiac point-of-care ultrasound or echocardiography confirms the presence of a pericardial effusion and can evaluate for tamponade. Fibrinous strands in the pericardial space and pericardial thickening suggest TB pericarditis.
- Features of TB pericarditis on diagnostic pericardiocentesis:
 - Exudate
 - Elevated ADA (≥ 30 IU/L)
 - Elevated white cells with lymphocytes predominantly, pericardial fluid lymphocyte: neutrophil ratio ≥ 1
 - Positive TB-NAAT, microscopy and TB culture
- Histologic examination of pericardial biopsy
- Investigate for TB at other sites (e.g. send sputum for TB-NAAT, U-LAM in eligible PLWH).

The diagnosis of TB pericarditis is “definite” when TB bacilli are present in a smear or culture of pericardial fluid, and/or TB bacilli or caseating granulomata are found on histological examination of pericardium. A diagnosis of “probable” TB pericarditis is made when there is evidence of pericarditis in a patient with TB elsewhere and/or a lymphocytic pericardial exudate with elevated ADA and/or a good response to anti-tuberculosis treatment.

NOTE: In areas with a high burden of HIV and TB, it may be safer for the patient to start empiric TB treatment before establishing a definitive diagnosis than to undergo diagnostic pericardiocentesis.

MEDICINE TREATMENT

Treatment of TB pericarditis is as for pulmonary TB (see Section 27.1.1: Tuberculosis, pulmonary and lymphadenitis).

Note: Adolescents 12 to < 15 years with TB pericarditis are **NOT** eligible for a shorter 4-month treatment regimen (see Figure 27.4 above).

If definite or probable TB pericarditis, ADD:

- Corticosteroids (intermediate-acting), e.g.:
- e.g.: Prednisone, oral, 120 mg daily for 1 week. Then taper gradually over the next 6 weeks (refer to dosing regimen tabulated below).
- Prednisone, oral, 120 mg daily for 1 week. Then taper gradually over the next 6 weeks (refer to dosing regimen tabulated below).

Weeks	Dosing Regimen
Week 1	120 mg/day
Week 2	90 mg/day
Week 3	60 mg/day
Week 4	30 mg/day

	Week 5	15 mg/day
	Week 6	5 mg/day
CAUTION In PLWH, perform a thorough clinical examination before starting corticosteroids to exclude Kaposi's sarcoma and other HIV-related cancers. In PLWH started on corticosteroids, antiretroviral therapy should be initiated promptly in accordance with Section 10.1: Antiretroviral treatment.		
REFERRAL • Suspected pericardial tamponade • Constrictive pericarditis		

Section 27.8 Tuberculous, osteoarticular

STG – New addition

New STG guidance on the management of osteoarticular TB has been added as tabulated below.

27.8 TUBERCULOSIS, OSTEOARTICULAR

B90.0, B90.2

DESCRIPTION

Osteoarticular TB is extrapulmonary *M. tuberculosis* infection of the bone and/or joints. TB infection can involve any joint and is usually limited to one joint, such as the hip or knee, at a point in time. TB infection of the bone is called TB osteomyelitis, and any bone may be affected. Symptoms of TB joint or bone infection include swelling, pain and loss of function. The affected joint or bone is usually not red or warm, thus differentiating it from septic arthritis. There may be associated constitutional symptoms of fever and weight loss. In people with delayed presentation of TB bone or joint infection, there may be significant deformity.

TB osteomyelitis that involves the vertebral column is referred to as spinal TB. Spinal TB may present with pain, muscle spasm, rigidity, neurological signs, fever and loss of weight. Spinal TB may lead to severe neurological complications such as paraplegia from spinal cord compression. Spinal TB is characterised by loss of vertebral body bone density and slow bone erosion, with the disc space preserved for a long time, which differentiates it from pyogenic infection. Collapse of adjacent vertebral bodies may lead to angulated kyphosis (also known as gibbus deformity). Local spread of TB infection may occur into the soft paravertebral tissue to form a cold "psoas abscess".

GENERAL MEASURES

Diagnosis

- » Imaging (e.g. X-ray, CT scan) may be suggestive of TB.
- » Tissue biopsy and/or aspiration of pus may be performed.
- » TB-NAAT, smear microscopy, or TB culture of tissue biopsy or aspirated material are confirmatory.
- » Investigate for TB at other sites (e.g. CXR, send sputum for TB-NAAT, U-LAM in eligible PLWH).

MEDICINE TREATMENT

Treatment of TB of the bone and/or joints is as for pulmonary TB (see Section 27.1.1: Tuberculosis, pulmonary and lymphadenitis). Treat with standard combination tuberculosis therapy and extend the duration of therapy to 9 months (2 months intensive phase, 7 months continuation phase).

Adolescents 12 to < 15 years with TB of the bone and/or joints are **NOT** eligible for a shorter 4-month treatment regimen (see Figure 27.4 above).

Section 27.9 Tuberculosis, meningitis

Corticosteroids, IV dexamethasone - HIV-negative adults with TB meningitis (any grade): Added

Corticosteroids, oral prednisolone - HIV-negative adults with TB meningitis (any grade): Added
Corticosteroids, IV dexamethasone - adults with HIV and TB meningitis of any grade, with CD4 count ≤ 200 cells/mm³: Not Added
Corticosteroids, oral prednisolone - adults with HIV and TB meningitis of any grade, with CD4 count ≤ 200 cells/mm³: Not Added
Corticosteroids, IV dexamethasone - adults with HIV and TB meningitis of any grade, with CD4 count > 200 cells/mm³: Added
Corticosteroids, oral prednisolone - adults with HIV and TB meningitis of any grade, with CD4 count > 200 cells/mm³: Added

The use of oral/IV corticosteroids for the management of TB meningitis was approved for addition to the EML in accordance with the NEMLC recommendation from the evidence review detailed below. A copy of the complete evidence review may be accessed at the end of this report or on the NHI webpage.

Key Recommendations (if more appropriate, describe in narrative form)

Type of ERC recommendation	We recommend against the option and for the alternative (strong)		We suggest not to use the option or to use the alternative (conditional)		We suggest using the option (conditional)		We recommend the option (strong)	
	☐		✓ See recommendation 2		✓ See recommendation 3		✓ See recommendation 1 and 4	
High level summary of conclusions	1. In HIV-negative adults with TB meningitis of any grade, we recommend <u>using</u> corticosteroids. 2. In adults with HIV and TB meningitis of any grade, with CD4 count ≤ 200 cells/mm³, we suggest <u>not using</u> corticosteroids. 3. In adults with HIV and TB meningitis of any grade, with CD4 count >200 cells/mm³, we <u>suggest</u> using corticosteroids. 4. In children, with or without HIV, with TB meningitis of any grade, we recommend <u>using</u> corticosteroids.							
NEMLC Ratification	Date		Comments/Recommendation					
	26 Mar 2026		NEMLC ratified the ERCs recommendation as detailed above, pending agreement with the national TB and HIV programs. (Program confirmation received by email communication April 2026).					
Therapeutic Interchange Considerations (if applicable)*	If YES:	Alternative medicine/s name (INN)	Alternative/s SAHPRA registered?	Formulation/s	Equipotent dose/ Dose range and dosing interval		If NO, tick box	
							✓	
Trigger for review								

STG Update

STG guidance on the management of drug-sensitive TB has been subject to editorial updates as detailed below and transferred from AH Chp 14 Neurological conditions to Chp 26 Tuberculosis.

AMENDED FROM	AMENDED TO
14.8.1.1 TUBERCULOUS MENINGITIS (TBM) A17.0† + (G01*) DIAGNOSIS CSF findings are extremely variable. Generally, lymphocytes predominate, however, polymorphs predominate initially in about a third of patients.	27.9 TUBERCULOSIS, MENINGITIS A17.0/G00.8/G00.9/G02.8/G03.9 DESCRIPTION TB meningitis is infection of the meninges by <i>M. tuberculosis</i> . TB meningitis is associated with high morbidity and mortality.

Protein is usually > 1 g/L and glucose is usually low. In cases where the differential diagnosis between bacterial and tuberculous meningitis is in doubt, lumbar puncture should be repeated 2–3 days later while still on ceftriaxone. If the aetiology is bacterial, considerable improvement in CSF findings may be expected, but with untreated tuberculous meningitis, the cell counts and protein levels will be the same or higher as the original CSF findings; and the glucose level will be the same or lower. MEDICINE TREATMENT Treat with standard combination tuberculosis therapy according to National protocol and extend duration of therapy to 9 months (2 months intensive phase, 7 months continuation phase). See Section16.9: Tuberculosis, Pulmonary for details. In HIV-negative individuals: Corticosteroid use may be of benefit in reducing neurological deficit in patients with grade II to III disease (focal neurological disease, depressed levels of consciousness, or a Glasgow Coma Scale of 14 or less). • Dexamethasone, IV, dosing as follows: Weeks Dosing regimen <table><tr><td>Initial dose 0.3-0.4 mg/kg/day for 2 weeks.</td></tr><tr><td>Week 3 0.2 mg/kg daily.</td></tr><tr><td>Week 4 0.1 mg/kg daily.</td></tr><tr><td>Week 5 to 8 4 mg/day, tapering daily dose by 1 mg each week.</td></tr></table> OR • Corticosteroids (intermediate-acting) e.g.: • Prednisone, oral, 60 mg daily for 2 weeks. - o Then taper gradually over the next 6 weeks (see Appendix II for an example of a dose reduction regimen). In people with HIV: Note: There is uncertainty whether the use of corticosteroids is beneficial in PLWH with TBM.	Initial dose 0.3-0.4 mg/kg/day for 2 weeks.	Week 3 0.2 mg/kg daily.	Week 4 0.1 mg/kg daily.	Week 5 to 8 4 mg/day, tapering daily dose by 1 mg each week.	Patients may present with headache, confusion and decreased consciousness. On examination, they may have meningism. Patients with suspected TB meningitis should be referred to hospital urgently. DIAGNOSIS » Diagnosis of TB meningitis is based on clinical presentation and cerebrospinal fluid (CSF) analysis following lumbar puncture, with or without evidence of TB disease elsewhere. » If TB meningitis is suspected, treatment should be initiated without awaiting bacteriological proof of diagnosis. » Imaging (e.g. CT brain) should be performed prior to lumbar puncture if there is concern for raised intracranial pressure. » CSF findings are variable, but findings suggestive of TB meningitis include: - Elevated lymphocytes (30 – 300/mm3). Note that polymorphs predominate initially in about a third of patients. - Elevated protein (usually > 1 g/L). - Low glucose. - Negative cryptococcal antigen test. - Positive TB-NAAT and/or TB culture on CSF. - In cases where the differential diagnosis between bacterial and tuberculous meningitis is in doubt, lumbar puncture should be repeated 2–3 days later while still on ceftriaxone. If the aetiology is bacterial, considerable improvement in CSF findings is expected. With untreated tuberculous meningitis, the cell counts and protein levels will be the same as, or higher than, the original CSF findings; and the glucose level will be the same or lower. - TB meningitis severity can be graded as follows: - Grade I: Alert, orientated, without focal neurological deficit - Grade II: Glasgow Coma score 10 to 14 with or without focal neurological deficit, or Glasgow Coma score of 15 with focal neurological deficit. - Grade III: Glasgow Coma score less than 10 with or without focal neurological deficit GENERAL MEASURES - Hospitalise all patients with presumed TBM. - Monitor respiratory rate and pattern, pulse rate, blood pressure and oxygen saturation. - Monitor fluid and electrolyte status, particularly serum sodium, and manage hyponatraemia appropriately (Refer Chapter 7, Section 7.2.4 Hyponatraemia). - Monitor neurological status regularly, including level of consciousness, pupil responses and focal neurological signs. - A rapid deterioration in level of consciousness may indicate worsening hydrocephalus, hyponatraemia or cerebral infarction. Review serum sodium urgently and consider repeat neuroimaging. - Seizures may occur acutely and survivors of TBM may develop epilepsy. Monitor for seizures. To manage status epilepticus and seizures, refer to Chapter 14, sections 14.4. Epileptic seizures, 14.5 Status epilepticus and 14.6 Epilepsy. Choice of antiseizure medication
Initial dose 0.3-0.4 mg/kg/day for 2 weeks.					
Week 3 0.2 mg/kg daily.					
Week 4 0.1 mg/kg daily.					
Week 5 to 8 4 mg/day, tapering daily dose by 1 mg each week.					

	should include consideration of the drug interactions with rifampicin and other anti-TB medicines. - Ensure adequate nutrition and refer for nutritional support. Enteral feeding may be required in patients with impaired consciousness or swallowing. - Refer for rehabilitative support, including physiotherapy, occupational therapy and speech therapy. MEDICINE TREATMENT Treatment of TB meningitis is as for pulmonary TB (see Section 27.1.1: Tuberculosis, pulmonary and lymphadenitis). Treat with standard combination tuberculosis therapy and extend the duration of therapy to 9 months (2 months intensive phase, 7 months continuation phase). Adolescents 12 to < 15 years with TB meningitis are NOT eligible for a shorter 4-month treatment regimen (see Figure 27.4 above) In adults without HIV and PLWH with CD4 count > 200 cells/mm³ with TB meningitis of any grade <u>ADD</u>: • Dexamethasone, IV, dosing as follows: <table border="1"> <thead> <tr> <th>Weeks</th><th>Dosing Regimen</th></tr> </thead> <tbody> <tr> <td>Initial Dose</td><td>0.3 – 0.4 mg/kg/day for 2 weeks</td></tr> <tr> <td>Week 3</td><td>0.2 mg/kg daily</td></tr> <tr> <td>Week 4</td><td>0.1 mg/kg daily</td></tr> <tr> <td>Week 5 to 8</td><td>4mg/day, tapering daily dose by 1 mg each week</td></tr> </tbody> </table> OR ▪ Oral corticosteroids (intermediate-acting) • e.g.: Prednisone, oral, 60 mg daily for 2 weeks. ○ Then taper gradually over the next 6 weeks. See Appendix II for an example of a dose reduction regimen. In PLWH with CD4 count ≤ 200 cells/mm³ and TB meningitis of any grade: Adjunctive corticosteroids should not be routinely used in PLWH with CD4 counts ≤200 cells/mm³ and TB meningitis, as current evidence does not demonstrate clinical benefit.	Weeks	Dosing Regimen	Initial Dose	0.3 – 0.4 mg/kg/day for 2 weeks	Week 3	0.2 mg/kg daily	Week 4	0.1 mg/kg daily	Week 5 to 8	4mg/day, tapering daily dose by 1 mg each week
Weeks	Dosing Regimen										
Initial Dose	0.3 – 0.4 mg/kg/day for 2 weeks										
Week 3	0.2 mg/kg daily										
Week 4	0.1 mg/kg daily										
Week 5 to 8	4mg/day, tapering daily dose by 1 mg each week										

Section 27.10 Drug-resistant TB

STG –New addition

STG guidance on the management of drug-resistant TB has been added as detailed below.

General measures – contraception

In response to external comment received, a recommendation that women of childbearing potential be encouraged to use effective contraception for the duration of DR-TB treatment has been added to the STG.

TB preventive therapy for contacts of patients diagnosed with DR-TB

Recommendations on TB preventive therapy in adult and adolescent (≥ 15 years) contacts of patients diagnosed with DR-TB has not been included in the STG as the use of TB preventative therapy in this cohort has not yet been reviewed by NEMLC.

27.10 DRUG-RESISTANT TB

U50, U50.9, U50.91

See the National Department of Health Updated Clinical Reference Guide: Clinical Management of **Rifampicin-Resistant Tuberculosis**, September 2023

DESCRIPTION

Table 27.6 below presents key definitions and terminology for drug-resistant tuberculosis.

Table 27.6: Terminology and definitions associated with DR-TB

Drug Resistance Terminology	
Monoresistant TB	Resistant to only one anti-TB medicine, without resistance to other drugs
Rifampicin-resistant TB (RR-TB)	Resistant to rifampicin $\pm$ resistance to another anti-TB medicines
Multidrug resistant TB (MDR-TB)	Resistant to rifampicin AND isoniazid ($\pm$ resistance to other anti-TB drugs)
Pre-extensively drug-resistant TB (Pre-XDR-TB)	Resistant to rifampicin ($\pm$ resistant to isoniazid) AND resistant to fluoroquinolones
Extensively drug-resistant TB (XDR)	Resistant to: • Rifampicin ($\pm$ resistant to isoniazid), AND • At least one fluoroquinolone (levofloxacin or moxifloxacin) AND • Bedaquiline OR linezolid

Table 26.5: Terminology and definitions associated with DR-TB

GENERAL MEASURES

- » Ensure that appropriate infection prevention and control measures are implemented at the facility, including:
 - adequate ventilation,
 - isolation of patients with confirmed or suspected infectious pulmonary TB, and
 - use of personal respiratory protection by healthcare workers (e.g. respirator masks).
- » Counsel and educate patients about the disease and its treatment, including treatment duration.
- » Explain the importance of completing treatment.
- » Advise against the use of tobacco and excessive alcohol.
- » Institute measures to prevent TB transmission in homes, including:
 - Instruct patients to cover their mouth and nose with their sleeve or a tissue when coughing or sneezing. After that, they should wash their hands and throw their tissue in the bin.
 - Windows and doors must be kept open (weather permitting) to increase the ventilation.
 - Where possible, sleep alone and not in a room with other household members.
 - While the patient is still considered infectious, provide them with surgical masks to wear at home, during transportation and medical consultations.
 - Refrain from having visitors in the home.
- » Screen all contacts for signs and symptoms of TB, and collect sputum for TB-NAAT to detect TB disease and determine susceptibility. A contact is any person who has shared the same enclosed space with a person with pulmonary TB (e.g. the TB source patient), for one or more nights OR for frequent or extended daytime periods. The exposure must have occurred while the source patient was not on TB treatment OR if the source patient is on treatment the exposure must have occurred during the three months before the source patient started TB treatment
- » Women and girls of childbearing potential should be encouraged to use effective contraception for the duration of DR-TB treatment to avoid becoming pregnant.

Section 27.10.1 Isoniazid monoresistant TB

STG Update

STG guidance on the management of isoniazid monoresistant TB has been subject to editorial updates as detailed below and transferred from AH Chp 16 Respiratory conditions to Chp 27 Tuberculosis.

Isoniazid-resistant TB –mutations

The need to distinguish between katG or inhA mutations to guide treatment decisions regarding the use of high-dose isoniazid and ethionamide have not been referenced in the STG, as standard RR-TB treatment regimens no longer include high-dose isoniazid or ethionamide.

Isoniazid monoresistance – delayed detection

In response to an external comment received, the following guidance has been added when there is a delay in detecting isoniazid resistance: *“If isoniazid monoresistance is detected > 28 days after starting treatment with RHZE for drug-susceptible TB, repeat TB-NAAT testing to rapidly assess for rifampicin resistance.”* The ongoing management of these patients should be discussed with an expert.

AMENDED FROM	AMENDED TO
16.11.1 ISONIAZID MONORESISTANT TB A15.0-9/A16.0-5/A16.7-9/A17.0-1/A17.8-9/A18.0-8/A19.0-2/A19.8-9 + (B20.0) + (U50.00-01/U50.10-11) Isoniazid monoresistant TB is TB disease caused by <i>M. tuberculosis</i> complex that is resistant to isoniazid but susceptible to rifampicin. MEDICINE TREATMENT <u>Confirmed isoniazid monoresistant TB:</u> • RHZE at standard dosing, AND • Levofloxacin, oral, daily: ○ 30–45 kg: 750 mg ○ ≥46 kg: 1000 mg <u>Confirmed isoniazid monoresistant TB AND contraindication to isoniazid:</u> • Rifampicin, oral, 10 mg/kg daily. AND • Ethambutol, oral, 15 mg/kg daily. AND • Pyrazinamide, oral, 25 mg/kg daily. AND • Levofloxacin, oral, daily: ○ 30–45kg: 750 mg ○ ≥46kg: 1000 mg Treatment should be given for at least 6 months.	27.10.1 ISONIAZID MONORESISTANT TB U50.00, U50.1, U50.10, U50.11 DESCRIPTION Isoniazid monoresistant TB is TB disease caused by <i>M. tuberculosis</i> that is resistant to isoniazid but susceptible to rifampicin. If isoniazid monoresistant TB is detected by TB-NAAT, collect another sample to determine fluoroquinolone susceptibility (see Figure 27.1 and Figure 27.2). If isoniazid monoresistance is detected > 28 days after starting treatment with RHZE for drug-susceptible TB, repeat TB-NAAT testing to rapidly assess for rifampicin resistance. MEDICINE TREATMENT Treatment should be given for at least 6 months. <u>Confirmed isoniazid monoresistant TB and fluoroquinolone susceptible::</u> • RHZE at standard dosing daily for 6 months AND ○ Levofloxacin, oral, daily for 6 months: ○ 30 to <46 kg: 750 mg ○ ≥46 kg: 1000 mg. <u>Confirmed isoniazid monoresistant TB AND fluoroquinolone susceptible with isoniazid contraindication:</u> ○ Rifampicin, oral, 10 mg/kg daily for 6 months. AND ○ Ethambutol, oral, 15 mg/kg daily for 6 months. AND ○ Pyrazinamide, oral, 25 mg/kg daily for 6 months. AND ○ Levofloxacin, oral, daily for 6 months: ○ 30 to < 46kg: 750 mg ○ ≥46kg: 1000 mg REFERRAL

	» If isoniazid AND fluoroquinolone resistance is detected, discuss with an expert. » If isoniazid resistance is detected late in a patient not responding to drug-susceptible TB treatment, discuss with an expert
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Section 27.10.2 Rifampicin resistant, Pre-XDR and XDR TB

Gabapentin - Linezolid-induced peripheral neuropathy: Not added

Pregabalin Linezolid-induced peripheral neuropathy,: Not added

External comment received to include the use of gabapentin and/or pregabalin for the management of linezolid-induced peripheral neuropathy, as potential alternatives to the EML recommended options of amitriptyline (*risk of additive QT prolongation, increasing the likelihood of torsades de pointes when co-administered with certain second-line TB medications*) and carbamazepine (*hepatic enzyme inducer, potentially reducing plasma concentrations of second-line anti-TB agents*). The Committee noted recently updated safety concerns¹¹ with gabapentin and pregabalin and recommend that these medicines be subject to NEMLC evidence reviews. Gabapentin and pregabalin for the management of drug-induced neuropathic pain, have been included in the list of topics for prioritisation for review as part of the review of AH Chp 25 Pain Section 25.1.4 Neuropathic pain. Pregabalin and gabapentin are currently included in the T&Q EML for refractory neuropathy or those intolerant to standard of care. DRTB patients with linezolid-induced peripheral neuropathy may therefore access pregabalin via the T&Q EML. A statement indicating this has been included in the STG.

Delamanid - anti-tuberculosis medicines used in RR- and Pre-XDR-TB individualised regimens: Added
 Delamanid has been added to the EML for RR-TB and Pre-XDR-TB for patients who are not eligible for the BPAL-L regimen and who may require individualised regimens. Delamanid is used in clinical practice in pregnant women, who are not eligible for BPAL-L, and children requiring treatment for RR- and Pre-XDR-TB, and is included in the national TB guidelines for RR-TB.¹² Inclusion on the EML is supported by results from the recently published BEAT TB study.¹³

NEMLC recommendation:

Key Recommendations

Type of ERC recommendation	We recommend against the option and for the alternative (strong)	We suggest not to use the option or to use the alternative (conditional)	We suggest using the option (conditional)	We recommend the option (strong)
	☐	☐	X	☐
High level summary of conclusions	It is recommended that delamanid be included on the EML for the management of DR-TB in all requiring individualised treatment regimens (including in children, adolescents, adults and pregnant or breastfeeding women).			

¹¹ Iacobucci G. New safety warnings for gabapentinoids, benzodiazepines, and z drugs. BMJ. 2026 Jan 9;392:s50. doi: 10.1136/bmj.s50. PMID: 41513263.

¹² National Department of Health. Clinical Management of **Rifampicin-Resistant Tuberculosis**, September 2023.

¹³ Conradie F, Badat T, Poswa A, Rajaram S, Kooverjee S, et.al. A Pragmatic Trial of a 6-month strategy for rifampicin-resistant tuberculosis. NEJM. 2026; 394: 2429-2439.

NEMLC Ratification	Date		Comments/Recommendation			
EML Status	EML		Non-EML – contingent on stated reference price threshold in Rand Value		Non-EML	
	X		☐		☐	
Therapeutic Interchange Considerations (if applicable)*	If YES:	Alternative medicine/s name (INN)	Alternative/s SAHPRA registered?	Formulation/s	Equipotent dose/ Dose range and dosing interval	If NO, tick box
						X
Trigger for review						

Para-aminosalicylic acid (PAS) - anti-tuberculosis medicines used in RR- and Pre-XDR-TB individualised regimens: Added

NEMLC supported the inclusion of para-aminosalicylic acid (PAS) to the EML, following approval of a historic use submission. PAS has been used in clinical practice for many years, and is included in both WHO and national TB guidelines for patients requiring individualised TB treatment regimens, for whom the standard BPAL-L regimen is not appropriate.

High-dose isoniazid - anti-tuberculosis medicines used in RR- and Pre-XDR-TB individualised regimens: Added

High-dose isoniazid has been included on the STG list of anti-tuberculosis medicines that may be used in individualised regimens for RR- and Pre-XDR-TB. The use of isoniazid for the treatment of TB is long established on the EML, and has been included in the STG for comprehensiveness.

WHO groupings of medicines used in RR- and Pre-XDR-TB individualised regimens:

An external request to include the WHO groups A-C for medicines used in individualised RR-,Pre-XDR-TB and XDR-TB regimens has not been adopted as no reference is made to this grouping in the STG text, and the STG does not specify the design of individualised regimens. The STG refers to programmatic guidance and expert referral to the National Clinical Advisory Committee (NCAC) for individualised regimens.

BPAL regimen – linezolid dose rounding

For the management of RR-TB, the WHO guideline¹⁴ recommends a linezolid dose of 450mg daily for individuals weighing 36-46kg which would involve the crushing and mixing of the 600mg tablet to

¹⁴ WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment 2022, IGO. update. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0. <https://www.who.int/publications/i/item/9789240063129>.

formulate the requisite dose. This dose guidance from the WHO has been adopted by the National TB programme in the National DR-TB guideline,¹⁵ as tabulated below:

"Dissolving of crushed adult tablets or capsule content in 10 mL of water is required for administering this dose. The number of mL in the table reflects the dose to provide. This avoids fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (use of dispersible tablets is preferred)."
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For pragmatic reasons, the recommended dose of linezolid has been rounded for ease of implementation of the 600mg tablet formulation i.e. for individuals weighing 30-35.9kg a recommended dose of 300mg [equivalent to half of 600mg tablet] and for individuals ≥36kg 600mg [equivalent to 1 X 600mg tablet], and has been published in a subsequent clinical reference guide¹⁶ - this dose rounding guidance has been included in the STG update.

BPAL-L regimen – age thresholds

NEMLC has applied an age threshold of 15 years and older for eligibility for the BPAL-L regimen, in consultation with the TB programme to facilitate ease of implementation. This decision is an update to the NELMC recommendation included in the previously approved adolopment of the WHO guideline¹⁷, accessible online on the NHI webpage.

STG Update

STG guidance on the management of rifampicin resistant, pre-XDR and XDR TB has been subject to editorial updates as detailed below and transferred from AH Chp 16 Respiratory conditions to Chp 27 Tuberculosis.

Diagnosis - targeted next generation sequencing (tNGS)

In response to an external comment received, reference to targeted next generation sequencing (tNGS) testing as part of DR-TB reflex testing has been added to the STG. tNGS testing has been rolled out nationwide to facilitate more rapid detection of drug resistance.

AMENDED FROM	AMENDED TO:
16.11.2 RIFAMPICIN RESISTANT, Pre-XDR and XDR TB A15.0-9/A15.7-8/A16.0-5/A16.7-9/A17.0-1/A17.8-9/A18.0-7/A18.8/A19.0-2/ A19.8-9 + (B20.0) + (U50.00-01/U50.20-21/U50.30-31)	27.10.2 RIFAMPICIN RESISTANT, Pre-XDR and XDR TB U50.0, U50.2, U50.20, U50.21, U50.5
Never treat for drug-resistant TB without laboratory confirmation, either by molecular or phenotypic (culture and sensitivity) results.	DESCRIPTION Rifampicin resistant tuberculosis (RR-TB) is TB disease caused <i>M. tuberculosis</i> that is resistant to rifampicin, with or without resistance to other anti-TB drugs. Pre-XDR-TB is TB disease caused by <i>M. tuberculosis</i> that is resistant to rifampicin (with or without resistance to isoniazid) and to at least one fluoroquinolone (either levofloxacin or moxifloxacin). Extensively drug-resistant TB (XDR-TB) is TB disease caused by <i>M. tuberculosis</i> that is resistant to rifampicin AND at least one fluoroquinolone (levofloxacin or moxifloxacin) AND either bedaquiline or linezolid.

¹⁵ National Department of Health. Clinical management of RR-TB. Updated clinical reference guide. September 2023. Accessible online: <https://www.health.gov.za/wp-content/uploads/2023/10/Updated-RR-TB-Clinical-Guidelines-September-2023.pdf>

¹⁶ Shorter RR-TB regimen (BPAL-L) in patients ≥ 15 yrs October 2024. Version 3, updated February 2026 based on Clinical Management of Rifampicin-Resistant Tuberculosis: Updated Clinical Reference Guide, September 2023, Circular 2/23: Implementation of BPAL-L regimen and Circular 1/2026: Clinical Management of Rifampicin-resistant Tuberculosis in Pregnancy and Breastfeeding, South African National Department of Health. Accessible online: <https://eur03.safelinks.protection.outlook.com/?url=https%3A%2F%2Furl.za.m.mimecastprotect.com%2Fs%2FumWfCqj5DOHzo7oycZfYfErgFh%3Fdomain%3Dmic.uct.ac.za&data=05%7C02%7Czahiera.adam%40health.gov.za%7C1bd3712e20e941ddf36f08dedb67856a%7Ca517371cf316484cac5c98b76127790a%7C0%7C0%7C639189435296952413%7CUnknown%7CTWFpbGZsb3d8eyJFbXB0eU1hcGkiOnRydWUsIlY9IjoiwlJlAuMDAwMCIsIiAiOiJXaW4zMlslkFOljoITWVpbCIsIldUIjoyfQ%3D%3D%7C0%7C%7C%7C&sdata=tY%2BjLsUjfDTNFSshNAAmMunW0Cj1jsIA4%2FeZauwYIM%3D&reserved=0>

¹⁷ BPAL-M regimen: NDoH. Review - Adolopment_WHO_DRTB_Guidelines_4May2023_Final.

DESCRIPTION Rifampicin resistant tuberculosis (RR-TB) is diagnosed when there is resistance of <i>M. tuberculosis</i> to rifampicin, with or without resistance to other anti-TB drugs. RR-TB is diagnosed exclusively on culture and sensitivity assays or TB nucleic acid amplification tests (TB-NAAT). While some TB-NAAT assays test for both rifampicin and isoniazid resistance, Xpert® MTB/RIF Ultra, a type of TB-NAAT, only tests for rifampicin resistance. However, rifampicin resistance detected by Xpert® MTB/RIF Ultra is sufficient to start a patient on RR treatment, pending confirmation of RR-TB by line probe assay. Pre XDR-TB is TB disease caused by a strain of <i>M. tuberculosis</i> that is resistant to rifampicin (with or without INH resistance) and at least one fluoroquinolone (either levofloxacin or moxifloxacin). Extensively drug-resistant TB (XDR-TB) is TB disease caused by a strain of <i>M. tuberculosis</i> that is resistant to rifampicin AND at least one fluoroquinolone (levofloxacin or moxifloxacin) AND either bedaquiline or linezolid. Confirmation of pre XDR- and XDR-TB requires line probe assay and drug susceptibility testing. GENERAL MEASURES Screen all close contacts for signs and symptoms to detect early disease. MEDICINE TREATMENT Drug resistant TB prophylaxis The effectiveness of preventive therapy in adults exposed to drug resistant TB bacteria is not currently known. Consult a specialist for management. RR-TB and Pre XDR-TB treatment Consult the most recent national drug-resistant TB programme guidelines. Treatment for 6–18 months is required. Management of drug-resistant TB should be conducted in dedicated drug-resistant TB clinics and hospitals with appropriate infection control measures. XDR-TB treatment Patients with XDR-TB should be discussed with the National Clinical Advisory Committee (Email: NCAC@witshealth.co.za) and referred to a TB hospital for an individualised regimen of at least 4 effective medicines, based on susceptibility tests and treatment history. Infection control to prevent airborne transmission is essential to prevent nosocomial transmission.	DIAGNOSIS All people with signs and symptoms of TB should have a specimen sent for TB-NAAT testing. Some TB-NAAT assays test for both rifampicin and isoniazid resistance (e.g. BD MAX™ MDR-TB). Xpert® MTB/RIF Ultra, a type of TB-NAAT, only tests for rifampicin resistance. A rifampicin resistant result detected by Xpert® MTB/RIF Ultra, or other TB-NAAT, is sufficient to start a patient on RR-TB treatment. However, all people who test positive for <i>M. tuberculosis</i> with rifampicin resistance must have an additional specimen sent for DR-TB reflex testing which may include Xpert® MTB/XDR testing for fluoroquinolone resistance, targeted next generation sequencing (tNGS), TB microscopy and culture, and phenotypic drug susceptibility testing for bedaquiline and linezolid if culture positive. MEDICINE TREATMENT RR -TB and Pre-XDR-TB treatment Consult the most recent national drug-resistant TB programme guidelines. Most people with RR- or Pre-XDR-TB will be eligible to receive the 6-month BPAL-L regimen. Non-pregnant adults and adolescents (≥ 15 years) with pulmonary or non-severe extrapulmonary) RR- or Pre-XDR-TB: BPAL-L regimen • Bedaquiline, oral, 400 mg daily for 2 weeks. Followed by bedaquiline, oral, 100 mg, daily from week 3 to week 24 AND • Pretomanid, oral, 200 mg daily for 24 weeks AND • Linezolid, oral, daily for 24 weeks ○ 30 – 35.9 kg: 300 mg ○ ≥ 36 kg: 600mg AND • Levofloxacin, oral, daily for 24 weeks ○ 30 to < 46 kg: 750mg ○ ≥ 46 kg: 1000 mg ○ NOTE: If fluoroquinolone resistance is detected (e.g. Pre-XDR-TB), stop levofloxacin and continue treatment with bedaquiline, pretomanid and linezolid for the remaining duration of the 24 week course. CAUTION The following patient groups are ineligible for the BPAL-L regimen: » People with severe extrapulmonary RR- or Pre-XDR-TB (e.g. TB meningitis, osteoarticular TB, or disseminated or miliary TB). » People with an RR-TB strain that is resistant to bedaquiline, linezolid, pretomanid or delamanid. » Pregnant women and children or adolescents < 15 years. Refer to the most recent National Department of Health programmatic guidelines and circulars for further management guidance. Common adverse drug reactions associated with medicines included in the BPAL-L regimen
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Table 27.7: Adverse drug reactions associated with BPAL-L			
Adverse drug reaction		Most likely drug responsible	Management
Anaemia		Linezolid	If Hb < 8 g/dL in first 8 weeks of BPAL-L treatment: Interrupt linezolid treatment, monitor and consider blood transfusion if clinically appropriate. Linezolid must be used for at least 2 months for the BPAL-L regimen to be considered effective. If linezolid must be interrupted, discuss with NCAC/expert. If Hb < 8 g/dL after 8 weeks of BPAL-L: linezolid can be stopped provided there has been a clinical response (e.g. reduction in symptoms, weight gain, or culture conversion). If clinical response inadequate, discuss with NCAC/expert.
Thrombocytopenia		Linezolid	If platelets < 50 x 10 ⁹ /L: Stop linezolid until thrombocytopenia improves, exclude other causes, and discuss further management with NCAC/expert.
Neutropenia		Linezolid	If neutrophils < 0.75 x 10 ⁹ /L: Stop linezolid until neutropenia improves, exclude other causes, and discuss further management with NCAC/expert.
Peripheral neuropathy		Linezolid	Drug-induced peripheral neuropathy can be irreversible if the offending drug is not stopped promptly. If neuropathy interferes with daily activities, stop linezolid. If this occurs before 8 weeks of therapy, discuss with an expert. For milder forms of neuropathy treat symptomatically and try to continue linezolid until at least 8 weeks of therapy with close monitoring for deterioration in symptoms. Reduce the dose or discontinue linezolid if symptomatic neuropathy occurs after 8 weeks. For symptomatic management of neuropathy avoid amitriptyline, which may prolong the QT interval in association with other DRTB medicines, and carbamazepine, which may interact with other TB medicines. Special access to pregabalin or gabapentin may be granted on recommendation by local pharmacy and therapeutics committees (PTCs) for these patients.
Visual impairment		Linezolid	If there is a decline in visual acuity, withhold linezolid and refer patient to ophthalmologist for further evaluation.

	QTcF prolongation (QTcF = Fridericia corrected QT interval)	Bedaquiline, moxifloxacin, pretomanid, delamanid, levofloxacin	- If QTcF $\geq$ 450 ms and symptomatic (e.g. syncope, fainting, chest pain, palpitations, dizziness or loss of consciousness), hospitalise patient and withhold all medicines that may prolong QT until cause of symptoms has been assessed. - If QTcF $\geq$ 450 ms but $<$ 470 ms with no symptoms: continue routine monthly QT monitoring. Discontinue other QT-prolonging medications where possible. - If QTcF $\geq$ 470 ms but $<$ 500 ms with no symptoms: repeat ECG at rest on the same day. If still $\geq$ 470 ms but $<$ 500 ms and asymptomatic, repeat ECG weekly until stable. Check TSH and check and correct electrolytes. Discontinue other QT-prolonging medications where possible. - If QTcF $\geq$ 500 ms with no symptoms repeat ECG at rest on the same day. If still $\geq$ 500 ms, withhold all QT-prolonging medicines and all TB medicines. Check TSH and check and correct electrolytes, Discuss patient with expert.
	Arthralgia, arthritis	Fluoroquinolones, bedaquiline	Manage symptomatically with non-pharmacological measures (e.g. physical therapy, massage) and analgesia.
	Hyperlactataemia, lactic acidosis	Linezolid	Hospitalise patient with hyperlactataemia or lactic acidosis and stop linezolid immediately.
	Hepatotoxicity (e.g. nausea, vomiting, right upper quadrant pain, jaundice)	Bedaquiline, fluoroquinolones, pretomanid	- Monitor LFTs. - If elevated ALT, do full LFTs and INR and rule out other potential causes of hepatitis. - Stop BPaL-L and all potentially hepatotoxic medicines if ALT $>$ 5 times the upper limit of normal (ULN) irrespective of symptoms, or if $>$ 3 times the ULN and patient has symptoms of DILI. - Start background regimen of linezolid, clofazimine, terizidone and delamanid. - Wait for ALT to decrease to $<$ 100 IU/L before considering re-challenge. - Re-challenge sequentially with treatment dosages of levofloxacin, followed by pretomanid, followed by bedaquiline, every 5 to 7 days, with monitoring of liver function before introducing the next medicine. - Once successfully re-challenged, stop clofazimine, terizidone and delamanid and

			continue BPAL-(L). If re-challenge is unsuccessful, discuss with an expert.
	Skin reactions	All agents	Treatment can be continued if rash is mild. Stop treatment if rash is severe e.g. blistering, mucosal involvement, fever, feeling unwell or hepatitis. Patients with a severe rash must be hospitalised. Patients with a severe rash should be discussed with NCAC/expert.
Patients who are not eligible for the BPAL-L regimen or in whom bedaquiline, linezolid or pretomanid are prematurely and permanently discontinued due to toxicity may require an individualised regimen. Discuss these patients with a TB expert. Examples of anti-tuberculosis medicines used in RR- and Pre-XDR-TB individualised regimens include: ○ Levofloxacin ○ Bedaquiline ○ Linezolid ○ Clofazimine ○ Terizidone ○ Ethambutol ○ Delamanid ○ Pyrazinamide ○ Ethionamide ○ Para aminosalicylic acid ○ High-dose isoniazid XDR-TB treatment There is no standardised treatment for XDR-TB. Patients with XDR-TB should be discussed with the National Clinical Advisory Committee (Email: NCAC@witshealth.co.za) and referred to a TB hospital. These patients require an individualised regimen of at least 4 effective medicines, selected from the list above, based on susceptibility tests and treatment history, and potentially including amikacin and a carbapenem. Infection control to prevent airborne transmission is essential to prevent nosocomial transmission.			

South African National Department of Health
Brief Report of NEMLC Limited Review¹
Corticosteroids for the treatment of tuberculous pericarditis
May 2026

Medicine details:

Medicine Class	Corticosteroids	<i>If applicable Please consider therapeutic interchange policy</i>
Medicine/s name -INN: - South African name (if differs from INN)	Prednisone Prednisolone Dexamethasone	http://www.whocc.no/atc_ddd_in dex/
Medicine/s (ATC5):	H02AB07 H02AB06 H02AB02	http://www.whocc.no/atc_ddd_in dex/
Indication (ICD-10 code):	A18.0	https://www.health.gov.za/icd- 10-master-industry-table/
SAHPRA Approved	Yes	SAHPRA registered health products database https://medapps.sahpra.org.za:60 06/
Dosage form/s	tablet, suspension, injection	
Route of administration/s	Oral, IV injection	
Patient population	Adults and children with and without HIV with tuberculous pericarditis and/or pericardial effusion	
Prevalence and/or incidence of condition	66% of patients with pulmonary TB have signs of pericardial abnormality on echocardiography at the start of anti-TB treatment.[1] 47% of patients have pericardial effusion at TB diagnosis.[1] 12% of patients with pulmonary TB have features of constrictive pericarditis at diagnosis.[1]	<i>May refer to estimates or routine data (DHIS, StatsSA), not necessarily published data.</i>
Level of Care	Hospital level	
Prescriber level	Doctor prescribed	

¹ This template was informed by examples of previous NEMLC limited reviews, input from the Essential Drug Programme Oversight Group and the NEMLC Medicine Review Template which was updated with support through the Evidence-to-Decision (E2D) project which is a collaboration between National Department of Health, the South African Medical Research Council and the University of Stellenbosch.

Current Standard of Care

In adults: Antituberculosis drugs for 6 months. No recommendation regarding use of corticosteroids is provided in the Standard Treatment Guidelines (STGs). National Tuberculosis Management guidelines (2014) recommend the use of corticosteroids in adults with extrapulmonary tuberculosis, including pericarditis.

In children: Antituberculosis drugs for 6 months plus corticosteroids in suspected or proven tuberculous pericarditis.

Executive Summary

- ➔ In sub-Saharan Africa, tuberculous pericarditis is associated with all-cause mortality of 9.1 per 100 person-years (Mayosi, 2014).[2]
- ➔ The current Adult Hospital standard treatment guidelines make no recommendation regarding the use of corticosteroids in people with tuberculous pericarditis. However, National Tuberculosis Management guidelines (2014) recommend the use of corticosteroids in adults with tuberculous pericarditis.
- ➔ The current Paediatric Hospital standard treatment guidelines and Management of Tuberculosis in Children and Adolescents: A Clinical Guideline (2024), while acknowledging the limited evidence in children, recommend the use of corticosteroids in children with tuberculous pericarditis.
- ➔ We conducted an updated rapid systematic review of the evidence for the use of corticosteroids in the management of tuberculous pericarditis in HIV-negative children and adults, as well as in children and adults with HIV (PWH). Only guidelines, systematic reviews with meta-analyses, and randomised controlled trials were included.
- ➔ We identified two clinical practice guidelines:
 - Clinical practice guidelines from WHO (2025) and ATS/CDC/ERS/IDSA (2025) included the same primary studies, but did not stratify results by HIV status, and had not updated recommendations since 2016/2017.
 - The WHO (2025) clinical practice guideline recommended that in patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used. (Conditional recommendation, very low certainty of evidence)
 - The ATS/CDC/ERS/IDSA (2025) clinical practice guideline suggested that initial adjunctive corticosteroid therapy not be routinely used in patients with tuberculous pericarditis (Conditional recommendation, very low certainty of evidence).
- ➔ We identified three systematic reviews. The most up-to-date and relevant systematic review which stratified results by HIV-status (Wiysonge, 2017), was considered to be of low-quality on AMSTAR2 assessment. Key findings from this review include:
 - In adults without HIV and with tuberculous pericarditis:
 - Corticosteroids probably reduce deaths from pericarditis (RR 0.39 [95% CI 0.19 to 0.80], moderate certainty evidence) and may reduce all-cause deaths (RR 0.80 [95% CI 0.59 to 1.09], low certainty evidence) and the need for repeat pericardiocentesis (RR 0.85 [95% CI 0.70 to 1.04], low certainty evidence).
 - It is uncertain whether corticosteroids have any effect on the incidence of cancer, hospitalisation, development of constrictive pericarditis, or the need for pericardiectomy (very low certainty evidence).
 - In adult PWH with tuberculous pericarditis:
 - Corticosteroids may reduce constrictive pericarditis (RR 0.55 [95% CI 0.26 to 1.16], low certainty evidence) and hospitalization (RR 0.80 [95% CI 0.59 to 1.09], low certainty evidence).
 - Corticosteroids may make little or no difference to the need for repeat pericardiocentesis (RR 1.02 [95% 0.89 to 1.18], low certainty evidence).
 - It is uncertain whether corticosteroids have any effect on deaths from pericarditis, all-cause deaths, the need for pericardiectomy or the development of cancer (very low certainty evidence).
 - These findings are based largely on data from one RCT, in which the majority of PWH with tuberculous pericarditis were not on ART and had CD4 counts ≤ 350 cells/mm³.
- ➔ Two RCTs were identified in the search, both of which were included in the systematic review. However, since the systematic review included only limited safety outcomes, the safety outcomes from the largest RCT were reviewed (Mayosi, 2014). Key findings include:

- More participants in the prednisolone group developed candida and other opportunistic infections than in the placebo group, though this was not statistically significant. - Prednisolone, as compared with placebo, was associated with an increased incidence of cancer (1.05 vs. 0.32 cases per 100 person-years; HR 3.27; 95% CI, 1.07 to 10.03; p = 0.03). This increase was due to a higher incidence of HIV-related cancers in the prednisolone group than in the placebo group (0.73 vs. 0.08 per 100 person-years; HR 9.04; 95% CI, 1.14 to 71.33; p = 0.04), particularly Kaposi's sarcoma and non-Hodgkin's lymphoma. This increase may be related to the co-administration of immunotherapy (<i>M. indicus pranii</i>) in this RCT.
➔ Given the important benefits of reducing death in people without HIV, and in reducing hospitalisation and the development of constrictive pericarditis in PWH, we recommend the use of corticosteroids in adults with tuberculous pericarditis while acknowledging the low certainty evidence. - In PWH, a thorough clinical examination should be performed before starting corticosteroids to exclude HIV-related cancers. - In PWH, antiretroviral therapy should be initiated promptly in accordance with standard treatment guidelines.
➔ No data in children with or without HIV and tuberculous pericarditis were identified. Given the important benefits associated with corticosteroids in adults with tuberculous pericarditis, we suggest using corticosteroids in children with tuberculous pericarditis.

Key Recommendations

Type of ERC recommendation	We recommend against the option and for the alternative (strong)		We suggest not to use the option or to use the alternative (conditional)		We suggest using the option (conditional)		We recommend the option (strong)	
	☐		☐		☒ See recommendation 2		☒ See recommendation 1	
High level summary of conclusions	1. In adults with or without HIV, and with tuberculous pericarditis, we recommend using corticosteroids. 2. In children with or without HIV, and with tuberculous pericarditis, we suggest using corticosteroids.							
NEMLC Ratification	Date		Comments/Recommendation					
	4 June 2026		NEMLC ratified the ERC recommendation as above.					
Therapeutic Interchange Considerations (if applicable)*	If YES:	Alternative medicine/s name (INN)	Alternative/s SAHPRA registered?	Formulation/s	Equipotent dose/ Dose range and dosing interval		If NO, tick box	
							✓	
Trigger for review	Additional clinical trial data or safety signals.							

*Depending on the review and number of products, an annexure may need to be included

Background and rationale

The standard treatment guidelines (STGs) for tuberculosis are being updated and consolidated into a single chapter to outline the various manifestations of TB disease. Currently, the adult hospital and primary healthcare STGs provide no specific guidance for the management of tuberculous pericarditis. Tuberculous pericarditis is an extrapulmonary manifestation of tuberculosis. It is associated with all-cause mortality of 9.1 per 100 person-years in the IMPI trial conducted in sub-Saharan Africa.[2] The paediatric hospital level STGs Chapter 4 – Cardiovascular system recommends antituberculosis drugs for 6 months plus corticosteroids in suspected or proven tuberculous pericarditis (Figure 1). No differential guidance is provided by HIV status.

CHAPTER 4	CARDIOVASCULAR SYSTEM
MEDICINE TREATMENT	
If suspected or proven TB pericarditis, give antituberculosis drugs for 6 months plus corticosteroids.	
• Prednisone, oral, for 6 weeks: ○ Week 1: 2 mg/kg/day, ○ Week 2: 1.5 mg/kg/day, ○ Week 3: 1 mg/kg/day, ○ Week 4: 1 mg/kg/day, ○ Week 5: 0.5 mg/kg/day, ○ Week 6: 0.25 mg/kg/day.	
LoE III ^{1,14}	

Figure 1. Paediatric Hospital Level Standard Treatment Guidelines. Chapter 4. Cardiovascular system. Pericardial effusion. (The references for this recommendation are the trials by Mayosi, 2014 and Strang, 1987[2,3])

The National Tuberculosis Management Guidelines (2014) recommend the use of corticosteroids in adults with extrapulmonary tuberculosis, including pericarditis (Figure 2). No differential guidance is provided by HIV status.

7.5.2 Steroids The use of corticosteroids is recommended in extra-pulmonary tuberculosis, particularly for TB meningitis and pericarditis. High dose steroid treatment for 2-4 weeks and the taper off gradually over several weeks depending on clinical progress is recommended. The response to treatment is assessed clinically.
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Figure 2. National Tuberculosis Management Guidelines 2014. Page 42 of 120. Adjunctive treatment.

The largest study on the use of corticosteroids in tuberculous pericarditis was published in 2014, subsequent to the 2014 National Tuberculosis Management Guidelines. Recently, data on the differential effect of steroids in people with and without HIV in the setting of other extrapulmonary manifestations of tuberculosis has emerged. Therefore, in order to update and consolidate the tuberculosis STGs a rapid review of use of corticosteroids in tuberculous pericarditis was undertaken.

Purpose/Objective i.e., PICO question:

PICO 1

Population Subgroups	HIV-negative adults and children with tuberculous pericarditis
Intervention(s)	Corticosteroids (prednisone or prednisolone) plus standard anti-TB treatment
Comparator(s)	Anti-tuberculous treatment (ATT) alone or with placebo
Outcome(s)	Mortality, constrictive pericarditis, adverse events
Study types	Guidelines, systematic reviews with meta-analysis, randomised controlled trials

PICO 2

Population Subgroups	Adults and children living with HIV and tuberculous pericarditis
Intervention(s)	Corticosteroids (prednisone or prednisolone) plus anti-TB treatment
Comparator(s)	Anti-tuberculosis treatment (ATT) alone or with placebo
Outcome(s)	Mortality, constrictive pericarditis, adverse events
Study types	Guidelines, systematic reviews with meta-analysis, randomised controlled trials

Methods

1. Data Sources

Clinical practice guidelines: We searched for relevant clinical practice guidelines from the American Thoracic Society and World Health Organization.

Systematic reviews and randomised controlled trials: We searched PubMed for guidelines, systematic reviews, and randomised controlled trials.

2. Search Strategy

The following search terms were used:

((TB pericarditis) OR (tuberculous pericarditis)) OR (tuberculosis pericarditis)) AND (corticosteroids)
PubMed searches were filtered by guideline, systematic review, meta-analysis and randomised controlled trials.

3. Study selection and eligibility criteria, data extraction and analysis, and evidence synthesis

The study screening, selection and data extraction, analysis and evidence was conducted by 1 reviewer. Evidence was synthesised narratively.

4. Assessment of methodological quality

The most recent and up-to-date systematic review was appraised by one reviewer using AMSTAR.[4]

5. GRADE assessment

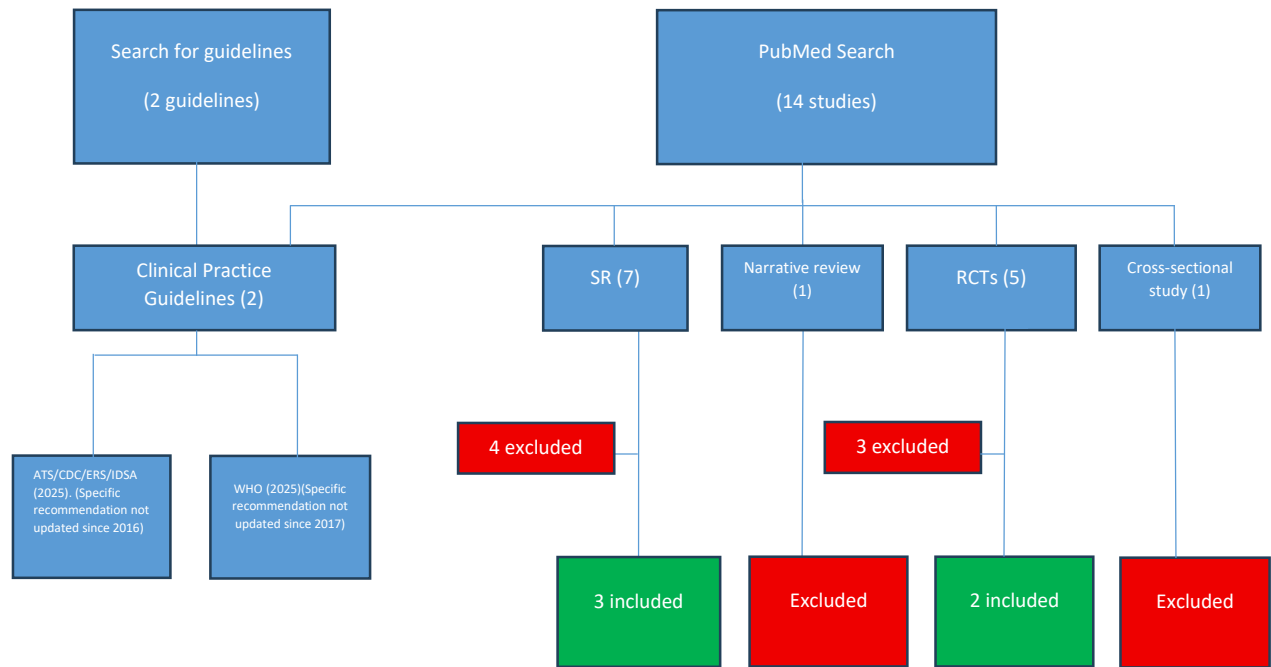
We adopted the GRADE (Grading of Recommendations Assessment, Development and Evaluation) assessment in the systematic review.

Results

1. Result of the search

The search results are illustrated in **Figure 3. Search Flow Chart**. Specific reasons for inclusion or exclusion of studies identified in the search are listed in **Appendix 1**.

Figure 3. Search Flow Chart



Abbreviations: ATS, American Thoracic Society; CDC, Centers for Disease Control and Prevention; ERS, European Respiratory Society; IDSA, Infectious Diseases Society of America; WHO, World Health Organisation; SR, systematic review; RCTs, randomised controlled trials

2. Description of included studies

2.1. Clinical Practice Guidelines

Two clinical practice guidelines were identified. Both clinical practice guidelines had not updated specific recommendations related to corticosteroid use in tuberculous pericarditis since 2016-2017. These guidelines with their respective recommendations are summarised in **Table 1**. Importantly, effect estimates by HIV status are not provided in either guideline's summary of findings tables. Summary of findings tables from the guidelines are included in **Appendix 2**.

Table 1. Summary of the recommendations from clinical practice guidelines identified

Guideline	Recommendation	Justification	Subgroup considerations	Studies included in the systematic review	Outcomes considered
WHO Consolidated guidelines on tuberculosis. Module 4: Treatment and care. 2025.	In patients with tuberculous pericarditis, an initial adjunct corticosteroid therapy <u>may be used</u>. (Conditional recommendation, very low certainty of evidence) This recommendation was first put forward in the guidelines update of 2017. They are copied without modification into this consolidated document and appear exactly as in the 2017 guidelines.	In patients with tuberculous pericarditis, evidence from studies in the systematic review showed a benefit to steroid treatment with regard to death, constrictive pericarditis and treatment adherence. When the studies were considered individually, the largest (1400 patients) and most recent study – the IMPI study – showed no benefit with steroids. However, a complicating factor in these findings is HIV infection. In the IMPI study, 67% of subjects were HIV-positive and only 14% were on ART. This raises the question as to whether immunosuppressed patients may have had a different benefit from steroids when compared to HIV-negative people or persons living with HIV who are on ART. In the IMPI study, a supplemental analysis was done of the HIV-negative patients only and a small mortality benefit was shown with steroid treatment. However, the relationship between HIV infection and steroids is complex. In another smaller study of 58 subjects, all of whom were HIV-positive, steroids were found to reduce mortality. It is of note that the other studies in the review did not address HIV and mortality. The panel considered that the benefit in preventing constrictive pericarditis outweighed the potential harms of corticosteroid therapy.	With regard to the use of steroids in tuberculous pericarditis, in one study an increase in HIV-related cancers (non-Hodgkins' lymphoma and Kaposi sarcoma) was observed. However, this increase appears to be caused by co-administration of immunotherapy (<i>M. indicus pranii</i>).	Strang et al. 1987 Strang et al. 1988 Hakim Et Al. 2000 Mayosi et al. 2014 Reuter et al. 2006	Mortality (5 studies) Treatment adherence (2 studies) Constrictive pericarditis (3 studies)
Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis, 2016. Update on the Treatment of Drug-Susceptible and Drug-Resistant Tuberculosis. An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline, 2025.	We suggest initial adjunctive corticosteroid therapy <u>not be</u> routinely used in patients with tuberculous pericarditis (Conditional recommendation; very low certainty of evidence).	Based on small studies that have shown mortality and morbidity benefits, corticosteroids have previously been universally recommended in combination with a standard 6-month regimen for treating tuberculous pericarditis; however, a recent placebo-controlled randomized clinical trial with 1400 participants did not find a difference in the combined primary endpoint of the trial, which included mortality, cardiac tamponade, or constrictive pericarditis, between patients treated with adjunctive corticosteroids vs placebo. A subgroup analysis, however, did suggest a benefit in preventing constrictive pericarditis. Similarly, a systematic review conducted to obtain evidence in support of this guideline did not find a statistically significant benefit in terms of mortality or constrictive pericarditis from the use of corticosteroids. Therefore, we suggest that adjunctive corticosteroids should not be used routinely in the treatment of patients with pericardial tuberculosis.	However, selective use of corticosteroids in patients who are at the highest risk for inflammatory complications might be appropriate. Such patients might include those with large pericardial effusions, those with high levels of inflammatory cells or markers in pericardial fluid, or those with early signs of constriction.	Strang et al. 1987 Strang et al. 1988 Hakim Et Al. 2000 Mayosi et al. 2014 Reuter et al. 2006	Mortality (5 studies) Treatment adherence (2 studies) Constrictive pericarditis (3 studies)

2.2. Systematic reviews

Three systematic reviews were identified in the search (**Table 2**). The Cochrane systematic review by Wiysonge, 2017 was considered to be the most up-to-date and relevant as analyses presented are stratified by HIV status.

Table 2. Characteristics of systematic reviews identified

Systematic review	Year Published	Studies included	Subgroup analysis by HIV status	Comment
George et al.[5]	2018	Strang, 1987 Strang, 1988 Hakim, 2000 Mayosi, 2014 Reuter, 2006	No	
Wiysonge et al.[6]	2017 (reviewed in 2019 and considered up-to-date with respect to intervention of corticosteroids)	Schrire, 1959 Hakim, 2000 Strang, 2004a (10-year follow-up study of Strang 1987) Strang, 2004b (10-year follow-up study of Strang 1988) Reuter, 2006 Mayosi, 2014	Yes	Most up-to-date and relevant AMSTAR quality appraisal: Low-quality (Appendix 3)
Ntsekhe et al. [7]	2003	Schrire, 1959 Strang, 1987 Strang, 1988 Hakim, 2000	Yes	

2.2.1. Wiysonge, 2017[6]

This is an update of an earlier Cochrane systematic review published in 2002. This systematic review included seven randomised controlled trials (RCTs) or quasi-RCTs, all from sub-Saharan Africa, including the largest RCT conducted to date. Six trials comprising 1926 participants evaluated corticosteroids in tuberculous pericarditis.[2,8-11] Characteristics of these studies are summarised in **Table 3**. Four trials, comprising 1841 participants, were considered to be at low risk of bias. Three trials, comprising 118 participants, were considered to be at high risk of bias (**Figure 4**). Five trials enrolled participants with tuberculous pericardial effusion and one trial enrolled participants with tuberculous pericardial constriction. The corticosteroids evaluated included cortisone (1 trial), prednisone and triamcinolone hexacetonide (1 trial), and prednisolone (4 trials). The length of follow-up across trials ranged from 1 to 10 years. Only 2 trials included adults and children, with only 7 participants < 15 years included in the systematic review.[8]

In the systematic review, analyses were stratified by HIV status. Data on HIV status were not available in three trials that were conducted in South Africa before the onset of the HIV epidemic.[8,9] The participants in these trials were assumed to be HIV negative for the purposes of the systematic review. One trial enrolled only people with HIV (PWH).[10] Two trials enrolled both PWH and HIV-negative people. [2,11] More than half of all participants included in the systematic review were PWH (1018/1926, 52.9%), however only 19.9% were on antiretroviral therapy at enrolment. In the largest trial included in the systematic review, which comprised 939 PWH, baseline CD4 was available for 633 of 939 participants (67.4%). In these participants, the median CD4 count was 144 cells/mm³; 103 participants (16.3%) had a CD4 count < 50 cells/mm³; 295 participants (46.6%) had a CD4 count between 50 and 199 cells/mm³, 144 participants (22.7%) had a CD4 count between 200 to 350 cells/mm³, and 91 participants (14.4%) had CD4 cell counts > 350 cells/mm³. [12]

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Hakim 2000	+	+	+	+	+	?	+
Liebenberg 2016	+	+	?	+	-	?	+
Mayosi 2014	+	+	+	+	+	+	+
Reuter 2006	?	-	+	?	-	?	+
Schrire 1959	-	-	-	-	?	?	+
Strang 2004a	+	+	+	+	+	?	+
Strang 2004b	+	+	+	+	+	?	+

Figure 4. Risk of bias summary from systematic review

(Note: The study by Liebenberg 2016 included in Figure 4 below is relevant to a different research question with colchicine as the intervention)

Table 3. Summary of studies included in Wiysonge, 2017

Study and Location	Methods	Participants	Interventions	Outcomes
Schire 1959 Cape Town, South Africa	Alternate allocation of 28 participants to adjuvant steroids or no steroids	28 adult participants with pericardial effusion who were on antituberculous chemotherapy for suspected tuberculous pericarditis. The trial authors did not provide the characteristics of the included participants, and did not specify the antituberculous drugs used. No participants with HIV. Definite TB: Not reported	Intervention • Cortisone with a loading dose of 300 mg and maintenance dose of 100 mg daily for several weeks was prescribed for 14 participants. - At a later date, prednisolone 60 mg/day with a maintenance dose of 20 mg was substituted. Control • No corticosteroids. The trial authors did not specify the length of follow-up.	Constriction requiring pericardiectomy
Hakim 2000 Harare, Zimbabwe	Computer-generated randomization list Double blind placebo controlled trial	58 HIV-positive adults with pericardial effusion who were on antituberculous chemotherapy for suspected tuberculous pericarditis. Inclusion criteria: (a) age 18 to 55 years; (b) residence in Harare city to ensure good follow up; (c) HIV seropositive; (d) no diagnosis of tuberculosis within the past two years; (e) large pericardial effusion on echocardiography (> 1 cm anteriorly and > 1 cm posteriorly; and (f) pericardial aspirate with > 50% lymphocytes and protein content > 30 g/L. Exclusion criteria: (a) antituberculous treatment started more than 48 hours before recruitment; (b) corticosteroid treatment within previous one month; (c) presence of Kaposi's sarcoma or any other malignancy; (d) coexisting life threatening disease; (e) bacterial pneumonia; (f) pregnancy; (g) cavitating pulmonary tuberculosis; and (h) other causes of pericardial effusion. All patients received a standard short course anti tuberculous regimen in accordance with national guidelines. This included rifampicin, isoniazid, pyrazinamide, and ethambutol for two months, followed by rifampicin and isoniazid for a further four months in standard doses. 0 participants on ART Definite TB: 38%	Intervention • Prednisolone for the first 6 weeks of antituberculous chemotherapy. • Dose for adults: 60 mg for the first week and tapering by 10 mg every week. Control • Placebo.	Primary outcomes • Death. • Resolution of pericardial effusion. Secondary outcomes • Resolution of pretreatment symptoms and signs, and ECG changes. • Corticosteroid-related adverse effects.

Study and Location	Methods	Participants	Interventions	Outcomes
Strang 2004a Umtata, South Africa (Follow-up of Strang, 1987)	Central randomization Double blind placebo- controlled study	143 participants with suspected tuberculous constrictive pericarditis aged 5 years and older. Only 2 participants were younger than 15 years of age. The participants in the treatment and control groups were well-matched in terms of clinical characteristics and completion of antituberculous chemotherapy. Those consenting to take part were all prescribed the same 6-month standard antituberculosis regimen of streptomycin, isoniazid, rifampicin, and pyrazinamide daily for 14 weeks as an in-patient, followed by isoniazid and rifampicin daily up to 6 months. Assumed no participants with HIV. Definite TB: 10%	Intervention • Prednisolone for the first 11 weeks of antituberculous chemotherapy. The dose for children aged 5 to 9 years was 30 mg daily for weeks 1 to 4; 15 mg daily for weeks 5 to 8; 7.5 mg daily for weeks 9 to 10; and 2.5 mg daily for week 11. Regarding children aged 10 to 14 years, the dose was 45 mg for weeks 1 to 4; 22.5 mg for weeks 5 to 8; 7.5 mg for weeks 9 to 10; and 2.5 mg for week 11. The dose for adults was 60 mg for the first 4 weeks; 30 mg for weeks 5 to 8; 15 mg for weeks 9 to 10; and 5 mg for week 1. Control • Matching placebo.	• Death. • Death from pericarditis. • Favourable clinical status at 24 months. • Pericardiectomy.
Strang 2004b Umtata, South Africa (Follow-up of Strang, 1988)	Central randomization Double blind placebo- controlled study Factorial design	240 participants aged 5 years or more diagnosed as having active tuberculous pericardial effusion. Only 5 participants were younger than 15 years of age. The participants in the treatment and control groups were well-matched in terms of their clinical characteristics and completion of antituberculous chemotherapy. Those consenting to take part were all prescribed the same 6-month standard antituberculosis regimen of streptomycin, isoniazid, rifampicin, and pyrazinamide daily for 14 weeks as an in-patient, followed by isoniazid and rifampicin daily up to 6 months. Assumed no participants with HIV. Definite TB: 60%	Intervention 1 • Complete open surgical drainage on admission. Control 1 • No open drainage. Intervention 2 • Prednisolone for the first 11 weeks of antituberculous chemotherapy. The dose for children aged 5 to 9 years was 30 mg daily for weeks 1 to 4; 15 mg daily for weeks 5 to 8; 7.5 mg daily for weeks 9 to 10; and 2.5 mg daily for week 11. Regarding children aged 10 to 14 years, the dose was 45 mg for weeks 1 to 4; 22.5 mg for weeks 5 to 8; 7.5 mg for weeks 9 to 10; and 2.5 mg for week 11. The dose for adults was 60 mg for the first 4 weeks; 30 mg for weeks 5 to 8; 15 mg for weeks 9 to 10; and 5 mg for week 1. Control 2 • Matching placebo.	• Death. • Death from pericarditis. • Favourable clinical status at 24 months. • Tamponade requiring pericardiocentesis. • Constriction. • Pericardiectomy.

Study and Location	Methods	Participants	Interventions	Outcomes
Reuter 2006 Cape Town, South Africa	Computer-generated randomization list Double-blind placebo-controlled study	57 participants, aged 17 to 66 years, with large pericardial effusions on echocardiography, pericardial aspirate with protein content > 30 g/L, and pericardial fluid adenosine deaminase (ADA) activity > 35 U/L; 23 females and 34 males; 40 had microbiological or histological evidence of TB or both, and 17 patients were diagnosed by clinical and supportive laboratory data. 21 (37.0%) were HIV-positive. No PWH were on ART. A standard short-course anti-tuberculous regimen was initiated according to national guidelines, namely a combination of rifampicin, isoniazid, pyrazinamide and ethambutol for two months, followed by rifampicin and isoniazid for a further four months. Patients were discharged on anti-tuberculous therapy and pyridoxine, with or without adjunctive prednisone. HIV-positive patients also received daily oral cotrimoxazole; due to the prevailing national policy at the time of this study, none of these patients received antiretroviral therapy. Definite TB: not reported	Intervention 1 • 200 mg (5 mL) intrapericardial triamcinolone hexacetonide. Triamcinolone was injected directly into the pericardium just prior to the removal of the indwelling catheter. Due to limited resources, an oral placebo was not used in conjunction with the intrapericardial triamcinolone. 17 participants were in this arm, 6 (35%) were HIV-positive. Intervention 2 • Oral prednisone plus intrapericardial placebo (5 mL 0.9% saline solution). Oral prednisone was started at 60 mg/day for 4 weeks, followed by 30 mg/day for 4 weeks, 15 mg/day for 2 weeks and 5 mg/day for 1 week. There were 16 participants in this arm, 9 (56%) were HIV-positive. Control • Placebo (5 mL intrapericardial 0.9% saline). 24 participants were included in this arm, and 6 (25%) were HIV-positive. We excluded data from the intrapericardial triamcinolone arm from this review.	Primary outcome • All-cause mortality. Secondary outcomes • Death attributed to pericarditis. • Disability related to pericardial disease at 1 year (defined as a history of restricted physical activity using New York Heart Association functional classification.) • Effusive constriction. • Fibrous constrictive pericarditis requiring pericardiectomy.

Study and Location	Methods	Participants	Interventions	Outcomes
Mayosi 2014 Multiple sites in South Africa, Mozambique, Malawi, Uganda, Sierra Leone, Zimbabwe, Kenya, and Nigeria	Computer-generated randomization list Double-blind placebo-controlled 2x2 factorial study	1400 participants (67% HIV-positive) 18 years of age or older, evidence of definite or probable tuberculous pericarditis, and had begun antituberculous treatment less than 1 week before enrolment. 83% of participants had pericardial effusion. 17% had constriction. 22% of PWH were on ART. Trial participants received antimicrobial treatment for tuberculosis and antiretroviral treatment for HIV according to World Health Organization (WHO) guidelines; management during the trial was revised as recommended treatment practices evolved. Definite TB: 17%	Intervention 1 • Prednisolone for 6 weeks at a dose of 120 mg per day in the first week, 90 mg per day in the second week, 60 mg per day in the 3rd week, 30 mg per day in the 4th week, 15 mg per day in the 5th week, and 5 mg per day in the 6th week. Control 1 • Identical placebo for 6 weeks at a dose of 120 mg per day in the 1st week, 90 mg per day in the 2nd week, 60 mg per day in the 3rd week, 30 mg per day in the 4th week, 15 mg per day in the 5th week, and 5 mg per day in the 6th week Intervention 2 • <i>M. indicus pranii</i> preparation (CADI-Mw injection, Cadila Pharmaceuticals) in 5 doses: at the time of enrolment and at 2 weeks, 4 weeks, 6 weeks, and 3 months. The 1st dose was given as 2 injections of 0.1 mL (containing 0.5 Å~ 109 organisms) in each deltoid region of the upper arm; the 4 subsequent doses were given as a single injection of 0.1 mL. Control 2 • Identical placebo in 5 doses: at the time of enrolment and at 2 weeks, 4 weeks, 6 weeks, and 3 months. The 1st dose was given as 2 injections of 0.1 mL in each deltoid region of the upper arm; the 4 subsequent doses were given as a single injection of 0.1 mL.	Primary outcome • Composite of death or 1st occurrence of cardiac tamponade requiring pericardiocentesis or constrictive pericarditis. Secondary outcomes • Individual components of the primary outcome. • Hospitalization. Safety outcomes • Opportunistic infections. • Cancer. • CD4+ T-lymphocyte cell count (measure of immunosuppression) and immune reconstitution inflammatory syndrome (in HIV-positive).

2.3 Randomised controlled trials (RCTs)

Two RCTs were identified in the search.[2,8] Both studies were included in the Wiysonge(2017) systematic review and the effectiveness results for these two studies are not discussed further. Since the identified systematic review included only limited safety outcomes, the safety outcomes from the largest RCT are included.

The largest RCT was the IMPI trial, which utilised a 2 x 2 factorial double-blind design and was conducted in multiple centres across Sub-Saharan Africa.[2] The study enrolled 1400 adults with definite or probable tuberculous pericarditis to receive either prednisolone (n = 706) or placebo (n = 694) for 6 weeks, and either *M.indicus prannii* immunotherapy or placebo, in addition to standard anti-tuberculous therapy. The primary outcome was a composite of death or the first episode of cardiac tamponade requiring pericardiocentesis or constrictive pericarditis. Two thirds of participants were PWH, and across study arms <15% of PWH were on antiretroviral medication at randomisation. In the Wiysonge (2017) systematic review the IMPI trial was assessed to be at low risk of bias.

3. Effectiveness and/or safety results

3.1 PICO 1: Corticosteroids plus standard anti-tuberculous treatment compared to anti-tuberculous treatment alone or with placebo in HIV-negative adults with tuberculous pericarditis

Table 4. Summary of findings table for HIV-negative people from Wiysonge, 2017

Summary of findings for the main comparison. Corticosteroids for tuberculous pericarditis in HIV-negative people						
Population: HIV-negative people with tuberculous pericarditis Settings: any setting Intervention: corticosteroids Comparison: placebo						
Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Placebo	Steroids				
Death from all causes	22 per 100	18 per 100 (13 to 24)	RR 0.80 (0.59 to 1.09)	660 (4 trials)	⊕⊕⊕⊕ low ^{1,2}	Steroids may reduce the risk of deaths from all causes among HIV-negative people.
Death from pericarditis	8 per 100	3 per 100 (1 to 6)	RR 0.39 (0.19 to 0.80)	660 (4 trials)	⊕⊕⊕⊕ moderate ²	Steroids probably reduce the risk of deaths from pericarditis among HIV-negative people.
Constrictive pericarditis	10 per 100	7 per 100 (3 to 15)	RR 0.72 (0.34 to 1.55)	281 (2 trials)	⊕⊕⊕⊕ very low ^{2,3,4}	It is uncertain whether steroids have an effect on the risk of constriction among HIV-negative people.
Repeat pericardiocentesis	40 per 100	34 per 100 (28 to 41)	RR 0.85 (0.70 to 1.04)	492 (2 trials)	⊕⊕⊕⊕ low ^{1,4}	Steroids may reduce the risk of repeat drainage of the pericardium among HIV-negative people.
Cancer	1 per 100	1 per 100 (0 to 12)	RR 0.85 (0.05 to 13.80)	256 (1 trial)	⊕⊕⊕⊕ very low ^{3,5}	It is uncertain whether steroids have an effect on the risk of cancer among HIV-negative people.
Abbreviations: CI: confidence interval; RR: risk ratio.						
GRADE Working Group grades of evidence High certainty: further research is very unlikely to change our confidence in the estimate of effect. Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low certainty: we are very uncertain about the estimate.						

¹We downgraded by 1 for imprecision: the CI ranges from a large clinical benefit to a small increase in harm.

²We downgraded by 1 for study limitations: one trial was at high risk of bias.

³We downgraded by 2 for imprecision: the CI ranges from clinically important benefits to a large increase in harm.

⁴We downgraded by 1 for selective reporting: data were only reported by 2 of the 4 trials that recruited HIV-negative people.

⁵We downgraded by 1 for selective reporting: data were only reported by 1 of the 4 trials that recruited HIV-negative people.

In addition, only 1 trial reported on hospitalisation. It is uncertain whether corticosteroids reduced the risk of hospitalisation in people without HIV (RR 0.98, 95% CI 0.57 to 1.70, 256 participants, 1 trial, very low certainty evidence).

The effects of corticosteroids on risk of pericardiectomy in people without HIV is also uncertain (RR 0.91, 95% CI 0.58 to 1.41; 432 participants; 4 trials; very low certainty evidence).

3.2 PICO 2: Corticosteroids plus standard anti-tuberculous treatment compared to anti-tuberculous treatment alone or with placebo in adults with HIV and tuberculous pericarditis

Table 5. Summary of findings table for PWH from Wiysonge, 2017

Summary of findings 2. Corticosteroids for tuberculous pericarditis in HIV-positive people

Population: HIV-positive people with tuberculous pericarditis. Most patients (80%) not on antiretroviral drugs

Settings: any setting

Intervention: corticosteroids

Comparison: placebo

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Placebo	Corticosteroids				
Death from all causes	17 per 100	15 per 100 (6 to 40)	RR 0.91 (0.34 to 2.42)	575 (3 trials)	⊕⊕⊕⊕ very low ^{1,2}	It is uncertain whether steroids have an effect on the risk of deaths from all causes among people living with HIV.
Death from pericarditis	4 per 100	4 per 100 (2 to 10)	RR 1.07 (0.46 to 2.54)	517 (2 trials)	⊕⊕⊕⊕ very low ^{1,3}	It is uncertain whether steroids have an effect on the risk of deaths from pericarditis among people living with HIV.
Constrictive pericarditis	6 per 100	4 per 100 (2 to 7)	RR 0.55 (0.26 to 1.16)	575 (3 trials)	⊕⊕⊕⊕ low ¹	Steroids may reduce the risk of developing constriction among people living with HIV.
Repeat pericardiocentesis	60 per 100	61 per 100 (53 to 71)	RR 1.02 (0.89 to 1.18)	517 (2 trials)	⊕⊕⊕⊕ low ^{3,5}	Steroids may have little or no effect on the risk of repeat pericardiocentesis among people living with HIV.
Cancer	1 per 100	1 per 100 (0 to 8)	RR 1.62 (0.27 to 9.77)	502 (1 trial)	⊕⊕⊕⊕ very low ^{1,3}	It is uncertain whether steroids have an effect on the risk of cancer among people living with HIV.

Abbreviations: CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence

High certainty: further research is very unlikely to change our confidence in the estimate of effect.

Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low certainty: we are very uncertain about the estimate.

¹We downgraded by 2 for imprecision: the CI ranges from substantial clinical benefits to substantial harm.

²We downgraded by 1 for unexplained heterogeneity ($\text{Chi}^2 = 3.82$, $\text{df} = 1$ ($P = 0.05$); I^2 statistic = 74%).

³We downgraded by 1 for selective reporting: only 2 of the 3 studies that recruited HIV-positive people reported data.

⁴We downgraded by 1 for study limitations: 1 study had a high risk of bias.

⁵We downgraded by 1 for imprecision: the CI ranges from a small beneficial effect to clinically important harms.

Corticosteroids may reduce the risk of hospitalisation in PWH (RR 0.80, 95% CI 0.59 to 1.09; 502 participants, 1 trial, low certainty evidence).

It is uncertain whether corticosteroids have an effect on risk of pericardiectomy in PWH (RR 2.10, 95% CI 0.10 to 44.40; 15 participants, 1 trial, very low certainty evidence)

It is uncertain whether corticosteroids have an effect on the risk of opportunistic infections in PWH (RR 0.95, 95% CI 0.61 to 1.48; 517 participants, 2 trials, very low certainty evidence).

The IMPI trial, which contributed to the majority of participants with HIV in the Wiysonge 2017 systematic review, included a subgroup analyses of the effect of prednisolone on the primary composite outcome by CD4 count (**Figure 5**).

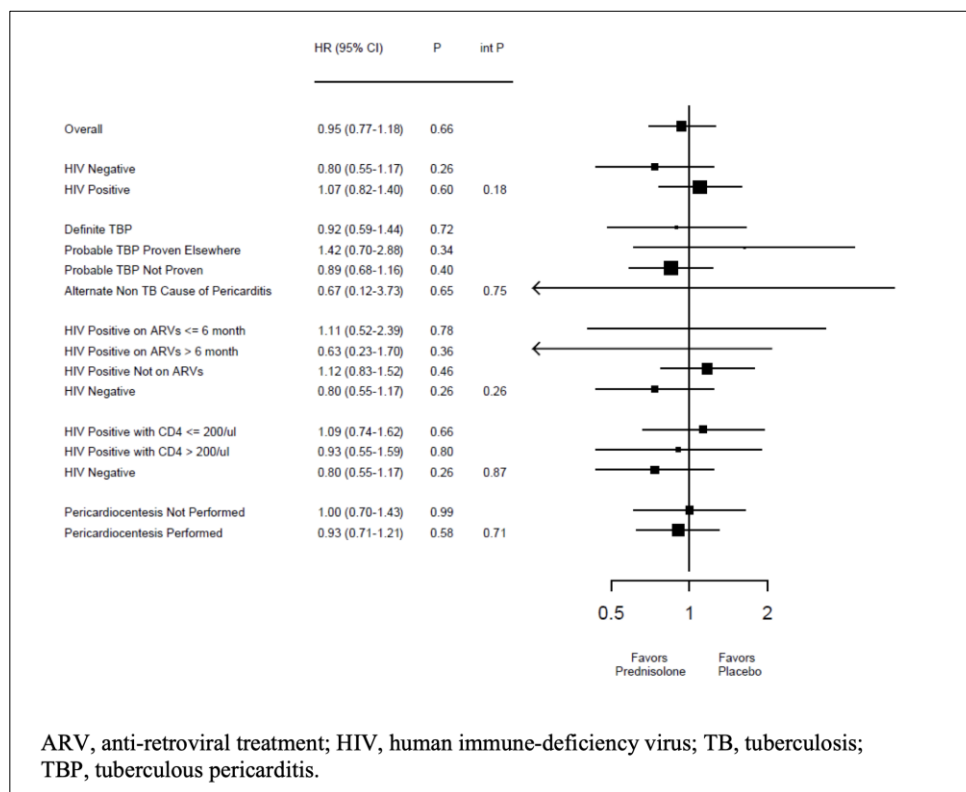


Figure 5. Forest Plot of Effect on Primary Composite Outcome by Key Subgroups for the Prednisolone Comparison from Mayosi, 2014

3.3 Safety Outcomes from Mayosi, 2014[2]

Table 6. Effects of prednisolone on Safety Outcomes from Mayosi, 2014

Outcome	Prednisolone (N = 706)		Placebo (N = 694)		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	no. of events/100 person-yr	no. of patients (%)	no. of events/100 person-yr		
Opportunistic infection	78 (11.0)	6.89	68 (9.8)	5.91	1.16 (0.84–1.61)	0.36
Candida infection	54 (7.6)	4.68	36 (5.2)	3.01	1.52 (1.00–2.32)	0.05
Cancer	13 (1.8)	1.05	4 (0.6)	0.32	3.27 (1.07–10.03)	0.03
HIV-related cancer	9 (1.3)	0.73	1 (0.1)	0.08	9.04 (1.14–71.33)	0.04
Immune reconstitution disease	2 (0.3)	0.16	1 (0.1)	0.08	2.02 (0.18–22.28)	0.56

More participants in the prednisolone group developed candida and other opportunistic infections than in the placebo group, though this was not statistically significant. There were very few cases of immune reconstitution inflammatory syndrome (IRIS) in the trial overall, 2 cases of IRIS occurred in the prednisolone group and 1 in the placebo group. Prednisolone, as compared with placebo, was associated with an increased incidence of cancer (1.05 vs. 0.32 cases per 100 person-years; HR 3.27; 95% CI, 1.07 to 10.03; $p = 0.03$). This increase was due to a higher incidence of HIV-related cancers in the prednisolone group than in the placebo group (0.73 vs. 0.08 per 100 person-years; HR 9.04; 95% CI, 1.14 to 71.33; $p = 0.04$). The various cancers are summarised in **Table 7**. Nine of

the 13 cases of cancer in the prednisolone group occurred in participants who also received *M. indicus pranii*. Kaplan-Meier estimates of time to cancer occurrence for all four comparisons in the trial are shown in **Figure 6**. It should be noted that based on the suggestion of a clinical interaction between prednisolone and *M. indicus pranii* on cancer incidence, in the Wiysonge 2017 systematic review for the outcome of cancer, only data from the group that took 1 active intervention (i.e. prednisolone and placebo) were included, and data from the group that received both interventions was excluded.

Table 7. Causes of Malignancy Prednisolone vs. Placebo

Cause of malignancy	Prednisolone 706/1400		Placebo 649/1400		P value*
	n	%	n	%	
All malignancies (Patient could have multiple malignancies)	13	1.8	4	0.6	0.05
Kaposi	7	1.0	1	0.1	0.07
Non Hodgkin's lymphoma	2	0.3	0	0.0	0.50
Gastric / colon cancer	1	0.1	0	0.0	>0.99
Progression of pre-existing malignancy	1	0.1	1	0.1	>0.99
Other	2	0.3	2	0.3	>0.99

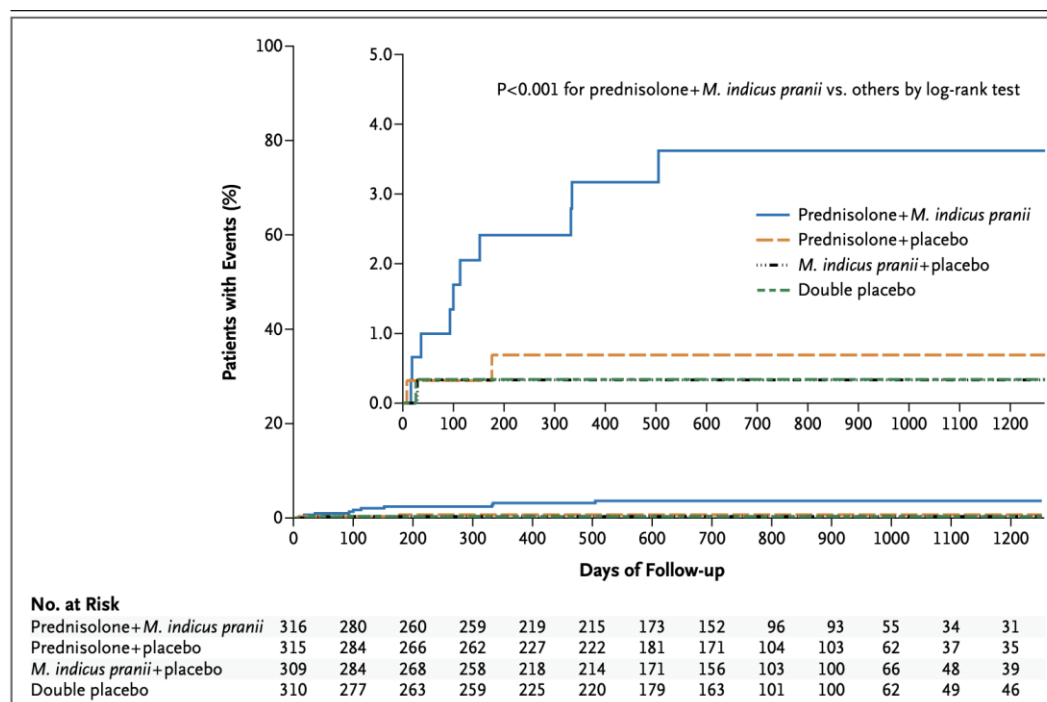


Figure 6. Time to cancer occurrence by study arm from Mayosi, 2014

Costs

The management of TB pericarditis will be a new STG addition to the Adult Hospital publication. As the national TB guidelines recommend the use of corticosteroids in TB pericarditis, we anticipate a minimal incremental budget impact with this recommendation. Costs have been calculated using the oral prednisone dose regimen from Mayosi (2014) RCT as this includes the largest patient cohort. Equivalent doses of dexamethasone IV for patients unable to take oral therapy, were obtained using the online steroid conversion calculator: https://www.mdcalc.com/calc/2040/steroid-conversion-calculator?drug_dosage=90

Table 8. Direct cost of corticosteroids in the treatment of tuberculous pericarditis in adults

TB PERICARDITIS - cost of corticosteroids as adjunctive therapy (ADULTS)					
Dexamethasone IV					
STG dosing guidance		Formulation	Price per ampoule (Rands)	Equivalent number of amps per week	Cost per week (Rands)
Week 1	18mg	4mg/mL as 1mL inj	6,83	35	239,05
Week 2	13,5mg			28	191,24
Week 3	9mg			21	143,43
Week 4	4,5mg			14	95,62
Week 5	2,3mg			7	47,81
Week 6	0,8mg			7	47,81
Cost per course					R764,96
Prednisone oral					
STG dosing guidance		Formulation	Price per tablet (Rands)	Equivalent number of tablets per day	Cost per week (Rands)
Week 1	120mg/day	5mg tablet	0,19	24	31,92
Week 2	90mg/day			18	23,94
Week 3	60mg/day			12	15,96
Week 4	30mg/day			6	7,98
Week 5	15mg/day			3	3,99
Week 6	5mg/day			1	1,33
Cost per course					R85,12
Notes:					
1. Dexamethasone dose conversion based on equivalent dose of oral prednisone using Mayosi 2014 regimen https://www.mdcalc.com/calc/2040/steroid-conversion-					
2. Doses rounded to nearest ampoule/tablet					
3. Prices based on MHPL (Feb 2026)					
4. Where dose ranges recommended - max dose applied for costing					
5. For prednisone, ave price per tablet applied as multiple products on tender					

As the use of adjunctive corticosteroids is already included in the paediatric STGs as standard of care, there is no anticipated incremental budget impact associated with this recommendation (**Table 9**).

Table 9. Direct cost of corticosteroids in the treatment of tuberculous pericarditis in children by weight band (based on current dosing guidance in Paediatric STG)

Assumed weight per patient				10kg			20kg			30kg					
Formulation	Price per pack (Rands)	STG dosing guidance		Dose per week (mg)	Equivalent number of bottles per patient	Cost per course (Rands)	Dose per week (mg)	Equivalent number of bottles per patient	Cost per course (Rands)	Dose per week (mg)	Equivalent number of bottles per patient	Cost per course (Rands)			
15mg/5mL solution (50mL pack) = 150mg per bottle	95,21	Week 1	2mg/kg/day	140	3		280	6		420	9				
		Week 2	1.5mg/kg/day	105			210			315					
		Week 3	1mg/kg/day	70			140			210					
		Week 4	1mg/kg/day	70			140			210					
		Week 5	0.5mg/kg/day	35			70			105					
		Week 6	0.25mg/kg/day	17,5			35			52,5					
				437,5			R285,63		875			R571,26	1312,5		R856,89
Notes:															
1. Based on 3 weight bands (10kg, 20kg and >=30kg)															
2. Total dose per course rounded to nearest full pack															
3. Prices based on MHPL (Feb 2026)															

Key findings

- In adults without HIV and with tuberculous pericarditis:
 - Corticosteroids probably result in a reduction in deaths from pericarditis (moderate certainty evidence) and may reduce deaths from all causes and the need for repeat pericardiocentesis (low certainty evidence).
 - It is uncertain whether corticosteroids have any effect on the incidence of cancer, hospitalisation, development of constrictive pericarditis, or the need for pericardiectomy.
- In adult PWH not on ART with CD4 counts ≤ 350 cells/mm³ with tuberculous pericarditis:
 - Corticosteroids may reduce constrictive pericarditis and hospitalization (low certainty evidence).
 - Corticosteroids may make little or no difference to the need for repeat pericardiocentesis (low certainty evidence)
 - It is uncertain whether corticosteroids have any effect on deaths from pericarditis, deaths from all causes, the need for pericardiectomy or the development of cancer (very low certainty evidence).
- In the largest RCT conducted to date, key findings relevant to safety outcomes include:
 - More participants in the prednisolone group developed candida and other opportunistic infections than in the placebo group, though this was not statistically significant.
 - Prednisolone, as compared with placebo, was associated with an increased incidence of cancer, particularly HIV-related cancers (Kaposi's sarcoma and non-Hodgkin's lymphoma). This increase may be related to co-administration of immunotherapy (*M. indicus pranii*) in this RCT.
- No data in adult PWH on ART or with higher CD4 cell counts was identified and in these patients the results from adults without HIV may be more applicable.
- No data in children with or without HIV and tuberculous pericarditis was identified.

Conclusion and Recommendation

Given the important benefits of corticosteroids in reducing deaths in adults without HIV, and in reducing hospitalisations and the development of constrictive pericarditis in PWH, we recommend the use of corticosteroids in tuberculous pericarditis, acknowledging the low certainty evidence. In PWH, a thorough clinical examination should be performed before starting corticosteroids to exclude HIV-related cancers and antiretroviral therapy should be initiated promptly in accordance with standard treatment guidelines to mitigate the potential signal of harm observed in the largest RCT.

While no data in children with or without HIV and tuberculous pericarditis was identified, given the important benefits associated with the use of corticosteroids in adults with tuberculous pericarditis, we suggest using corticosteroids in children with tuberculous pericarditis.

Review Team

The following people were involved in this review (alphabetical by surname):

Name	Affiliation(s)	Role and Contribution	Interest declaration
Jessica Taylor (Lead author)	University of Cape Town	Literature search, quality appraisal, data synthesis, drafting report	None
Zahiera Adam	Clinton Health Access Initiative (CHAI) and NDoH	Costing, QA and recommendation	None
Prof Karen Cohen	Division of Clinical Pharmacology, University of Cape Town	QA, expert guidance and recommendation	None
Dr Halima Dawood	Infectious Diseases Unit, Greys Hospital	Expert guidance	None
Dr Jeremy Nel	Division of Infectious Diseases, Department of Medicine, University of the Witwatersrand	QA, expert guidance and recommendation	None

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Appendix 1: Search results and reasons for exclusion

	Reference	Study Type	Included/Excluded	Reason
1.	Imazio M, Gaita F, LeWinter M. Evaluation and Treatment of Pericarditis: A Systematic Review. JAMA. 2015 Oct 13;314(14):1498-506. doi: 10.1001/jama.2015.12763. Erratum in: JAMA. 2015 Nov 10;314(18):1978. doi: 10.1001/jama.2015.14947. Erratum in: JAMA. 2016 Jan 5;315(1):90. doi: 10.1001/jama.2015.16998. Dosage error in article text. PMID: 26461998.	Systematic review	Excluded	Incorrect population - Not specific to tuberculous pericarditis
2.	López-López JP, Posada-Martínez EL, Saldarriaga C, Wyss F, Ponte-Negretti CI, Alexander B, Miranda-Arboleda AF, Martínez-Sellés M, Baranchuk A; Neglected Tropical Diseases, Other Infectious Diseases Affecting the Heart (the NET-Heart Project). Tuberculosis and the Heart. J Am Heart Assoc. 2021 Apr 6;10(7):e019435. doi: 10.1161/JAHA.120.019435. Epub 2021 Mar 18. PMID: 33733808; PMCID: PMC8174360.	Narrative review	Excluded	Incorrect study type
3.	George IA, Thomas B, Sadhu JS. Systematic review and meta-analysis of adjunctive corticosteroids in the treatment of tuberculous pericarditis. Int J Tuberc Lung Dis. 2018 May 1;22(5):551-556. doi: 10.5588/ijtld.17.0341. PMID: 29663961.	Systematic review	Included	
4.	Wiyongse CS, Ntsekhe M, Thabane L, Volmink J, Majombozi D, Gumede F, Pandie S, Mayosi BM. Interventions for treating tuberculous pericarditis. Cochrane Database Syst Rev. 2017 Sep 13;9(9):CD000526. doi: 10.1002/14651858.CD000526.pub2. PMID: 28902412; PMCID: PMC5618454.	Systematic review	Included	
5.	Diallo A, Diallo BD, Diallo OH, Carlos-Bolumbu M, Camara M, Sidikiba S. Corticosteroids for reducing tuberculosis mortality in persons living with HIV: a systematic review and meta-analysis using reconstructed individual patient data. BMJ Glob Health. 2025 Aug 14;10(8):e017923. doi: 10.1136/bmjgh-2024-017923. PMID: 40813100; PMCID: PMC12352167	Systematic review	Excluded	Incorrect population – pericardial, meningeal and pleural tuberculosis
6.	Ntsekhe M, Wiyongse C, Volmink JA, Commerford PJ, Mayosi BM. Adjuvant corticosteroids for tuberculous pericarditis: promising, but not proven. QJM. 2003 Aug;96(8):593-9. doi: 10.1093/qjmed/hcg100. PMID: 12897345.	Systematic review	Included	
7.	Mayosi BM, Ntsekhe M, Volmink JA, Commerford PJ. Interventions for treating tuberculous pericarditis. Cochrane Database Syst Rev. 2002;(4):CD000526. doi: 10.1002/14651858.CD000526. Update in: Cochrane Database Syst Rev. 2017 Sep 13;9:CD000526. doi: 10.1002/14651858.CD000526.pub2. PMID: 12519546.	Systematic review	Excluded	2017 update included (Wiyongse et al.)
8.	Mayosi BM, Volmink JA, Commerford PJ. Interventions for treating tuberculous pericarditis. Cochrane Database Syst Rev. 2000;(2):CD000526. doi: 10.1002/14651858.CD000526. Update in: Cochrane Database Syst Rev. 2002;(4):CD000526. doi: 10.1002/14651858.CD000526. PMID: 10796550.	Systematic Review	Excluded	2017 update included (Wiyongse et al.)
9.	Reuter H, Burgess LJ, Louw VJ, Doubell AF. Experience with adjunctive corticosteroids in managing tuberculous pericarditis. Cardiovasc J S Afr. 2006 Sep-Oct;17(5):233-8. PMID: 17117227.	Randomised controlled trial	Excluded	Incorrect intervention/comparison – intrapericardial corticosteroid therapy vs. oral corticosteroid vs. intrapericardial placebo
10.	Strang JI, Nunn AJ, Johnson DA, Casbard A, Gibson DG, Girdling DJ. Management of tuberculous constrictive pericarditis and tuberculous pericardial effusion in Transkei: results at 10 years follow-up. QJM. 2004 Aug;97(8):525-35. doi: 10.1093/qjmed/hch086. PMID: 15256610.	10-year follow-up of 2 randomised controlled trials	Included	.
11.	Mayosi BM, Ntsekhe M, Bosch J, Pogue J, Gumede F, Badri M, Jung H, Pandie S, Smieja M, Thabane L, Francis V, Thomas KM, Thomas B, Awotedu AA, Magula NP, Naidoo DP, Damasceno A, Banda AC, Mutyaba A, Brown B, Ntuli P, Mntla P, Ntintyane L, Ramjee R, Manga P, Kirenga B, Mondo C, Russell JB, Tsitsi JM, Peters F, Essop MR, Barasa AF, Mijinyawa MS, Sani MU, Olunuga T, Ogah O, Adebiyi A, Aje A, Ansa V, Ojji D, Danbauchi S, Hakim J, Matenga J, Yusuf S. Rationale and design of the Investigation of the Management of Pericarditis (IMPI) trial: a 2 × 2 factorial randomized double-blind multicenter trial of adjunctive prednisolone and Mycobacterium m immunotherapy in tuberculous pericarditis. Am Heart J. 2013 Feb;165(2):109-15.e3. doi: 10.1016/j.ahj.2012.08.006. Epub 2012 Dec 13. PMID: 23351812.	Randomised controlled trial protocol	Excluded	Incorrect study design - protocol
12.	Liebenberg JJ, Dold CJ, Olivier LR. A prospective investigation into the effect of colchicine on tuberculous pericarditis. Cardiovasc J Afr. 2016 Nov/Dec;27(6):350-355. doi: 10.5830/CVJA-2016-035. PMID: 27965998; PMCID: PMC5412665.	Randomised controlled trial	Excluded	Incorrect comparator - colchicine
13.	Mayosi BM, Ntsekhe M, Bosch J, Pandie S, Jung H, Gumede F, Pogue J, Thabane L, Smieja M, Francis V, Joldersma L, Thomas KM, Thomas B, Awotedu AA, Magula NP, Naidoo DP, Damasceno A, Chitsa Banda A, Brown B, Manga P, Kirenga B, Mondo C, Mntla P, Tsitsi JM, Peters F, Essop MR, Russell JB, Hakim J, Matenga J, Barasa AF, Sani MU, Olunuga T, Ogah O, Ansa V, Aje A, Danbauchi S, Ojji D, Yusuf S; IMPI Trial Investigators. Prednisolone and Mycobacterium indicus pranii in tuberculous pericarditis. N Engl J Med. 2014 Sep 18;371(12):1121-30. doi: 10.1056/NEJMoa1407380. Epub 2014 Sep 1. PMID: 25178809; PMCID: PMC4912834.	Randomised controlled trial	Included	Primary study included in systematic review
14.	Wiyongse CS, Ntsekhe M, Gumede F, Siwa K, Blackett KN, Commerford PJ, Volmink JA, Mayosi BM. Contemporary use of adjunctive corticosteroids in tuberculous pericarditis. Int J Cardiol. 2008 Mar 14;124(3):388-90. doi: 10.1016/j.ijcard.2006.12.060. Epub 2007 Apr 18. PMID: 17445921.	Cross-sectional study	Excluded	Incorrect study type

Appendix 2.

Summary of findings table from WHO Guideline WHO Consolidated guidelines on tuberculosis. Module 4: Treatment and care.

PICO 7

Author(s): Lelia Chaisson

Question: Adjuvant corticosteroids compared with TB treatment without corticosteroids for tuberculous pericarditis

Bibliography: Strang JI et al. Lancet 1987; Strang JI et al. Lancet 1988; Hakim JG et al. Heart 2000; Mayosi BM et al. N Engl J Med 2014; Reuter H et al. Cardiovasc J S Afr. 2006

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adjuvant corticosteroids	TB treatment without corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Death												
5	randomized trials	not serious	serious ¹	serious ²	serious ³	none ⁴	142/897 (15.8%)	142/882 (16.1%)	RR 0.54 (0.23 to 1.26)	74 fewer per 1000 (from 42 more to 124 fewer)	⊕○○○ VERY LOW	CRITICAL
Treatment adherence												
2	randomized trials	serious ⁵	very serious ¹	serious ⁵	not serious	none	744/888 (83.8%)	785/907 (86.5%)	RR 0.91 (0.75 to 1.12)	78 fewer per 1000 (from 104 more to 216 fewer)	⊕○○○ VERY LOW	IMPORTANT
Constrictive pericarditis												
3	randomized trials	not serious	not serious	not serious	very serious ³	none	36/768 (4.7%)	56/747 (7.5%)	RR 0.72 (0.32 to 1.58)	21 fewer per 1000 (from 43 more to 51 fewer)	⊕⊕○○ LOW	IMPORTANT

CI: confidence interval; RR: risk ratio.

1. Inconsistent findings between studies. Death $I^2 = 70\%$; adherence $I^2 = 89\%$. Older studies show larger effects.
2. Although not alone a reason for downgrading (only in context of the concern for publication bias), we considered the older studies not necessarily reflecting the populations seen in practice today.
3. The effects at the ends of the confidence interval would lead to different clinical decisions; in addition, the sample sizes are smaller than the optimal information size.
4. Publication bias is possible – small studies show a large effect. However, these studies are also older, and the enrolled populations may differ, accounting for the difference in the effects.
5. Different definitions of adherence were used by different studies.

Summary of findings table from the *Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis, 2016*.

Evidence profile 14

Date: 05/16/2014

PICO Question 7: Does the use of adjuvant corticosteroids in tuberculous pericarditis provide mortality and morbidity benefits?

Comparison: systemic corticosteroid therapy versus placebo.

Quality assessment							N of patients		Effect		Certainty in the Evidence	Importance
N of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Steroids	placebo	Relative (95% CI)	Absolute (95% CI)		
Death												
5 studies	randomized trials	not serious	very serious ¹	not serious	serious ²	none	142/897 (15.8%)	142/882 (16.1%)	RR 0.54 (0.23 to 1.26)	74 fewer per 1000 (from 42 more to 124 fewer)	 VERY LOW	CRITICAL
Adherence												
2 studies	randomized trials	serious ²	very serious ¹	serious ¹	not serious	none	744/888 (83.8%)	785/907 (86.5%)	RR 0.91 (0.75 to 1.12)	78 fewer per 1000 (from 104 more to 216 fewer)	 VERY LOW	IMPORTANT
Constrictive pericarditis												
3 studies	randomized trials	not serious	not serious	not serious	very serious ²	none	36/768 (4.7%)	56/747 (7.5%)	RR 0.72 (0.32 to 1.58)	21 fewer per 1000 (from 43 more to 51 fewer)	 LOW	IMPORTANT

MD – mean difference, RR – relative risk

Events:

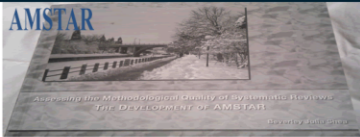
1. Inconsistent findings between studies. Death $I^2 = 70\%$; Adherence $I^2 = 89\%$.
2. The effects at the ends of the confidence interval would lead to different clinical decisions; in addition, the sample sizes are smaller than the optimal information size.
3. Different definitions of adherence were used by different studies.

Evidence Profile References:

- Strang JI, Kakaza HH, Gibson DG, Girding DJ, Nunn AJ, Fox W. Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. *Lancet* 1987; 2(8573): 1418-22.
- Strang JI, Kakaza HH, Gibson DG, et al. Controlled clinical trial of complete open surgical drainage and of prednisolone in treatment of tuberculous pericardial effusion in Transkei. *Lancet* 1988; 2(8614): 759-64.
- Hakim JG, Temouth I, Mushang E, Sizya S, Robertson V, Malin A. Double blind randomized placebo controlled trial of adjunctive prednisolone in the treatment of effusive tuberculous pericarditis in HIV seropositive patients. *Heart* 2000; 84(2): 183-8.
- Mayosi BM, Ntsokhe M, Smeja M. Immunotherapy for tuberculous pericarditis. *N Engl J Med* 2014; 371(26): 2534.
- Reuter H, Burgess LJ, Lowe VJ, Doull AF. Experience with adjunctive corticosteroids in managing tuberculous pericarditis. *Cardiovasc J S Afr*. 2006 Sep-Oct;17(5):233-8.

Appendix 3: AMSTAR assessment

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Article Name:

Interventions for treating tuberculous pericarditis (Cochrane Review). 2017 is a Low quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes Yes Yes Yes Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No
4. Did the review authors use a comprehensive literature search strategy?	Yes Yes Yes Yes Yes Yes Yes Yes
5. Did the review authors perform study selection in duplicate?	Yes Yes
6. Did the review authors perform data extraction in duplicate?	Yes Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes Yes Yes
8. Did the review authors describe the included studies in adequate detail?	Partial Yes Yes Yes Yes Yes Yes Yes Yes Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? RCT	Yes
NRSI	0 Yes Yes Yes Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? RCT	Yes
NRSI	Yes Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes Yes Yes

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

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South African National Department of Health
Brief Report of NEMLC Limited Review¹
Corticosteroids for the treatment of tuberculous meningitis (TBM)
February 2026

Medicine details:

Medicine Class	Corticosteroids	<i>If applicable Please consider therapeutic interchange policy</i>
Medicine/s name -INN: - South African name (if differs from INN)	Prednisone Prednisolone Dexamethasone	http://www.whocc.no/atc_ddd_index/
Medicine/s (ATC5):	H02AB07 H02AB06 H02AB02	http://www.whocc.no/atc_ddd_index/
Indication (ICD-10 code):	A17.0	https://www.health.gov.za/icd-10-master-industry-table/
SAHPRA Approved	Yes	SAHPRA registered health products database https://medapps.sahpra.org.za:6006/
Dosage form/s	tablet, suspension, solution for injection	
Route of administration/s	oral, intravenous	
Patient population	Adults and children with and without HIV	
Prevalence and/or incidence of condition	Overall, in 2012, 6.8 cases per 100 000 persons. In people living with HIV 34.9 cases per 100 000 persons. (Britz et al. PloS One. 2016)	<i>May refer to estimates or routine data (DHIS, StatsSA), not necessarily published data.</i>
Level of Care	Hospital level (initiation) Primary Healthcare (continuation)	
Prescriber level	Doctor initiated	

¹ This template was informed by examples of previous NEMLC limited reviews, input from the Essential Drug Programme Oversight Group and the NEMLC Medicine Review Template which was updated with support through the Evidence-to-Decision (E2D) project which is a collaboration between National Department of Health, the South African Medical Research Council and the University of Stellenbosch.
Limited Review_Corticosteroids for TBM_v1.0_26 Mar 2026_final

Current Standard of Care

In adults: Combination anti-tuberculosis treatment for 9 months duration. In people without HIV, with grade II to III TBM, adjunctive corticosteroids are recommended. No recommendation is currently made for corticosteroid use in people living with HIV (PWH) and TBM.

In children: Combination anti-tuberculosis treatment for 6 to 9 months duration. In all children, irrespective of HIV status or TBM grade, adjunctive corticosteroids are recommended.

Executive Summary

- TB meningitis (TBM) is associated with significant mortality, with a pooled case fatality rate of 53% in people with HIV (PWH) and 22% in HIV-negative people.[1]
- The current standard treatment guidelines recommend the use of corticosteroids in HIV-negative adults with Grade II² or III TBM, and in children with TBM, only. These recommendations are based on a 2008 Cochrane systematic review [2]
- We conducted an updated rapid systematic review of the evidence for the use of corticosteroids in the management of TBM in HIV-negative children and adults, as well as in children and adults with HIV. Only guidelines, systematic reviews with meta-analyses, and randomised controlled trials published subsequent to 2008 (and not included in the previous reference) were included.
- We identified three clinical practice guidelines:
 - Clinical practice guidelines from WHO (2025) and ATS/CDC/ERS/IDSA³ (2025) recommend using corticosteroids in people with TBM, irrespective of TBM grade, and without any differential recommendation based on HIV status. These recommendations had not been updated since 2016-2017.[3,4]
 - The Tuberculous Meningitis International Research Consortium clinical practice guideline (2026) was identified as the most up-to-date clinical practice guideline for the management of TBM. [5] This guideline recommends using adjunctive corticosteroid therapy for TBM in people without HIV (strong recommendation, high certainty of evidence). In the absence of an effective alternative adjunctive therapy for HIV-associated tuberculous meningitis, and based on the safety and potential effectiveness of corticosteroids, they recommend using corticosteroids on a case-by-case basis in PWH (weak recommendation, high certainty of evidence).
- We identified one updated Cochrane systematic review and meta-analysis of adjunctive corticosteroids in predominantly HIV-negative adults and children with TBM.[6] Key findings include:
 - Corticosteroids reduce mortality moderately (RR 0.75, 95% CI 0.65 to 0.87, high certainty of evidence).
 - This reduction in mortality is consistent across all grades of the disease.
 - Corticosteroids may reduce severe disability (RR 0.92, 95% CI 0.71 to 1.20, low certainty of evidence).
 - Corticosteroids result in little to no difference in serious adverse events (RR 0.88, 95% CI 0.67 to 1.17).
 - Therefore, we recommend using corticosteroids in HIV-negative adults, and children, with any grade of TBM.

² British Medical Research Council Staging. Grade I TBM: No focal neurological signs, Glasgow Coma Scale (GCS) 15; Grade II TBM: GCS 11 to 14 or GCS 15 with focal neurological deficits; Grade III TBM: GCS $\leq$ 10.

³ American Thoracic Society/United States Centers for Disease Control and Prevention/Infectious Diseases Society of America, the European Respiratory Society.

- We identified one systematic review and meta-analysis from the Tuberculous Meningitis International Research Consortium clinical practice guideline (2026) and one randomised controlled trial (RCT) of adjunctive corticosteroids in adult PWH with TBM.[5,7] The methods and GRADE assessment underpinning the systematic review and meta-analysis from the clinical practice guideline were poorly reported. Key findings include:
 - Corticosteroids may result in lower mortality (RR 0.90, 95% CI 0.77 to 1.05).
 - Corticosteroids may increase severe disability, but the confidence interval is very wide (RR 1.34, 95% 0.65 to 2.87).
 - Corticosteroids did not increase serious adverse events.
 - These findings are based largely on data from the one RCT identified, in which the majority of PWH and TBM had a CD4 cell count ≤ 200 cell/mm³.
 - It is biologically plausible that in PWH with TBM and relatively preserved CD4 counts, the mortality benefit of adjunctive corticosteroids would approximate that observed in HIV-negative patients.
 - The exact CD4 count at which this mortality benefit would approximate that observed in HIV-negative individuals has not been established, and there is insufficient data to define this threshold.
 - Given the high mortality of TBM, the absence of demonstrated harm associated with corticosteroids, and the potential for a small mortality benefit specifically in PWH with higher CD4 counts, withholding corticosteroids from all PWH may not be appropriate.
 - We pragmatically suggest, based on expert opinion and aligned with the National Department of Health programmatic definitions of advanced HIV disease (AHD), that corticosteroids be used in PWH with TBM and CD4 cell counts > 200 cells/mm³.
 - In PWH with TBM and CD4 cell counts ≤ 200 cells/mm³ we suggest not using corticosteroids.
- In children with HIV and TBM
 - No randomized controlled trials evaluating corticosteroids in children with HIV and TBM were identified.
 - There is currently no direct evidence to indicate that children with HIV and TBM fail to derive a mortality benefit comparable to that observed in HIV-negative children with TBM.
 - In children, with or without HIV, with TB meningitis, we recommend using corticosteroids.

Key Recommendations *(if more appropriate, describe in narrative form)*

Type of ERC recommendation	We recommend against the option and for the alternative (strong)		We suggest not to use the option or to use the alternative (conditional)		We suggest using the option (conditional)		We recommend the option (strong)	
	☐		✓ See recommendation 2		✓ See recommendation 3		✓ See recommendation 1 and 4	
High level summary of conclusions	1. In HIV-negative adults with TB meningitis of any grade, we recommend using corticosteroids. 2. In adults with HIV and TB meningitis of any grade, with CD4 count ≤ 200 cells/mm³, we suggest not using corticosteroids. 3. In adults with HIV and TB meningitis of any grade, with CD4 count >200 cells/mm³, we suggest using corticosteroids. 4. In children, with or without HIV, with TB meningitis of any grade, we recommend using corticosteroids.							
NEMLC Ratification	Date		Comments/Recommendation					
	26 Mar 2026		NEMLC ratified the ERCs recommendation as detailed above, pending agreement with the national TB and HIV programs. <i>(Program confirmation received by email communication April 2026).</i>					
Therapeutic Interchange Considerations (if applicable)*	If YES:	Alternative medicine/s name (INN)	Alternative/s SAHPRA registered?	Formulation/s	Equipotent dose/ Dose range and dosing interval		If NO, tick box	
							✓	
Trigger for review								

Background and rationale

The current Adult Hospital standard treatment guidelines recommend the use of adjunctive corticosteroids alongside standard anti-tuberculosis therapy in adults with grade II to III tuberculous meningitis (TBM) **(Figure 1)**. This recommendation (level of evidence IIa) is based on evidence from Prasad et al.'s 2008 Cochrane review which demonstrate that corticosteroids can reduce the risk of neurological deficits and death in adults with TBM.[2] However, in adults living with HIV co-infected with TBM, the standard treatment guidelines highlight ongoing uncertainty regarding the benefits of corticosteroids therapy (level of evidence IIa, Prasad et al. Cochrane. 2008).[2] The 2008 Cochrane systematic review on which these recommendations are based was subsequently updated in 2016 and more recent studies in people living with HIV (PWH) have emerged as of 2023. [6,7]

The current Paediatric Hospital standard treatment guidelines recommend the use of adjunctive corticosteroids alongside standard anti-tuberculosis therapy in all children irrespective of HIV status or grade of TBM. No reference or level of evidence for this recommendation is provided (Figure 2).

This rapid review aims to evaluate the most up to date evidence for adjunctive corticosteroid therapy in people with TBM, and to inform a more refined and specific recommendation in PWH.

MEDICINE TREATMENT	
Treat with standard combination tuberculosis therapy according to National protocol and extend duration of therapy to 9 months (2 months intensive phase, 7 months continuation phase). See Section 16.9: Tuberculosis, Pulmonary for details.	
In HIV-negative individuals:	
Corticosteroid use may be of benefit in reducing neurological deficit in patients with grade II to III disease (focal neurological disease, depressed levels of consciousness, or a Glasgow Coma Scale of 14 or less).	
Dexamethasone, IV, dosing as follows:	
Weeks	Dosing regimen
Initial dose	0.3-0.4 mg/kg/day for 2 weeks.
Week 3	0.2 mg/kg daily.
Week 4	0.1 mg/kg daily.
Week 5 to 8	4 mg/day, tapering daily dose by 1 mg each week.
OR	
- Corticosteroids (intermediate-acting) e.g.: LoE:IIa^{vi} - Prednisone, oral, 60 mg daily for 2 weeks. - Then taper gradually over the next 6 weeks (see Appendix II for an example of a dose reduction regimen). LoE:IVb^{vi}	
In people with HIV:	
Note: There is uncertainty whether the use of corticosteroids is beneficial in PLWH with TBM. LoE:IIa^{ix}	
LoE:IIa^{ix}	

Figure 1. Adult Hospital. Chapter 14 Neurological Disorders. 14.8.1.1 TB meningitis

CHAPTER 10	TUBERCULOSIS
Steroid therapy:	
- Prednisone, oral, 2 mg/kg as a single daily dose for 4 weeks. - Maximum daily dose: 60 mg. - Taper to stop over further 2 weeks.	

Figure 2. Paediatric Hospital. Chapter 10 Tuberculosis. Section 10.4: Meningitis, tuberculosis (TBM) in children

Purpose/Objective i.e., PICO question (if relevant):

PICO 1

Population Subgroups	HIV-negative adults and children with TBM
Intervention(s)	Corticosteroids (prednisone, prednisolone or dexamethasone) plus standard anti-TB treatment
Comparator(s)	Anti-tuberculous treatment (ATT) alone or with placebo
Outcome(s)	Mortality, severe disability, adverse events
Study types	Guidelines, systematic reviews with meta-analysis, randomised controlled trials

PICO 2

Population Subgroups	Adults and children living with HIV co-infected with TBM
Intervention(s)	Corticosteroids (prednisone, prednisolone or dexamethasone) plus anti-TB treatment
Comparator(s)	Anti-tuberculous treatment (ATT) alone or with placebo
Outcome(s)	Mortality, severe disability, adverse events
Study types	Guidelines, systematic reviews with meta-analysis, randomised controlled trials

Methods

1. Data Sources

Clinical practice guidelines: We searched for relevant clinical practice guidelines from the American Thoracic Society and World Health Organization.

Systematic reviews and randomised controlled trials: We searched PubMed for guidelines, systematic reviews, and randomised controlled trials.

2. Search Strategy

The following search terms were used:

((TB meningitis) OR (tuberculous meningitis)) OR (tuberculosis meningitis) AND (corticosteroids)

We restricted our search to studies published from 2004, since the most recent study included in the 2008 Prasad et al. Cochrane review referenced in the current standard treatment guidelines was from 2004. PubMed searches were filtered by year (from 2004), guideline, systematic review, meta-analysis and randomised controlled trials.

3. Study selection and eligibility criteria, data extraction and analysis, and evidence synthesis

The study screening, selection and data extraction, analysis and evidence was conducted by 1 reviewer. Evidence was synthesised narratively.

Results

1. Result of the search

Three clinical practice guidelines were identified: the ATS/CDC/ERS/IDSA⁴ Clinical Practice Guideline (2025), the World Health Organisation (WHO) consolidated guidelines on tuberculosis. Module 4: Treatment and care (2025), and the Tuberculous Meningitis International Research Consortium guideline (2026).[3-5] In both the ATS/CDC/ERS/IDSA and WHO guidelines, specific recommendations relating to corticosteroids use in TBM have not been updated since 2016 – 2017.

The PubMed search identified 23 studies and 1 clinical practice guideline from the European Respiratory Society 2009. Of the 23 studies identified, there were 9 systematic reviews, 13 randomised controlled trials (RCTs) and 1 retrospective cohort study. Of the 9 systematic reviews, only 1 (Prasad (2016)) was eligible for inclusion.[6] Of the 13 RCTs, 3 were eligible for inclusion: Thwaites (2004); Malhotra (2009); Donovan, (2023).[7-9]

The WHO and ATS/CDC/ERS/IDSA clinical practice guidelines were based on systematic reviews of the same 5 primary studies.[8-12] The Tuberculous Meningitis International Research Consortium guideline included all 5 of these studies, 8 of 9 primary studies included in the Prasad (2016) systematic review, and the most recent RCT identified by Donovan (2023).[7] This clinical practice guideline was therefore the most up-to-date guideline and selected for inclusion.

The search results are illustrated in **Figure 3. Search Flow Chart**. Specific reasons for inclusion or exclusion of studies identified in the search are listed in **Appendix 1**. **Appendix 2** includes a comparison of the specific recommendations and primary studies included in the WHO, ATS/CDX/ERS/IDSA and Tuberculous Meningitis International Research Consortium guidelines.

⁴ American Thoracic Society/United States Centers for Disease Control and Prevention/Infectious Diseases Society of America, the European Respiratory Society.

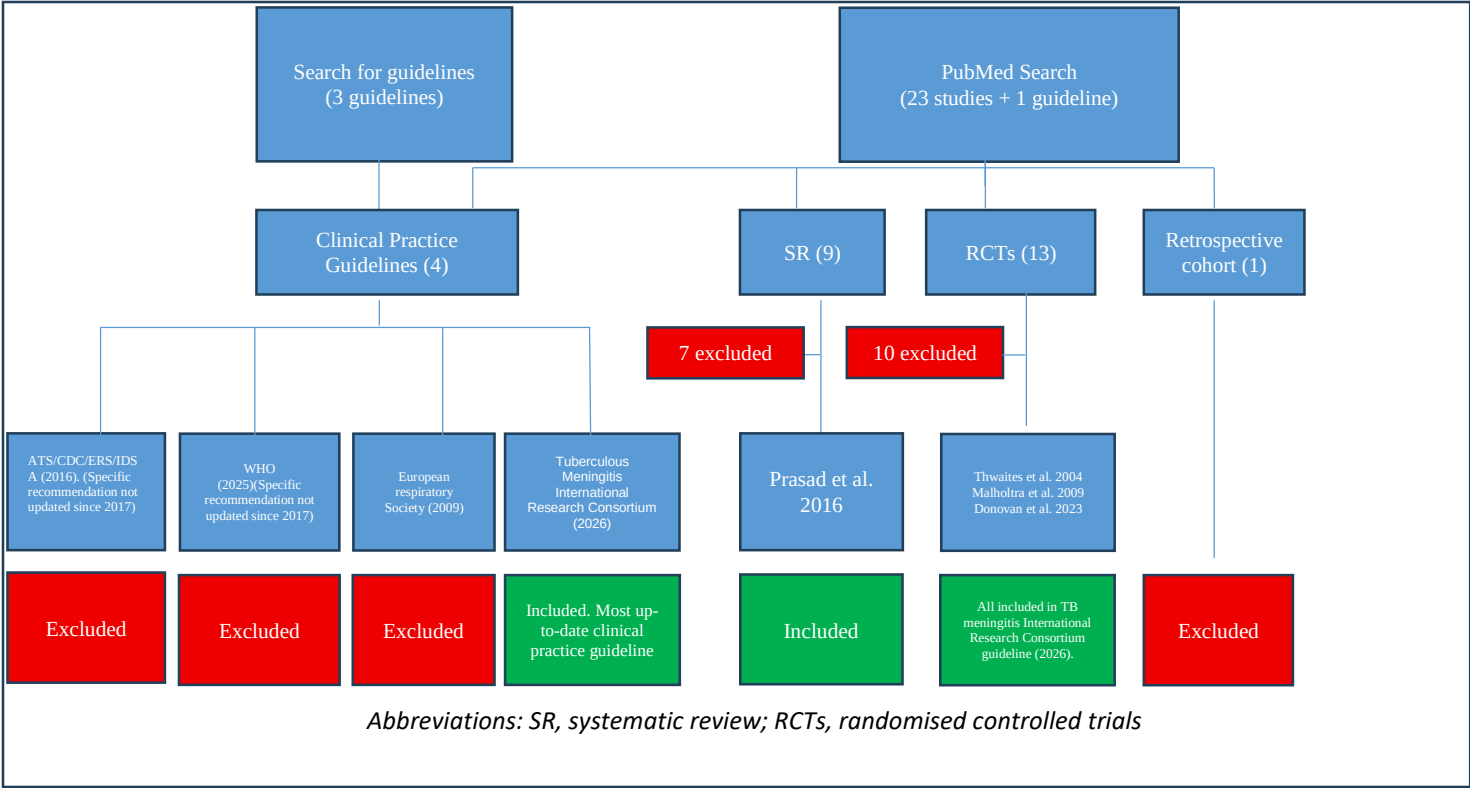


Figure 3. Search Flow Chart

2. Description of included studies

2.1. Clinical Practice Guidelines

The Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026) was considered the most up-to-date clinical practice guideline which included subgroup considerations by HIV status. The recommendations from this guideline are summarised in **Table 1**. Insufficient detail was provided in the clinical practice guideline concerning the underlying systematic review methodology and GRADE assessment, therefore, the quality of the underlying systematic review was not assessed. The results of the systematic review and meta-analyses are reported in **Results Section 3**.

Table 1. Summary of the recommendation from the Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026)

Recommendation	Justification	Subgroup considerations	Studies included in the systematic review (9)	Outcomes considered	AGREE II
In people without HIV, we recommend the use of adjunctive corticosteroid therapy. (strong recommendation, high certainty of evidence) In the absence of an effective alternative adjunctive therapy for HIV-associated tuberculous meningitis, and the safety and potential effectiveness of corticosteroids, we recommend their use on a case-by-case basis in people living with HIV (weak recommendation, high certainty evidence).	Corticosteroids reduced case fatality, especially in children and adults without HIV. There is no signal for a change in disability among survivors in these groups. In people living with HIV and tuberculous meningitis, the benefits of corticosteroids are uncertain.	Separate recommendations for those with and without HIV.	O'Toole (1969)[7] Girgis (1991)[13] Kumaravelu (1994)[10] Chotmongkol (1996)[11] Schoeman (1997)[12] Lardizabal (1998)[14] Malhotra (2009)[9] Thwaites (2004)[8] Donovan (2023)[7]	Mortality Morbidity	Overall: 60 % Domain 1- Scope and Purpose: 90% Domain 2 – Stakeholder involvement: 57% Domain 3 - Rigour of development: 61% Domain 4 – Clarity of presentation: 67% Domain 5 - Applicability: 32% Domain 6 – Editorial independence: 64%

2.2. Systematic reviews

One systematic review was eligible for inclusion, Prasad (2016).[6] This systematic review is the update of the Prasad (2008) Cochrane systematic review.[2]

This systematic review evaluated the effects of adjunctive corticosteroids on death and severe disability in people with tuberculous meningitis. It included only RCTs that compared corticosteroids plus ATT with ATT treatment alone, and which included death or disability as an outcome.

Nine RCTs with 1337 participants were included. The 9 RCTs were: O'Toole (1969); Girgis (1991); Kumaravelu (1994); Chotmongkol (1996); Schoeman (1997); Lardizabal (1998); Thwaites (2004); Prasad (2006 (unpublished data only); Malhotra (2009).[8-15] The characteristics of these RCTs are summarised in **Table 2**. All but one of the RCTs included in the Prasad (2016) systematic review are included in the Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026). The Prasad (2006) trial (unpublished data) is not included in the Tuberculous Meningitis International Research Consortium Clinical Practice Guideline,

One RCT included only young children.[12] Two RCTs included adults and children.[13,15] Six RCTs included only adults or adults and adolescents ≥ 14 years of age. Only one RCT reported on HIV-co-infection.[8] One RCT included prolonged follow-up to 5 years. At least 5 RCTs were considered to be at high risk of bias (including the unpublished data from the Prasad (2006) RCT).[9,10,13,14] Three RCTs had unclear risk of bias.[11,12,15] One RCT was considered to be at low risk of bias (**Figure 4**).[8]

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (death)	Blinding of outcome assessment (disabling neurological deficit at the end of follow-up)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Chotmongkol 1996	?	+	+	+	?	?	?
Girgis 1991	+	?	?	?	-	?	?
Kumarvelu 1994	+	-	?	+	-	-	?
Lardizabal 1998	?	?	?	+	-	+	+
Malhotra 2009	+	?	?	+	-	+	+
O'Toole 1969	?	+	+	+	+	+	?
Prasad 2006	+	+	+	+	?	?	-
Schoeman 1997	?	?	?	+	+	?	+
Thwaites 2004	+	+	+	+	+	+	+

Figure 4. Risk of bias summary from Prasad (2016) systematic review

Table 2. Summary of studies included in Prasad (2016) systematic review

Study	Methods	Participants	Interventions	Outcomes
O'Toole 1969	Randomized parallel group 2-arm study with allocation ratio 1:1. Length of follow-up: unclear.	Setting: Infectious Diseases Hospital, Calcutta, India - tertiary referral centre. Number of participants: 23 participants in total, 11 females, 12 males; 11 received dexamethasone, 12 received no steroid. Inclusion criteria: not explicitly specified, but the trial authors state that due to the trial institution's admissions policy only participants with a short history or acute signs and symptoms of meningitis were selected; due to limited bed availability only moderate to severely unwell participants were included (MRC Stage II and III). All age groups were included. Treatment allocation was stratified for age and disease severity. HIV status: not reported.	1. ATT plus dexamethasone given for up to 4 weeks in an adult dose of 9 mg/day during the first week, 6 mg/day during the second week, 3 mg/day during the third week, and 1.5 mg/day during the 4th week; dose for children was calculated according to their body surface area (no more details available). 2. ATT alone. ATT: isoniazid intramuscular or oral (10 mg/kg/day, except in children < 2 years of age who received 20 mg/kg/day) and streptomycin (20 mg/kg/day, maximum 1 g), duration not specified	1. Death at the end of follow-up (duration unclear). 2. Number with elevated CSF opening pressure on days 1, 4, 7, and 14. 3. CSF sugar, protein, and cell count on days 1, 4, 7, 14, 21, and 28 in decreasing number of participants, depending apparently on the surviving number. Number with residual deficits not given. Surviving participants all been described as "significantly improved". 4. Adverse events recorded: upper gastrointestinal bleed, invasive bacterial infection, hypoglycaemia, and hypothermia. 5. Resolution of CSF findings
Girgis 1991	Randomized parallel group, 2-arm study with allocation ratio: 1:1. Length of follow-up: 24 months.	Setting: Abbassia Fever Hospital, Cairo, Egypt - tertiary referral centre. Number of participants: 280 participants; 158 males, 122 females; 145 received dexamethasone, 135 received no steroid. Age: all ages included, 37% aged 0 to 5 years, 22% aged 5 to 16 years. Inclusion criteria: clinically diagnosed tuberculous meningitis based on history and examination (duration of illness > 30 days, consisting of fever, headache, vomiting, altered sensorium, generalized weakness or cranial nerve deficits); comparison of first and second CSF findings; and a poor response to antibacterial therapy for 48 hrs. Exclusion criteria: not reported. HIV status: not reported.	1. ATT plus dexamethasone given intramuscularly (12 mg/day to adults and 8 mg/day to children weighing < 25 kg) for 3 weeks and then tapered during the next 3 weeks). 2. ATT alone. ATT: isoniazid (10 mg/kg/day, maximum 600 mg) intramuscularly for 2 weeks then orally for 2 years, streptomycin intramuscular (25 mg/kg/day, maximum 1000 mg) for 6 weeks, and ethambutol oral (25 mg/kg/day, maximum 1200 mg) for 6 weeks, then 15 mg/kg/day for 2 years.	1. Death during 2-year follow-up. 2. Residual neurological sequelae. 3. Neurological complications developing during therapy. 4. CSF leucocytes, glucose, and protein on day 15 and day 30 after initiation of treatment. Trial authors reported case-fatality rate, which by definition includes all deaths caused by tuberculous meningitis, but not deaths attributed to other causes. They did not report whether any death during the follow-up period was considered to be due to any cause other than tuberculous meningitis.
Kumarvelu 1994	Randomized parallel group 2-arm study with allocation ratio 1:1. Length of follow-up: 3 months.	Setting: all India Institute of Medical Sciences (AIIMS), New Delhi, India - tertiary referral centre. Number of participants: 47 participants; 22 females, 25 males; 24 received dexamethasone, 23 received no steroid. Inclusion criteria: aged over 10 years; clinically diagnosed tuberculous meningitis (meeting any 3 of the following criteria). 1. Fever, headache, neck stiffness for 2 weeks. 2. CSF profile of > 20 cells/mm predominantly lymphocytes, protein > 1 g/L, and sugar < 2/3 of corresponding blood sugar with no malignant cells on cytological examination and bacteria/fungi on culture. 3. Head contrast-enhanced CT showing basal exudates or hydrocephalus. 4. Clinical, radiological, or histological evidence of extracranial TB). All stages of severity and any duration of disease included. Exclusion criteria: aged < 10 years, received ATT for more than 4 weeks prior to admission, received corticosteroids before admission. HIV status: not reported.	1. ATT plus dexamethasone (intravenous 16 mg/day in 4 divided doses for 7 days, then oral tablet 8 mg/ day for 21 doses, and in children 0.6 mg/kg/day for 7 days, reducing to 0.3 mg/kg/day for 21 days). 2. ATT alone. ATT: rifampicin (450 mg), isoniazid (300 mg), and pyrazinamide (1500 mg) all oral daily; for those weighing < 30 kg 15 mg/kg, 10 mg/kg, and 30 mg/kg respectively. Duration of treatment: 1 year.	1. Death at 3 months. 2. Major sequelae (totally dependent for activities of daily living) at 3 months. 3. Minor sequelae (activities of daily living with no or minimal assistance) at 3 months. 4. Adverse effects. 5. Time to recover from altered sensorium, from fever, and from headache.
Chotmongkol 1996	Randomized parallel group study. Length of follow-up: 6 months but post-study follow-up continued for 16 to 45 months (mean = 30 months).	Setting: Sringarind Hospital, Khon Kaen, Thailand - tertiary referral centre. Number of participants: 59 participants; 27 females, 32 males; 29 received prednisolone, 30 received no steroid. Inclusion criteria: age > 15 years; clinically diagnosed tuberculous meningitis (characteristic clinical features with typical CSF profile consisting of lymphocytic meningitis with low glucose level and elevated protein), all stages of disease included. Exclusion criteria: children <15 years old, HIV-positive, VDRL positive for syphilis, cryptococcal antigen positive, CSF positive for bacterial or fungal infection on latex agglutination or culture, malignant cells in CSF. HIV status: HIV-positive participants excluded.	1. ATT plus prednisolone orally on tapering dosage for 5 weeks (week 1 = 60 mg, week 2 = 45 mg, week 3 = 30 mg; week 4 = 20 mg, week 5 = 10 mg). 2. ATT alone. ATT: isoniazid oral (300 mg), rifampicin oral (600 mg, 450 mg for those weighing < 50 kg), pyrazinamide oral (1500 mg), and streptomycin intramuscular (750 mg) for the first 2 months; followed by isoniazid and rifampicin in above dosage for 4 months.	1. Death at the end of 6 months. 2. Residual neurological deficits at the end of 6 months. 3. Time until resolution of fever. 4. Time until disappearance of headache. Adverse events recorded were gastrointestinal bleeding and hyperglycaemia.
Schoeman 1997	Randomized parallel group 2-arm study with allocation ratio 1:1. Length of follow-up: 6 months.	Setting: Tygerberg Hospital, Tygerberg, South Africa. Number of participants: 141 randomized (gender balance not specified); 70 received prednisolone and 71 received no steroid. Inclusion criteria: children (age limit not specified); diagnosis of tuberculous meningitis based on history and "typical CSF changes" with at least 2 of the following: strongly positive (> 15 mm) Mantoux test, chest x-ray suggesting TB or CT head showing basal enhancement and acute hydrocephalus. Only MRC Stage II and III included. HIV status: not reported.	1. ATT plus prednisolone (given to first 16 participants in a dose of 2 mg/kg/day and to the remaining 54 participants in a dose of 4 mg/kg/day (once in the morning); decision to double the dose after the first 16 participants). 2. ATT alone. ATT: isoniazid (20 mg/kg/day), rifampicin (20 mg/kg/day), ethionamide (20 mg/kg/day), and pyrazinamide (40 mg/kg/day) for 6 months.	1. Deaths at 6 months. 2. Disability (mild and severe) at 6 months. 3. Serious side effects.++ 4. Baseline and pulse pressure of lumbar CSF. 5. Changes in ventricular size in CT. 6. Proportion of participants with successful treatment of raised intracranial pressure. 7. Proportion of participants with basal ganglia infarcts, tuberculomas, meningeal enhancement, and enlarged subarachnoid spaces.

Study	Methods	Participants	Interventions	Outcomes
Lardizabal 1998	Randomized parallel group, 2-arm study with allocation ratio 1:1 Length of follow-up: 2 months	Setting: University of the Philippines College of Medicine, tertiary care facility, single centre Number of participants: 58 participants; 31 males and 27 females; 29 received dexamethasone, 29 received no steroid. Inclusion criteria: aged 18 years and above; probable tuberculous meningitis diagnosed using ASEAN Neurological Association criteria based on the following. 1. Insidious onset fever for at least 1 week, headache and vomiting, with or without nuchal rigidity followed by altered consciousness, cranial nerve palsies, or long tract signs. 2. CSF profile of lymphocyte predominance, elevated protein and reduced glucose. 3. CSF negative for cryptococcal antigen plus 1 or more of the following: basilar/meningeal enhancement on contrast CT scanning, active pulmonary disease, positive purified protein derivative (PPD), history of contact with TB; confirmed tuberculous meningitis based on positive CSF culture or microscopy, or both. 4. British MRC stages II and III disease. Exclusion criteria 1. Aged under 18. 2. British MRC stage I TB meningitis, or bacterial or fungal meningitis diagnosed on CSF culture. 3. Pregnancy or lactation. 4. History of diabetes mellitus or hypertension. 5. Upper gastrointestinal bleeding, or history of peptic ulcer disease in the previous month. 6. Raised bilirubin, SGPT or serum creatinine.	1. ATT plus dexamethasone (16 mg/day for 3 weeks (first 5 days intravenous thereafter orally or via nasogastric tube); after 3 weeks corticosteroid was tapered by 4 mg decrements every 5 days). 2. ATT alone. ATT: rifampicin (10 to 15 mg/kg/day), isoniazid (5 to 10 mg/kg/day), pyrazinamide (15 to 30 mg/kg/day), and ethambutol (15 to 20 mg/kg/day) for the first 2 months; thereafter, rifampicin and isoniazid only for 10 months; total treatment duration 12 months; route of administration was not stated. An H2-antagonist (famotidine or ranitidine) was given during the period of corticosteroid administration.	1. Death on days 15, 30, and 60 post-randomization. 2. Functional independence assessed by attending doctor on admission and 60 days after randomization: Functional Independence Measure (FIM) used assesses self-care, sphincter control, mobility, locomotion, and social cognition on a 7-point scale. 3. Potential adverse reactions to corticosteroids including weakness, oedema, hypertension, euphoria, psychosis, epigastric discomfort, Cushingoid facies, hirsutism, acne, insomnia, and increased appetite.
Thwaites 2004	Randomized parallel group 2-arm study with allocation ratio 1:1. Length of follow-up: 9 months (initial report), followed by a 5-year follow-up trial.	Setting: Pham Ngoc Thach Hospital for Tuberculosis and Lung Disease and the Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam - two tertiary referral centres. Number of participants: 545 randomized, 331 males, 214 females; 274 received dexamethasone, 271 received placebo. Inclusion criteria: aged over 14 years, clinical meningitis (defined as combination of nuchal rigidity and CSF abnormalities). Tuberculous meningitis defined as "definite" if acid-fast bacilli were seen in CSF, "probable" if at least 1 of the following present: suspected active pulmonary TB on chest radiography, acid-fast bacilli in any specimen other than CSF, clinical evidence of extrapulmonary TB, and "possible" if at least 4 of the following were present: history of TB, predominance of lymphocytes in CSF, duration of illness more than 5 days, ratio of CSF to plasma glucose less than 0.5, altered consciousness, yellow CSF, focal neurological signs. Exclusion criteria: contraindication to corticosteroids; received more than 1 dose of any corticosteroid, or more than 30 days of ATT immediately before the trial. HIV status: 98/545 HIV-positive, 44/274 (16.1%) in dexamethasone group, 54/271 (19.9%) in placebo group. Three participants in the dexamethasone group, and eight participants in the placebo group were not tested for HIV.	1. ATT plus dexamethasone, dose stratified by disease severity*. 2. ATT plus placebo. ATT: For previously untreated participants: oral isoniazid (5 mg/kg), rifampicin (10 mg/kg), pyrazinamide (25 mg/kg, maximum, 2 g/day), and intramuscular streptomycin (20 mg/kg, maximum 1 g/day) for 3 months followed by 6 months of isoniazid, rifampicin, and pyrazinamide at the same daily doses; ethambutol (20 mg/kg; maximum 1.2/day) substituted for streptomycin in HIV-positive participants and was added to the regimen for 3 months for participants previously treated for TB. *Grade II and III disease: intravenous dexamethasone sodium phosphate given 0.4 mg/kg/day for week 1, 0.3 mg/kg/d for week 2, 0.2 mg/kg/d for week 3, and 0.1 mg/kg/day for week 4, and then oral dexamethasone for 4 weeks decreasing by 1 mg each week. Grade I disease: intravenous dexamethasone sodium phosphate 0.3 mg/kg/day for week 1 and 0.2 mg/kg/day for week 2 followed by 4 weeks of oral dexamethasone (0.1 mg/kg/day for week 3 then a total of 3 mg/day, decreasing by 1 mg each week).	Assessed at 9 months post-randomization. 1. Death or severe disability. 2. Adverse events: hepatitis; gastrointestinal bleeding, bacterial sepsis, septic shock, brain herniation syndrome, decreased visual acuity, hyponatraemia, hyperglycaemia, hypertension, vertigo, deafness, Cushingoid features, pruritis, polyarthralgia, streptomycin reaction, rifampicin flu, rash, and others. 3. Coma clearance time. 4. Fever clearance time. 5. Time to discharge. 6. Time to relapse. 7. Presence of focal neurological deficit (9 months post-randomization). Assessed during 5-year follow-up study (9 months to 5 years post-randomization). 1. Death. 2. Disability status. 3. TB relapse.
Prasad 2006	Double-blind, randomized, concurrent placebo-controlled parallel group trial. Length of follow-up: 18 months. A 10-year follow-up was planned but not completed.	Setting: All India Institute of Medical Sciences, New Delhi, India - tertiary referral centre. Number of participants: 87 participants; 39 females, 48 males; 41 received dexamethasone, 46 received placebo. Inclusion criteria: clinically diagnosed tuberculous meningitis based on meeting these 3 criteria. 1. Gradual onset of any 2 of fever, progressive headache, or impaired consciousness with at least 1 symptom of 3 weeks duration. 2. At least 1 sign of meningeal irritation for example, neck stiffness, Kernig's sign, Brudzinski's sign (except in deeply comatose cases). 3. CSF profile characteristic of tuberculous meningitis (containing more than 0.02 Å~ 109 cells per litre with predominant lymphocytes , protein more than 1 g/Pl, sugar less than two-thirds of simultaneous blood sugar). Exclusion criteria: 1. Alternative diagnosis (including non-tubercular infection, malignancy) made on CSF testing or imaging. 2. Treatment with steroids regularly for more than 10 days used during the current illness. 3. Liver disease or gout. 4. History of gastric or duodenal ulcer, gastrointestinal haemorrhage, malignant hypertension. 5. Pregnant women. HIV status: not specified.	1. ATT plus dexamethasone 0.15 mg per kg body weight (up to a maximum of 4 mg) every 6 hours for 3 weeks then tapered gradually. 2. ATT plus placebo (0.9% saline). ATT: oral (through nasogastric tube in unconscious participants) administration of isoniazid 10 mg/kg up to 300 mg, rifampicin 15 mg/kg up to 450 mg, and pyrazinamide 30 mg/kg for participants less than 30 kg and 1500 mg for participants over 30 kg daily, plus pyridoxine 50 mg daily. Total duration was 9 months	Outcomes identified in trial protocol 1. Treatment success, defined as resolution of meningitic symptoms and achievement of good neurologic function and stability of this state for 3 consecutive months. 2. All-cause death in the first 3 months. 3. Secondary treatment failure. 4. Adverse events related to ATT or dexamethasone, for example deranged liver function tests, hypertension, hyperglycaemia, secondary infection, rash, gastrointestinal bleeding. Outcomes reported in results 1. Death. 2. Non-disabling neurological deficit. 3. Disabling neurological deficit. 4. Bad outcome (death plus disabling neurological deficit). 5. Any deficit (non-disabling neurological deficit plus disabling neurological deficit).

Study	Methods	Participants	Interventions	Outcomes
Malhotra 2009	Randomized parallel group 3-arm study with allocation ratio 1:1:1. Length of follow-up: 10 months.	Setting: Chhatrapati Shahuji Maharaj Medical University (CSMMU), Lucknow, India - tertiary referral centre. Number of participants: 91 participants; 48 males, 43 females (6 participants randomized but lost to follow-up); 32 randomized to dexamethasone (1 lost to follow-up), 33 randomized to methylprednisolone (3 lost to follow-up), 32 randomized to no steroid (2 lost to follow-up). Inclusion criteria: age > 14 years; meningitis syndrome; tuberculous meningitis defined as "definite" if acid-fast bacilli were seen in CSF, "probable" if one or more than one of the following present: suspected active pulmonary TB on chest radiography, acid-fast bacilli in any specimen other than CSF, clinical evidence of extrapulmonary TB, and "possible" if at least 4 of the following were present: history of TB, predominance of lymphocytes in CSF, duration of illness > 5 days, ratio of CSF to plasma glucose < 0.5, altered consciousness, yellow CSF, or focal neurological signs. Exclusion criteria: age < 14 years; HIV-positive; contraindication to corticosteroids; received corticosteroid or ATT before presentation at the CSMMU, evidence of space occupying lesion on CT brain, refused consent.	1. ATT + dexamethasone (intravenous for 4 weeks as (at 0.4, 0.3, 0.2 and 0.1 mg/kg/day during weeks 1, 2, 3, 4 respectively); daily oral dose for following 4 weeks as 4, 3, 2, 1 mg/day on weeks 5, 6, 7, 8 respectively). 2. ATT + methylprednisolone (intravenous for 5 days (1 g/day for participants weighing > 50kg and 20 mg/kg/day for participant weighing < 50 kg). 3. ATT alone. ATT: rifampicin (15 mg/kg/day), isoniazid (10 mg/kg/day), pyrazinamide (30 mg/kg/day) and either ethambutol (20 mg/kg/day) or streptomycin (15 mg/kg/day) for 2 months and isoniazid (10 mg/kg/day) for 7 months.	Assessed at 6 months post-randomization. 1. Death or severe disability. 2. Adverse events: hepatitis; anti-epileptic toxicity, gastro-intestinal bleeding, paradoxical tuberculoma. 3. Deterioration in vision, development of new focal neurological deficit and new-onset seizures.

2.3 Randomised controlled trials (RCTs)

Only one additional RCT published subsequent to the Prasad (2016) systematic review was identified.[7] This RCT is included in the Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026).

This RCT was a double-blind, placebo-controlled trial that included only adults living with HIV and TBM. Participants were recruited from the Hospital for Tropical Diseases and Pham Ngo Thach Hospital for Tuberculosis and Lung Disease in Ho Chi Minh City, Vietnam and from Dr Cipto Mangunkusumo National Reference Hospital and Persahabatan National Respiratory Referral Hospital in Jakarta, Indonesia. Eligible participants were 18 years or older, living with HIV, had been clinically diagnosed with TBM based on ≥ 5 days of meningitis symptoms and cerebrospinal fluid abnormalities, and had started ATT. Participants were further classified as having definite, probable, and possible TBM.

Enrolled participants were randomly assigned in a 1:1 ratio to receive a 6- to 8-week tapering course of dexamethasone or placebo in addition to 12 months of standard ATT and antiretroviral therapy (ART). Randomisation was computer-generated using randomly permuted block sizes of 4 and 6. Randomisation was stratified by participating site and modified Medical Research Council tuberculous meningitis severity grade⁵.

First-line ATT followed Vietnamese and Indonesian national guidelines. Rifampin (10mg/kg/24 hrs; maximum 600mg), isoniazid (5mg/kg/24hrs; maximum 300mg), pyrazinamide (25mg/kg/24hrs; maximum 2g) and ethambutol (20mg/kg/24 hrs; maximum 1.2g) were given the first 2 months of treatment, provided drug resistance was not suspected or proven. Pyrazinamide was then stopped and rifampin, isoniazid and ethambutol were continued until at least 12 months of ATT in total had been completed. In ART naïve participants, ART was started 6 to 8 weeks after initiation of ATT according to national guidelines.

Participants with grade II or III TBM randomised to the intervention arm received intravenous dexamethasone for 4 weeks (0.4 mg per kilogram of body weight per day for the first week, 0.3 mg per kilogram per day for the second week, 0.2 mg per kilogram per day for the third week, and 0.1 mg per kilogram per day for the fourth week) and then oral dexamethasone for 4 weeks, starting at 4 mg per day and decreasing by 1 mg each week. Participants with grade I TBM randomised to the intervention arm received intravenous dexamethasone for 3 weeks (0.3 mg per kilogram per day for the first week, 0.2 mg per kilogram per day for the second week, and 0.1 mg per kilogram per day for the third week) and then oral dexamethasone for 3 weeks, starting at 3 mg per day and decreasing by 1 mg each week.

The primary endpoint was death from any cause during the 12 months after randomisation. Secondary endpoints included neurological disability (defined as a modified Rankin scale score of 3-5) at 12 months after randomisation and neurological immune reconstitution inflammatory syndrome (IRIS) during the first 6 months. Additional secondary endpoints assessed at 12 months after randomisation included first new neurologic event or death, HIV-associated cancer, use of open-label glucocorticoid treatment for any reason, shunt surgery, and serious adverse events.

The study sample size calculation assumed a 9-month mortality of 40% in the dexamethasone arm and a hazard ratio of death for the dexamethasone arm compared to the placebo arm of 0.69. An estimated 520 PWH with TBM were required for 80% power, allowing 5% loss to follow-up.

Between 25 May 2017 and 29 April 2021, 520 participants were enrolled, with 263 participants randomly assigned to the dexamethasone arm and 257 participants randomly assigned to placebo arm. Almost half (49%) of participants were ART naïve. In participants with a baseline CD4 count ($n = 484$), 51.9% ($n = 251$) had a baseline

⁵ Modified Medical Research Council tuberculous meningitis severity grade: Grade I, Glasgow coma scale (GCS) of 15 with no focal neurological deficit; Grade II, GCS 11 to 14 OR GCS 15 with focal neurological deficit; Grade III, GCS ≤ 10 with or without focal neurological deficit.

CD4 count ≤ 50 cells per cubic millimetre. The median age of participants was 36 years. Overall, 40.8% of participants had definite TBM, 48.7% had probable TBM and 10% had possible TBM. The majority of participants (86%) had grade I or II disease. In total, 16 participants (10 in the dexamethasone arm and 6 in the placebo arm) had multidrug-resistant TBM.

Overall this RCT was assessed to be at low risk of bias (**Appendix 3**)

3. Results: Effectiveness and/or safety

3.1 PICO 1: Corticosteroids plus standard anti-tuberculous treatment compared to anti-tuberculous treatment alone or with placebo in HIV-negative adults and children with TBM

3.1.1 Outcome 1: Mortality and Outcome 2: Severe disability

3.1.1.1 Guideline: Tuberculous Meningitis International Research Consortium Clinical Practice Guideline, 2026.

Clinical Practice Guideline (2026). Corticosteroids be used as an adjunctive agent for TBM irrespective of HIV status.

Certainty assessment							No of patients		Effect	
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	corticosteroids	no corticosteroids	Relative (95% CI)	Absolute (95% CI)
Mortality (follow-up: range 9 months to 12 months)										
9	Randomised trials, ¹⁰⁵⁻¹¹³	Not serious	Not serious	Not serious	Not serious	None	316/910 (34.7%)	367/860 (42.7%)	RR 0.81 (0.72-0.92)	79 fewer per 1,000 (from 34 fewer to 125 fewer)
Morbidity as defined by modified Rankin Scale 3-5 (compared to 0-2) amongst survivors with follow-up from 9 to 12 months)										
8	Randomised trials, ¹⁰⁵⁻¹¹²	Not serious	Serious	Not serious	Not serious	None	102/589 (17.3%)	100/490 (20.4%)	RR 0.85 (0.66-1.09)	31 fewer per 1,000 survivors (from 78 fewer to 16 more)

CI=confidence interval. OR=odds ratio. RR=risk ratio. TBM=tuberculous meningitis.

Note: these estimates are based on ALL RCTs including 2 RCTs that enrolled 614 PWH.

Insufficient methodological detail was provided in the clinical practice guideline to allow appraisal of the underpinning systematic review. The transparency of the guideline's GRADE assessment was limited, as explicit justifications for decisions to downgrade (or not downgrade) the certainty of evidence were not reported. Consequently, the certainty of evidence ratings are not presented here.

3.1.1.2 Systematic review: Prasad (2016)

Table 4. Summary of findings table from Prasad (2016) systematic review

Summary of findings for the main comparison. Any corticosteroid compared to control for tuberculous meningitis					
Any corticosteroid compared to control for tuberculous meningitis					
Participant or population: adults or children with tuberculous meningitis on tuberculosis (TB) chemotherapy					
Settings: hospital care					
Intervention: any corticosteroid					
Comparison: placebo or no corticosteroid					
Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk*	Corresponding risk			
	Control	Corticosteroid			
Follow-up to 2 to 24 months					
Death	41 per 100	31 per 100 (27 to 36)	RR 0.75 (0.65 to 0.87)	1337 (9 trials)	⊕⊕⊕⊕ high 1,2,3,4,5
Disabling neurological deficit	8 per 100	7 per 100 (6 to 10)	RR 0.92 (0.71 to 1.20)	1314 (8 trials)	⊕⊕⊕⊕ low 6,7,8
Follow-up to 5 years					
Death	47 per 100	44 per 100 (37 to 53)	RR 0.93 (0.78 to 1.12)	545 participants (1 trial)	⊕⊕⊕⊕ moderate 9,10
Disabling neurological deficit	15 per 100	14 per 100 (7 to 25)	RR 0.91 (0.49 to 1.69)	244 (1 trial)	⊕⊕⊕⊕ very low 10,11,12
*The assumed risk is from the median control group risk across studies. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; RR: risk ratio; TB: tuberculosis.					
1	Not downgraded for risk of bias. There are few uncertainties regarding allocation concealment or sequence generation in one of the two largest studies, but the largest trial was high quality and effects between these two trials were consistent.				
2	Not downgraded for inconsistency: low statistical heterogeneity, and the forest plot shows a consistent benefit.				
3	Not downgraded for indirectness in relation to age: all the participants in Schoeman 1997 and 59% of the participants in Girgis 1991 were children, and the effect is consistent with the other large trial, Thwaites 2004, which included participants aged 14 and over.				
4	Not downgraded for indirectness for HIV status: one trial included 98 HIV-positive participants, with no obvious qualitative heterogeneity when compared to HIV-negative participants (Thwaites 2004). If making recommendations for HIV-positive participants only, a guidelines panel may wish to downgrade on indirectness.				
5	Not downgraded for serious imprecision: the overall meta-analysis is adequately powered to detect this effect but is only adequately powered when the trials at unclear or high risk of bias are included. The effect is clinically important.				
6	Downgraded by one for risk of bias: four of the eight trials were at high risk of bias due to lack of blinding of outcome assessors, which could impact on the interpretation of assessments of disability.				
7	Not downgraded for indirectness: trials included children, adults, some HIV-positive people, and people from different continents.				
8	Downgraded by one for imprecision: effects range from clinically important benefits of 29% reduction to 20% increase in disability.				
9	Not downgraded on risk of bias or imprecision: number of participants followed up was high: 91% at five years.				
10	Downgraded by one for indirectness. This was a single trial conducted in a high-quality health care unit in a population with high levels of infectious diseases endemicity and poverty. The attenuation of the effect may be less marked in populations with lower exposure to infectious diseases and other causes of reduced life expectancy associated with poverty. The authors were not able to establish the cause of death in most of the people who died after 9 months follow-up, and so it is not possible to assess whether these deaths were related to tuberculous meningitis or to other causes.				
11	Not downgraded on risk of bias. Although the assessors were not blind to the allocation, and some assessments were conducted by telephone, the numbers of disabled participants in the two groups were the same, and it is unlikely that systematic bias in the observers is present.				
12	Downgraded by two for imprecision. There were few events, and the confidence interval ranges from substantive harms to substantive benefits.				

The effect of corticosteroids appeared to be consistent across all grades of the disease although this analysis is underpowered (Grade I TBM RR 0.50, 95% CI 0.29 to 0.85; six trials, 305 participants); Grade II (RR 0.72, 95% CI 0.56 to 0.93; seven trials, 581 participants); and Grade III (RR 0.69, 95% CI 0.54 to 0.88; eight trials, 651 participants).

3.1.2 Outcome 3: Adverse events

3.1.2.1 Guideline: Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026).

No summary of findings table for adverse events was included in the publication.

3.1.2.2 Systematic review: Prasad (2016)

No summary of findings table for adverse events was included in the publication. There was no difference in incidence of hyperglycaemia/glycosuria, hepatitis, gastrointestinal bleeding, or invasive bacterial infection (**Figure 5**).

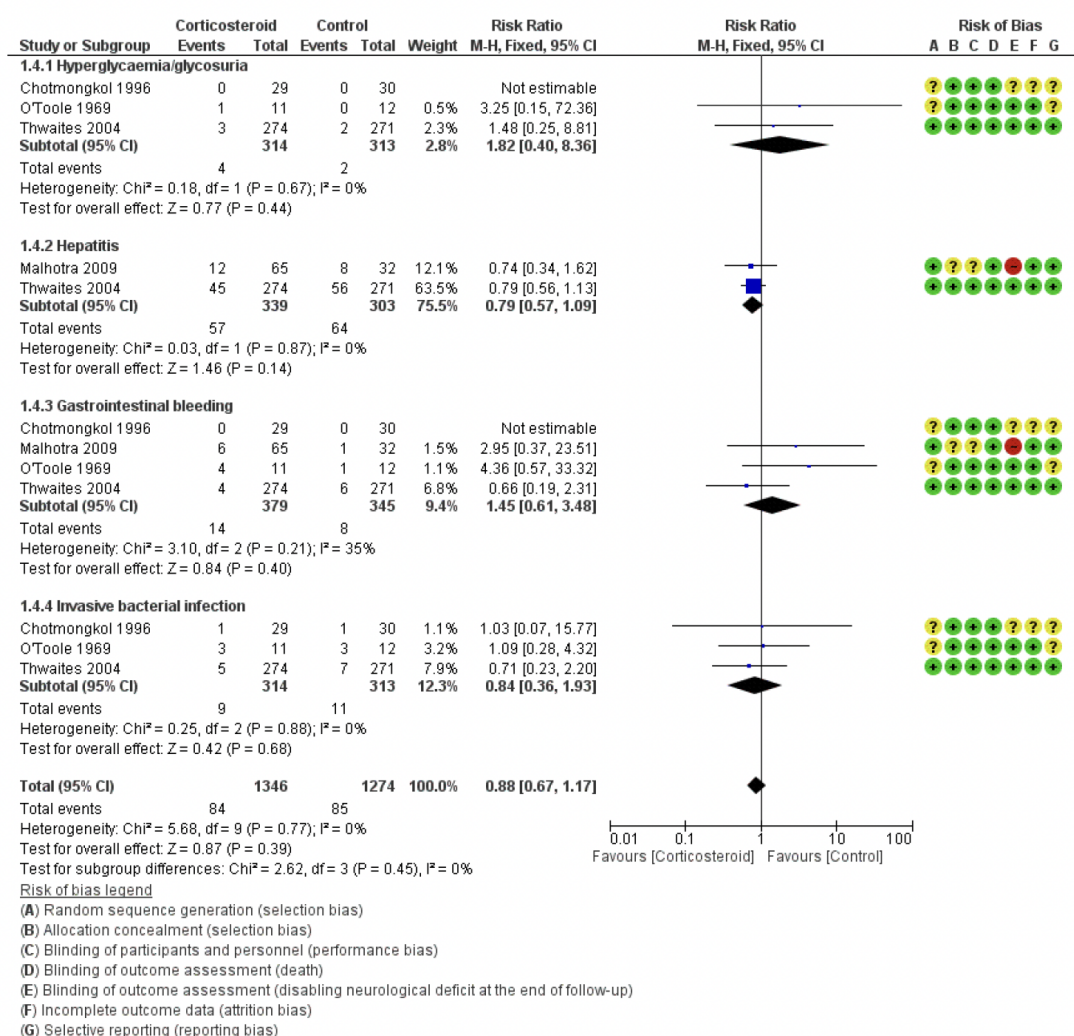


Figure 5. Forest plot of comparison any corticosteroid versus control, outcome adverse events from Prasad (2016)

3.2 PICO 2: Corticosteroids plus standard anti-tuberculous treatment compared to anti-tuberculous treatment alone or with placebo in adults and children living with HIV and co-infected with TBM

3.2.1 Outcome 1 and 2: Mortality and severe disability

3.2.1.1 Guideline: Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026)

Table 5. Summary of findings table from Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026). Corticosteroids used as an adjunctive agent for TBM with HIV co-infection.

Certainty assessment							№ of patients		Effect	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	no corticosteroids	Relative (95% CI)	Absolute (95% CI)
Mortality (follow-up: range 9 months to 12 months)										
2	Randomised trials ^{111,112}	Not serious	Not serious	Not serious	Not serious	None	143/307 (46·6%)	163/311 (52·4%)	RR 0·90 (0·77 to 1·05)	52 fewer per 1,000 (from 121 fewer to 26 more)
Morbidity as defined by modified Rankin Scale 3-5 (compared to 0-2) amongst survivors with follow-up from 9 to 12 months)										
2	Randomised trials ^{111,112}	Not serious	Not serious	Not serious	Not serious	None	15/147 (10·2%)	10/131 (7·6%)	RR 1·34 (0·62 to 2·87)	25 more per 1,000 (from 41 fewer to 93 more)

CI=confidence interval. OR=odds ratio. RR=risk ratio. TBM=tuberculous meningitis.

Note: The two RCTs included in the systematic review and meta-analysis are Thwaites (2004) which included 98 PWH and Donovan (2023) which included 520 PWH. [7,8] Neither of these RCTs enrolled children < 14 years of age.

Insufficient methodological detail was provided in the clinical practice guideline to allow appraisal of the underpinning systematic review. The transparency of the guideline's GRADE assessment was limited as explicit justifications for decisions to downgrade (or not downgrade) the certainty of evidence were not reported. For example, despite a low event rate and wide confidence interval for the morbidity outcome, the certainty of evidence was not downgraded for imprecision. Consequently, the reported certainty of evidence ratings are not presented here.

3.2.1.2 Systematic review: Prasad (2016)

No summary of findings table for PWH specifically was included in the publication. In a subgroup analysis by HIV status, only one RCT specifically mentioned that 98 participants were PWH. Analyses stratifying the outcomes of death and disabling neurological deficit in PWH did not detect any large differences and showed no apparent effect of HIV status on the effect estimates, but the analysis is underpowered.

Table 6. Any corticosteroid versus control stratified by HIV status from Prasad (2016)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1	534	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.66, 1.02]
1.1 HIV-positive	1	98	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.67, 1.20]
1.2 HIV-negative	1	436	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.58, 1.06]
2 Disabling neurological deficit	1	534	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.73, 1.79]
2.1 HIV-positive	1	98	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.08, 19.07]
2.2 HIV-negative	1	436	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.73, 1.80]
3 Death or disabling residual neurological deficit	1	545	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.76, 1.09]
3.1 HIV-positive	1	98	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.68, 1.20]
3.2 HIV-negative	1	447	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.74, 1.14]

3.2.1.3 Randomised controlled trial: Donovan (2023)

Death occurred in 116 of 263 participants (44.1%) in the dexamethasone group and in 126 of 257 participants (49.0%) in the placebo group (HR 0.85; 95% CI 0.66 to 1.10; $p = 0.22$) (RR 0.90; 95% CI 0.75 to 1.08; $p = 0.26$; 49 fewer per 1000 (122 fewer to 39 more per 1000)). No benefit associated with dexamethasone was observed in any prespecified subgroup in the intention-to-treat population, including modified MRC disease-severity grade, or CD4 cell count at enrolment. However, in subgroup analyses by diagnostic category, the apparent benefit of corticosteroids appeared to be driven by participants classified as having possible tuberculous meningitis, although the small size of this subgroup and the issue of multiple testing limit the interpretability of this finding (Table 7).

Table 7. Death from any cause in pre-specified subgroups of PWH in the intention-to-treat population adapted from Donovan (2023)

Subgroup	Dexamethasone (n = 263)	Placebo (n = 257)	Hazard Ratio (95% CI)
Overall	116/263	126/257	0.85 (0.66–1.10)
Modified MRC disease-severity grade			
I	22/99	28/97	0.72 (0.41–1.25)
II	60/125	68/126	0.82 (0.58–1.16)
III	34/39	30/34	1.03 (0.63–1.69)
Diagnostic category			
Definite tuberculous meningitis	48/108	49/104	0.90 (0.61–1.35)
Probable tuberculous meningitis	61/129	61/124	0.91 (0.64–1.30)
Possible tuberculous meningitis	5/24	15/28	0.34 (0.12–0.94)
ART status at enrolment			
No previous ART	64/133	64/122	0.85 (0.60–1.21)
>3 months of ART	20/46	26/58	0.96 (0.54–1.72)
ART of undetermined duration	19/58	19/48	0.80 (0.42–1.51)
CD4 cell count at enrolment (1)			
≤ 50 per cubic millimetre	67/126	67/125	0.96 (0.69–1.35)
51–100 per cubic millimetre	12/45	19/44	0.52 (0.25–1.06)
101–200 per cubic millimetre	14/36	13/35	1.04 (0.49–2.22)
>200 per cubic millimetre	11/37	15/36	0.70 (0.32–1.52)
CD4 cell count at enrolment (2)*			
≤ 50 per cubic millimetre	67/126	67/125	0.96 (0.69–1.35)
>50 per cubic millimetre	37/118	47/118	0.79 (0.56–1.11)

*Note: the effect estimates for CD4 cell count at enrolment (2) were conducted post-hoc by the reviewer.

3.2.2 Outcome 2: Adverse events

3.2.2.1 Guideline: Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026)

No summary of findings table for adverse events was included in the publication.

3.2.2.2 Systematic review: Prasad (2016)

No summary of findings table for adverse events in PWH was included in the publication.

3.2.2.3 Randomised controlled trial: Donovan (2023)

The numbers of participants with at least one serious adverse event were similar between the dexamethasone group compared to the placebo group (73% vs. 75.5%, $p = 0.52$). Fewer participants had serious neurologic adverse events in the dexamethasone group than in the placebo group (36.1% vs. 44.7%). These serious neurologic adverse events included depressed consciousness and new focal neurologic signs.

Gastrointestinal bleeding events and other adverse events possibly, probably, or definitely related to glucocorticoids occurred with a similar incidence in the two trial groups. The incidence of clinical grade 3 or 4 adverse events (including hyperglycaemia and psychiatric disorders), adverse events leading to interruptions in ATT or ART (including sepsis), and grade 3 or 4 laboratory abnormalities was similar in the two groups, except for elevated ALT levels, which occurred more often in the dexamethasone arm than in the placebo arm (13.7% versus 7.8%).

Table 8. Serious adverse events from Donovan (2023)

Event	Dexamethasone (N=263)		Placebo (N=257)	
	no. of participants (%)	no. of events	no. of participants (%)	no. of events
Any selected serious adverse event	192 (73.0)	486	194 (75.5)	442
Nervous system disorder	95 (36.1)	128	115 (44.7)	147
Infection or infestation	60 (22.8)	79	50 (19.5)	63
Metabolism or nutrition disorder	51 (19.4)	66	59 (23.0)	68
Respiratory, thoracic, or mediastinal disorder	39 (14.8)	40	37 (14.4)	39
Hepatobiliary disorder	38 (14.4)	44	29 (11.3)	29
Gastrointestinal disorder	32 (12.2)	33	21 (8.2)	25
Blood or lymphatic system disorder	20 (7.6)	23	17 (6.6)	17
Investigation†	14 (5.3)	14	9 (3.5)	9
General disorder or administration-site condition	14 (5.3)	15	7 (2.7)	7
Vascular disorder	10 (3.8)	10	11 (4.3)	11
Skin or subcutaneous-tissue disorder	12 (4.6)	13	5 (1.9)	6
Cardiac disorder	7 (2.7)	7	4 (1.6)	4
Renal or urinary disorder	4 (1.5)	4	6 (2.3)	6
Musculoskeletal or connective-tissue disorder	4 (1.5)	4	2 (0.8)	2
Psychiatric disorder	3 (1.1)	3	1 (0.4)	1
Eye disorder	0	0	3 (1.2)	3
Endocrine disorder	1 (0.4)	1	2 (0.8)	2
Ear or labyrinth disorder	1 (0.4)	1	1 (0.4)	1
Injury, poisoning, or procedural complication	1 (0.4)	1	1 (0.4)	1
Immune system disorder	0	0	1 (0.4)	1

* Events were summarized according to the system organ class of the *Medical Dictionary for Regulatory Activities* hierarchy. The number of participants with any adverse events and specific events were summarized and compared between the two trial groups on the basis of chi-square tests or (if the expected number in one of the table cells was <1) Fisher's exact test.

† Abnormal results of investigations were reported.

Costs

As the use of adjunctive corticosteroids is already included in the paediatric STG as standard of care, there is no change in recommendation and no resultant incremental budget impact. The historic absence of a definitive recommendation for the use of corticosteroids for the treatment of TBM in PLWH is likely to have resulted in discretionary clinical judgement being applied in clinical practice. An accurate assessment of any budget impact is not possible, however, we do not anticipate any significant incremental budget impact with the CD4 stratified treatment approach included in our recommendation above.

TBM - cost of corticosteroids as adjunctive therapy (PAEDIATRICS)								
Prednisolone oral								
Formulation	Price per pack (Rands)	STG dosing guidance		Assumed weight per patient (kg)	Dose per day (mg)	Dose per course (mg)	Equivalent number of bottles per patient	Cost per course (Rands)
15mg/5mL solution (50mL pack) = 150mg per bottle	95,21	Weeks 1 -4	2mg/kg/day	10	20	560	5	R444,31
		Weeks 5-6	1mg/kg/day		10	140		
		Weeks 1 -4	2mg/kg/day	20	40	1120	10	R952,10
		Weeks 5-6	1mg/kg/day		20	280		
		Weeks 1 -4	2mg/kg/day	>30	60	1680	14	R1 332,94
		Weeks 5-6	1mg/kg/day		30	420		
Notes: 1. Based on 3 weight bands (10kg, 20kg and >/=30kg) 2. Total dose per course rounded to nearest full pack 3. Prices based on MHPL (Feb 2026) 4. Weeks 5-6 dose taper calculated at 50% of treatment dose for pragmatic reasons								
TBM - cost of corticosteroids as adjunctive therapy (ADULTS)								
Dexamethasone IV								
STG dosing guidance		Formulation	Price per ampoule (Rands)	Daily dose for 70kg (mg)	Equivalent number of amps per day	Cost per week (Rands)		
Week 1	0.3-0.4mg/kg/day	4mg/mL as 1mL inj	6,83	28	7	334,67		
Week 2	0.3-0.4mg/kg/day			28	7	334,67		
Week 3	0.2mg/kg/day			14	4	191,24		
Week 4	0.1mg/kg/day			7	2	95,62		
Week 5	4mg/day			4	1	47,81		
Week 6	3mg/day			3	1	47,81		
Week 7	2mg/day			2	1	47,81		
Week 8	1mg/day			1	1	47,81		
Cost per course						R1 147,44		

Prednisone oral (ADULTS)					
STG dosing guidance		Formulation	Price per tablet (Rands)	Equivalent number of tablets per day	Cost per week (Rands)
Week 1	60mg/day	5mg tablet	0,19	12	15,96
Week 2	60mg/day			12	15,96
Week 3	40mg/day			8	10,64
Week 4	25mg/day			5	6,65
Week 5	20mg/day			4	5,32
Week 6	15mg/day			3	3,99
Week 7	10mg/day			2	2,66
Week 8	5mg/day			1	1,33
Cost per course					R62,51
Notes: 1. Based on 70kg adult for weight-based dosing 2. Doses rounded to nearest ampoule/tablet 3. Prices based on MHPL (Feb 2026) 4. Where dose ranges recommended - max dose applied for costing 5. For prednisone, ave price per tablet applied as multiple products on tender					

Key findings and discussion

- In adults and children with TBM who are HIV-negative[6]:
 - Corticosteroids reduce mortality moderately (RR 0.75, 95% CI 0.65 to 0.87, high certainty of evidence). This reduction in mortality is consistent across all grades of the disease.
 - Corticosteroids may reduce severe disability (RR 0.92, 95% CI 0.71 to 1.20, low certainty of evidence).
 - Corticosteroids result in little to no difference in serious adverse events (RR 0.88, 95% CI 0.67 to 1.17).
- In adult PWH and TBM:
 - Corticosteroids may result in lower mortality (RR 0.90, 95% CI 0.77 to 1.05).[5]
 - Corticosteroids may increase severe disability, but the confidence interval is very wide (RR 1.34, 95% 0.65 to 2.87).[5]
 - Corticosteroids did not increase serious adverse events (73% vs. 75.5%, p = 0.52).[7]
 - These findings are predominantly based on data from one RCT in which the majority of PWH and TBM had CD4 cell count ≤ 200 cell/mm³.
 - It is biologically plausible that in PWH with TBM and relatively preserved CD4 counts, the mortality benefit of adjunctive corticosteroids would approximate that observed in HIV-negative patients.
 - The exact CD4 count at which this mortality benefit would approximate that observed in HIV-negative individuals has not been established, and there is insufficient data to define this threshold.
 - Given the high mortality of TBM, the absence of demonstrated harm associated with corticosteroids, and the potential for a small mortality benefit, specifically in those PWH with higher CD4 counts, withholding corticosteroids from all PWH may not be appropriate.

- We pragmatically suggest, based on expert opinion and aligned with the National Department of Health programmatic definitions of advanced HIV disease (AHD), that corticosteroids be used in PWH with TBM and CD4 cell counts > 200 cells/mm³. In PWH with TBM and CD4 cell counts ≤ 200 cells/mm³ we suggest not using corticosteroids.
- In children with HIV and TBM
 - No randomized controlled trials evaluating corticosteroids in children with HIV and TBM were identified. Consequently, there is currently no direct evidence to indicate that children with HIV and TBM fail to derive a mortality benefit comparable to that observed in HIV-negative children with TBM.

Recommendations

- In HIV-negative adults with TB meningitis of any grade, we recommend using corticosteroids.
- In adults with HIV and TB meningitis, with CD4 count ≤ 200 cells/mm³, we suggest not using corticosteroids.
- In adults with HIV and TB meningitis, with CD4 count >200 cells/mm³, we suggest using corticosteroids.
- In children, with or without HIV, with TB meningitis of any grade, we recommend using corticosteroids.

Review Team

The following people were involved in this review:

Name	Affiliation	Role and Contribution	Interest declaration
Jessica Taylor	University of Cape Town	PICO; Title, abstract and full text screening; Write-up, referencing and appendices; Quality appraisal, Clinical expertise; Formulation of recommendations; Quality assurance	None
Zahiera Adam	CHAI, Affordable Medicines Directorate, NDoH	Costing; Quality assurance; Formulation of recommendations	None
Gayle Tatz	University of Cape Town	Clinical expertise; Formulation of Recommendations	None
Halima Dawood	Infectious diseases specialist, Greys Hospital, KZN	Clinical expertise; Formulation of recommendations	None
Jeremy Nel	Infectious diseases specialist, Helen Joseph Hospital and the University of the Witwatersrand.	Clinical expertise; Formulation of recommendations	None
Karen Cohen	University of Cape Town	Clinical expertise; Formulation of recommendations	None

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- [3] WHO Guidelines Approved by the Guidelines Review Committee. WHO consolidated guidelines on tuberculosis: Module 4: Treatment and care. Geneva: World Health Organization © World Health Organization 2025.; 2025.
- [4] Saukkonen JJ, Duarte R, Munsiff SS, et al. Updates on the Treatment of Drug-Susceptible and Drug-Resistant Tuberculosis: An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2025;211(1):15-33.
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- [6] Prasad K, Singh MB, Ryan H. Corticosteroids for managing tuberculous meningitis. *Cochrane Database Syst Rev*. 2016;4(4):Cd002244.
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Appendix 1: Search results and reasons for exclusion

	Reference	Study Type	Included/Excluded	Reason
1.	Prasad K, Singh MB, Ryan H. Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev. 2016 Apr 28;4(4):CD002244. doi: 10.1002/14651858.CD002244.pub4. PMID: 27121755; PMCID: PMC4916936.	Systematic review	Included	
2.	Thwaites GE, Nguyen DB, Nguyen HD, Hoang TQ, Do TT, Nguyen TC, Nguyen QH, Nguyen TT, Nguyen NH, Nguyen TN, Nguyen NL, Nguyen HD, Vu NT, Cao HH, Tran TH, Pham PM, Nguyen TD, Stepniewska K, White NJ, Tran TH, Farrar JJ. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med. 2004 Oct 21;351(17):1741-51. doi: 10.1056/NEJMoa040573. PMID: 15496623.	Randomised controlled trial	Included	
3.	Donovan J, Bang ND, Imran D, Nghia HDT, Burhan E, Huong DTT, Hiep NTT, Ngoc LHB, Thanh DV, Thanh NT, Wardhani ALS, Maharani K, Gasmara CP, Hanh NHH, Oanh PKN, Estiasari R, Thu DDA, Kusumaningrum A, Dung LT, Giang DC, Ha DTM, Lan NH, Chau NVV, Nguyet NTM, Gekus RB, Thuong NTT, Kestelyn E, Hamers RL, Phu NH, Thwaites GE; ACT HIV Investigators. Adjunctive Dexamethasone for Tuberculous Meningitis in HIV-Positive Adults. N Engl J Med. 2023 Oct 12;389(15):1357-1367. doi: 10.1056/NEJMoa2216218. PMID: 37819954; PMCID: PMC7615197.	Randomised controlled trial	Included	
4.	Thwaites G, Fisher M, Hemingway C, Scott G, Solomon T, Innes J; British Infection Society. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. J Infect. 2009 Sep;59(3):167-87. doi: 10.1016/j.jinf.2009.06.011. Epub 2009 Jul 4. PMID: 19643501.	Guideline	Excluded	Never updated. More up-to-date clinical practice guidelines available.
5.	Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD002244. doi: 10.1002/14651858.CD002244.pub3. Update in: Cochrane Database Syst Rev. 2016 Apr 28;4:CD002244. doi: 10.1002/14651858.CD002244.pub4. PMID: 18254003.	Systematic review	Excluded	2016 update included.
6.	Critchley JA, Young F, Orton L, Garner P. Corticosteroids for prevention of mortality in people with tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis. 2013 Mar;13(3):223-37. doi: 10.1016/S1473-3099(12)70321-3. Epub 2013 Jan 29. PMID: 23369413.	Systematic review	Excluded	Incorrect population – includes any TB diagnosis, not specifically TBM.
7.	Thuong NTT, Heemskerk D, Tram TT, Thao LTP, Ramakrishnan L, Ha VTN, Bang ND, Chau TTH, Lan NH, Caws M, Dunstan SJ, Chau NVV, Wolbers M, Mai NTH, Thwaites GE. Leukotriene A4 Hydrolase Genotype and HIV Infection Influence Intracerebral Inflammation and Survival From Tuberculous Meningitis. J Infect Dis. 2017 Apr 1;215(7):1020-1028. doi: 10.1093/infdis/jix050. PMID: 28419368; PMCID: PMC5426373.	Randomised controlled trial	Excluded	Non-interventional, mechanistic study nested within randomised controlled trial.
8.	Saluja A, Vibha D, Pandit AK, Shukla G, Srivastava AK, Tripathi M, Srivastava MVP, Prasad K, Dwivedi SN. Comparison of dexamethasone regimens in tubercular meningitis (TBM): a randomized open label clinical trial. J Infect Dev Ctries. 2023 Dec 31;17(12):1769-1774. doi: 10.3855/jidc.17563. PMID: 38252729.	Randomized controlled trial	Excluded	Incorrect intervention and comparator – oral and intravenous dexamethasone.
9.	Diallo A, Diallo BD, Diallo OH, Carlos-Bolumbu M, Camara M, Sidikba S. Corticosteroids for reducing tuberculosis mortality in persons living with HIV: a systematic review and meta-analysis using reconstructed individual patient data. BMJ Glob Health. 2025 Aug 14;10(8):e017923. doi: 10.1136/bmjgh-2024-017923. PMID: 40813100; PMCID: PMC12352167.	Systematic review	Excluded	Incorrect population – includes any TB diagnosis, not specifically TBM.
10.	Malhotra HS, Garg RK, Singh MK, Agarwal A, Verma R. Corticosteroids (dexamethasone versus intravenous methylprednisolone) in patients with tuberculous meningitis. Ann Trop Med Parasitol. 2009 Oct;103(7):625-34. doi: 10.1179/000349809X12502035776315. PMID: 19825284.	Randomised controlled trial	Included	
11.	Prasad K, Volmink J, Menon GR. WITHDRAWN: Steroids for treating tuberculous meningitis. Cochrane Database Syst Rev. 2007 Jul 18;(1):CD002244. doi: 10.1002/14651858.CD002244.pub2. Update in: Cochrane Database Syst Rev. 2008 Jan 23;(1):CD002244. doi: 10.1002/14651858.CD002244.pub3. PMID: 17836701.	Systematic review	Excluded	Study withdrawn
12.	Madani N, Dendane T, Zekraoui A, Abidi K, Zegwagh AA, Aboual R. Effects of corticosteroids on adults with tuberculous meningitis admitted to intensive care unit: a propensity score analysis. Rev Med Interne. 2009 Jan;30(1):12-9. French. doi:10.1016/j.revmed.2008.06.023. Epub 2008 Aug 15. PMID: 18706739.	Retrospective cohort study	Excluded	Incorrect study type
13.	Rustami R, Ganien AR, Dian S, Apriani L, Achmad TH, van der Ven AJ, Born G, Aarnoutse RE, van Crevel R. Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial. Lancet Infect Dis. 2013 Jan;13(1):27-35. doi: 10.1016/S1473-3099(12)70264-5. Epub 2012 Oct 25. PMID: 23103177.	Randomised controlled trial	Excluded	Incorrect intervention – moxifloxacin and rifampicin.
14.	Kalita J, Misra UK, Prasad S, Bhoi SK. Safety and efficacy of levofloxacin versus rifampicin in tuberculous meningitis: an open-label randomized controlled trial. J Antimicrob Chemother. 2014 Aug;69(8):2246-51. doi:10.1093/jac/dku103. Epub 2014 Apr 20. PMID: 24752957.	Randomised controlled trial	Excluded	Incorrect intervention – levofloxacin.
15.	Moloughgi K, Sheybani F, Naderi H, Mirfeizi Z, Morovatdar N, Baradaran A. Central nervous system infections in patients with systemic lupus erythematosus: a systematic review and meta-analysis. Lupus Sci Med. 2022 Jan;9(1):e000560. doi: 10.1136/lupus-2021-000560. PMID: 34980679; PMCID: PMC8724813.	Systematic review	Excluded	Incorrect population – systemic lupus erythematosus.
16.	Verma R, Chakraborty R. A Clinico-Immunological Perspective of Paradoxical Reaction in HIV-ve Tuberculous Meningitis with Therapeutic Possibilities. Neurol India. 2025 Jul 1;73(4):678-691. doi: 10.4103/neuro-india.Neurol-India-D-24-00443. Epub 2025 Jul 24. PMID: 40705281.	Systematic review	Excluded	Incorrect population - people with TBM with paradoxical reactions
17.	Green JA, Tran CT, Farrar JJ, Nguyen MT, Nguyen PH, Dinh SX, Ho ND, Ly CV, Tran HT, Friedland JS, Thwaites GE. Dexamethasone, cerebrospinal fluid matrix metalloproteinase concentrations and clinical outcomes in tuberculous meningitis. PLoS One. 2009 Sep 30;4(9):e7277. doi: 10.1371/journal.pone.0007277. PMID: 19789647; PMCID: PMC2748711.	Randomised controlled trial	Excluded	Non-interventional, mechanistic study nested within Thwaites, 2008 randomised controlled trial.
18.	Simmons CP, Thwaites GE, Quyen NT, Chau TT, Mai PP, Dung NT, Stepniewska K, White NJ, Hien TT, Farrar J. The clinical benefit of adjunctive dexamethasone in tuberculous meningitis is not associated with measurable attenuation of peripheral or local immune responses. J Immunol. 2005 Jul 1;175(1):579-90. doi:10.4049/jimmunol.175.1.579. PMID: 15972695.	Randomised controlled trial	Excluded	Mechanistic study nested within Thwaites, 2008 randomised controlled trial
19.	Contopoulos-Ioannidis DG, Ioannidis JP. Claims for improved survival from systemic corticosteroids in diverse conditions: an umbrella review. Eur J Clin Invest. 2012 Mar;42(3):233-44. doi: 10.1111/j.1365-2362.2011.02584.x. Epub 2011. Aug 31. PMID: 21880039.	Systematic review	Excluded	Incorrect population – any indication for corticosteroids
20.	Misra UK, Kalita J, Nair PP. Role of aspirin in tuberculous meningitis: a randomized open label placebo controlled trial. J Neurol Sci. 2010 Jun 15;293(1-2):12-7. doi: 10.1016/j.jns.2010.03.025. Epub 2010 Apr 24. PMID: 20421121.	Randomised controlled trial	Excluded	Incorrect intervention – aspirin.
21.	Schoeman JF, Springer P, van Rensburg AJ, Swanevelder S, Hanekom WA, Haslett PA, Kaplan G. Adjunctive thalidomide therapy for childhood tuberculous meningitis: results of a randomized study. J Child Neurol. 2004 Apr;19(4):250-7. doi: 10.1177/088307380401900402. PMID: 15163089.	Randomised controlled trial	Excluded	Incorrect intervention – thalidomide.
22.	Nguyen TH, Tran TH, Thwaites G, Ly VC, Dinh XS, Ho Dang TN, Dang QT, Nguyen DP, Nguyen HP, To SD, Nguyen vV, Nguyen MD, Campbell J, Schultz C, Parry C, Torok ME, White N, Nguyen TC, Tran TH, Stepniewska K, Farrar JJ. Dexamethasone in Vietnamese adolescents and adults with bacterial meningitis. N Engl J Med. 2007 Dec 13;357(24):2431-40. doi: 10.1056/NEJMoa070852. PMID: 18077808.	Randomised controlled trial	Excluded	Incorrect population – bacterial meningitis.
23.	Garg RK, Pandey S, Mahdi RA, Singhal S. Movement Disorders in Central Nervous System Tuberculosis: A Systematic Review. Can J Neurol Sci. 2025 Sep 29;1-10. doi: 10.1017/cjn.2025.10436. Epub ahead of print. PMID: 41017616.	Systematic review	Excluded	Incorrect population – people with TBM and with movement disorders
24.	Beardsley J, Hoang NLT, Kibengo FM, Tung NLN, Binh TQ, Hung LQ, Chieraki W, Thwaites GE, Chau NVV, Nguyen TTT, Gekus RB, Day JN. Do Intracerebral Cytokine Responses Explain the Harmful Effects of Dexamethasone in Human Immunodeficiency Virus-associated Cryptococcal Meningitis? Clin Infect Dis. 2019 Apr 24;68(9):1494-1501. doi: 10.1093/cid/ciy725. PMID: 30169607; PMCID: PMC6481995.	Randomised controlled trial	Excluded	Incorrect population – cryptococcal meningitis

Appendix 2. Summary of clinical practice guidelines and recommendations

Clinical Practice Guideline	Recommendation	Justification	Subgroup considerations	Studies included in the systematic review	Outcomes considered
Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026)	In people without HIV, we recommend the use of adjunctive corticosteroid therapy, (Strong recommendation, high certainty of evidence) In the absence of an effective alternative adjunctive therapy for HIV-associated tuberculous meningitis, and the safety and potential effectiveness of corticosteroids, we recommend their use on a case-by-case basis in people living with HIV (weak recommendation, high certainty evidence)	Corticosteroids reduced case fatality, especially in children and adults without HIV. There is no signal for a change in disability among survivors in these groups. In people living with HIV and tuberculous meningitis, the benefits of corticosteroids are uncertain.	Separate recommendations for those with and without HIV.	O'Toole RD et al. Ann Intern Med 1969 Girgis N et al. Pediatr Infect Dis J 1991 Kumarvelu S et al. Tuber Lung Dis 1994 Chotmongkol V et al. J Med Assoc Thai 1996 Schoeman JF et al. Pediatrics 1997 Lardizabal DV et al. Philippine Journal of Neurology 1998 Malhotra HS et al. Ann Trop Med Parasitol 2009 Thwaites GE et al. N Engl J Med 2004 Donovan J et al. N Engl J Med 2023	Mortality Morbidity
WHO consolidated guidelines on tuberculosis. Module 4: Treatment and care. (2025). (Note: specific recommendation not updated since 2017)	4.1 In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6 – 8 weeks should be used. (Strong recommendation, moderate certainty of evidence) This recommendation was first put forward in the 2017 guideline update and are copied without modification into the 2025 guideline update.	In patients with tuberculous meningitis, evidence from randomized controlled trials in the systematic review showed lower rates of mortality, death or severe disability, and disease relapse when patients were treated with steroids in addition to anti-TB treatment. The benefits in terms of mortality increased with the increasing TB meningitis stage (i.e. increasing severity of disease).	Steroids should be given regardless of the severity of meningitis. No subgroup consideration by HIV status.	Kumarvelu S et al. Tuber Lung Dis 1994 Chotmongkol V et al. J Med Assoc Thai 1996 Schoeman JF et al. Pediatrics 1997 Malhotra HS et al. Ann Trop Med Parasitol 2009 Thwaites GE et al. N Engl J Med 2004	Mortality Death or severe disability Relapse Adverse events

		Additionally, rates of adverse events and severe adverse events, including severe hepatitis, were lower in the patients receiving steroids.			
ATS/CDC/ERS/IDSA ⁶ Clinical Practice Guideline (2025) (Note: specific recommendation not updated since 2016)	Recommendation 8. We recommend initial adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6 – 8 weeks for patients with tuberculous meningitis (strong recommendation, moderate certainty in evidence)	Our updated systematic review found a mortality benefit from the use of adjuvant corticosteroids.	No subgroup consideration by severity of TB meningitis or HIV status.	Kumaravelu S et al. Tuber Lung Dis 1994 Chotmongkol V et al. J Med Assoc Thai 1996 Schoeman JF et al. Pediatrics 1997 Malhotra HS et al. Ann Trop Med Parasitol 2009 Thwaites GE et al. N Engl J Med 2004	Mortality Death or severe disability Relapse Adverse events

⁶ American Thoracic Society/United States Centers for Disease Control and Prevention/Infectious Diseases Society of America, the European Respiratory Society.

Appendix 3. Risk of bias assessment Donovan (2023)

Unique ID	Donovan et. al. 2023	Study ID	DOI:10.1056/NEJMoa2216218	Assessor	JT
Ref or Label		Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Adjunctive dexamethasone	Comparator	Placebo	Source	Journal article(s)
Outcome	Mortality	Results	HR 0.85	Weight	1
Domain	Signalling question		Response	Comments	
Bias arising from the randomization process	1.1 Was the allocation sequence random?		Y	Randomization computer-generated using randomly permuted blocks of 4 and 6. Randomization of participants performed using trained clinical staff, with 24-hour availability using Web-based software.	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y		
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N		
	Risk of bias judgement		Low		
Bias due to deviations from intended interventions	2.1. Were participants aware of their assigned intervention during the trial?		N		
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N		
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?		NA		
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA		
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA		
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y		
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA		

	Risk of bias judgement	Low	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Death of any cause - objective
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	Not specifically stated
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N	Death of any cause - objective
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Low	

South African National Department of Health

NATIONAL ESSENTIAL MEDICINES LIST COMMITTEE

DELAMANID – MDR/RR-TB

Medicine details

Medicine Class	No
Medicine/s name INN:	Delamanid
Medicine/s (ATC5):	J04AK06
Indication (ICD-10 code):	U50.0, U50.2, U50.20, U50.21, U50.5
SAHPRA Approved	Yes
Dosage form/s	Tablet
Route of administration/s	Oral
Patient population	Children, adolescents and adults (including pregnant or breastfeeding women) with multidrug-resistant/rifampicin-resistant tuberculosis (RR-MDR/RR-TB)
Prevalence and/or incidence of condition	In 2024, the estimated prevalence of MDR/RR-TB among TB cases in South Africa was 3.6% in new cases and 17% in previously treated cases. The estimated burden of MDR/RR-TB was 14,000 incident cases, corresponding to an incidence of 21 per 100,000 population per year. ¹
Level of Care	Primary Healthcare
Prescriber level	Doctor prescribed

Current Standard of Care

Delamanid is included in the National TB Programme guidelines for the management of MDR/RR-TB.¹ Delamanid, in combination with other anti-TB medicines, is used as part of individualised treatment regimens for MDR/RR-TB in children, adolescents, adults and pregnant or breastfeeding women not eligible for BPAL-L. Delamanid, in combination with other anti-TB medicines, is used as part of individualised rescue regimens for bedaquiline-resistant TB in children, adolescents, adults and pregnant or breastfeeding women.

Executive Summary

- Delamanid is included in the National TB Programme Guidelines and is used, in combination with other appropriate anti-TB medicines, as part of individualised or rescue regimens for children, adolescents, adults, and pregnant or breastfeeding women with MDR/RR-TB not eligible for BPAL-L or with bedaquiline-resistant TB.
- Delamanid has not been formally evaluated by the NEMLC. The development of updated Tuberculosis Standard Treatment Guidelines (STGs) in 2025/2026 required consideration of its inclusion in the Essential Medicines List (EML).
- Given the widespread programmatic use of delamanid in South Africa since 2019, it was not considered an efficient use of resources to undertake a full de novo evidence review to support inclusion in the EML. Instead, a limited review was conducted to evaluate current international guideline recommendations and supporting evidence for the use of delamanid in the treatment of MDR/RR-TB.

¹ World Health Organization. *Global tuberculosis report 2025*. Geneva: World Health Organization; 2025.

- The World Health Organisation (WHO) consolidated guidelines on tuberculosis, Module 4: Treatment and Care,^{2,3} which were considered to be of high-quality by AGREE-II assessment, and a recently published randomised control trial, the BEAT TB study, were reviewed.
- WHO Consolidated guideline recommendations relevant to delamanid include:
 - Recommendation 1.2. WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine (BDLLfxC) in MDR/RR-TB patients with or without fluoroquinolone resistance. (*Conditional recommendation, very low certainty of evidence*)
 - This recommendation applies to people with diagnosed pulmonary TB of all ages, including children, adolescents, PLHIV, and pregnant and breastfeeding women.
 - Recommendation 3.1. In MDR or RR-TB patients on longer regimens, all three Group A agents (refer table below), and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents (including delamanid) are added to complete it. (*Conditional recommendation, very low certainty of evidence*).
 - Recommendation 3.8. Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens. (*Conditional recommendation, moderate certainty of evidence*). In children with MDR/RR-TB aged below 3 years delamanid may be used as part of longer regimens. (*Conditional recommendation, very low certainty of evidence*)
 - Although the WHO recommendations are conditional and based on very low to moderate certainty evidence, they reflect the limited treatment options available for drug-resistant TB and the need to maximise the number of likely effective medicines in an individualised regimen.
- The BEAT Tuberculosis trial, which enrolled pregnant and breastfeeding women and children ≥ 6 years, showed that the efficacy of the 6- month bedaquiline, linezolid, delamanid, clofazimine and/or levofloxacin regimen was non-inferior to a 9-month or longer regimen to treat RR-TB, including fluoroquinolone-resistant TB. Safety outcomes were also similar.
 - Of the 170 female participants (42.2%), 9 (5.3%) were pregnant at baseline: one was in the first trimester, six were in the second trimester, and two were in the third trimester. One participant became pregnant during the trial. All pregnancies resulted in singleton live births, with one premature delivery. Among the pregnant participants, two serious adverse events occurred which were not related to treatment. One pregnant participant in the trial-strategy group had a recurrence of tuberculosis disease.
 - Thirty participants (7.4%) were 8 to 17 years of age. All participants younger than 18 years of age had a successful outcome at the end of treatment and the end of follow-up. Delamanid was discontinued in one child because of neuropsychiatric adverse reactions.
 - The BEAT Tuberculosis provides evidence for a shorter treatment option of comparable duration to BPAL-L for these vulnerable populations.
- Inclusion of delamanid on the Essential Medicines List aligns with current evidence-based WHO recommendations and will ensure availability of an important treatment option for patients requiring individualised management of drug-resistant tuberculosis.

Key Recommendations

Type of ERC recommendation	We recommend against the option and for the alternative (strong)		We suggest not to use the option or to use the alternative (conditional)		We suggest using the option (conditional)		We recommend the option (strong)	
	☐		☐		X		☐	
High level summary of conclusions	It is recommended that delamanid be included on the EML for people with DR-TB requiring individualised treatment regimens, including in children, adolescents, adults and pregnant or breastfeeding women.							
NEMLC Ratification	Date		Comments/Recommendation					
EML Status	EML		Non-EML – contingent on stated reference price threshold in Rand Value			Non-EML		
	X		☐			☐		
Therapeutic Interchange Considerations (if applicable)*	If YES:	Alternative medicine/s name (INN)	Alternative/s SAHPRA registered?	Formulation/s		Equipotent dose/ Dose range and dosing interval		If NO, tick box
								X
Trigger for review	New evidence for safety or efficacy							

REVIEW TEAM

Review contributors as detailed below:

Name & Affiliation	Declaration of Interests	Defining the PICO	Protocol development	Literature search	Study selection	Data extraction & characteristics of	Quality appraisal	Data analysis	GRADE assessment	Write up and referencing	Clinical Expertise &	Quality assurance
Jessica Taylor	None to declare	n/a	n/a	n/a	X	n/a	n/a	n/a	n/a	X	X	X
Zahiera Adam	None to declare	n/a	n/a	n/a	X	n/a	n/a	n/a	n/a	X		X
Jane Riddin	None to declare	n/a	n/a	n/a	X	n/a	n/a	n/a	n/a	X		X

Background and rationale

Delamanid is a first-in-class bicyclic nitroimidazole that was first approved by the European Medicines Agency in 2014. In 2019, the South African Health Products Regulatory Authority (SAHPRA) registered delamanid for use, in combination with other anti-tuberculosis medicines, for the treatment of adults with pulmonary multidrug-resistant tuberculosis (MDR-TB) when an effective treatment regimen cannot be constructed because of drug resistance or intolerance. Since then, delamanid has been included in various treatment regimens recommended by the South African National Tuberculosis Programme. Delamanid is listed on the Master Health Product List as a non-EML medicine and is available for procurement in the public sector. It has not previously undergone formal evaluation by the National Essential Medicines List Committee (NEMLC) for inclusion in the National Essential Medicines List (EML). Current South African programmatic guidelines for the management of RR-TB recommend delamanid in combination with other anti-TB medicines, as part of individualised treatment regimens for people with RR-TB not eligible for a 6-month BPaL-L² regimen. People not eligible for BPaL-L include pregnant women, children and adolescents < 15 years, and adults with severe extrapulmonary DR-TB. In addition, individualised regimens containing delamanid may be required by some adults with limited treatment options due to drug resistance, such as bedaquiline-resistance, or toxicity.

In 2025/2026, the development of dedicated tuberculosis chapters for the Primary Healthcare, Adult Hospital, as well as update of the Paediatric Hospital Standard Treatment Guidelines (STGs) was undertaken. The objective was to update treatment recommendations and ensure alignment, as far as possible, with national tuberculosis programme guidance. This process necessitated consideration of the inclusion of delamanid in the EML for the management of drug-resistant tuberculosis. Given the widespread programmatic use of delamanid in South Africa since 2019, it was not considered an efficient use of resources to undertake a full de novo evidence review to support inclusion in the EML. Instead, this limited review was conducted to evaluate current international guideline recommendations and the supporting evidence for the use of delamanid in the treatment of drug-resistant tuberculosis.

Methods

1. Data Sources

The World Health Organization (WHO) consolidated guidelines for the treatment of tuberculosis were identified and recommendations relevant to delamanid were extracted. Additionally, the recently published BEAT TB study (Conradie et.al. 2026) was identified.⁴

Results

Description of included studies

1.1. Clinical Practice Guidelines

- World Health Organization: Consolidated Guidelines on Tuberculosis:
 - WHO 2025. Consolidated Guidelines on Tuberculosis: Module 4: Treatment – Drug-resistant tuberculosis treatment.
 - This guideline was appraised as being of high quality using the AGREE II tool (overall quality of this guideline score of 6)

²A 6-month regimen of bedaquiline, linezolid, pretomanid with or without levofloxacin.

Domain	
Scope and purpose	21 (100%)
Stakeholder involvement	17 (77.8%)
Rigour of development	49 (85.4%)
Clarity of presentation	17 (77.8%)
Applicability	23(79.2%)
Editorial Independence	12 (83.3%)

1.2. RCTs

Conradie et.al. 2026⁴

Study ID	Country	Type of study	Primary outcome	Study Duration	Intervention	Comparison	Age Median (IQR)	Sample Size
Conradie, et.al. 2026	South Africa: Durban Gqeberha	Phase 3, open-label, pragmatic, randomised, controlled non-inferiority trial.	The primary efficacy end point was a successful outcome (cure or completion of treatment) at the end of treatment and 76 weeks after randomisation. The primary safety end point was adverse events of grade 3 or higher.	76 weeks	Bedaquiline, linezolid, delamanid, and levofloxacin OR clofazimine OR both for 6 months.	9-month South African standard-of-care treatment for rifampicin-resistant tuberculosis*	35 (28.0 – 43.0) < 18 years: 30 (7.4%)	Intervention: 203 Control: 200 61% susceptible to fluoroquinolones

*At study start and throughout, the South African standard treatment for RR-TB was a 9-month, all-oral regimen consisting of bedaquiline (used for 6 months), linezolid (used for first 2 months), levofloxacin, ethambutol, high-dose isoniazid (for 4 months, extended to 6 months if the patient remains sputum smear positive at the end of 4 months), pyrazinamide and clofazimine, followed by treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide (for 5 months). If fluoroquinolone resistance was diagnosed, then an 18-month regimen of bedaquiline, linezolid, clofazimine, terizidone and delamanid was given.

Effectiveness and/or safety

WHO Consolidated guidelines on Tuberculosis: Module 4: Treatment. Guideline Recommendations:

RECOMMENDATION	ADDITIONAL COMMENTS
Recommendation 1.2. WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine (BDLLfxC) in MDR/RR-TB patients with or without fluoroquinolone resistance. <i>(Conditional recommendation, very low certainty of evidence)</i>	- Drug susceptibility testing (DST) for fluoroquinolones is strongly encouraged in people with MDR/RR-TB. Although it should not delay the initiation of the BDLLfxC, the test results should guide the decision on whether levofloxacin or clofazimine should be retained. - This recommendation applies to the following: - People with MDR/RR-TB or pre-XDR-TB (i.e. MDR/RR-TB and resistance to fluoroquinolones). - Patients with less than 1 month of previous exposure to bedaquiline, linezolid, delamanid or clofazimine. When exposure is greater than 1 month, these patients may still receive the regimen if resistance to

	the specific medicines involved in such exposure has been ruled out. ○ People with diagnosed pulmonary TB of <u>all ages, including children, adolescents, PLHIV, and pregnant and breastfeeding women.</u> ○ People with all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular TB, or disseminated forms of TB with multiorgan involvement. ○ Children and adolescents who do not have bacteriological confirmation of TB or resistance patterns but who do have a high likelihood of MDR/RR-TB (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB). ● When resistance to fluoroquinolones is unknown, the regimen should be started as BDLLfxC and then adjusted based on the DST results. In cases of quinolone susceptibility, clofazimine should be dropped and the regimen started or continued as bedaquiline, delamanid, linezolid and levofloxacin (BDLLfx). In cases of resistance to fluoroquinolones, levofloxacin should be dropped and the regimen started or continued as bedaquiline, delamanid, linezolid and clofazimine (BDLC). The rationale for this recommendation is based on the evidence and considerations described in detail in the following two subsections. Data from an RCT (BEAT Tuberculosis trial: NCT04062201) showed that the efficacy and safety of the BDLLfxC regimen was similar to that of the control arm regimen (WHO-recommended 9-month or longer regimens), and offers advantages based on its shorter duration and lower pill burden than the comparators. It was judged that implementing this regimen was probably feasible and acceptable, with equity probably improved, and that implementing this regimen was probably suitable for most population groups, including pregnant and breastfeeding women, children and PLHIV.
Recommendation 3.1. In MDR or RR-TB patients on longer regimens, all three Group A agents (refer table), and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of treatment if bedaquiline is stopped. If only	Group A: fluoroquinolones (levofloxacin and moxifloxacin), bedaquiline and linezolid were considered highly effective and strongly recommended for inclusion in all regimens unless contraindicated. Group B: clofazimine and cycloserine or terizidone were conditionally recommended as agents of second choice. Group C: included all other medicines that can be used when a regimen cannot be composed with Group A or

one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. <i>(Conditional recommendation, very low certainty of evidence).</i>	Group B agents. The medicines in Group C are ranked by the relative balance of benefit to harm usually expected of each. Anti-TB medicine grouping <table><thead><tr><th>Groups and steps</th><th>Medicine</th><th>Abbreviation</th></tr></thead><tbody><tr><td rowspan="4">Group A: Include all three medicines</td><td>Levofloxacin or moxifloxacin</td><td>Lfx Mfx</td></tr><tr><td>Bedaquiline^{b,c}</td><td>Bdq</td></tr><tr><td>Linezolid^d</td><td>Lzd</td></tr><tr><td></td><td></td></tr><tr><td rowspan="2">Group B: Add one or both medicines</td><td>Clofazimine</td><td>Cfz</td></tr><tr><td>Cycloserine or terizidone</td><td>Cs Trd</td></tr><tr><td rowspan="8">Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used</td><td>Ethambutol</td><td>E</td></tr><tr><td>Delamanid^e</td><td>Dlm</td></tr><tr><td>Pyrazinamide^f</td><td>Z</td></tr><tr><td>Imipenem–cilastatin or meropenem^g</td><td>Ipm–Cln Mpm</td></tr><tr><td>Amikacin (or streptomycin)^h</td><td>Am (S)</td></tr><tr><td>Ethionamide or prothionamideⁱ</td><td>Eto Pto</td></tr><tr><td>P-aminosalicylic acid^j</td><td>PAS</td></tr><tr><td></td><td></td></tr></tbody></table> Group A: fluoroquinolones (levofloxacin and moxifloxacin), bedaquiline and linezolid were considered highly effective and strongly recommended for inclusion in all regimens unless contraindicated. Group B: clofazimine and cycloserine or terizidone were conditionally recommended as agents of second choice. Group C: included all other medicines that can be used when a regimen cannot be composed with Group A or Group B agents. The medicines in Group C are ranked by the relative balance of benefit to harm usually expected of each.	Groups and steps	Medicine	Abbreviation	Group A: Include all three medicines	Levofloxacin or moxifloxacin	Lfx Mfx	Bedaquiline ^{b,c}	Bdq	Linezolid ^d	Lzd			Group B: Add one or both medicines	Clofazimine	Cfz	Cycloserine or terizidone	Cs Trd	Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E	Delamanid ^e	Dlm	Pyrazinamide ^f	Z	Imipenem–cilastatin or meropenem ^g	Ipm–Cln Mpm	Amikacin (or streptomycin) ^h	Am (S)	Ethionamide or prothionamide ⁱ	Eto Pto	P-aminosalicylic acid ^j	PAS		
Groups and steps	Medicine	Abbreviation																																	
Group A: Include all three medicines	Levofloxacin or moxifloxacin	Lfx Mfx																																	
	Bedaquiline ^{b,c}	Bdq																																	
	Linezolid ^d	Lzd																																	
Group B: Add one or both medicines	Clofazimine	Cfz																																	
	Cycloserine or terizidone	Cs Trd																																	
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E																																	
	Delamanid ^e	Dlm																																	
	Pyrazinamide ^f	Z																																	
	Imipenem–cilastatin or meropenem ^g	Ipm–Cln Mpm																																	
	Amikacin (or streptomycin) ^h	Am (S)																																	
	Ethionamide or prothionamide ⁱ	Eto Pto																																	
	P-aminosalicylic acid ^j	PAS																																	
Recommendation 3.8. Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens. <i>(Conditional recommendation, moderate certainty of evidence)</i> In children with MDR/RR-TB aged below 3 years delamanid may be used as part of longer regimens. <i>(Conditional recommendation, very low certainty of evidence)</i>	To answer the PICO question on the use of delamanid in children aged below 3 years, data were reviewed by the guideline development group 2021 from a Phase 1, open-label, age de-escalation trial designed to assess the pharmacokinetics, safety and tolerability of delamanid administered twice daily for 10 days in children with MDR/RR-TB on treatment with an optimized background regimen (protocol 242–12–232) and from the corresponding open-label extension study (protocol 242–12–233). Data from cohorts 1 (age 12–17 years), 2 (age 6–11 years), 3 (age 3–5 years) and 4 (age 0–2 years) for both protocols were reviewed. Exposures in the 0–2-year age group were lower than those of children aged 3 years and older, necessitating a modelling or simulation approach to dosing. No cardiac safety signals distinct from those reported in adults were observed in children aged 0–2 years. However, consideration of these																																		

	findings should take into account that children had lower drug exposures than adults. Pharmacodynamic simulations suggested that clinically meaningful changes in QT (i.e. prolongation) would be unlikely in children aged below 3 years, even if higher doses were used to reach drug exposures comparable to those achieved in adults. CNS effects (paraesthesia, tremors, anxiety, depression and insomnia) were included in the delamanid label for both adults and children as important potential safety concerns for the drug. In March 2021, the study sponsor released a statement of intent to modify the labelling to include hallucinations as an adverse reaction. This new safety signal has been more prevalent among children than adults, with 15 reports in 14 children aged 2 – 16 years in India, the Phillippines, South Africa, Tajikistan and Ukraine. Children experiencing this safety signal included some with extensively resistant forms of TB (MDR/XDR-TB) treated with delamanid under programmatic conditions (12 reports) and children enrolled in a clinical trial studying delamanid for TB prevention (3 reports). Seven of the 15 reports were for children also receiving cycloserine (under programmatic conditions). The guideline development group noted the importance of side-effects involving the CNS in young children, considering their dynamic brain development. In addition to data from the trials, data from a paediatric DR-TB individual participant data were analysed descriptively (24 231 records from all six WHO regions, the majority from India and South Africa). The search was conducted in April 2020. Just under 20 000 of these records were used for a matched analysis of treatment outcomes in children being treated for DR-TB. The paediatric DR-TB IPD included only seven children aged below 3 years treated with delamanid, 14 children aged 3–6 years and 69 children aged 6–12 years. All 21 children aged below 6 years were successfully treated. The number of children was insufficient for a matched analysis.
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The BEAT Tuberculosis trial³, a phase 3 open-label pragmatic randomised controlled non-inferiority trial in South Africa, assessed a 6-month treatment strategy for pulmonary RR-TB. Eligible participants had pulmonary tuberculosis with resistance to rifampicin with or without resistance to isoniazid or fluoroquinolones (or both). Children ≥ 6 years, and pregnant or breastfeeding women were eligible. Participants were randomly assigned to a regimen consisting of bedaquiline, linezolid, delamanid, and levofloxacin or clofazimine or both for 6 months (the trial strategy); or 9-months of South African standard of care at the time (control strategy). In the trial-strategy group, when the results of fluoroquinolone susceptibility testing were available either levofloxacin (if the results showed fluoroquinolone resistance) or clofazimine (if the results showed fluoroquinolone susceptibility) was discontinued. If the susceptibility results were available at the time of randomization, either levofloxacin or clofazimine was not initiated. At study start and throughout, the South African standard treatment for RR-TB was a 9-month, all-oral regimen consisting of bedaquiline (used for 6 months), linezolid (used for first 2 months), levofloxacin, ethambutol, high-dose isoniazid (for 4 months, extended to 6 months if the patient remains sputum smear positive at the end of 4 months), pyrazinamide and clofazimine, followed by treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide (for 5 months). If fluoroquinolone resistance was diagnosed in the control strategy arm, then an 18-month regimen of bedaquiline, linezolid, clofazimine, terizidone and delamanid was given. The primary efficacy outcome was successful treatment outcome (cure or completion of treatment) at the end of treatment and at 76 weeks after randomisation. Cure was defined as adequate treatment adherence ($\geq 80\%$ of doses taken) and two negative sputum specimens obtained before the end of treatment, at least 14 days apart. Completion of treatment was defined as adequate adherence without evidence of treatment failure (defined as lack of sputum culture conversion, bacteriologic reversion, or substitution of two or more drugs because of adverse effects) but no record of two or more consecutive negative sputum specimens obtained at least 14 days apart. The primary safety endpoint was an adverse event of grade 3 or higher. The composite efficacy-safety end point was a successful outcome at end of follow-up and no adverse events of grade 3 or higher during treatment. The primary efficacy analysis was performed in the intention-to-treat population. For the primary analysis, the between group difference (risk difference) in the percentage of participants who met criteria for the primary end point (a successful outcome) at the end of treatment and at 76 weeks after randomisation was compared. Non-inferiority was determined if the upper boundary of the 95% confidence interval for the risk difference was less than 10 percentage points. A total sample size of 400 patients would provide 87.3% power to show non-inferiority assuming a proportion cure of 0.60 in the control strategy and 0.65 in the study strategy (an absolute increase of 0.05) or 89.4% assuming a proportion cure of 0.65 in the control strategy and 0.7 in the study strategy. Between August 2019 and October 2022, 403 participants were randomised. The median age was 35 years, and 30 participants (7.4%) were 8 to 17 years of age. A total of 205 participants (50.9%) were PLHIV, with a median CD4 count of 194 cells/mm³.

Outcome – Successful outcome (Cure or completion of treatment):

Successful outcome at the end of treatment and at 76 weeks: 86.1% (174 of 202) in trial-strategy group, and 86% (172 of 200) in control group; adjusted risk difference: -0.2 percent points 95% CI -6.9 to 6.5; $p=0.001$ for non-inferiority.

Treatment effects did not appear to vary by age, sex, HIV status, status of sputum smear at baseline (positive vs. negative), presence of cavities on chest radiography, or fluoroquinolone resistance although the trial was not powered to rule out differences across subgroups. All participants younger than 18 years of age had a successful

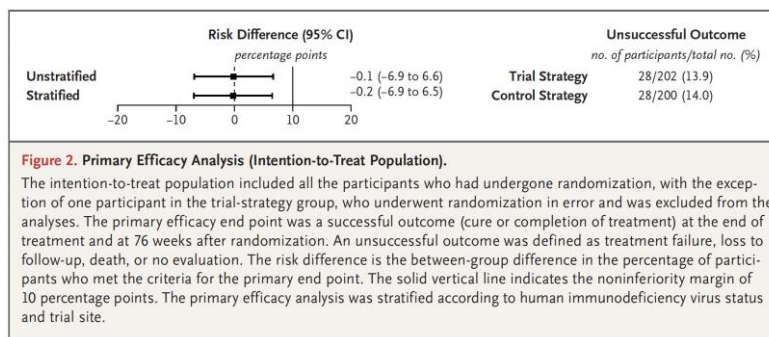
³ Conradie F, Badat T, Poswa A, Rajaram S, Kooverjee S, et.al. A Pragmatic Trial of a 6-month strategy for rifampicin-resistant tuberculosis. NEJM. 2026; 394: 2429-2439.

outcome at the end of treatment and the end of follow-up. One pregnant participant in the trial-strategy group had a recurrence of tuberculosis disease.

Table 2. Primary Efficacy Analysis (Intention-to-Treat Population).*

Variable	Trial Strategy (N = 202)	Control Strategy (N = 200)	Total (N = 402)
	<i>number (percent)</i>		
Primary end point: successful outcome at end of treatment and at end of follow-up	174 (86.1)	172 (86.0)	346 (86.1)
Cure at end of treatment and at end of follow-up	160 (79.2)	162 (81.0)	322 (80.1)
Cure at end of treatment and negative culture at last visit	14 (6.9)	10 (5.0)	24 (6.0)
Unsuccessful outcome at end of treatment	14 (6.9)	22 (11.0)	36 (9.0)
Treatment failure	7 (3.5)	10 (5.0)	17 (4.2)
Lost to follow-up during treatment	2 (1.0)	4 (2.0)	6 (1.5)
Died during treatment	4 (2.0)	7 (3.5)	11 (2.7)
Not evaluated because of withdrawn consent	1 (0.5)	1 (0.5)	2 (0.5)
Unsuccessful outcome at end of follow-up	14 (6.9)	6 (3.0)	20 (5.0)
Recurrence after cure at end of treatment	10 (5.0)	4 (2.0)	14 (3.5)
Died after cure at end of treatment	4 (2.0)	2 (1.0)	6 (1.5)

* The intention-to-treat population included all the participants who had undergone randomization, with the exception of one participant in the trial-strategy group, who underwent randomization in error and was excluded from the analyses. Participants were followed for 76 weeks after randomization. A successful outcome was defined as cure or completion of treatment. An unsuccessful outcome was defined as treatment failure (lack of sputum culture conversion, bacteriologic reversion, or substitution of two or more drugs because of adverse effects), loss to follow-up, death, or no evaluation.



Outcome – Adverse events:

Adverse events (grade 3 or higher) that occurred during treatment: 31.2% (63 of 202) in trial-strategy group and 37% (74 of 200) in control group. Among the pregnant participants, two serious adverse events occurred which were not related to treatment. Delamanid was discontinued in one child because of neuropsychiatric adverse reactions.

Table 3. Safety (Safety Population).^a

Adverse Event	Trial Strategy (N = 202)	Control Strategy (N = 200)	Total (N = 402)	Risk Difference (95% CI) [†]
Grade ≥3 event	69 (34.2)	76 (38.0)	145 (36.1)	3.8 (-5.5 to 13.2)
Grade ≥3 event during treatment	63 (31.2)	74 (37.0)	137 (34.1)	5.8 (-3.4 to 15.1)
Treatment-related grade ≥3 event [‡]	52 (25.7)	56 (28.0)	108 (26.9)	2.3 (-6.4 to 10.9)
Serious adverse event at any time	45 (22.3)	44 (22.0)	89 (22.1)	-0.3 (-8.4 to 7.8)
Serious adverse event during treatment	38 (18.8)	42 (21.0)	80 (19.9)	2.2 (-5.6 to 10.0)
Notable event [§]	36 (17.8)	31 (15.5)	67 (16.7)	-2.3 (-9.6 to 5.0)
Death at any time	10 (5.0)	10 (5.0)	20 (5.0)	0.0 (-4.2 to 4.3)
Death during treatment	6 (3.0)	8 (4.0)	14 (3.5)	1.0 (-2.6 to 4.6)
Death after treatment	4 (2.0)	2 (1.0)	6 (1.5)	-1.0 (-3.3 to 1.4)
Anemia leading to treatment discontinuation	10 (5.0)	8 (4.0)	18 (4.5)	-1.0 (-5.0 to 3.1)
Anemia leading to blood transfusion	20 (9.9)	11 (5.5)	31 (7.7)	-4.4 (-9.6 to 0.8)
Grade ≥3 liver abnormality	4 (2.0)	9 (4.5)	13 (3.2)	2.5 (-0.9 to 6.0)
Peripheral neuropathy leading to treatment discontinuation	10 (5.0)	7 (3.5)	17 (4.2)	-1.5 (-5.4 to 2.5)
Optic neuropathy leading to treatment discontinuation	7 (3.5)	2 (1.0)	9 (2.2)	-2.5 (-5.3 to 0.4)
QTcF ≥480 msec	12 (5.9)	19 (9.5)	31 (7.7)	3.6 (-1.7 to 8.8)
QTcF ≥500 msec	5 (2.5)	7 (3.5)	12 (3.0)	1.0 (-2.3 to 4.4)
Treatment-related serious adverse events [‡]				
Related to linezolid	20 (9.9)	16 (8.0)	36 (9.0)	-1.9 (-7.5 to 3.7)
Related to bedaquiline	4 (2.0)	7 (3.5)	11 (2.7)	1.5 (-1.7 to 4.7)
Related to levofloxacin	3 (1.5)	4 (2.0)	7 (1.7)	0.5 (-2.0 to 3.1)
Related to clofazimine	6 (3.0)	7 (3.5)	13 (3.2)	0.5 (-2.9 to 4.0)
Related to delamanid	2 (1.0)	2 (1.0)	4 (1.0)	0.0 (-1.9 to 2.0)

^a The safety population included all the participants who had undergone randomization and received at least one dose of the assigned treatment. QTcF denotes corrected QT interval calculated with the use of Fridericia's formula.

[†] The risk difference is the difference in percentage points.

[‡] Included are events that were at least possibly related to treatment.

[§] Notable events included grade 3 or 4 cardiotoxic effects, increase in aspartate aminotransferase or alanine aminotransferase level, pregnancy, and peripheral neuropathy.

Outcomes – pregnancy outcomes

Of the 170 female participants (42.2%), 9 (5.3%) were pregnant at baseline: one was in the first trimester, six were in the second trimester, and two were in the third trimester. One participant became pregnant during the trial. All pregnancies resulted in singleton live births, with one premature delivery.

Costs

Delamanid is currently procured as a non-EML medicine for use in the public sector.

Product	Brand As Per Contract	Supplier Name	Price*
Delamanid; 50mg; Tablet; 48 Tablets	DELTIBA	Viatrix Healthcare (Pty) Ltd	R1498.4

MHPL (Jul 2026)

As delamanid is already being used for select MDR/RR-TB regimens in the public sector in accordance with the National RR-TB guideline, we do not anticipate any incremental budget impact through its listing on the EML.

Discussion and Conclusion

Current South African National TB programme guidelines for the management of RR-TB recommend delamanid, in combination with other appropriate anti-TB medicines, as part of individualised or rescue regimens for children, adolescents, adults, and pregnant or breastfeeding women with MDR/RR-TB not eligible for BPAL-L, or when drug resistance or toxicity, necessitate an individualised approach.

The WHO classifies delamanid as a Group C medicine and recommend using it to construct effective longer individualised MDR/RR-TB regimens when Group A and Group B medicines are insufficient due to resistance or toxicity. Although the WHO recommendations are conditional and based on very low to moderate certainty

evidence, they reflect the limited treatment options available for drug-resistant TB and the need to maximise the number of likely effective medicines in an individualised regimen.

The recently published BEAT-Tuberculosis trial provides additional evidence supporting the inclusion of delamanid in a shorter, all-oral regimen for RR-TB. Importantly, the trial enrolled patient groups who are not eligible for the current South African standard-of-care BPAL-L regimen, including pregnant and breastfeeding women and children under 15 years of age, thereby providing evidence for a shorter treatment option of comparable duration to BPAL-L for these vulnerable populations.

Inclusion of delamanid on the Essential Medicines List aligns with current evidence-based WHO recommendations and will ensure availability of an important treatment option for patients requiring individualised management of drug-resistant tuberculosis.

References

¹ National Department of Health. Management of Rifampicin-Resistant Tuberculosis. November 2023. <https://www.health.gov.za/wp-content/uploads/2023/10/Updated-RR-TB-Clinical-Guidelines-September-2023.pdf>

² The World Health Organization (WHO) Consolidated Guidelines on Tuberculosis: Module 4: Treatment – Drug-resistant tuberculosis treatment (2022). <https://iris.who.int/server/api/core/bitstreams/b4112461-7e9c-403c-808f-055f1dc3a54b/content>

³ The World Health Organization (WHO) Consolidated Guidelines on Tuberculosis: Module 5 – Management of tuberculosis in children and adolescents (2022). <https://iris.who.int/server/api/core/bitstreams/6212d328-f45e-4905-ae32-e0161d4f0029/content>

⁴ Conradie F, Badat T, Poswa A, Rajaram S, Kooverjee S, et.al. A Pragmatic Trial of a 6-month strategy for rifampicin-resistant tuberculosis. NEJM. 2026; 394: 2429-2439.

South African National Department of Health

HISTORICALLY ACCEPTED USE REVIEW: Para-aminosalicylic acid (PAS)

Executive Summary

Date: July 2026

Medicine(s) (INN): Para-aminosalicylic acid (PAS) (4-aminosalicylic acid)

Medicine(s) (ATC): J04AA01

Indication/s (ICD10 code/s): Drug-resistant TB (DR-TB) (U50, U50.9, U50.91)

Patient population/s: Children and adults with DR-TB with limited treatment options requiring individualised and/or rescue regimens.

Prevalence of condition/s:

Level of Care: individualised regimens as advised by the National clinical advisory committee (NCAC), then down referred to PHC for ongoing care

Prescriber Level: Doctor initiated

Current Standard(s) of Care: PAS is included in the NDoH TB guidelines for use in individualised DR-TB regimens when other medicines are unlikely to be effective because of resistance and/or are not tolerated.

Background:

The Tuberculosis (TB) Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) are being updated, with a focus to align with the National Department of Health (NDoH) TB Guidelines and Recommendations.

Para-aminosalicylic acid (PAS) is included in the National Department of Health Clinical Management of Rifampicin-Resistant Tuberculosis – updated Clinical Reference Guide (2023).¹ PAS is classified as a Group C medication by the World Health organisation². The Group C medications are medications added to complete individualised DR-TB regimens, where medicines from Group A and B cannot be used because they are unlikely to be effective because of resistance and/or are not tolerated.

Group A	Levofloxacin or moxifloxacin
	Bedaquiline
	Linezolid
Group B	Clofazimine
	Cycloserine or terizidone
Group C	Ethambutol
	Delamanid
	Pyrazinamide
	Imipenem-cilastatin or meropenem
	Amikacin (or streptomycin)
	Ethionamide or prothionamide
	P-aminosalicylic acid

PAS has historically been used in the management of TB since the 1940s.³ PAS is listed on the Current Master Health Product list as non-EML, although it has never been considered for EML inclusion.

Methods:

The WHO Drug-Resistant TB (DR-TB) Guidelines will be evaluated to understand the evidence supporting the use of PAS in individualised DR-TB regimens.

Summary of Evidence:

Specific indications for PAS have been included in WHO TB guidelines for management of DR-TB since 1997.⁴

Clinical Practice Guideline (CPG) recommendations:

Guideline	Recommendations	AGREE II assessment
World Health Organisation: Consolidated Guidelines on Tuberculosis. Module 4: Treatment and Care - 2025	Recommendation 3.1. In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. <i>(Conditional recommendation, very low certainty of evidence)</i>	97% <i>See annexure 1</i>
	Recommendation 3.13. P-aminosalicylic acid may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. <i>(Conditional recommendation against use, very low certainty of evidence)</i> <i>This recommendation has been in place since 2019</i> <i>(PAS showed effectiveness only in regimens without bedaquiline, linezolid, clofazimine or delamanid, and are thus proposed only when other options to compose a regimen are not possible)</i>	

Historically accepted use Criteria

SECTION A		
	Criteria	Comment
1	The medicine is included in the World Health Organization (WHO) Model Essential Medicines List, either as a core or complementary item, for the indication requested.	YES NO ☒ X ☐
2	The medicine is currently registered by South African Health Products Regulatory Authority (SAHPRA).	YES NO ☒ X ☐

3	A documented rapid literature review identified no new safety concerns or new evidence of lack of efficacy.	YES NO X <i>PAS is associated with <u>known</u> higher incidence of adverse reactions. Data from the Individual Patient Data Meta-Analysis (iPD) found that 12.2% of patients had adverse effects attributed to PAS.⁵</i> Use of PAS remains limited to exceptional individualised regimens where safer alternatives are not clinically appropriate.
4	The anticipated costs and usage are not likely to result in a substantial impact on the budget.	YES NO X <i>Comment:</i> <i>PAS 4g sachets (30s); R1250*</i> <i>*MHPL July 2026</i> Para-aminosalicylic acid (PAS) is included in the National Department of Health Clinical Management of Rifampicin-Resistant Tuberculosis – updated Clinical Reference Guide (2023)⁶ and already being used to manage patients with DR-TB and limited treatment options requiring individualised regimens. We therefore do not anticipate any incremental budget impact.
SECTION B		
1	There is evidence prior to 2007* of safety and efficacy for the recognised indication (a systematic review/meta-analysis, or at least one critically appraised controlled trial.) <i>Information after 2007 would need to be subject to standard review processes for a new inclusion.</i>	YES NO X <i>See above: Used to treat TB since 1940s.</i>
OR		
2	It is included as part of standard of care in a critically appraised clinical practice guideline (CPGs) of adequate quality, for the particular indication.	YES NO X <i>See above: CPG recommendations</i>
AND		
3	It is currently use in practice for this indication.	YES NO X <i>Comment:</i> Para-aminosalicylic acid (PAS) is included in the National Department of Health Clinical Management of Rifampicin-Resistant Tuberculosis – updated Clinical Reference Guide (2023)

Modified Evidence to Decision Framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF BENEFIT	What is the size of the effect for beneficial outcomes? Large ☐ Moderate ☐ Small ☒ None ☐	
EVIDENCE OF HARMS	What is the size of the effect for harmful outcomes? Large ☐ Moderate ☒ Small ☐ None ☐	PAS is associated with known higher incidence of adverse reactions. Data from the Individual Patient Data Meta-Analysis (iIPD) found that 12.2% of patients had adverse effects attributed to PAS. ⁵
QUALITY OF EVIDENCE	What is the certainty/quality of evidence? High ☐ Moderate ☐ Low ☐ Very low ☒ <i>High quality:</i> confident in the evidence <i>Moderate quality:</i> mostly confident, but further research may change the effect <i>Low quality:</i> some confidence, further research likely to change the effect <i>Very low quality:</i> findings indicate uncertain effect	Limited evidence in the DR-TB setting
BENEFITS & HARMS	Do the desirable effects outweigh the undesirable harms? Favours intervention ☒ Favours control ☐ Intervention = Control <i>or</i> Uncertain ☒	PAS showed effectiveness only in regimens without bedaquiline, linezolid, clofazimine or delamanid, and is thus proposed only when better options to compose a regimen are not possible. In these situations, desirable effects outweigh the undesirable harm.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes ☐ No ☒	
FEASIBILITY	Is implementation of this recommendation feasible? Yes ☒ No ☐ Uncertain ☐	Currently being used for individualised regimens only.
RESOURCE USE	How large are the resource requirements? More intensive ☐ Less intensive ☐ No impact ☒	Currently being used for individualised regimens only.. No incremental budget impact is anticipated.

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
VALUES, PREFERENCES, ACCEPTABILITY	Is there important uncertainty or variability about how much people value the options? Minor ☐ Major ☐ Uncertain ☒ Is the option acceptable to key stakeholders? Yes ☒ No ☐ Uncertain ☐	Request from TB programme to list PAS in STGs to improve access. PAS is already being used for individualised regimens only by the local TB programme.
	Would there be an impact on health inequity? Yes ☒ No ☐ Uncertain ☐	Formally updating the EML status in line with National TB guidelines will aid in facilitating equitable access.

RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative (strong)	We suggest not to use the option (conditional)	We suggest using either the option or the alternative (conditional)	We suggest using the option (conditional)	We recommend the option (strong)
				X	
Recommendation: It is recommended that para-aminosalicylic acid be included on the EML to complete individualised DR-TB regimens, where medicines from Group A and B cannot be used because they are unlikely to be effective due to resistance and/or are not tolerated. Rationale: Para-aminosalicylic acid (PAS) is included in the National Department of Health Clinical Management of Rifampicin-Resistant Tuberculosis – updated Clinical Reference Guide (2023)⁷, recommended by the WHO, and already being used to manage patients with DR-TB and limited treatment options. Use is limited to individualised DR-TB regimens where other EML alternatives are not clinically appropriate. Level of Evidence: Very low certainty evidence Review indicator: New efficacy or safety data					
NEMLC RECOMMENDATION: NEMLC recommended the inclusion of PAS on the EML to complete individualised DR-TB regimens, where medicines from Group A and B cannot be used because they are unlikely to be effective due to resistance and/or are not tolerated.					
Monitoring and evaluation considerations:					
Research priorities:					

Annexure 1:

• World Health Organisation: Consolidated Guidelines on Tuberculosis. Module 4: Treatment and Care - 2025²

		Appraiser 1	Rationale	Domain total	Domain score
Scope & Purpose	Q1	7	Objectives clearly stated.	21	100%
	Q2	7	Clinical questions defined using PICO.		
	Q3	7	Target population clearly described.		
Stakeholder Involvement	Q4	7	Multidisciplinary GDG.	20	94%
	Q5	6	Patient values considered; direct involvement less explicit.		
	Q6	7	Target users identified.		
Rigour of Development	Q7	7	Systematic searches described.	55	98%
	Q8	7	Selection criteria predefined.		
	Q9	7	GRADE used to assess certainty.		
	Q10	7	EtD framework used.		
	Q11	7	Benefits and harms balanced.		
	Q12	7	Recommendations linked to evidence.		
	Q13	7	External review documented.		
	Q14	6	Updating described but interval not explicit.		
Clarity of Presentation	Q15	7	Recommendations specific.	21	100%
	Q16	7	Management options presented.		
	Q17	7	Key recommendations identifiable.		
Applicability	Q18	6	Implementation barriers partly addressed.	26	92%
	Q19	7	Implementation tools provided.		
	Q20	7	Resource implications considered.		
	Q21	6	Monitoring guidance limited in core guideline.		
Editorial Independence	Q22	7	Funding independent.	14	100%
	Q23	7	Conflicts managed transparently.		
Overall Assessment					97%

References

¹ National Department of Health. Clinical Management of Rifampicin-Resistant Tuberculosis: Updated Clinical Reference Guide. September 2023. <https://www.health.gov.za/wp-content/uploads/2023/10/Updated-RR-TB-Clinical-Guidelines-September-2023.pdf>

² World Health Organization. WHO Consolidated Guidelines on Tuberculosis. Module 4: Treatment and Care. Updated 2025. <https://iris.who.int/server/api/core/bitstreams/f663f086-5d97-4355-beea-0635d47f1227/content>

³ Lehmann J. Para-aminosalicylic acid in the treatment of tuberculosis. *Lancet*. 1946, 1(6384):15.

⁴ Crofton J, Chaulet P, Maher D, et.al. Guidelines for the Management of Drug-Resistant Tuberculosis. World Health Organization. 1997. <https://iris.who.int/server/api/core/bitstreams/a0cb51ce-893e-425a-b62f-cadd522bd397/content>

⁵ Ahmad N, Ahuja SD, Akkerman OW, Alffenaar JC, Anderson LF, Baghaei P, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Lancet*. 2018;392(10150):821–834. doi:10.1016/S0140-6736(18)31644-1.

⁶ National Department of Health. Clinical Management of Rifampicin-Resistant Tuberculosis: Updated Clinical Reference Guide. September 2023. <https://www.health.gov.za/wp-content/uploads/2023/10/Updated-RR-TB-Clinical-Guidelines-September-2023.pdf>

⁷ National Department of Health. Clinical Management of Rifampicin-Resistant Tuberculosis: Updated Clinical Reference Guide. September 2023. <https://www.health.gov.za/wp-content/uploads/2023/10/Updated-RR-TB-Clinical-Guidelines-September-2023.pdf>