

PHC Chapter 23: Tuberculosis

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23.1 DRUG-SUSCEPTIBLE TUBERCULOSIS (DS-TB)

A15–A19

* 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 or failure to thrive, 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-NAATs 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 and children, a negative TB-NAAT is not an adequate 'rule out' test. Most children with TB disease will not have microbiological confirmation of TB, particularly children with severe or extrapulmonary disease. Negative TB-NAAT and culture results should be reviewed in the context of the history and clinical and radiological findings of the child. Treatment may be started if overall picture suggests TB, even if the TB-NAAT or culture is negative.

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 PLWH with signs and symptoms of pulmonary and/or extrapulmonary TB seen in an outpatient setting with:

- A CD4 $\leq$ 200 or $\leq$ 25% (if < 5 years) within the last 6 months **OR**
- Advanced HIV disease **OR**
- Current serious illness warranting admission to hospital.

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).

23.1.1 PERINATAL TUBERCULOSIS

P37.0

*Notifiable condition.

DESCRIPTION

Perinatal tuberculosis (TB) is defined as TB acquired either congenitally (in-utero or during birth), or postnatally within the first 3 months of life.

- » Congenital TB:
 - Transplacental transmission – usually due to maternal extrapulmonary or disseminated TB.
 - Via swallowed or aspirated maternal blood or amniotic fluid during labour or delivery – usually due to maternal extrapulmonary TB.
- » Postnatal TB:
 - Inhalation of the bacilli during the neonatal period from a close contact with infectious pulmonary TB (PTB) – usually the mother but also other household contacts or visitors.

An infant may be the first identified person with TB. If the mother has not been diagnosed with TB, she should be assessed for TB immediately.

History of Exposure

An infant has had significant exposure to a person with infectious TB if:

- » The infant was born to a mother with TB and the mother:
 - started TB treatment within 2 months before delivery **OR**
 - demonstrates poor clinical response to TB treatment **OR**
 - is TB smear or acid-fast bacilli (AFB) or culture positive at delivery **OR**
 - is diagnosed with TB soon after delivery.
- » The infant shared an enclosed space with an adult or adolescent with pulmonary TB for ≥ 1 night **OR** for frequent or extended daytime periods (e.g. at school or creche). 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.

Clinical Presentation

- » The clinical presentation may vary from asymptomatic or vague symptoms to severe acute or chronic illness.

- » Symptom onset in young infants is often acute over days. Infants with congenital TB may become symptomatic within the first days of life but typically become ill between 2 and 4 weeks of age. Some may be diagnosed as late as five months of age.
- » The signs of perinatal TB can be non-specific and include poor feeding, fever, lethargy, irritability, growth faltering.
- » Congenital TB often presents with acute respiratory distress, jaundice, hepatosplenomegaly, abdominal signs, poor feeding and failure to thrive and/or a clinical picture of “neonatal sepsis”.
- » Postnatal TB often presents with cough, tachypnoea, wheeze or stridor.
- » Given the high risk of TB disease, the non-specific clinical presentation of infants, and high morbidity and mortality, there should be a low threshold for rapid referral of unwell TB-exposed neonates and young infants.

MEDICINE TREATMENT

See Figure 23.1: Management of the newborn exposed to TB.

For infants with significant TB exposure, but no indication of active TB, see Section 23.3.1: Tuberculosis preventive therapy for drug-susceptible tuberculosis exposure for initiation of TPT by a medical officer at primary care level.

GENERAL MEASURES

- » All healthy newborns should receive BCG at discharge from the delivery unit regardless of HIV status or TB exposure status.
 - BCG is a live, attenuated *M.bovis* vaccine which is killed by anti-TB medicines.
 - If the baby starts TPT or TB treatment in the first 6 weeks of life, the BCG vaccine must be repeated one day after completion of TPT or TB treatment.
 - Babies with HIV should receive the repeat BCG dose after completion of TPT or TB treatment if they are on ART, clinically well, and have a CD4 > 25%.
- » Check HIV status of the mother and, if positive, test the infant for HIV with a HIV PCR.
- » Screen all other household contacts for TB.
- » Monitor the nutritional status of the neonate closely.

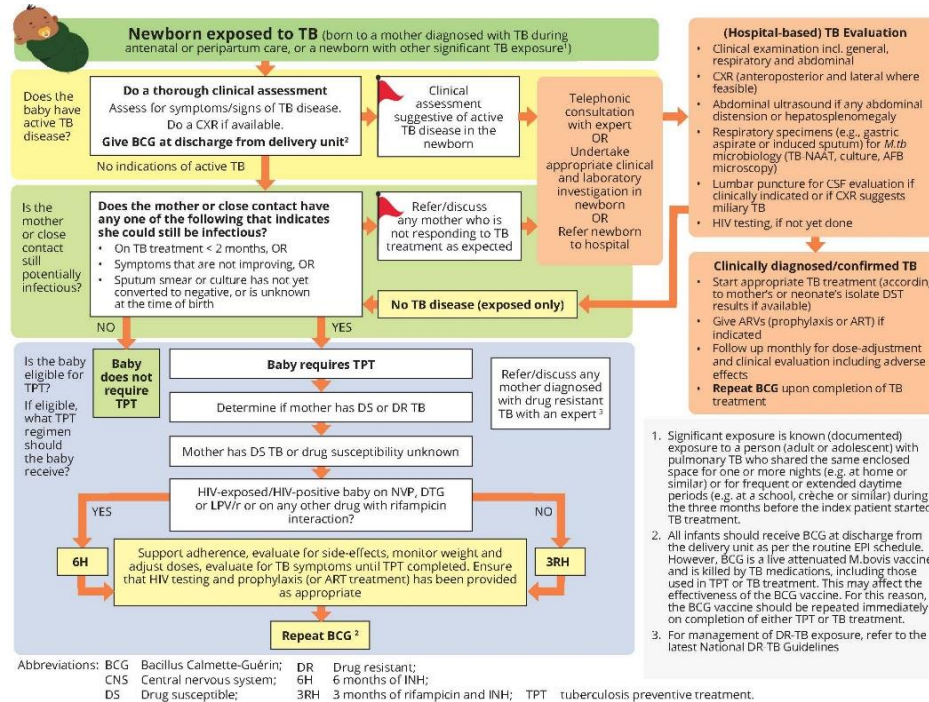


Figure 23.1: Management of the newborn exposed to TB

REFERRAL

- » All infants with a significant TB exposure with a clinical assessment suggestive of TB for hospital TB work-up.
- » All infants with significant TB exposure with no indication of active TB to a medical officer at primary care level for initiation of TPT (see Section 23.3.1 Tuberculosis Preventive Therapy for Drug-susceptible Tuberculosis Exposure).
- » Perinatal TB with a history of exposure to a person diagnosed with drug-resistant TB – discuss with an expert.

23.1.2 TUBERCULOSIS IN CHILDREN AND ADOLESCENTS <15 YEARS

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

DESCRIPTION

Tuberculosis (TB) is a chronic, granulomatous disease caused by *M. tuberculosis*.

Most children develop TB after inhalation of droplets containing *M. tuberculosis*, which have been coughed or exhaled by adults or adolescents with infectious pulmonary TB (e.g. the source patient). It is critical to identify the source patient with TB that the child was exposed to. Identify and screen all other child contacts of the source patient and offer TB preventive therapy (TPT) if appropriate.

Children < 2 years or living with HIV or severely malnourished may have few or atypical symptoms and are at high risk of rapid progression of TB disease with quick deterioration. Do not delay investigations for TB.

DIAGNOSIS

Signs and symptoms may include:

- » cough, acute (especially in infants or immunocompromised children) or persistent, unremitting cough for > 14 days that persists despite treatment;
- » loss of appetite;
- » unexplained weight loss or failure to thrive including insufficient weight gain and growth faltering;
- » lack of energy, child is less playful;
- » unexplained fever (> 38°C) for ≥ 2 weeks;
- » drenching night sweats that are excessive and soak the bed or clothes;
- » noisy breathing or wheeze which may be as a result of airway compression by lymph nodes;
- » lymphadenopathy (especially cervical and matted lymph nodes);
- » hepatosplenomegaly;

- » consolidation and pleural effusion on chest examination;
- » back pain, limp or difficulty walking, lower limb weakness, or spinal deformity.

Any child presenting with symptoms and signs suggestive of pulmonary TB is regarded as a case of TB if there is

- » A chest X-ray suggestive of TB: hilar or mediastinal adenopathy, with or without parenchymal opacification, and/or bronchopneumonia.

AND/OR

- » History of significant TB exposure **OR** positive tuberculin skin test (TST) e.g. Mantoux.
 - History of significant TB exposure. A child or adolescent is considered to have had a significant TB exposure if within the 12 months before presentation with presumed TB, they shared an enclosed space with an adult or adolescent with pulmonary TB for ≥ 1 night OR for frequent or extended daytime periods (e.g. at school or creche). 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.
 - Tuberculin skin test (TST), e.g. Mantoux:
 - A positive test: TST induration ≥ 10 mm or ≥ 5 mm in children living with HIV (CLHIV) or malnourished children.
 - A positive TST confirms a child has been infected with TB but does not differentiate between TB infection and TB disease.
 - A negative TST does not exclude TB infection or TB disease and a decision not to start TB treatment should not be based on a negative TST test.
 - A TST may be falsely negative in the presence of malnutrition, immunosuppression, e.g. HIV, steroid therapy, cancer chemotherapy, following overwhelming viral infection, e.g. measles or post vaccination. In these circumstances a TST induration ≥ 5 mm may be regarded as positive.
 - A TST provides no additional information in a child who is known to have a significant TB exposure.

Always collect sputum, induced sputum, gastric aspirates and/or nasopharyngeal aspirates for TB-NAAT and TB culture, or stool for GeneXpert. A positive TB-NAAT and/or culture on early morning gastric aspirate, expectorated sputum, induced sputum, nasopharyngeal aspirate and other clinical specimens confirms TB disease. A negative TB-NAAT or TB culture does not rule out TB disease, particularly in children with severe or extrapulmonary disease. Negative results should be reviewed in the context of the history and clinical and radiological findings. Treatment may be started if overall picture suggests TB, even if the TB-NAAT or culture is negative. If the child is not severely ill and there is uncertainty about diagnosis, especially if low risk (>2 years of age, not living with HIV, not

severely malnourished), consider treating the most likely non-TB condition, and follow-up in 1 - 2 weeks to reassess weight and symptoms. The parent/caregiver should be encouraged to return earlier if there is any deterioration of symptoms. This decision should consider the ability of the child to return for reassessment.

Determine HIV status for all children with presumed TB if the last test was negative or HIV status is unknown. Urine lipoarabinomannan (U-LAM) may also be used to diagnose TB disease in children or adolescents with HIV (CALHIV). Perform a U-LAM in symptomatic CALHIV seen in an outpatient setting with current serious illness requiring hospital admission or a CD4 count ≤ 200 or $\leq 25\%$ (if < 5 years) within the last 6 months or who have advanced HIV disease.

Refer to Management of Tuberculosis in Children and Adolescents. A Clinical Guideline for the Diagnosis and Treatment of Drug-susceptible TB in Children and Adolescents in South Africa. September 2024¹: ***TB Treatment Decision Algorithm (page 29)***

GENERAL MEASURES

- » When a child is diagnosed with any form of TB, the parents and other household members should be evaluated to identify undiagnosed TB.
- » Identify and screen all other child contacts of the source patient with TB and offer TB preventive therapy (TPT) if appropriate and only after TB disease is excluded.
- » Children with TB usually have paucibacillary disease and pose a low risk of infection to adults and other children.
- » However, children or adolescents who are sputum AFB smear-microscopy or TB-NAAT positive, or older children (≥ 8 years) and adolescents with adult-type pulmonary TB (e.g. cavities on chest X-ray) pose higher infection risk to others.
 - All contacts of these children with TB should be evaluated for TB symptoms, and where TB disease is excluded, TPT may be indicated.
- » Ensure that appropriate infection prevention and control measures are implemented at the facility with an adult, older child or adolescent with TB, including:
 - Adequate ventilation.
 - Isolation of older children, adolescents or adults with confirmed or suspected infectious pulmonary TB.
 - Use of personal respiratory protection by healthcare workers (e.g. respiratory masks).
- » Institute measures to prevent TB transmission in homes with an older child with TB:
 - 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.
- During the first two weeks of treatment when 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.
- » Monitor the nutritional status (e.g. measure and plot weight, height, mid-upper arm circumference) of the child at baseline and during follow-up to assess response to treatment and to adjust treatment dosing.
- » Energy needs increase in children with TB. Advise the caregiver on how to meet additional energy needs using food available at home. Refer for nutrition support.
- » At every visit ensure the caregiver can confidently crush, mix and give the correct volume of medicines themselves.
- » At every visit, monitor for any worsening or changes in signs and symptoms of TB that may necessitate further discussion or referral.
- » At every visit, monitor for adverse drug reactions.
- » Follow-up chest X-rays should not be performed routinely unless there is clinical deterioration or poor clinical response to TB treatment.
- » In children with good clinical response to treatment who cannot adequately expectorate, repeat sputum testing is rarely required.
- » Repeat sputum testing is required in children who are smear or culture positive at TB diagnosis. Monitor these children for smear or culture conversion, as in adults.
- » Repeat sputum testing is also required in children with clinical deterioration, or after new exposure to a source patient with drug-resistant TB.
- » TB-NAAT should not be used to monitor response to treatment.
- » Note the TB diagnosis, anthropometry, and outcome of each follow-up visit in the Road-to-Health booklet and treatment card.
- » Ensure vaccinations are up to date.

MEDICINE TREATMENT

Refer to Management of Tuberculosis in Children and Adolescents. A Clinical Guideline for the Diagnosis and Treatment of Drug-susceptible TB in Children and Adolescents in South Africa. September 2024¹

The specific TB treatment regimen is determined by drug susceptibility results for the child, as well as the person with TB that the child was in contact with (e.g. drug-susceptible TB, drug-resistant TB) and the site of TB disease. The duration of TB treatment is determined by the site of TB disease, disease severity at the start of therapy, and treatment response towards the end of

treatment. Disease severity is based on clinical, radiological, and microbiological features. In CALHIV, treatment duration is also determined by duration on ART and HIV viral load.

Children and adolescents with non-severe drug-susceptible PTB and drug-susceptible cervical TB lymphadenitis are treated with a shortened 4-month treatment regimen (2 months intensive phase and 2 months continuation phase), provided they adhere to therapy and respond appropriately. CALHIV who meet eligibility criteria based on ART and viral suppression are also eligible for a shortened 4-month regimen. See Table 23.1: Determining eligibility for shortened course DS-TB treatment regimen, below.

Children and adolescents with severe pulmonary disease, extrapulmonary disease (except isolated cervical TB lymphadenitis), miliary TB, and TB meningitis (TBM) have severe disease, and are **NOT** eligible for shortened regimens.

If unsure regarding which duration of therapy to provide, provide a longer therapy course.

Table 23.1: Eligibility for shortened course DS-TB treatment regimen.

DETERMINE ELIGIBILITY FOR SHORTENED COURSE DS-TB TREATMENT REGIMEN	
Work through steps 1-6 below to assess eligibility to start shortened course of DS-TB treatment:	
INCLUSION CRITERIA FOR SHORT-COURSE	EXCLUSION CRITERIA FOR SHORT-COURSE
STEP 1. AGE OF THE CHILD	
- If no CXR available: child between ages of 3 months to < 8 years - If CXR available: child between ages of 3 months and less than 15 years	- Child is under 3 months old - Child is aged 8 years or older & CXR is not available - Child is aged 15 years or older
STEP 2. SITE AND FEATURES OF DISEASE	
- PTB - Cervical lymphadenitis - Simple TB pleural effusion - First episode	- Extrapulmonary TB - Disseminated TB - Miliary TB - TB meningitis - TB bone or joint - Previous TB treatment
STEP 3. HIV STATUS	
- HIV negative - CLHIV on ART for at least 3 months AND VL < 1000 in the last 3 months	- Newly diagnosed HIV - On ART for < 3 months - Unsuppressed VL (VL ≥ 1000 in the last 3 months)
STEP 4. CLINICAL AND NUTRITIONAL STATUS	
Clinically well without severe acute malnutrition	- Any danger signs* - Severe acute malnutrition (weight-for-height Z-score (WHZ) < -3 OR mid upper arm circumference (MUAC) < 11.5 cm, or bilateral pitting oedema) - Asymmetric or persistent wheezing
STEP 5. RADIOLOGICAL SEVERITY (if x-ray available)	
- Uncomplicated hilar lymphadenopathy: with no airway obstruction/compression - Uncomplicated TB pleural effusion - Consolidation/opacification: < 1 lobe involved - No cavities - No miliary pattern	- Complicated hilar lymphadenopathy: i.e., airway obstruction/ compression, deviation and/or hyperinflation or collapse. - Complicated TB pleural effusion: i.e., loculated effusion, empyema or associated pneumothorax - Consolidation/opacification: ≥ 1 lobe involved - Cavities - Miliary infiltrates
STEP 6. BACTERIOLOGICAL SEVERITY	
No sputum sample that is AFB smear positive	AFB smear positive on sputum sample
 	
If NO exclusion criteria, child is ELIGIBLE for shortened TB treatment regimen: start short-course regimen (4 months in total). If ANY exclusion criteria, child is NOT ELIGIBLE for shortened TB treatment regimen: start 6-12 months TB treatment. Decide on duration according to site of disease/HIV status.	
IF ON SHORT COURSE, REASSESS ELIGIBILITY AT THE END OF MONTH 1 AND 4	
- Adherent to TB treatment - MONTH 1: TB signs and symptoms improved - MONTH 4: All TB signs & symptoms resolved and appropriate/improving weight trend	- Non-adherent to treatment - MONTH 1: TB signs and symptoms persisting (not improved) - MONTH 4: TB signs and symptoms have not completely resolved or weight trend not improving
 	
Treatment may be stopped once child completed 4 months. Extend treatment to 6 months.	

NOTE:

- » If no chest X-ray (CXR) is available to confirm that the radiological criteria outlined in Table 23.1 for non-severe pulmonary TB are met, children and adolescents aged ≥ 15 years are **NOT** eligible for the shorter 4-month treatment regimen.
- » Children and adolescents < 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.
- » Children and adolescents < 15 years who are not eligible for the shortened treatment regimen should receive the standard six-month drug-susceptible TB treatment regimen outlined below.
- » If there is any uncertainty about whether a child or adolescent is eligible for treatment shortening or not, rather treat for the full 6 months.
- » In children and adolescents with TB lymphadenitis, if cervical lymph nodes did not decrease in size by month 4 of treatment, continue to 6 months of treatment. Refer patients for further investigation 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.

Danger signs that require urgent attention and preclude use of the shortened regimen

<u>General danger signs</u> • Unable to drink or breastfeed • Vomiting everything • Convulsions • Unconscious or lethargic • Any signs of shock	<u>Signs of severe dehydration (2 of the following)</u> • Unconscious or lethargic • Sunken eyes • Unable to drink or drinking poorly • Skin pinch goes back very slowly
<u>Signs of severe respiratory illness (any of the following)</u> • Chest indrawing • Stridor in calm child • Oxygen saturation $< 92\%$ on room air • Central cyanosis	<u>Signs of meningitis (any of the following)</u> • Neck stiffness • Bulging fontanelle • Restless, continuously irritable <u>Signs of severe anaemia (any of the following)</u> • Severe palmar pallor • HB < 7 g/dl

Table 23.2: TB dosing chart for children and adolescents <15 years with confirmed or clinically diagnosed drug-susceptible non-severe pulmonary TB, severe pulmonary TB, and extrapulmonary TB (excluding TBM/CNS TB/ Military TB)

	Intensive phase Once daily, 7 days a week		Continuation phase Once daily, 7 days a week		
Target dose (dose range) (mg/kg/day)	Duration 2 months		Non-severe TB Duration: 2 months	Severe PTB and most EPTB Duration: 4 months	Bone & joint TB Duration: 10 months
	Isoniazid (H): 10 (7-15), Rifampicin (R): 15 (10-20), Pyrazinamide (Z): 35 (30-40), Ethambutol (E): 20 (15-25)				
Formulation	RHZ 75/50/150mg dispersible tablet (scored) OR 75/50/150mg/4ml suspension *	E 400mg tablet (not scored) OR 400mg/8ml suspension #	RH 75/50mg Dispersible tablet (scored) OR 75/50mg/4ml suspension*		
Body Weight (kg)					
< 2	Obtain expert advice				
2 – 2.9	½ tab	1 ml	½ tab		
3 – 3.9	¾ tab (3 ml)	1.5 ml	¾ tab (3 ml)		
4 – 7.9	1 tab	2.5 ml	1 tab		
8 – 11.9	2 tabs	½ tab or 4 ml	2 tabs		
12 – 15.9	3 tabs	¾ tab or 6 ml	3 tabs		
16 – 24.9	4 tabs	1 tab or 8 ml	4 tabs		
≥ 25	RHZE 150/75/400/275 mg tablet		Choose one of below options		
			RH 150/75 mg tablet	RH 300/150 mg tablet	
25 – 29.9	2 tabs		2 tabs		1 tab
30 – 34.9	3 tabs		3 tabs		-
35 – 64.9	4 tabs		4 tabs		2 tabs
≥ 65	5 tabs		5 tabs		-
Children should be taught and encouraged to swallow whole tablets or, if required, fractions of tablets so as to avoid large volumes of liquid medication					
* To make an oral suspension, for weight band 3 – 3.9 kg, for each dose, disperse 1 x RHZ 75/50/150 mg tablet (2 months intensive phase) or 1 x RH 75/50 mg tablet (continuation phase) in 4 ml of water, administer 3 ml, discard unused suspension. For other weight bands, an oral suspension can be made by dispersing the required number of tablets & fractions of tablets in a small amount of water (5-10 ml) and administering all of the suspension to the child orally or via nasogastric tube.					
# Oral suspension is preferred to ensure accurate dosing. For each oral suspension 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.					

AND

Breastfed infants, children > 8 years of age, CALHIV, malnourished children, and children with existing neuropathy should receive pyridoxine in addition to TB treatment. Acute malnutrition refers to wasting (weight-for-length/height z score less than -2); mid upper arm circumference (MUAC) less than 12.5 cm; or bilateral pitting oedema.

- Pyridoxine, oral, daily for 6 months.
 - Body weight < 6 kg: 6.25 mg (¼ tablet).
 - Body weight ≥ 6 kg but age < 5 years: 12.5 mg (½ tablet).
 - Age ≥ 5 years: 25 mg (1 tablet).

CAUTION

In CALHIV on dolutegravir-based ART and rifampicin-containing TB treatment, dolutegravir is dosed by weight-band **twice daily (12 hourly)**. Continue twice daily dosing of dolutegravir until 2 weeks after stopping rifampicin. Refer Chapter 11: Human Immunodeficiency Virus infection.

Common adverse drug reactions associated with DS-TB medicines in children:

Table 23.3: Common adverse effects of TB medicines in children

Adverse effect	Responsible drug	Management
Hepatotoxicity (e.g. jaundice, new or persistent nausea, vomiting, tender or enlarged liver)	Pyrazinamide, ethionamide, isoniazid, rifampicin.	• Stop TB treatment and other hepatotoxic drugs (e.g. antiretroviral or cotrimoxazole) immediately. • Refer urgently.
Gastrointestinal intolerance (e.g. nausea, vomiting, abdominal pain)	Most DS-TB medicines	• If jaundiced or tender, enlarged liver, or new/persistent vomiting, stop all anti-TB treatment immediately and refer urgently. • If nausea/vomiting only after taking TB treatment without jaundice or tender/enlarged liver, advise to take treatment after eating or at night. If symptoms persist after 1 week, discuss/refer.
Joint pain	Pyrazinamide	Symptomatic treatment with paracetamol 15 mg/kg (maximum 1g) 6 hourly as needed for 5 days.
Peripheral neuropathy (e.g. tingling pain or burning or	Isoniazid	Ensure taking pyridoxine: ○ Body weight < 6 kg: 6.25 mg (¼ tablet)

numbness in hands and feet)		- Body weight ≥ 6 kg but age < 5 years: 12.5mg (1/2 tablet) daily - Age ≥ 5 years old: 25mg (1 tablet) daily If already on pyridoxine or not responding – discuss/refer all cases. Note: Drug-induced peripheral neuropathy can be irreversible if the offending drug is not stopped promptly.
Orange urine	Rifampicin	Reassure the child or adolescent and caregivers that this is normal and to be expected while taking rifampicin. No intervention required.
Rash	All DS-TB medicines	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 medicines and refer urgently to hospital.
Optic neuritis (e.g. change in vision or visual impairment)	Ethambutol	Stop ethambutol immediately. Refer to ophthalmology for urgent assessment.

LoE:IIb²

Refer to Management of Tuberculosis in Children and Adolescents. A Clinical Guideline for the Diagnosis and Treatment of Drug-susceptible TB in Children and Adolescents in South Africa. September 2024: Section 14.4 Management of Adverse Drug Events.

REFERRAL

- » Refer all cases of extrapulmonary TB (other than simple TB pleural effusion and TB lymphadenitis) and disseminated TB (including miliary TB) for further investigations not available at primary care (e.g. lumbar puncture, ultrasound).
- » All children and adolescents who cannot be managed on an ambulatory basis.
- » Children with previously treated TB requiring re-treatment.
- » Children and adolescents with poor response to TB treatment.
- » Adverse drug reactions (ADR) requiring single drug combinations.
- » If the adult or adolescent with TB the child is or was exposed to has drug-resistant TB (DR TB), refer the child or discuss with an expert.

23.1.3 TUBERCULOSIS (TB) IN ADULTS AND ADOLESCENTS ≥ 15 YEARS

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

TB guidelines are updated regularly. Consult the most recent National Tuberculosis Control Programme Guidelines.

DESCRIPTION

Pulmonary tuberculosis (PTB) refers to infection of the lung tissue or airways caused by *M. tuberculosis* and may present with cough, fever, weight loss and night sweats. Extrapulmonary TB (EPTB) refers to *M. tuberculosis* infection occurring outside the lungs such as the lymph nodes, pleura, pericardium, central nervous system and bones and joints. EPTB is more common in PLWH. EPTB may also present with weight loss, night sweats, and fever, as well as other symptoms depending 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 23.4 Common presenting signs and symptoms of EPTB

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.
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.
TB empyema	» Similar to pleural effusion, but aspiration reveals thick pus.
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).
TB pericarditis	» 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).
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.
Disseminated/miliary TB	» Fever. » Cough. » Generalised lymphadenopathy. » Hepatomegaly. » Consider in febrile patients presenting with HIV wasting syndrome.
TB abdomen/peritoneum	» Ascites with no signs of portal hypertension. » Possible palpable abdominal masses. » Possible bowel obstruction.
Urogenital TB	» Dysuria, urinary frequency, or urgency » Haematuria » Sterile pyuria » Pelvic, flank or perineal pain » Infertility in men and women

DIAGNOSIS

PTB is diagnosed on sputum by TB-NAAT, smear microscopy, or TB culture.

In people with suspected TB:

- » 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 23.2, 23.3 and 23.4 below.
- » All patients with *M. tuberculosis* (MTB) detected on TB-NAAT require additional sputum to be sent at baseline for smear microscopy for acid-fast bacilli (AFB) to allow for monitoring of treatment.
- » Patients who are at risk of drug-resistant TB (e.g. previous episode of TB treatment, prisoners, health care 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

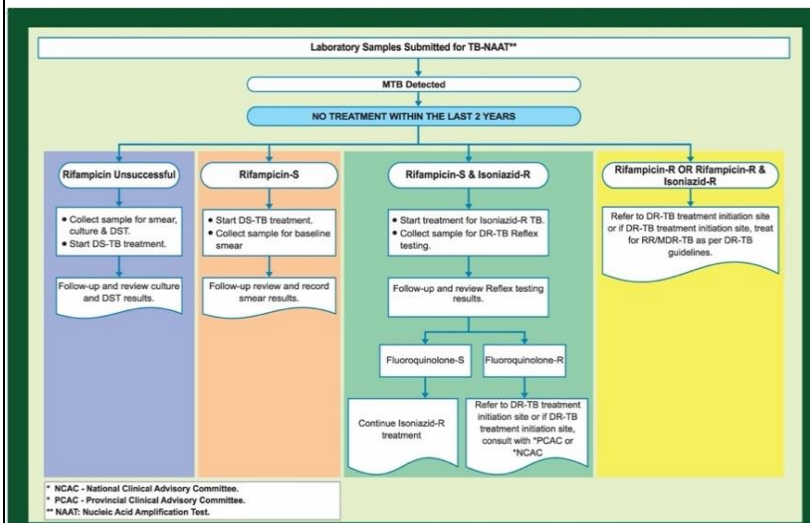


Figure 23.2: TB-NAAT Diagnostic Algorithm 1 - Guidance on managing TB-NAAT "MTB detected" results in patients NOT treated for TB within the last 2 years (Source: NDoH TB Program)

Patients treated for TB within the last 2 years

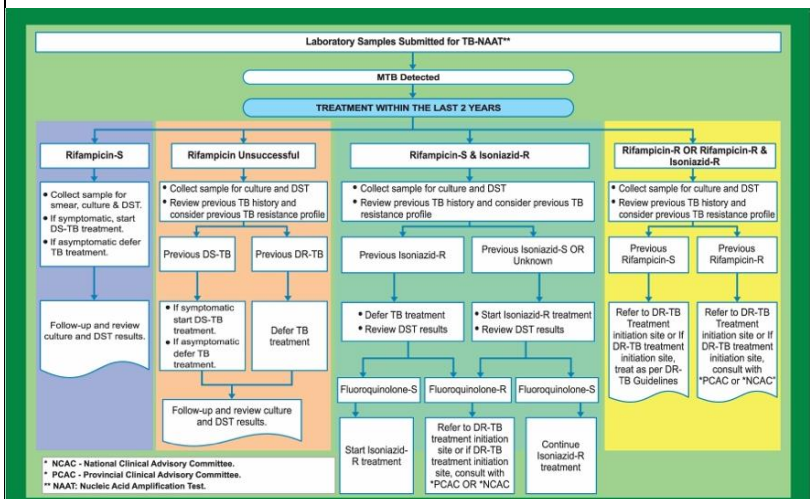


Figure 23.3: TB-NAAT Diagnostic Algorithm 2 - Guidance on managing TB-NAAT "MTB detected" results in patients treated for TB within the last 2 years (Source: NDoH TB Program)

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.

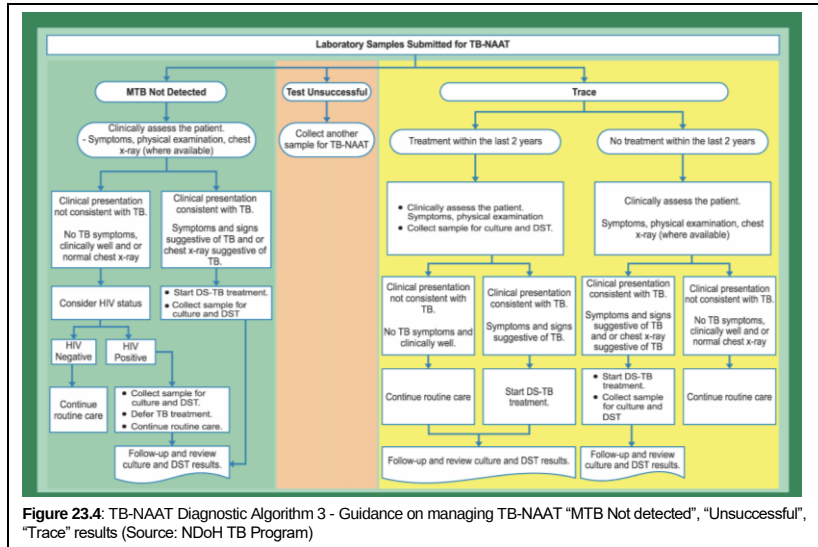


Figure 23.4: TB-NAAT Diagnostic Algorithm 3 - Guidance on managing TB-NAAT "MTB Not detected", "Unsuccessful", "Trace" results (Source: NDoH TB Program)

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 need empiric anti-tuberculosis therapy.

- » Perform a U-LAM test in 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 shared the same enclosed space with an adult or adolescent with pulmonary TB (e.g. the source patient), for ≥ 1 night 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.
- » Explain the importance of completing treatment.
- » Advise against the use of tobacco and excessive alcohol.
- » If more than two doses of treatment are missed, extra effort should be made to identify and manage any problems the patient might have.

Monitoring

- » Patients with pulmonary TB 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 23.5 below for the timing of sputum examinations and the recommended actions based on results.
- » 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.

Table 23.5. Sputum smear microscopy monitoring in patients with drug-susceptible TB

Timing of sputum examination	End of Intensive Phase
	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

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 23.5 below).

Treatment for known or presumed drug-susceptible PTB:

- Rifampicin/isoniazid/pyrazinamide/ethambutol, oral, daily for 2 months.

Followed by

- Rifampicin/isoniazid, oral, daily for 4 months.
 - Weigh the patient frequently and adjust the dose according to current weight.
 - Administer the total daily amount of each medicine in one dose and not as divided doses.

Table 23.5: Weight-based dosing guidance for adults and adolescents ≥ 15 years with drug-susceptible TB

Body weight	Two months intensive phase	Four months continuation phase (Extend continuation phase to 7 months for TB meningitis and osteoarticular TB)	
	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, oral, 25 mg, 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 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 11.1: Antiretroviral therapy, adults and adolescents for guidance on managing interaction with other types of ART, 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 treatment phase:

- RHZE: Administer standard weight-based dosing with RHZE on Monday, Wednesday, Friday.
- RH: Administer standard weight-based dosing with 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 with RH.

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Common adverse drug reactions associated with DS-TB medicines:
Table 23.6: Common adverse drug reactions associated with DS-TB medicines in adolescents and 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 – refer to hospital for urgent (same day) ALT and further management.
Gastrointestinal intolerance (nausea, vomiting, anorexia)	Most DS TB medicines	Exclude drug-induced liver injury/hepatitis – refer for urgent (same day) ALT and further management. 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 Section 20 Pain).
Peripheral neuropathy (e.g. tingling pain or)	Isoniazid	Initiate or increase pyridoxine to 50 mg daily.

burning or numbness in hands and feet)		Note: Doses of pyridoxine > 100 mg daily may cause or worsen peripheral neuropathy and should be avoided. See Section 15.10.3 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 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 medicines and refer urgently to hospital.
Thrombocytopenia and/or purpura or petechial rash	Rifampicin	If petechial rash, refer to hospital for urgent (same day) platelet count. If thrombocytopenia, stop rifampicin.
Optic neuritis (e.g. change in vision or visual impairment)	Ethambutol	Stop ethambutol immediately. Refer to ophthalmology for urgent assessment.
Also see: Medicine Information Centre: Management of suspected drug-induced rash, kidney injury and liver injury in adult patients on DS-TB treatment and/or antiretroviral treatment. November 2024 https://mic.uct.ac.za/sites/default/files/media/documents/mic_uct_ac_za/2157/ade-booklet.pdf		

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REFERRAL

- » All suspected cases of extrapulmonary TB (other than microbiologically confirmed TB lymphadenitis and simple TB pleural effusion) should be referred for diagnosis and further management.
- » All patients who cannot be managed on an ambulatory basis because of clinical severity, infection and prevention control challenges in the home, and/or unstable social circumstances, requiring intensive multidisciplinary management.
- » All patients with poor response to TB treatment, including non-resolving TB pleural effusions. Suspect an incorrect diagnosis of TB pleural effusion if the effusion does not improve on the CXR after 3 months of treatment, or if the patient deteriorates.
- » Patients with suspected adverse drug reactions (ADR) requiring hospitalisation (e.g. drug-induced liver injury, severe cutaneous adverse reactions), single drug combinations, or individualised regimens.

23.2 DRUG-RESISTANT TUBERCULOSIS (DR-TB)

U50, U50.9, U50.91

See the National Department of Health Updated Clinical Reference Guide: Clinical Management of **Rifampicin-Resistant Tuberculosis**, September 2023⁴

DESCRIPTION

Key definitions and terminology for drug-resistant tuberculosis:

Table 23.7: Key definitions and terminology for drug-resistant TB

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

DIAGNOSIS

All people with signs and symptoms of TB should have specimens sent as part of the diagnostic work-up. 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, and in children stool). TB-NAAT testing is also used to rapidly determine drug susceptibility. 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 (NGS), TB microscopy, culture, and phenotypic drug susceptibility testing for bedaquiline and linezolid if culture positive.

Many children will not have microbiological confirmation of DR-TB by TB-NAAT or culture due to paucibacillary or extrapulmonary disease. In these children, DR-TB is suspected based on evidence of TB disease (e.g. history,

clinical examination, and radiological investigations) and a recent DR-TB exposure or if the child is not responding to first-line TB treatment despite good adherence. In these children, treatment should be based on the drug susceptibility testing results of the *M. tuberculosis* strain from the most likely source patient.

Suspect drug-resistant TB when any of the features listed below is present:

- » Contact with a known source patient with drug-resistant TB or high-risk source patient, e.g., recently released from prison or not improving on DS-TB therapy.
- » A patient with confirmed treatment adherence that remains smear positive after 2 months of 1st line TB treatment.
- » Any patient with TB who failed to improve or got worse on TB treatment.
- » Patients who were lost to follow-up on TB treatment (>2 months treatment interruption).
- » History of treatment interruption (<1 month) or relapse at some point during their TB therapy.
- » Patients with recurrent TB disease after completion of TB treatment (re-treatment case).

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 and educate patients and/or caregivers 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 by sputum collection for TB-NAAT to detect TB disease and determine susceptibility. A contact is any person that shared the same enclosed space with an adult or adolescent with pulmonary TB (e.g. the source patient), for ≥ 1 night 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.
- » For children, ensure the caregiver can confidently crush, mix and give the correct volume of medicines themselves at every visit.

23.2.1 ISONIAZID MONORESISTANT TUBERCULOSIS

A15.0-3/A15.7-8/A16.0-2/A16.4/A16.7-9 + (U50.00-01+U50.10-11) + (B20.0)
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 23.2 and 23.3). 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.

23.2.1.1 ISONIAZID MONORESISTANT TUBERCULOSIS IN ADULTS

A15.0-3/A15.7-8/A16.0-2/A16.4/A16.7-9 + (U50.00-01+U50.10-11) + (B20.0)
U50.00, U50.1, U50.10, U50.11

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
 - Body weight: 30 to < 46 kg: 750 mg
 - Body weight: ≥ 46 kg: 1000 mg

AND

Prophylactic 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.

Confirmed isoniazid monoresistant TB AND fluoroquinolone susceptible AND contraindication to isoniazid:

- Rifampicin, oral, 10 mg/kg daily.

AND

- Ethambutol, oral, 15 mg/kg daily.

AND

- Pyrazinamide, oral, 25 mg/kg daily.

AND

- Levofloxacin, oral, daily.
 - Body weight: 30 to < 46 kg: 750 mg
 - Body weight: ≥ 46 kg: 1 000 mg

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REFERRAL

- » All drug-resistant TB patients to medical officer at primary care level for initiation of therapy. If isoniazid AND fluoroquinolone resistance detected discuss with an expert.
- » If isoniazid resistance detected late in a patient non-responding to drug-susceptible TB treatment, discuss with an expert.

23.2.1.2 ISONIAZID MONORESISTANT TUBERCULOSIS IN CHILDREN < 15 YEARS

MEDICINE TREATMENT

Treatment should be given for at least 6 months.

Confirmed isoniazid mono-resistant TB and fluoroquinolone susceptible:

- RHZ plus E at standard weight-based dosing, oral, daily.

AND

- Levofloxacin, oral, daily.

AND

Breastfed infants, children > 8 years of age, CALHIV, malnourished children, and children with existing neuropathy should receive pyridoxine in addition to TB treatment. Acute malnutrition refers to wasting (weight-for-length/height z score less than -2); mid upper arm circumference (MUAC) less than 12.5 cm; or bilateral pitting oedema.

- Pyridoxine, oral, daily for 6 months.
 - Body weight < 6 kg: 6.25 mg (¼ tablet).
 - Body weight ≥ 6 kg but age < 5 years: 12.5 mg (½ tablet).
 - Age ≥ 5 years: 25 mg (1 tablet).

Table 23.8: TB dosing chart for children and adolescents <15 years with confirmed or clinically diagnosed isoniazid mono-resistant pulmonary and extrapulmonary TB (excl. TBM, CNS TB, Miliary TB, bone/joint TB)

	Single phase, 6 months duration Oral, 7 days a week		
Formulation	RHZ 75/50/150mg dispersible tablet (scored) OR 75/50/150mg/4ml suspension*	E 400mg tablet (not scored) OR 400mg/8ml suspension**	Levofloxacin 250 mg tablet OR 500 mg tablet OR 25 mg/ml suspension***
Body Weight (kg)			
Target dose (range; mg/kg/day)	Isoniazid (H): 10 (7–15) mg Rifampicin (R): 15 (10–20) mg Pyrazinamide (Z): 35 (30–40) mg Ethambutol (E): 20 (15–25) mg Levofloxacin: 15–20 mg		
3–3.9	¾ tab (3 ml)	1.5 ml	2 ml
4–4.9	1 tab	2.5 ml	
5–7.9	1 tab	2.5 ml	5 ml or ½ x 250 mg tablet
8–9.9	2 tabs	½ tab or 4 ml	10 mL or 1 x 250 mg tablet
10–11.9	2 tabs	½ tab or 4 ml	
12–12.9	3 tabs	¾ tab or 6 ml	
13–15.9	3 tabs	¾ tab or 6 ml	
16–24.9	4 tabs	1 tab or 8 ml	15 mL or 1 ½ x 250 mg tablet
≥ 25	RHZE 150/75/400/275 mg tablet		
25–29.9	2 tabs		1 x 500 mg tablet or 2 x 250 mg tablet or 20 mL
30–34.9	3 tabs		1 ½ x 500mg or 3 x 250mg tablets daily
35– < 45.9 kg	4 tabs		
46-65 kg	4 tabs		2 x 500mg or 4 x 250mg tablets daily
≥ 65	5 tabs		
Children should be taught and encouraged to swallow whole tablets or, if required, fractions of tablets so as to avoid large volumes of liquid medication.			

* To make an oral suspension, for weight band 3–3.9 kg, for each dose, disperse 1 x RHZ 75/50/150 mg tablet (2 months intensive phase) in 4 ml of water, administer 3 ml, discard unused suspension. For other weight bands, an oral suspension can be made by dispersing the required number of tablets & fractions of tablets in a small amount of water (5–10 ml) and administering all of the suspension to the child 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.

***For levofloxacin 25mg/ml suspension: Crush and disperse 1 x 250mg tablet in 10 mL water.

Confirmed isoniazid monoresistant TB AND fluoroquinolone susceptible AND contraindication to isoniazid:

- Rifampicin, oral, 10 mg/kg daily.

AND

- Ethambutol, oral, 15 mg/kg daily.

AND

- Pyrazinamide, oral, 25 mg/kg daily.

AND

- Levofloxacin, oral, daily.

REFERRAL

- » All drug-resistant TB patients to medical officer at primary care level for initiation of therapy. If isoniazid AND fluoroquinolone resistance detected discuss with an expert.
- » Discuss children with isoniazid-monoresistant TBM, miliary TB or bone/joint TB with an expert as they require a different regimen or duration of treatment.

23.2.2 RIFAMPICIN-RESISTANT, PRE-XDR AND XDR TUBERCULOSIS IN ADULTS AND ADOLESCENTS ≥ 15 YEARS

A15.0-3/A15.7-8/A16.0-2/A16.7-8 + (U50.00-01+U50.20-21) + (B20.0)/U50.0/U50.2/U50.20/U50.21/U50.5

DESCRIPTION

Rifampicin resistant tuberculosis (RR-TB) is TB disease caused by *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.

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 (e.g. lymphadenopathy or pleural effusion) 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.

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AND

- Levofloxacin, oral, daily for 24 weeks.
 - 30 to <46kg: 750 mg.
 - ≥ 46 kg: 1000 mg.

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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Table 23.9: Common adverse drug reactions associated with medicines included in the BPaL-L regimen

Adverse drug reaction	Most likely responsible drug	Management
Anaemia	Linezolid	If Hb < 8 g/dL in first 8 weeks of BPaL-L treatment: Interrupt linezolid treatment and refer to hospital for close monitoring and blood transfusion. 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 < $50 \times 10^9/L$: Stop linezolid until thrombocytopenia improves, exclude other causes, and discuss further management with NCAC/expert.
Neutropenia	Linezolid	If neutrophils < $0.75 \times 10^9/L$: 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 DR-TB 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 the 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, upper quadrant pain, jaundice)	Bedaquiline, fluoroquinolones, pretomanid	» Refer for urgent (same day) ALT. 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 rechallenge. » Rechallenge 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 rechallenged, stop clofazimine, terizidone and delamanid and continue BPaL-(L). If rechallenge 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. Refer patients with severe rash to hospital urgently.

LoE:IVbl^B

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/National Clinical Advisory Committee (NCAC).

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.

REFERRAL

- » All drug-resistant TB patients should be assessed by a medical officer at primary care level for initiation of therapy.
- » If Hb < 8 g/dL, refer for blood transfusion prior to starting linezolid.
- » Discuss patients not eligible for the BPAL-L regimen or in whom bedaquiline, linezolid or pretomanid are prematurely and permanently discontinued due to toxicity require an individualised regimen with a TB expert.
- » Patients unable to attend primary care facility for treatment (e.g. too weak to ambulate).
- » Patients with challenges to instituting infection control in their home.
- » Recurrent treatment interruption where previous outpatient treatment has been unsuccessful.
- » All patients with XDR-TB, to be discussed with an expert.
- » Patients not responding to appropriate TB treatment.
- » Patients presenting with adverse drug reactions (ADR) requiring admission and/or drug substitution.

23.2.3 RIFAMPICIN-RESISTANT (RR), PRE-XDR AND XDR TUBERCULOSIS, IN CHILDREN AND ADOLESCENTS < 15 YEARS

A15.0-3/A15.7-8/A16.0-2/A16.7-8 + (U50.00-01+U50.20-21) + (B20.0)

DESCRIPTION

Rifampicin resistant tuberculosis (RR-TB) is TB disease caused by *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 children and adolescents with signs and symptoms of TB should have a specimen sent for TB-NAAT testing. A rifampicin resistant result detected by Xpert® MTB/RIF Ultra, or other TB-NAAT, is sufficient to start a patient on RR-TB treatment. All children and adolescents who test positive for *M. tuberculosis* with rifampicin resistance must have additional specimens sent for DR-TB reflex testing that may include Xpert® MTB/XDR testing for fluoroquinolone resistance, targeted next generation sequencing (tNGS), TB microscopy, culture, and phenotypic drug susceptibility testing for bedaquiline and linezolid, if culture positive. Many children will not have microbiological confirmation due to paucibacillary or extrapulmonary disease. In children, without microbiological confirmation of RR-TB/Pre-XDR-TB, treatment should be based on the drug susceptibility of the *M. tuberculosis* strain from the most likely source case.

MEDICINE TREATMENT

- » The composition and duration of RR-TB/Pre-XDR-TB treatment regimens are based on drug susceptibility (or that of the most likely source patient) as well as site and severity of TB disease.

Severe TB disease in children < 15 years	Non-severe TB disease in children < 15 years
- Chest x-ray: bilateral disease (consolidation, infiltrates), or presence of cavities. - Mediastinal lymph nodes causing airway compression. - Extrapulmonary forms of disease other than isolated peripheral lymph nodes or simple pleural effusion.	- Isolated Peripheral lymphadenopathy. - Chest x-ray: unilateral disease (consolidation, infiltrates in < 1 lobe in total) without cavities. - Small/simple pleural effusions. - Mediastinal lymph nodes without airway compression

- » Regimens should include at least 4 drugs considered to be effective, with the addition of a 5th drug in severe disease.
- » Children with non-severe RR-TB/Pre-XDR-TB disease are likely to be successfully treated with 6-month regimens containing at least 4 effective drugs.
- » Children with more severe disease are likely to require longer treatment for 9 or 12 months.
- » There is no specified intensive or continuation phase for paediatric RR-TB/Pre-XDR-TB regimens and most drugs should be continued through treatment.
- » All-oral regimens must be prioritised, and child-friendly formulations of anti-TB medications should be used whenever possible.
- » Toxicity and feasibility of adverse effect monitoring for specific medicines, may limit the use of certain medicines.
- » Drug dosing is based on the child's weight, and dosing must be modified as children gain or lose weight.
- » All cases of RR-TB/Pre-XDR-TB with confirmed or presumed resistance to bedaquiline, clofazimine or linezolid (e.g. XDR-TB) should be referred to a paediatric RR-TB expert or infectious diseases specialist or to the National clinical advisory committee (NCAC) (Email: NCAC@witshealth.co.za).

Examples of anti-tuberculosis drugs used in RR-TB treatment

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

For treatment of RR and Pre-XDR-TB in children and adolescents < 15 years refer to National Department of Health. Updated Clinical Reference Guide: Clinical Management of Rifampicin-Resistant Tuberculosis. September 2023. Page 47.

REFERRAL

- » All children with suspected drug-resistant TB should be assessed by a medical officer at primary care level for initiation of therapy.
- » Hb < 8 g/dL - consult expert before starting linezolid.
- » Suspected CNS or miliary DR-TB.

- » If unsure of appropriate treatment regimen - Telephonic consultation with specialist.
- » Unfavourable social circumstances, inability to attend outpatient follow-up, recurrent treatment interruption.
- » Patients not responding to appropriate TB treatment.
- » Adverse drug reactions (ADR) requiring admission and/or drug substitution.

23.3 TUBERCULOSIS PREVENTIVE THERAPY (TPT) IN CHILDREN AND ADOLESCENTS

Z20.1

For TPT in PLWH refer to Section 11.2.2 Tuberculosis preventive therapy.

Screen all infants, children and adolescents with a history of significant exposure to a TB source patient. An infant, child or adolescent is considered to have had a significant TB exposure if within the 12 months before presentation with presumed TB, they shared an enclosed space with an adult or adolescent with pulmonary TB for ≥ 1 night OR for frequent or extended daytime periods (e.g. at school or creche). 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.

In addition, a newborn has had significant exposure to a person with infectious TB if the baby was born to a mother with TB and the mother:

- » started TB treatment within 2 months before delivery OR
- » demonstrates poor clinical response to TB treatment OR
- » is TB smear or acid-fast bacilli (AFB) or culture positive at delivery OR
- » is diagnosed with TB soon after delivery.

Screening includes history taking, clinical examination and appropriate investigations. Give full anti-tuberculosis treatment if the diagnosis of TB disease is confirmed or suspected (See Section 23.1.1: Perinatal Tuberculosis and Section 23.1.2: Tuberculosis in children and adolescents < 15 years). If there is a history of a significant exposure, and TB disease has been excluded, consider the need for TB preventive therapy (TPT).

Note: Never give TPT to children with active TB disease.

Indications for TPT:

- » All asymptomatic infants and children < 5 years and children or adolescents with HIV (CALHIV), who are clinically well, with a normal chest X-ray, irrespective of TST, in close contact with someone with infectious pulmonary TB should receive TPT.

NOTE: Previous TPT or TB treatment does not protect a child against subsequent TB exposure/infection. If there is a new exposure to someone with infectious pulmonary TB after completion of a course of TPT, the exposed child may be eligible for a repeat course of TPT. TPT should be repeated after each episode of documented TB exposure. In the case of a new exposure to someone with infectious pulmonary TB while the child is on TPT, the duration of TPT should continue for at least as long as the source case remains infectious.

23.3.1 TUBERCULOSIS PREVENTIVE THERAPY (TPT) AFTER DRUG-SUSCEPTIBLE TUBERCULOSIS EXPOSURE

MEDICINE TREATMENT

- » In HIV-negative children < 25kg, the priority regimen is 3RH (rifampicin plus isoniazid daily for 3 months).
- » In CALHIV, the preferred regimen is 6H (isoniazid daily for 6 months).

If HIV-negative or HIV-exposed not on nevirapine and < 25kg:

- Rifampicin/isoniazid 75/50 mg daily for 3 months.

Weight (kg)	RH (Daily) fixed dose combinations		Duration
	75/50 mg	If crushed and mixed in in water	
2 – 2.9	½ tablet	Mix 1 tablet in 4mL of water. Give only 2mL of this mixture.	3 months
3–3.9	¾ tablet	Mix 1 tablet in 4 mL of water. Give only 3 mL of this mixture.	
4–5.9	1 tablet	Mix 1 tablet in 4 mL of water and give ALL of this mixture.	
6–7.9	1 ½ tablets	Mix 1 ½ tablets in 5–10mL of water and give ALL of this mixture.	
8–11.9	2 tablets	Mix 2 tablets in 5–10mL of water and give ALL of this mixture.	
12–15.9	3 tablets	Mix 3 tablets in 5–10mL of water and give ALL of this mixture.	
16–24.9	4 tablets	Mix 4 tablets in in 5–10mL of water and give ALL of this mixture.	
≥ 25	Use adult formulations and doses		

AND

Breastfed infants, malnourished children, and children with existing neuropathy should receive pyridoxine in addition to 3RH. Acute malnutrition refers to wasting (weight-for-length/height z score less than -2); mid upper arm circumference less than 12.5 cm; or bilateral pitting oedema.

- Pyridoxine, oral, daily for 6 months.
 - Body weight < 6 kg: 6.25 mg (¼ tablet).
 - Body weight ≥ 6 kg but age < 5 years: 12.5 mg (½ tablet).

If CALHIV or HIV-exposed on nevirapine:

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

Weight (kg)	Daily isoniazid 100 mg tablet	Duration
2 - 3.4	¼ tablet	6 months
3.5–4.9	½ tablet	
5–7.4	¾ tablet	
7.5–9.9	1 tablet	
10–14.9	1 ½ tablets	
15–19.9	2 tablets	
20–24.9	3 tablets (or one 300 mg tablet)	
≥ 25	Use adult formulations (maximum dose 300 mg per day)	

AND

Breastfed infants, CALHIV, malnourished children, and children with existing neuropathy should receive pyridoxine in addition to 6H. Acute malnutrition refers to wasting (weight-for-length/height z score less than -2); mid upper arm circumference less than 12.5 cm; or bilateral pitting oedema.

- Pyridoxine, oral, daily for 6 months.
 - Body weight < 6 kg: 6.25 mg (¼ tablet).
 - Body weight ≥ 6 kg but age < 5 years: 12.5 mg (½ tablet).
 - Age ≥ 5 years: 25 mg (1 tablet).

LoE:IVb⁹

REFERRAL

- » All children with significant TB exposure to medical officer at primary care level to exclude TB disease and initiate TPT.

23.3.2 TUBERCULOSIS PREVENTIVE THERAPY (TPT) FOR DRUG-RESISTANT TUBERCULOSIS EXPOSURE

Isoniazid mono-resistance (rifampicin-susceptible):

- Rifampicin , oral, for 4 months.

LoE:IVb¹⁰

Daily dose		Dose calculation/preparation (depending on available rifampicin formulation)	Notes
< 10 years old	15 mg/kg daily	15 mg/ml solution Rifampicin 150mg capsule: open capsule into 10 ml of water.	If rifampicin alone is unavailable, discuss alternative with expert.
≥ 10 years old	10 mg/kg daily	30 mg/ml solution - Rifampicin 300mg capsule: open capsule into 10 ml of water. 60 mg/ml solution - Rifampicin 600mg capsule: open capsule into 10 ml of water.	

CAUTION

In CALHIV on dolutegravir-based ART and rifampicin TPT, dolutegravir is dosed by weight-band **twice daily (12 hourly)**. Continue twice daily dosing of dolutegravir until 2 weeks after stopping rifampicin. Refer to Chapter 11: Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome (HIV and AIDS).

Rifampicin mono-resistance (confirmed isoniazid-susceptible by culture-based drug sensitivity testing):

LoE:IVb¹¹

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

Weight (kg)	Daily isoniazid 100mg tablet	Duration
2 - 3.4	¼ tablet	6 months
3.5 – 4.9	½ tablet	
5 – 7.4	¾ tablet	
7.5 – 9.9	1 tablet	
10 – 14.9	1 ½ tablets	
15 – 19.9	2 tablets	
20 – 24.9	3 tablets (or one 300 mg tablet)	
≥ 25	Use adult formulations (maximum dose 300 mg per day)	

AND

Breastfed infants, CALHIV, malnourished children, and children with existing neuropathy should receive pyridoxine in addition to 6H. Acute malnutrition refers to wasting (weight-for-length/height z score less than -2); mid upper arm circumference less than 12.5 cm; or bilateral pitting oedema.

- Pyridoxine, oral, daily for 6 months.
 - Body weight < 6 kg: 6.25 mg (¼ tablet).
 - Body weight ≥ 6 kg but age < 5 years: 12.5 mg (½ tablet).
 - Age ≥ 5 years: 25 mg (1 tablet).

LoE:IVb¹²**Rifampicin-resistant TB (susceptible to fluoroquinolones):**

- Levofloxacin ^w 15–20 mg/kg daily for 6 months (maximum dose: 1000 mg).
- OR**
- Isoniazid, oral, 15–20 mg/kg daily for 6 months (maximum dose: 600 mg).
 - Only if susceptible to high-dose isoniazid (low-level INH resistance).

Weight	Levofloxacin 250 mg tablet (scored) OR 500 mg tablet (scored)		OR	Isoniazid 100 mg tablet OR 300 mg tablet	
	250 mg tablet*	500 mg tablet		100 mg tablet*	300 mg tablet
3 – 4.9 kg	2 mL			5 mL	
5 – 6.9 kg	5 mL or 0.5 tablet			1 tablet	
7 – 9.9 kg	1 tablet			1.5 tablets	
10 – 15.9 kg	1.5 tablets			2 tablets	
16 – 23.9 kg	2 tablets	1 tablet		3 tablets	1 tablet
24 – 29.9 kg	3 tablets	1.5 tablets		4 tablets	1.5 tablets
30 – 35.9 kg				4.5 tablets	
36 – 45.9 kg					
46 – 55.9 kg	4 tablets	2 tablets			2 tablets
56 – 69.9 kg					
≥ 70 kg					

*Dissolution 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.

AND

If isoniazid TPT, administer pyridoxine to all breastfed infants, malnourished children, CALHIV, or those with existing neuropathy. Acute malnutrition refers to wasting (weight-for-length/height z score less than -2); mid upper arm circumference less than 12.5 cm; or bilateral pitting oedema.

- Pyridoxine, oral, daily for 6 months:
 - Body weight < 6 kg: 6.25 mg (¼ tablet).
 - Body weight ≥ 6 kg but age < 5 years: 12.5 mg (½ tablet).
 - Age ≥ 5 years: 25 mg (1 tablet).

NOTE: Pyridoxine supplementation is not required with levofloxacin TPT.

If the person with infectious pulmonary TB, the child was in contact with has Pre-XDR-TB or XDR-TB, refer or discuss with a specialist. Ensure household infection control practices are observed. These children need close, ongoing follow-up for at least two years.

REFERRAL

- » All children with significant TB exposure to medical officer at primary care level to exclude TB disease and initiate TPT.

References:

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- ⁵ Levofloxacin, oral (with rifampicin, ethambutamol, pyrazinamide): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Levofloxacin, oral (in addition to rifampicin, pyrazinamide, and ethambutol) for isoniazid-resistant tuberculosis, September 2019. <http://www.health.gov.za/>
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- ⁶ 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: <https://eur03.safelinks.protection.outlook.com/?url=https%3A%2F%2Furl.za.m.mimecastprotect.com%2F%2FmWfCq5DQHzo7oycZYfErgFh%3Fdomain%3Dmic.uct.ac.za&data=05%7C02%7Czahiera.adam%40health.gov.za%7C1bd3712e20e941dd36f08dedb67856a%7Ca517371fc316484cac5c98b76127790a%7C0%7C0%7C639189435296952413%7CUkn0wn%7CTWfPbGZsb3d8eyJFbXB0eU1hcGkiOnRydWUsIlYiOiwiLjAuMDAwMCIslAiOiJXaW4zMlslkFOljiTWfPbClslldUjIvO%3D%3D%7C0%7C7C%7C7C&data=y%2BLSUjIdTfNShhNAAMunWOCj1slsIA4%2FeZauwYIM%3D&reserved=0>
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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

Primary Healthcare (PHC) Chapter 23 TUBERCULOSIS

Document Version Control

Report Version	Date	Detail
V1.1	29/09/2026	Ratified for publication
V1.0	30/07/2026	The PHC Chapter 23 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 PHC publication as well as some newly developed STGs.

Summary Tables

New STGs

Newly developed STGs added to the PHC publication include:

STG/SECTION	GUIDANCE PRODUCTS (Tick relevant)			
	PHC STGs & EML	AH STG & EML	PaedH STG & EML	TQ EML
Report Version 1.0				
23.1 Drug-susceptible tuberculosis	✓	✓		
23.1.1 Perinatal tuberculosis	✓			
23.2.1.2 Isoniazid mono-resistant tuberculosis in Children <15 year	✓			
23.3 Tuberculosis preventive therapy	✓			

Medicine Amendments

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							
23.1.1 Perinatal Tuberculosis	✓				Guidance on clinical presentation and referral to TPT section	ADDED	
23.1.2 Tuberculosis in children	✓		✓		General editorial amendments		

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							
and adolescents (<16 yrs)	✓		✓		Course duration	AMENDED	n/a
	✓		✓		Ethambutol	ADDED	n/a
	✓		✓		Rifampicin/Isoniazid 60/60mg formulation	DELETED	n/a
	✓		✓		Pyridoxine	AMENDED	
23.1.3 Tuberculosis in adults and adolescents (≥ 16 yrs)	✓	✓				Editorial amendments	n/a
23.2 Drug-resistant TB	✓	✓	✓			Editorial amendments	n/a
23.2.1 Isoniazid monoresistant tuberculosis	✓	✓	✓			Editorial amendments	n/a
23.2.1.2 Isoniazid monoresistant tuberculosis in children and and adolescents < 15 yrs <i>Confirmed isoniazid monoresistant TB</i>	✓		✓		Rifampicin/isoniazid/ pyrazinamide/ ethambutol (RHZE)	ADDED	
	✓		✓		Levofloxacin	ADDED	
	✓		✓		Pyridoxine	ADDED	
23.2.1.2 Isoniazid monoresistant tuberculosis in children and and adolescents < 15 yrs <i>Confirmed isoniazid monoresistant TB AND contraindication to isoniazid</i>	✓		✓		Rifampicin	ADDED	
	✓		✓		Pyrazinamide	ADDED	
	✓		✓		Ethambutol	ADDED	
	✓		✓		Levofloxacin	ADDED	
23.2.2 Rifampicin-resistant, pre-XDR and XDR tuberculosis in adults and adolescents ≥ 15 yrs	✓	✓				Editorial amendments	n/a
23.2.3 Rifampicin-resistant, pre-XDR and XDR tuberculosis in children and and adolescents < 15 yrs	✓		✓		Editorial amendments		
	✓		✓		Bedaquiline (BDQ)	ADDED	n/a
	✓		✓		Clofazimine (CFZ)	ADDED	n/a
	✓		✓		Delamanid (DLM)	ADDED	n/a
	✓		✓		Ethionamide (ETO)	ADDED	n/a
	✓		✓		High-dose isoniazid (hdINH)	ADDED	n/a
	✓		✓		Levofloxacin (LFX)	ADDED	n/a
	✓		✓		Linezolid (LZD)	ADDED	n/a
	✓		✓		Para-amino salicylic acid (PAS)	ADDED	n/a
	✓		✓		Terizidone (TRD)	ADDED	n/a
23.3.1 Tuberculosis preventive therapy for drug- susceptible tuberculosis exposure	✓		✓		3RH	ADDED	n/a

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							
23.3.2 Tuberculosis preventive therapy for drug- resistant tuberculosis exposure	✓		✓		Levofloxacin	ADDED	n/a

*Therapeutic Interchange

PHC Tuberculosis Chapter 23

General

Updates were made as far as possible to align with the National Programme Guidelines:

- Management of Tuberculosis in Children and Adolescents – A Clinical Guideline for diagnosis and treatment of Drug-susceptible TB in Children and Adolescents in South Africa, September 2024.¹
- Management of Tuberculosis in Children and Adolescents (0-15 years) – A quick Reference Guide.²
- Clinical Management of Rifampicin-Resistant Tuberculosis – Updated Clinical Reference Guide, September 2023.³
- National Guidelines on the Treatment of Tuberculosis Infection. February 2023.⁴
- National Department of Health. Updated Clinical Reference Guide: Clinical Management of Rifampicin-Resistant Tuberculosis. September 2023⁵.

Dosing tables were aligned with those in the National Programme TB Guidelines to ensure consistency in format and presentation.

Age Thresholds

Discrepancies with age cut-offs for children both for drug-susceptible and drug-resistant TB were noted between the National TB programmatic guidelines and the previously approved NEMLC recommendations. The NEMLC approved age cut-offs are retained.

- Drug-susceptible TB (DS-TB): Children eligible < 16 years eligible for treatment shortening. (SHINE Trial)⁶
- Drug-resistant TB (DR-TB): Children ≥ 14 years eligible for BPAL- (BPAL-L WHO adolopment review)⁶

¹ National Department of Health. Management of Tuberculosis in Children and Adolescents – A Clinical Guideline for diagnosis and treatment of Drug-susceptible TB in Children and Adolescents in South Africa, September 2024. https://knowledgehub.health.gov.za/system/files/elibdownloads/2024-10/Management%20of%20Paeds%20and%20Adol%20Tuberculosis%20Guideline%20v6%20202409118%20signed%20WEBview%20%281%29_0.pdf

² National Department of Health. Management of Tuberculosis in Children and Adolescents (0-15 years) – A quick Reference Guide, 2025. https://tbthinktank.org/wp-content/uploads/2025/09/Paeds-TB-Quick-Ref-Guide_Final_Sept-2025.pdf

³ 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>

⁴ National Department of Health. National Guidelines on the Treatment of Tuberculosis Infection. February 2023. https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-04/Health_Latent%2520TB%2520Infection_2023_web.pdf

⁵ National Department of Health. Updated Clinical Reference Guide: Clinical Management of Rifampicin-Resistant Tuberculosis. September 2023⁵. <https://www.health.gov.za/wp-content/uploads/2023/10/Updated-RR-TB-Clinical-Guidelines-September-2023.pdf>

⁶ DR-TB evidence review ratified by NEMLC in Mar 2023. https://www.health.gov.za/wp-content/uploads/2024/07/WHO-Guideline-Adolopment_Drug-Resistant-TB_4May2023_Final.pdf

Following discussion at NEMLC together with TB programme representatives, it was proposed that a common age cut off of 15 years be used for both drug-susceptible, and drug-resistant tuberculosis for pragmatic implementation. Thus, the STGs have aligned as follows:

- Drug-susceptible TB (DS-TB): Children eligible < 15 years eligible for treatment shortening.
- Drug-resistant TB (DR-TB): Children ≥ 15 years eligible for BPAL

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”.

Infection prevention and control measures

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

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 disease.⁴

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.

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 shared the same enclosed space with an adult or adolescent with pulmonary TB (e.g. the source patient), for ≥ 1 night 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.”

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 trial.^{Error! Bookmark not defined.} This contrasts with the WHO guideline⁷ which defines non-severe DS-TB as PTB confined to one lobe.

Treatment: Weight-based dosing guidance for RHZE

⁷ WHO operational handbook on tuberculosis. Module 4: treatment and care. Geneva: World Health Organization; 2025.

The NEMLC acknowledges that the dose guidance in sections relating to adults and adolescents ≥ 15 years with DS-TB 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.

The NEMLC also acknowledges the resultant discrepant dose guidance among similar weight bands across the paediatric and adult STG recommendations. These discrepancies in the STGs should be resolved once the final WHO weight banded dose guidance, is made available.

Section 23.1 Drug-susceptible tuberculosis (DS-TB)

STG – New addition

New STG guidance on drug-susceptible TB has been added as tabulated below.

23.1 DRUG-SUSCEPTIBLE TUBERCULOSIS

A15–A19

* 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 or failure to thrive, 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-NAATs 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 and children, a negative TB-NAAT is not an adequate 'rule out' test. Most children with TB disease will not have microbiological confirmation of TB, particularly children with severe or extrapulmonary disease. Negative TB-NAAT and culture results should be reviewed in the context of the history and clinical and radiological findings of the child. Treatment may be started if overall picture suggests TB, even if the TB-NAAT or culture is negative.

PLWH who have features of TB but are TB-NAAT negative require further investigation (e.g. chest X-ray, TB culture) and may need empiric anti-tuberculosis therapy. Perform a urine lipoarabinomannan (U-LAM) in PLWH with signs and symptoms of pulmonary and/or extrapulmonary TB seen in an outpatient setting with:

- A CD4 $\leq$ 200 or $\leq$ 25% (if $<$ 5 years) within the last 6 months **OR**
- Advanced HIV disease **OR**
- Current serious illness warranting admission to hospital.

Section 23.1.1 Perinatal tuberculosis

STG – New addition

New STG guidance on the management of perinatal TB has been added.

The following sections were added as aligned to the Paediatric Hospital Level STGs and EML:

- Description
- History of Exposure
- Clinical Presentation
- Referral to TPT section for patient exposed with no signs of active disease.
- Referral

All management of infants with TB exposure and clinical assessment of suggestive of TB, or TB exposure with no indication of active TB is to be referred for management at a Hospital Level.

Perinatal TB Preventative Therapy (TPT)

For Perinatal TPT, a cross-reference to the paediatric TPT section has been added.

The referral was added as follows

REFERRAL

- » All infants with a significant TB exposure with clinical assessment suggestive of TB for hospital TB work-up.
- » All infants with significant TB exposure with no indication of active TB to a medical officer at primary care level for initiation of TPT (see section 23.3.1 Tuberculosis Prevention Therapy for Drug-susceptible Tuberculosis Exposure).
- » Perinatal TB with a history of exposure to a person diagnosed with drug-resistant TB – discuss with an expert.

Section 23.1.2 Tuberculosis in children and adolescents (<15 years)

STG Update

STG guidance on the management of TB in children and adolescents (<15 years) has been amended.

Definition of a significant exposure: Added

The following text was added:

A child or adolescent is considered to have had a significant TB exposure if within the 12 months before presentation with presumed TB, they shared an enclosed space with an adult or adolescent with pulmonary TB for ≥ 1 night OR for frequent or extended daytime periods (e.g. at school or creche). 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.

Treatment course duration: Amended

For non-severe TB, the course of therapy was amended from a 4-month continuation phase to a 2-month continuation phase. This change was already NEMLC approved and incorporated in the Paediatric Hospital Level STGs and EML 2023 Edition. Additionally, this updated is in line with the National TB guidelines: Management of Tuberculosis in children and adolescents, as well as the WHO guidelines.⁸ This change is based on SHINE trial.⁹

Ethambutol: Added

The treatment regimens for children under the age of 8 years previously recommended a 3-drug intensive phase regimen of rifampicin, isoniazid and pyrazinamide. This has been updated to be a 4-drug intensive phase regimen, with ethambutol as the 4th drug. This is in line with the National TB guidelines: Management of Tuberculosis in children and adolescents.

The change is based on the SHINE trial⁵, where majority of patients received ethambutol as 4th drug. Change approved at NEMLC meeting in May 2024.

Rifampicin/Isoniazid 60/60mg formulation dosing table: Deleted

The World Health Organization (WHO) dispersible formulations of rifampicin, isoniazid and pyrazinamide (RHZ 75/50/150mg and RH 75/50mg) have been included as the preferential dosing formulation. The RH 60/60mg formulation historically included will no longer be included on tender, due to the preferential dispersible formulations

Pyridoxine: Amended

⁸ 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>

⁹ Turkova A, Wills GH, Wobudeya E, Chabala C, Palmer M, Kinikar A, et.al. Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children (SHINE). The New England Journal of Medicine. 2022, 386 (10): 911-922.

The pyridoxine indication and use were updated in line with the National TB Guidelines for Children and Adolescent.¹ The used was extended to include breastfed infants and children > 8 years. Additionally, a definition was provided for malnourished.

The text was amended as follows:

Breastfed infants, children > 8 years of age, CALHIV, malnourished children, and children with existing neuropathy should receive pyridoxine in addition to TB treatment. Acute malnutrition refers to wasting (weight-for-length/height z score less than -2); mid upper arm circumference (MUAC) less than 12.5 cm; or bilateral pitting oedema. - Pyridoxine, oral, daily for 6 months. - Body weight < 6 kg: 6.25 mg (¼ tablet). - Body weight ≥ 6 kg but age < 5 years: 12.5 mg (½ tablet). - Age ≥ 5 years: 25 mg (1 tablet).
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Common Adverse Drug Reactions: Added

Common adverse effects table added with cross-reference to appropriate management guidance.

Table inserted as follows:

Common adverse effects of TB medicines in children

Adverse effect	Responsible drug	Management
Hepatotoxicity (e.g. jaundice, new or persistent nausea, vomiting, tender or enlarged liver)	Pyrazinamide, ethionamide, isoniazid, rifampicin.	» Stop TB treatment and other hepatotoxic drugs (e.g. antiretroviral or cotrimoxazole) immediately. » For further management of refer to Management of Tuberculosis in Children and Adolescents. A Clinical Guideline for the Diagnosis and Treatment of Drug-susceptible TB in Children and Adolescents in South Africa. September 2024: Section 14.4 Management of Adverse Drug Events.
Gastrointestinal intolerance (e.g. nausea, vomiting, abdominal pain)	Most DSTB medicines	» If jaundiced or tender, enlarged liver, or new/persistent vomiting, stop all anti-TB treatment immediately and refer urgently. » If nausea/vomiting only after taking TB treatment without jaundice or tender/enlarged liver, advise to take treatment after eating or at night. If symptoms persist after 1 week, discuss/refer.
Joint pain	Pyrazinamide	Symptomatic treatment with paracetamol 15 mg/kg (maximum 1g) 6 hourly as needed for 5 days.
Peripheral neuropathy (e.g. tingling pain or burning or numbness in hands and feet)	Isoniazid	• Ensure taking pyridoxine: ○ Children < 6 kg: 6.25 mg (¼ tablet) ○ Children ≥ 6 kg but aged < 5 years old: 12.5 mg (½ tablet) daily. ○ Children: ≥ 5 years old: 25 mg (1 tablet) daily). - If already on pyridoxine and not responding – discuss/refer all cases. Note: Drug-induced peripheral neuropathy can be irreversible if the offending drug is not stopped promptly.
Dark or orange urine	Rifampicin	Reassure the child or adolescent and caregivers that this is normal and to be expected while taking rifampicin. No intervention required.
Rash	All DS-TB medicines	» 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 medicines and refer urgently to hospital.
Optic neuritis (e.g. change in vision or visual impairment)	Ethambutol	Stop ethambutol immediately. Refer to ophthalmology for urgent assessment.

Section 23.1.3 Tuberculosis in adults and adolescents (≥ 15 years)

STG Update

STG guidance on the management of TB in adults and adolescents (≥ 15 years) has been amended as tabulated below, with the addition of monitoring guidance.

AMENDED FROM	AMENDED TO														
17.4.1 PULMONARY TUBERCULOSIS (TB) IN ADULTS	23.1.3 TUBERCULOSIS IN ADULTS AND ADOLESCENTS (≥ 16 years)														
A15.0-3/A15.7-8/A16.0-2/A16.4/A16.7-9 + (B20.0)	A15.0-3/A15.7-8/A16.0-2/A16.4/A16.7-9 + (B20.0)														
DIAGNOSIS	TB guidelines are updated regularly.														
Pulmonary TB is diagnosed on sputum by TB nucleic acid amplification tests (TB-NAAT) such as Xpert® MTB/RIF Ultra, sputum smear, or culture.	Consult the most recent National Tuberculosis Control Programme Guidelines.														
» Send 1 sputum specimen for TB-NAAT.	DESCRIPTION														
- If TB-NAAT is unsuccessful: collect another sample and repeat TB-NAAT.	Pulmonary tuberculosis (PTB) refers to infection of the lung tissue or airways caused by <i>M. tuberculosis</i> and may present with cough, fever, weight loss and night sweats. Extrapulmonary TB (EPTB) refers to <i>M. tuberculosis</i> infection occurring outside the lungs such as the lymph nodes, pleura, pericardium, central nervous system and bones and joints. EPTB is more common in PLWH. EPTB may also present with weight loss, night sweats, and fever, as well as other symptoms depending 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.														
- If TB-NAAT is trace (only applies to Xpert® MTB/RIF Ultra): If the clinical presentation and chest X-ray are suggestive of TB, treat for drug-sensitive TB (DS-TB), and collect sputum specimen for TB culture and drug sensitivity testing (DST). If the patient is asymptomatic, with no abnormalities on chest X-ray, continue routine care with close follow-up for features of TB.	The most common sites of extrapulmonary TB are listed below along with commonly associated signs and symptoms:														
- If TB-NAAT is positive and susceptible to rifampicin: treat for DS-TB and send a sputum specimen for baseline smear microscopy (the smear is used for reporting, not for diagnosis).	<table border="1"> <thead> <tr> <th data-bbox="678 951 919 1001">Extrapulmonary TB type</th><th data-bbox="1003 951 1382 976">Common presenting signs/symptoms</th></tr> </thead> <tbody> <tr> <td data-bbox="678 1003 919 1138">TB lymphadenitis</td><td data-bbox="938 1003 1458 1138"> » Peripheral TB lymphadenopathy occurs in neck and armpits. Typically nodes are large (> 2 cm), tender, non-symmetrical, matted, firm to fluctuant and rapidly growing. » Audible wheeze or typical brassy cough caused by large mediastinal lymph nodes. </td></tr> <tr> <td data-bbox="678 1144 919 1341">TB pleural effusion (usually unilateral)</td><td data-bbox="938 1144 1458 1341"> » 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. </td></tr> <tr> <td data-bbox="678 1348 919 1415">TB empyema</td><td data-bbox="938 1348 1458 1415"> » Similar to pleural effusion, but aspiration reveals thick pus. </td></tr> <tr> <td data-bbox="678 1421 919 1535">TB of spine, bones and joints</td><td data-bbox="938 1421 1458 1535"> » 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). </td></tr> <tr> <td data-bbox="678 1541 919 1684">TB pericarditis</td><td data-bbox="938 1541 1458 1684"> » 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). </td></tr> <tr> <td data-bbox="678 1690 919 1885">TB meningitis</td><td data-bbox="938 1690 1458 1885"> » 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 </td></tr> </tbody> </table>	Extrapulmonary TB type	Common presenting signs/symptoms	TB lymphadenitis	» Peripheral TB lymphadenopathy occurs in neck and armpits. Typically nodes are large (> 2 cm), tender, non-symmetrical, matted, firm to fluctuant and rapidly growing. » Audible wheeze or typical brassy cough caused by large mediastinal lymph nodes.	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.	TB empyema	» Similar to pleural effusion, but aspiration reveals thick pus.	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).	TB pericarditis	» 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).	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
Extrapulmonary TB type	Common presenting signs/symptoms														
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TB pericarditis	» 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).														
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														
- If TB-NAAT is positive, susceptible to rifampicin and resistant to isoniazid: treat for isoniazid mono-resistant TB (See Section 17.4.4.1: Isoniazid mono-resistant tuberculosis in adults). Collect sputum sample for reflex testing of fluoroquinolone susceptibility.															
- If TB-NAAT is positive and rifampicin unsuccessful: start DS-TB treatment and collect another sputum sample for smear, culture and drug sensitivity testing (DST). Follow-up culture and DST results.															
- If TB-NAAT is positive and resistant to rifampicin (with or without isoniazid resistance): treat for rifampicin resistant TB and send sputum sample for further reflex testing and DST.															
- If TB-NAAT is negative and patient is living with HIV: send sputum for TB culture and perform chest X-ray. If CD4 <200 within the last 6 months and they have signs and symptoms of TB (pulmonary or extrapulmonary), the patient has advanced HIV disease or															

the patient is currently seriously ill and requiring hospitalization, perform urine LAM (U-LAM) test. - If TB-NAAT is negative and patient is HIV negative: treat with antibiotics and consider further investigation only if symptoms persist.	- vomiting - neck stiffness
Note: Patients with a history of TB can remain TB-NAAT positive for several years after completion of appropriate anti-TB treatment. To diagnose a new episode of TB in previously treated patients, send sputum for smear microscopy and culture instead.	Disseminated/miliary TB » Fever. » Cough. » Generalised lymphadenopathy. » Hepatomegaly. » Consider in febrile patients presenting with HIV wasting syndrome
	TB abdomen/peritoneum » Ascites with no signs of portal hypertension. » Possible palpable abdominal masses. » Possible bowel obstruction.

Table 23.4 Common presenting signs and symptoms of EPTB

DIAGNOSIS
PTB is diagnosed on sputum by TB-NAAT smear microscopy, or TB culture.

In people with suspected TB:

- » Send 1 sputum specimen for TB-NAAT
- » Manage results of TB-NAAT, based on the patient's previous history of TB, as outlined in Figure 23.2, 23.3 and 23.4 below.
- » All patients with *M. tuberculosis* (MTB) detected on TB-NAAT require additional sputum to be sent at baseline for smear microscopy for acid-fast bacilli (AFB) to allow for monitoring of treatment. TB-NAAT should not be used for monitoring of treatment.
- » Patients who are at risk of drug-resistant TB (e.g. previous episode of TB treatment, prisoners, health care 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.

GENERAL MEASURES

- » Counsel patients about the disease and infection control in the home. Explain the importance of completing treatment.
- » Advise against the use of tobacco and excessive alcohol.
- » If more than two doses of treatment are missed, extra effort should be made to identify and manage any problems the patient might have.

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

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

- » Use of alternative contraceptive methods, such as IUD or DMPA, should be advised.

OR

- » Women choosing to use a progestin-only subdermal implant should be advised to use additional contraception for the duration of TB therapy. See Section 11.1: Antiretroviral therapy, adults and adolescents.

CAUTION
Antiretroviral medicines frequently interact with TB medicines.
Consult the National Department of Health antiretroviral treatment guidelines.

Dose adjustment 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.

Intensive phase of treatment:

- Alternate day dosing of RH and RHZE.
 - Administer standard weight-based dosing of RH on Tuesday, Thursday, Saturday, Sunday.

Patients not treated for TB within the last 2 years

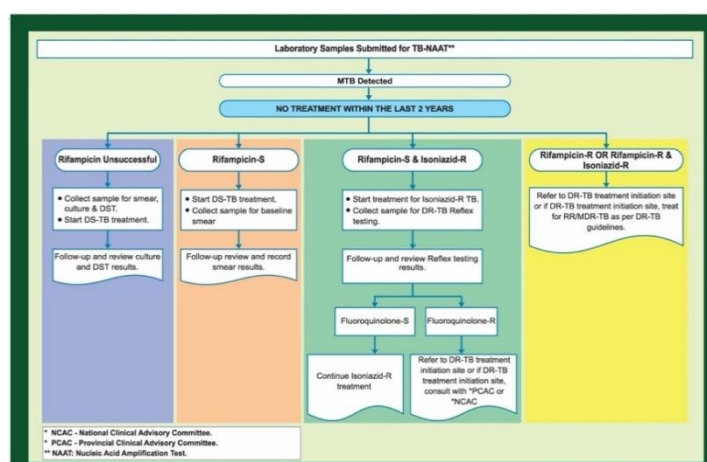


Figure 23.2 TB NAAT Diagnostic Algorithm 1 - Guidance on managing TB-NAAT "MTB detected" results in patients NOT treated for TB within the last 2 years (Source: NDoH TB Program)

AND

- Administer standard weight-based dosing with RHZE on Monday, Wednesday, Friday.

Continuation phase of treatment:

- Rifampicin and isoniazid
 - Do not require dose adjustment. Continue daily weight-based dosing of RH.

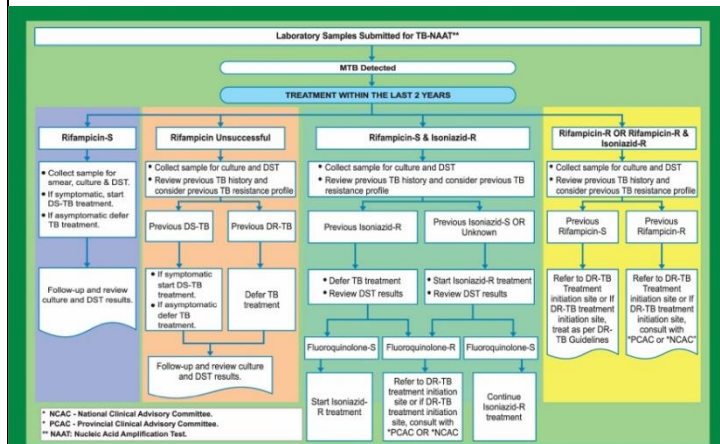
Adverse effects of TB medicines include:

- » Nausea:
 - Taking medicines with meals can minimise nausea.
 - Hepatitis must be excluded, if there is new onset nausea. Request serum alanine aminotransferase test urgently in these patients.
- » Hepatitis (drug induced liver injury):
 - Rifampicin, isoniazid and pyrazinamide may cause hepatitis. Cotrimoxazole and antiretrovirals (efavirenz, nevirapine, lopinavir + ritonavir) can also cause hepatitis.
 - Patient may present with jaundice and/or complaining of hepatitis symptoms (e.g. nausea, malaise, abdominal pain).
 - Refer to hospital for urgent (same day) ALT and further management.
 - If jaundiced, stop TB treatment and medicines known to cause hepatitis before referring. See Section: 11.1: Antiretroviral therapy, adults and adolescents (Rifampicin-based TB treatment).
- » New onset skin rash:
 - Refer if suspected drug rash.
- » Neuropathy:
 - Can be prevented by taking pyridoxine.
- » Arthralgia:
 - Exclude gout and treat symptomatically.

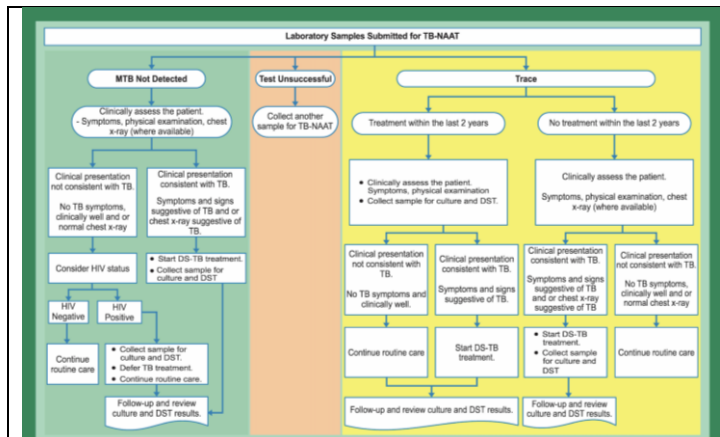
**17.4.1.2 TB CONTROL PROGRAMME:
MEDICINE REGIMENS IN
ADULTS**

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

Patients treated for TB within the last 2 years



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 need empiric anti-tuberculosis therapy.

- » Perform a U-LAM test in 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).

Treatment should be given once daily, **seven days per week**, in both the intensive and continuation phases.
R – Rifampicin
H – Isoniazid
Z or PZA– Pyrazinamide
E or EMB – Ethambutol

Pre-treatment body weight Kg	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
≥71kg	5 tablets		2 tablets

» Adhere to the correct dose and the duration of treatment.

» Weigh patient frequently and adjust the dose according to current weight.

» 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 shared the same enclosed space with an adult or adolescent with pulmonary TB (e.g. the source patient), for ≥ 1 night 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.

» Explain the importance of completing treatment.

» Advise against the use of tobacco and excessive alcohol.

» If more than two doses of treatment are missed, extra effort should be made to identify and manage any problems the patient might have.

Monitoring

» Patients with pulmonary TB 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 23.5 below for the timing of sputum examinations and the recommended actions based on results.

» 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.

Table 23.5. Sputum smear microscopy monitoring in patients with drug-susceptible TB

End of Intensive Phase	
Timing of sputum examinaiton	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 24 th 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

All adults and adolescents ≥ 16 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 23.5 below).

Treatment for known or presumed drug-sensitive PTB:

- Rifampicin/isoniazid/pyrazinamide/ethambutol, oral, daily for 2 months.

Followed by rifampicin/isoniazid, oral, daily for 4 months.

- Weigh the patient frequently and adjust the dose according to current weight.
- Administer the total daily amount of each medicine in one dose and not as divided doses.

Table 23.5: Weight-based dosing guidance for adults and adolescents ≥ 15 years with drug-susceptible TB

Body weight	Two months intensive phase	Four months continuation phase (Extend continuation phase to 7 months for TB meningitis and osteoarticular TB)	
	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, oral, 25 mg, 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 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 11.1 ART in adults and adolescents, for guidance on managing interaction with other types of ART, 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 treatment phase: • RHZE: Administer standard weight-based dosing with RHZE on Monday, Wednesday, Friday. • RH: Administer standard weight-based dosing with RH on Tuesday, Thursday, Saturday, Sunday. <table><tr><td></td><td>Sun</td><td>Mon</td><td>Tues</td><td>Wed</td><td>Thu</td><td>Fri</td><td>Sat</td></tr><tr><td>RHZE</td><td>Skip</td><td>Take</td><td>Skip</td><td>Take</td><td>Skip</td><td>Take</td><td>Skip</td></tr><tr><td>RH</td><td>Take</td><td>Skip</td><td>Take</td><td>Skip</td><td>Take</td><td>Skip</td><td>Take</td></tr></table> Continuation phase of treatment: • RH: No dose adjustment required. Continue daily weight-based dosing with RH.		Sun	Mon	Tues	Wed	Thu	Fri	Sat	RHZE	Skip	Take	Skip	Take	Skip	Take	Skip	RH	Take	Skip	Take	Skip	Take	Skip	Take
	Sun	Mon	Tues	Wed	Thu	Fri	Sat																		
RHZE	Skip	Take	Skip	Take	Skip	Take	Skip																		
RH	Take	Skip	Take	Skip	Take	Skip	Take																		
	Common adverse drug reactions associated with DS-TB medicines: <table><tr><th>Adverse effect</th><th>Responsible drug</th><th>Management</th></tr><tr><td>Hepatotoxicity (e.g. jaundice, nausea, malaise, abdominal pain)</td><td>Rifampicin, isoniazid, pyrazinamide</td><td>Exclude drug-induced liver injury/hepatitis – refer to hospital for urgent (same day) ALT and further management.</td></tr><tr><td>Gastrointestinal intolerance (nausea, vomiting, anorexia)</td><td>Most DS TB medicines</td><td>Exclude drug-induced liver injury/hepatitis – refer for urgent (same day) ALT and further management. 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.</td></tr><tr><td>Joint pain</td><td>Pyrazinamide</td><td>Exclude gout.</td></tr></table>	Adverse effect	Responsible drug	Management	Hepatotoxicity (e.g. jaundice, nausea, malaise, abdominal pain)	Rifampicin, isoniazid, pyrazinamide	Exclude drug-induced liver injury/hepatitis – refer to hospital for urgent (same day) ALT and further management.	Gastrointestinal intolerance (nausea, vomiting, anorexia)	Most DS TB medicines	Exclude drug-induced liver injury/hepatitis – refer for urgent (same day) ALT and further management. 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.												
Adverse effect	Responsible drug	Management																							
Hepatotoxicity (e.g. jaundice, nausea, malaise, abdominal pain)	Rifampicin, isoniazid, pyrazinamide	Exclude drug-induced liver injury/hepatitis – refer to hospital for urgent (same day) ALT and further management.																							
Gastrointestinal intolerance (nausea, vomiting, anorexia)	Most DS TB medicines	Exclude drug-induced liver injury/hepatitis – refer for urgent (same day) ALT and further management. 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 Section 20 Pain).
	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 15.10.3 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 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 medicines and refer urgently to hospital.
	Thrombocytopenia and/or purpura or petechial rash	Rifampicin	If petechial rash, refer to hospital for urgent (same day) platelet count. If thrombocytopenia, stop rifampicin.
	Optic neuritis (e.g. change in vision or visual impairment)	Ethambutol	Stop ethambutol immediately. Refer to ophthalmology for urgent assessment.
	<i>Also see: Medicine Information Centre: Management of suspected drug-induced rash, kidney injury and liver injury in adult patients on DS-TB treatment and/or antiretroviral treatment. November 2024</i> https://mic.uct.ac.za/sites/default/files/media/documents/mic_uct_ac_za/2157/ade-booklet.pdf Table 23.6: Common Adverse drug reactions associated with DS TB medicines REFERRAL » All suspected cases of extrapulmonary TB (other than microbiologically confirmed TB lymphadenitis and simple TB pleural effusion) should be referred for diagnosis and further management. » All patients who cannot be managed on an ambulatory basis because of clinical severity, infection and prevention control challenges in the home, and/or unstable social circumstances, requiring intensive multidisciplinary management. » All patients with poor response to TB treatment, including non-resolving TB pleural effusions. Suspect an incorrect diagnosis of TB pleural effusion if the effusion does not improve on the CXR after 3 months of treatment, or if the patient deteriorates. » Patients with suspected adverse drug reactions (ADR) requiring hospitalisation (e.g. drug-induced liver injury, severe cutaneous adverse reactions), single drug combinations, or individualised regimens.		

Section 23.2 Drug-resistant tuberculosis (DR-TB)

STG –Updated

STG guidance on the management of drug-resistant TB has been amended as tabulated below:

AMENDED FROM:	AMENDED TO:												
17.4.4 DRUG-RESISTANT TUBERCULOSIS (MDR TB)	23.2 DRUG-RESISTANT TB												
Drug-resistant TB (DR-TB) guidelines are updated regularly. Consult the most recent National DR-TB Programme Guidelines.	U50, U50.9, U50.91 See the National Department of Health Updated Clinical Reference Guide: Clinical Management of Rifampicin-Resistant Tuberculosis , September 2023												
DESCRIPTION Isoniazid mono-resistant TB is TB disease caused by <i>M. tuberculosis</i> that is resistant to isoniazid, but susceptible to rifampicin. Rifampicin resistant tuberculosis (RR-TB) is TB disease caused by <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 a strain of <i>M. tuberculosis</i> that is resistant to rifampicin 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.	DESCRIPTION Key definitions and terminology for drug-resistant tuberculosis. <table border="1" data-bbox="824 621 1464 1050"> <thead> <tr> <th data-bbox="824 621 1062 646">Drug Resistance Terminology</th><th data-bbox="1065 621 1464 646"></th></tr> </thead> <tbody> <tr> <td data-bbox="824 646 1062 697">Monoresistant TB</td><td data-bbox="1065 646 1464 697">Resistant to only one anti-TB drug, without resistance to other drugs</td></tr> <tr> <td data-bbox="824 697 1062 747">Rifampicin-resistant TB (RR-TB)</td><td data-bbox="1065 697 1464 747">Resistant to rifampicin ± resistance to another anti-TB drug</td></tr> <tr> <td data-bbox="824 747 1062 798">Multidrug resistant TB (MDR-TB)</td><td data-bbox="1065 747 1464 798">Resistant to rifampicin AND isoniazid (± resistance to other anti-TB drugs)</td></tr> <tr> <td data-bbox="824 798 1062 873">Pre-extensively drug-resistant TB (Pre-XDR-TB)</td><td data-bbox="1065 798 1464 873">Resistant to rifampicin (± resistant to isoniazid) AND resistant to fluoroquinolones</td></tr> <tr> <td data-bbox="824 873 1062 1050">Extensively drug-resistant TB (XDR-TB)</td><td data-bbox="1065 873 1464 1050">Resistant to: • Rifampicin (± resistant to isoniazid), AND • At least one fluoroquinolone (levofloxacin or moxifloxacin) AND • Bedaquiline OR linezolid </td></tr> </tbody> </table> Table 23.7: Key definitions and terminology for drug-resistant TB Diagnosis All people with signs and symptoms of TB should have specimens sent as part of the diagnostic work-up. Molecular tests (e.g. TB nucleic acid amplification tests, TB-NAAT), smear microscopy and TB culture are used to diagnose TB by identifying <i>M. tuberculosis</i> in sputum and other samples (e.g. urine, cerebrospinal fluid, pleural fluid, ascitic fluid, lymph node aspirate, and in children stool). TB-NAAT testing is also used to rapidly determine drug susceptibility. 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. All people who test positive for <i>M. tuberculosis</i> with rifampicin resistance will have DR-TB reflex testing that includes TB microscopy, culture, Xpert® MTB/XDR testing for fluoroquinolone resistance, and phenotypic drug susceptibility testing for bedaquiline and linezolid if culture positive. Many children will not have microbiological confirmation of DR-TB by TB-NAAT or culture due to paucibacillary or extrapulmonary disease. In these children, DR-TB is suspected based on evidence of TB disease (e.g. history, clinical examination, and radiological investigations) and a recent DR-TB exposure or if the child is not responding to first-line TB treatment despite good adherence. In these	Drug Resistance Terminology		Monoresistant TB	Resistant to only one anti-TB drug, without resistance to other drugs	Rifampicin-resistant TB (RR-TB)	Resistant to rifampicin ± resistance to another anti-TB drug	Multidrug resistant TB (MDR-TB)	Resistant to rifampicin AND isoniazid (± resistance to other anti-TB drugs)	Pre-extensively drug-resistant TB (Pre-XDR-TB)	Resistant to rifampicin (± resistant to isoniazid) AND resistant to fluoroquinolones	Extensively drug-resistant TB (XDR-TB)	Resistant to: • Rifampicin (± resistant to isoniazid), AND • At least one fluoroquinolone (levofloxacin or moxifloxacin) AND • Bedaquiline OR linezolid
Drug Resistance Terminology													
Monoresistant TB	Resistant to only one anti-TB drug, without resistance to other drugs												
Rifampicin-resistant TB (RR-TB)	Resistant to rifampicin ± resistance to another anti-TB drug												
Multidrug resistant TB (MDR-TB)	Resistant to rifampicin AND isoniazid (± resistance to other anti-TB drugs)												
Pre-extensively drug-resistant TB (Pre-XDR-TB)	Resistant to rifampicin (± resistant to isoniazid) AND resistant to fluoroquinolones												
Extensively drug-resistant TB (XDR-TB)	Resistant to: • Rifampicin (± resistant to isoniazid), AND • At least one fluoroquinolone (levofloxacin or moxifloxacin) AND • Bedaquiline OR linezolid												

	children, treatment should be based the drug susceptibility testing of the <i>M. tuberculosis</i> strain from the most likely source patient. Suspect drug-resistant TB when any of the features listed below is present: » Contact with a known source patient with drug-resistant TB or high-risk source patient, e.g., recently released from prison or not improving on DS-TB therapy. » A patient with confirmed treatment adherence that remains smear positive after 2 months of 1st line TB treatment. » Any patient with TB who failed to improve or got worse on TB treatment. » Patients who were lost to follow-up on TB treatment (>2 months treatment interruption). » History of treatment interruption (<1 month) or relapse at some point during their TB therapy. » Patients with recurrent TB disease after completion of TB treatment (re-treatment case). 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 and educate patients and/or caregivers 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 by sputum collection for TB-NAAT to detect TB disease and determine susceptibility. A contact is any person that shared the same enclosed space with an adult or adolescent with pulmonary TB (e.g. the source patient), for ≥ 1 night 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
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	duration of DR-TB treatment to avoid becoming pregnant. » For children, ensure the caregiver can confidently crush, mix and give the correct volume of medicines themselves at every visit.
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Section 23.2.1 Isoniazid monoresistant tuberculosis

Section 23.2.1.1 Isoniazid monoresistant tuberculosis in Adults

STG guidance on the management of isoniazid monoresistant TB in adults has been amended as tabulated below.

AMENDED FROM	AMENDED TO

17.4.4.1 ISONIAZID MONO-RESISTANT TUBERCULOSIS IN ADULTS A15.0-3/A15.7-8/A16.0-2/A16.4/A16.7-9 + (U50.00-01+U50.10-11) + (B20.0) MEDICINE TREATMENT <u>Confirmed isoniazid mono-resistant TB:</u> • RHZE at standard doses. (See Section 17.4.1: Pulmonary Tuberculosis (TB) in adults.) AND • Levofloxacin, oral, daily ○ 30–45 kg: 750 mg. ○ ≥46 kg: 1 000 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 to 45 kg: 750 mg ○ >46 kg: 1 000 mg Treatment should be given for at least 6 months. REFERRAL All drug resistant tb patients to medical officer at primary care level for initiation of therapy.	Isoniazid monoresistant Tuberculosis A15.0-3/A15.7-8/A16.0-2/A16.4/A16.7-9 + (U50.00-01+U50.10-11) + (B20.0) 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 23.2 and 23.3). 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. Isoniazid monoresistant Tuberculosis In Adults A15.0-3/A15.7-8/A16.0-2/A16.4/A16.7-9 + (U50.00-01+U50.10-11) + (B20.0) U50.00, U50.1, U50.10, U50.11 MEDICINE TREATMENT Treatment should be given for at least 6 months. <u>Confirmed isoniazid monoresistant TB and fluoroquinolone susceptible:</u> • RHZE, oral, daily at standard weight-based dosing for 6 months. AND • Levofloxacin, oral, daily ○ Body weight: 30 to < 46 kg: 750 mg ○ Body weight: ≥ 46 kg: 1000 mg AND Prophylactic 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. <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 to <46 kg: 750 mg ○ ≥46 kg: 1 000 mg REFERRAL » All drug-resistant TB patients to medical officer at primary care level for initiation of therapy. If isoniazid AND fluoroquinolone resistance detected discuss with an expert. » If isoniazid resistance detected late in a patient non-responding to drug-susceptible TB treatment, discuss with an expert.
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Section 23.2.1.2 Isoniazid monoresistant tuberculosis in Children <15 years

New STG added.

Confirmed isoniazid monoresistant TB:

Rifampicin/Isoniazid/Pyrazinamide/Ethambutol: Added

Levofloxacin: Added

Pyridoxine: Added

Confirmed isoniazid monoresistant TB and contraindication to isoniazid

Rifampicin: Added

Ethambutol: Added

Pyrazinamide: Added

Levofloxacin: Added

The following text was included:

MEDICINE TREATMENT

Treatment should be given for at least 6 months.

Confirmed isoniazid monoresistant TB:

- RHZ plus E at standard dosing daily

AND

- Levofloxacin, oral, daily

AND

Breastfed infants, children > 8 years of age, CALHIV, malnourished children, and children with existing neuropathy should receive pyridoxine in addition to TB treatment. Acute malnutrition refers to wasting (weight-for-length/height z score less than -2); mid upper arm circumference (MUAC) less than 12.5 cm; or bilateral pitting oedema.

- Pyridoxine, oral, daily for 6 months.
 - Body weight < 6 kg: 6.25 mg (¼ tablet).
 - Body weight ≥ 6 kg but age < 5 years: 12.5 mg (½ tablet).
 - Age ≥ 5 years: 25 mg (1 tablet).

Target dose (dose range) (mg/kg/day)	Duration 6 months		
	Isoniazid (H): 10 (7-15), Rifampicin (R): 15 (10-20), Pyrazinamide (Z): 35 (30-40), Ethambutol (E): 20 (15-25)		
Formulation	RHZ 75/50/150mg dispersible tablet (scored) OR 75/50/150mg/4ml suspension *	E 400mg tablet (not scored) OR 400mg/8ml suspension #	Levofloxacin 250 mg tablet OR 500 mg tablet OR 25 mg/ml suspension**
Body Weight (kg)			
< 2	Obtain expert advice		
2 – 2.9	½ tab	1 ml	2 ml
3 – 3.9	¾ tab (3 ml)	1.5 ml	3 ml
4 – 4.9	1 tab	2.5 ml	4 ml
5 – 5.9	1 tab	2.5 ml	5 ml or ½ x 250 mg tablet
6 – 7.9	1 tab	2.5 ml	6 ml
8 – 9.9	2 tabs	½ tab or 4 ml	7 ml
10 – 11.9	2 tabs	½ tab or 4 ml	10 mL or 1 x 250 mg tablet
12 – 12.9	3 tabs	¾ tab or 6 ml	
13 – 15.9	3 tabs	¾ tab or 6 ml	15 mL or 1 ½ x 250 mg tablet

16 – 24.9	4 tabs	1 tab or 8 ml	1 x 500 mg tablet or 2 x 250 mg tablet or 20 mL
≥ 25	RHZE 150/75/400/275 mg tablet		
25 – 29.9	2 tabs		1 ½ x 500mg or 3 x 250mg tablets daily
30 – 34.9	3 tabs		
35 – 64.9	4 tabs		2 x 500mg or 4 x 250 mg tablets daily
≥ 65	5 tabs		
Children should be taught and encouraged to swallow whole tablets or, if required, fractions of tablets so as to avoid large volumes of liquid medication * To make an oral suspension, for weight band 3 – 3.9 kg, for each dose, disperse 1 x RHZ 75/50/150 mg tablet (2 months intensive phase) or 1 x RH 75/50 mg tablet (continuation phase) in 4 ml of water, administer 3 ml, discard unused suspension. For other weight bands, an oral suspension can be made by dispersing the required number of tablets & fractions of tablets in a small amount of water (5-10 ml) and administering all of the suspension to the child 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. **For levofloxacin 25mg/ml suspension: Crush and disperse 1 x 250mg tablet in 10 mL water.			

Confirmed isoniazid monoresistant TB AND contraindication to isoniazid:

- Rifampicin, oral, 10 mg/kg daily.

AND

- Ethambutol, oral, 15 mg/kg daily.

AND

- Pyrazinamide, oral, 25 mg/kg daily.

AND

- Levofloxacin, oral, daily.

REFERRAL

- » All drug-resistant TB patients to medical officer at primary care level for initiation of therapy. If isoniazid AND fluoroquinolone resistance detected discuss with an expert.
- » Discuss children with isoniazid-monoresistant TBM, miliary TB or bone/joint TB with an expert as they require a different regimen or duration of treatment.

Section 23.2.2 Rifampicin-resistant, pre-XDR and XDR tuberculosis in adults and adolescents ≥ 15 years

Rifampicin-resistant, pre-XDR and XDR tuberculosis in adults and adolescents ≥ 15 years (6-month BPAL-L regimen)

– **Bedaquiline:** *ADDED*

Rifampicin-resistant, pre-XDR and XDR tuberculosis in adults and adolescents ≥ 15 years (6-month BPAL-L regimen)

– **Linezolid:** *ADDED*

Rifampicin-resistant, pre-XDR and XDR tuberculosis in adults and adolescents ≥ 15 years (6-month BPAL-L regimen)

– **Levofloxacin:** *ADDED*

Rifampicin-resistant, pre-XDR and XDR tuberculosis in adults and adolescents ≥ 15 years (6-month BPAL-L regimen)

– **Pretomanid:** *ADDED*

Rifampicin-resistant, pre-XDR and XDR tuberculosis in adults and adolescents ≥ 15 years (individualised regimens)

– **Clofazimine:** *RETAINED*

Rifampicin-resistant, pre-XDR and XDR tuberculosis in adults and adolescents ≥ 15 years (individualised regimens)

– **Terizidone:** *RETAINED*

Rifampicin-resistant, pre-XDR and XDR tuberculosis in adults and adolescents ≥ 15 years - **Delamanid: Added**
 Rifampicin-resistant, pre-XDR and XDR tuberculosis in adults and adolescents ≥ 15 years (individualised regimens)

– **Ethambutol: RETAINED**

Rifampicin-resistant, pre-XDR and XDR tuberculosis in adults and adolescents ≥ 15 years (individualised regimens)

– **Pyrazinamide RETAINED**

Rifampicin-resistant, pre-XDR and XDR tuberculosis in adults and adolescents ≥ 15 years (individualised regimens)

– **Ethionamide RETAINED**

Rifampicin-resistant, pre-XDR and XDR tuberculosis in adults and adolescents ≥ 15 years - **Para-aminosalicylic acid: Added**

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.¹⁰

A summary of the recently published BEAT TB study, in support of the use of delamanid in pregnant women is tabulated below:

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).							
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

¹⁰ National Department of Health. Clinical Management of **Rifampicin-Resistant Tuberculosis**, September 2023.

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 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 NCAC for individualised regimens.

BPAL regimen – linezolid dose rounding

For the management of RR-TB, the WHO guideline¹¹ recommends a linezolid dose of 450mg daily for individuals weighing 36-46kg which would involve the crushing and mixing of the 600mg tablet to formulate the requisite dose. This dose guidance from the WHO has been adopted by the National TB programme in the National DR-TB guideline,¹² 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)."

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 ≥ 36 kg 600mg [equivalent to 1 X 600mg tablet], and has been published in a subsequent clinical reference guide¹³ - this dose rounding guidance has been included in the STG update.

BPAL-L regimen – age thresholds

NEMLC has applied an age threshold of 14 years and older for eligibility for the BPAL-L regimen as determined in the NEMLC approved adoption of the WHO guideline. However, to align with TB programme and for pragmatic reasons, the age threshold will be 15 years both in drug-susceptible and drug-resistant TB.

¹¹ 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>.

¹² 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>

¹³ 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%2FumWfCqj5DOHzo7oycZyFfErgFh%3Fdomain%3Dmic.uct.ac.za&data=05%7C02%7Czahiera.adam%40health.gov.za%7C1bd3712e20e941ddf36f08dedb67856a%7Ca517371c1316484cac5e98b76127790a%67C0%7C0%7C639189435296952413%7CUnknown%7CTWFPbgZb3d8eylFbXB0eU1hcGkiOnRydWUslYlYjswlJwMDAwMCisilAiOiJXaW4zMislsKF0ljoitWFPbCisldUljoyfQ%3D%3D%7C0%7C%7C%7C&sdata=tY%2BjLsUjfdTNFShhNAAMMunWOCj1i1sLa22FeZauwYIM%3D&reserved=0>

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative. (strong)	We suggest not to use the option (conditional)	We suggest using either the option or the alternative (conditional)	We suggest using the option (conditional)	We recommend the option (strong)
				X	
Recommendation: The PHC/Adult hospital ERC suggests the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and a fluoroquinolone rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients. (Conditional recommendation, very low certainty of evidence) Although WHO recommend moxifloxacin for inclusion in their updated regimen (BPALM), the PHC/Adult hospital level committee suggest that levofloxacin to be used as fluoroquinolone of choice. Rationale: The recommended regimen is shorter in duration, less complex and may be cost-saving, particularly for those patients requiring treatment with current South African long regimens. Additionally, the recommended regimen was judged to probably be feasible and acceptable and to improve equity. However, the committee noted the very low quality of evidence on which WHO recommendations are based. In view of the paucity of evidence, the committee felt that the implementation of operational research and enhanced pharmacovigilance to detect safety signals is essential. Level of Evidence: Very low quality evidence Review indicator: New high quality evidence					
NEMLC RECOMMENDATION (30 March 2023): The committee supports the ERC's adapted recommendation as follows: We suggest the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and a fluoroquinolone rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients. (Conditional recommendation, very low certainty of evidence) Levofloxacin to be used instead of moxifloxacin as fluoroquinolone of choice for inclusion in the revised regimen.					
Monitoring and evaluation considerations Operational research and enhanced pharmacovigilance essential.					
Research priorities Shortened regimens for paediatric and pregnant populations					

STG Update

STG guidance on the management of rifampicin-resistant, pre-XDR and XDR TB in adults and adolescents ≥ 15 years has been amended as tabulated below.

For non-pregnant adults and adolescents (≥ 15 years) with pulmonary or non-severe extrapulmonary (e.g. lymphadenopathy or pleural effusion) RR- or Pre-XDR-TB, the shorter duration BPAL regimen is included in the STG in accordance with the NEMLC evidence review: Adolopment of WHO DRTB Guidelines published in May 2023, full review accessible online: https://www.health.gov.za/wp-content/uploads/2024/07/WHO-Guideline-Adolopment_Drug-Resistant-TB_4May2023_Final.pdf

AMENDED FROM: 17.4.4.2 RIFAMPICIN-RESISTANT TUBERCULOSIS (RR TB), IN ADULTS A15.0-3/A15.7-8/A16.0-2/A16.7-8 + (U50.00-01+U50.20-21) + (B20.0) Never treat for drug resistant TB without laboratory confirmation, either by molecular or phenotypic (culture and sensitivity) results.	AMENDED TO: 23.2.2 RIFAMPICIN-RESISTANT, PRE-XDR AND XDR TUBERCULOSIS IN ADULTS AND ADOLESCENTS ≥ 15 YEARS A15.0-3/A15.7-8/A16.0-2/A16.7-8 + (U50.00-01+U50.20-21) + (B20.0) U50.0, U50.2, U50.20, U50.21, U50.5
GENERAL MEASURES Counsel and educate patients about the disease and its treatment, including treatment duration. Screen all close contacts for signs and symptoms of drug-resistant TB and by sputum sampling to detect early disease. Infection control and cough etiquette is important to limit spread. 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 (NCAC - 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. REFERRAL All drug resistant TB atients to medical officer at primary care level for initiation of therapy.	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. 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 (e.g. lymphadenopathy or pleural effusion) 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 • Levofloxacin, oral, daily for 24 weeks. ◦ 30 to 46 kg: 750 mg. ◦ ≥ 46 kg: 1000 mg. 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		
	Table 23.9: Common adverse drug reactions associated with medicines included in the BPAL-L regimen		
	Adverse drug reaction	Drug responsible	Management
	Anaemia	Linezolid	If Hb < 8 g/dL in first 8 weeks of BPAL-L treatment: Interrupt linezolid treatment and refer to hospital for close monitoring and blood transfusion. 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	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 the 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	- Refer for urgent (same day) ALT. 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 before considering rechallenge. - Rechallenge 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 rechallenged, stop clofazimine, terizidone and delamanid and continue BPAL-(L). If rechallenge 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. Refer patients with severe rash to hospital urgently.

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 require an individualised regimen. Discuss these patients with a TB expert/National Clinical Advisory Committee (NCAC).

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.

REFERRAL

- » All drug-resistant TB patients to medical officer at primary care level for initiation of therapy.
- » If Hb < 8 g/dL, refer for blood transfusion prior to starting linezolid.
- » Patients not eligible for the BPAL-L regimen or in whom bedaquiline, linezolid or pretomanid are prematurely and permanently discontinued due to toxicity require an individualised regimen. Discuss these patients with a TB expert.

	» Patients unable to attend primary care facility for treatment (e.g. too weak to ambulate) » Patients with challenges to instituting infection control in their home. » Recurrent treatment interruption where previous outpatient treatment has been unsuccessful. » All patients with XDR-TB, to be discussed with an expert. » Patients not responding to appropriate TB treatment. » Patients presenting with adverse drug reactions (ADR) requiring admission and/or drug substitution.
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Section 23.2.3 Rifampicin-resistant (RR), pre-XDR and XDR tuberculosis in children and adolescents < 15 years

STG – STG Update

STG guidance on the management of rifampicin-resistant, pre-XDR and XDR TB in children has been updated.

The previous STG on DR-TB only referred to the TB programme guidelines for the management of DR-TB and included basic general measures and referral criteria. For this update the treatment for DR-TB was aligned with the National Department of Health Updated Clinical Reference Guide: Clinical Management of Rifampicin-Resistant Tuberculosis, September 2023¹⁴

Bedaquiline (BDQ): added

Clofazimine (CFZ): added

Delamanid (DLM): added

Ethionamide (ETO): added

High dose isoniazid (hdINH): added

Levofloxacin (LFX): added

Linezolid (LZD): added

Para-amino salicylic acid (PAS): added *(see historically accepted use document)*

Terizidone (TRD): added

See rationale and adoption document^{Error! Bookmark not defined.} of WHO DR-TB 2022 guidelines^{Error! Bookmark not defined.} in section 23.2.2 Rifampicin-resistant, pre-XDR and XDR tuberculosis in adults and adolescents ≥ 15 years. This decision included adolescents ≥ 16

years. The National TB Guidelines for Rifampicin-Resistant TB includes above mentioned medicines as treatment options for children under 15 years. It however indicates that there is no standardised treatment regimen for all children under 15 years of age; and composition and duration of treatment regimens is tailored to individual children and is based on resistance profile of the organism as well as site and severity of the RR-TB disease.

The WHO DR-TB 2022 guidelines made the following recommendations related to children:

¹⁴ 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>

- **Bedaquiline** should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more. *(Strong recommendation, moderate certainty of evidence).*
- **Bedaquiline** may also be included in longer MDR-TB regimens for patients aged 6–17 years. *(Conditional recommendation, very low certainty of evidence)* In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used. *(Conditional recommendation, very low certainty of evidence)*
- **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)*
- **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.

Delamanid

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.¹⁵ Inclusion on the EML is supported by results from the recently published BEAT TB study.¹⁶

NEMLC recommendation:

ERC Recommendation:								
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).							
NEMLC Ratification	Date		Comments/Recommendation					
EML Status	EML		Non-EML – contingent on stated reference price threshold in Rand Value				Non-EML	
	X		☐				☐	
Therapeutic Interchange	If YES:	Alternative medicine/s	Alternative/s SAHPRA registered?	Formulation/s	Equipotent dose/ Dose		If NO, tick box	

¹⁵ National Department of Health. Clinical Management of **Rifampicin-Resistant Tuberculosis**, September 2023.

¹⁶ 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.

	Considerations (if applicable) *		name (INN)			range and dosing interval	
							X
	Trigger for review						

Section 23.3 Tuberculosis preventive therapy (TPT) in children and adolescents

TPT indications retained as NEMLC approved:

Indications for TPT:

- » All asymptomatic children < 5 years and children and adolescents with HIV (CALHIV), who are clinically well, with a normal chest X-ray, irrespective of TST, in close contact with someone with infectious pulmonary TB should receive TPT.

Section 23.3.1 Tuberculosis preventive therapy (TPT) for drug-susceptible tuberculosis exposure

The STG guidance on the management of TPT has been updated.

3RH: Added

Rifampicin/isoniazid 75/50 mg daily for 3 months (3RH)

This use of 3RH is already included in the Paediatric Hospital Level STGs and EML for perinatal TB prophylaxis, and thus this would just be the extension to all children under 25 kg.

The WHO – Consolidated Guidelines on Tuberculosis: Management of tuberculosis in children and adolescents⁶ indicates a 3-month regimen of daily isoniazid plus rifampicin (3RH), in addition to 6-9 months daily isoniazid; regardless of HIV status. **(strong recommendation, moderate to high certainty in the estimates of effect).**

The WHO – Consolidated Guidelines – Module 1: Prevention¹⁷ indicates rifampicin plus isoniazid daily for 3 months should be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for children and adolescents aged < 15 years in countries with a high TB incidence. **(Strong recommendation, low-quality evidence).**

The WHO Prevention module¹⁷ indicates that the benefits of 3RH outweigh the harm, given its safer profile, higher completion rate than with isoniazid monotherapy and the availability of child-friendly fixed-dose combinations of rifampicin and isoniazid. Although the quality of the evidence was low, data on adult populations also support the benefits of 3RH. A systematic review of RCTs on preventive treatment options conducted in 2014¹⁸ showed that the efficacy and the risk for hepatotoxicity are similar for 3RH and isoniazid monotherapy.

¹⁷ WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment, second edition. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO.

¹⁸ Stagg HR, Zenner D, Harris RJ, Muñoz L, Lipman MC, Abubakar I. Treatment of latent tuberculosis infection: a network meta-analysis. Annals of Internal Medicine. 2014;161(6):419-428. doi:10.7326/M14-1019.

Additionally, it was noted that use of 3RH would require fewer resources, given the shorter duration of treatment, which would reduce the number of clinic visits required. The Guideline Development Group agreed that there is no important uncertainty or variation in clients' values and preferences. It also agreed that the acceptability of 3RH is high, given its shorter duration and long use by health-care workers for treatment of active TB disease.

3RH should be prescribed with caution to PLHIV who are on ART because of potential drug–drug interactions; the regimen cannot be co-administered with protease inhibitors or nevirapine.

The medicine treatment text was updated as follows to include the 3RH recommendations:

MEDICINE TREATMENT

- » In HIV-negative children < 25kg, the priority regimen is 3RH (rifampicin plus isoniazid daily for 3 months).
- » In CALHIV, the preferred regimen is 6H (isoniazid daily for 6 months).

If HIV-negative or HIV-exposed not on nevirapine and < 25kg:

- Rifampicin/isoniazid 75/50 mg daily for 3 months

Weight (kg)	RH (Daily) fixed dose combinations		Duration
	75/50 mg	If crushed and mixed in in water	
2 – 2.9	½ tablet	Mix 1 tablet in 4mL of water. Give only 2mL of this mixture.	3 months
3 – 3.9	¾ tablet	Mix 1 tablet in 4mL of water. Give only 3mL of this mixture.	
4 – 5.9	1 tablet	Mix 1 tablet in 4mL of water and give ALL of this mixture.	
6 – 7.9	1 ½ tablets	Mix 1 ½ tablets in 5-10mL of water and give ALL of this mixture.	
8 – 11.9	2 tablets	Mix 2 tablets in 5-10mL of water and give ALL of this mixture.	
12 – 15.9	3 tablets	Mix 3 tablets in 5-10mL of water and give ALL of this mixture.	
16 – 24.9	4 tablets	Mix 4 tablets in in 5-10mL of water and give ALL of this mixture.	
≥ 25	Use adult formulations and doses		

AND

Breastfed infants, malnourished children, and children with existing neuropathy should receive pyridoxine in addition to 3RH. Acute malnutrition refers to wasting (weight-for-length/height z score less than -2); mid upper arm circumference less than 12.5 cm; or bilateral pitting oedema.

- Pyridoxine, oral, daily for 6 months.
 - Body weight < 6 kg: 6.25 mg (¼ tablet).
 - Body weight ≥ 6 kg but age < 5 years: 12.5 mg (½ tablet).

If CALHIV or HIV-exposed on nevirapine:

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

isoniazid, 600 mg, 10 mg/kg daily for 6 months.		
Weight (kg)	Daily isoniazid 100mg tablet	Duration
2 - 3.4	¼ tablet	6 months
3.5 – 4.9	½ tablet	
5 – 7.4	¾ tablet	
7.5 – 9.9	1 tablet	
10 – 14.9	1 ½ tablets	
15 – 19.9	2 tablets	
20 – 24.9	3 tablets (or one 300 mg tablet)	
≥ 25	Use adult formulations (maximum dose 300 mg per day)	

AND

Breastfed infants, CALHIV, malnourished children, and children with existing neuropathy should receive pyridoxine in addition to 6H. Acute malnutrition refers to wasting (weight-for-length/height z score less than -2); mid upper arm circumference less than 12.5 cm; or bilateral pitting oedema.

- Pyridoxine, oral, daily for 6 months.
 - Body weight < 6 kg: 6.25 mg (¼ tablet).
 - Body weight ≥ 6 kg but age < 5 years: 12.5 mg (½ tablet).

- Age ≥ 5 years: 25 mg (1 tablet).

REFERRAL

» All children with significant TB exposure to medical officer at primary care level to exclude TB disease and initiate TPT.

Section 23.3.2 Tuberculosis preventative therapy (TPT) for drug-resistant tuberculosis exposure

STG – STG Update

Guidance on preventive therapy for drug-resistant TB contacts has been updated.

Isoniazid monoresistance (rifampicin-susceptible)

Rifampicin: Dosing table added

The following dosing table was added for guidance, in line with the NDoH Children and Adolescents (0-15 years) Quick Reference Guide, 2025.²

Daily dose		Dose calculation/preparation (depending on available rifampicin formulation)	Notes
< 10 years old	15 mg/kg daily	15 mg/ml solution • Rifampicin 150mg capsule: open capsule into 10 ml of water. 30 mg/ml solution • Rifampicin 300mg capsule: open capsule into 10 ml of water.	If rifampicin alone is unavailable, discuss alternative with expert.
≥ 10 years old	10 mg/kg daily		
		60 mg/ml solution • Rifampicin 600mg capsule: open capsule into 10 ml of water.	

Rifampicin-resistant TB (susceptible for fluoroquinolones):

Levofloxacin: Added.

Levofloxacin is included as a TPT treatment option for rifampicin-resistant TB (susceptible to fluoroquinolone) in the Paediatric Hospital Level STGs and EML. This option was aligned to be included in the PHC rifampicin-resistant TB TPT management.

Dosing table added for levofloxacin or isoniazid options as follows:

Weight	Levofloxacin 250 mg tablet (scored) OR 500 mg tablet (scored)		OR	Isoniazid 100 mg tablet OR 300 mg tablet	
	250 mg tablet	500 mg tablet		100 mg tablet	300 mg tablet
3–4.9 kg	2 mL*			5 mL*	
5–6.9 kg	5 mL* or 0.5 tablet			1 tablet	
7–9.9 kg				1.5 tablets	
10–15.9 kg	1 tablet			2 tablets	
16–23.9 kg	1.5 tablets			3 tablets	1 tablet
24–29.9 kg	2 tablets	1 tablet			
30–35.9 kg	3 tablets	1.5 tablets		4 tablets	1.5 tablets
36–45.9 kg				4.5 tablets	

46–55.9 kg	4 tablets	2 tablets			2 tablets
56–69.9 kg					
≥ 70 kg					
*Dissolution 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.					

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><tr><th>Groups and steps</th><th>Medicine</th><th>Abbreviation</th></tr><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>Ipem–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></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	Ipem–Cln Mpm	Amikacin (or streptomycin) ^h	Am (S)	Ethionamide or prothionamide ⁱ	Eto Pto	P-aminosalicylic acid ^j	PAS		
Groups and steps	Medicine	Abbreviation																																	
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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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Conradie et.al. 2026

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

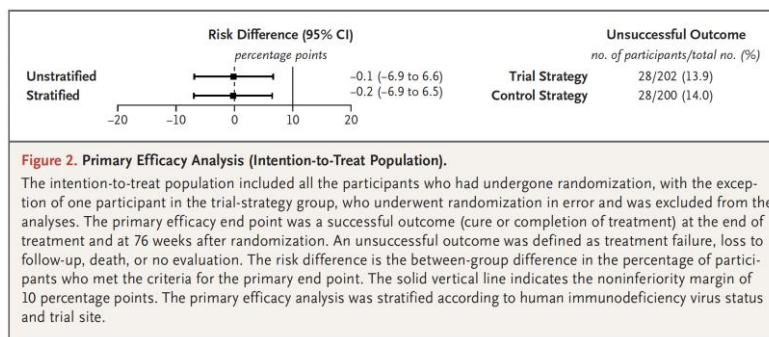
³ Conradie F, Badat T, Poswa A, Rajaram S, Kooverjee S, et.al. A Pragmatic Trial of a 6-month strategy for rifampicin-resistant tuberculosis. NEJM. 2026; 394: 2429-2439.

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> This recommendation has been in place since 2019 <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 (pIPD) 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.
EQUITY	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.		
Clarity of Presentation	Q14	6	Updating described but interval not explicit.	21	100%
	Q15	7	Recommendations specific.		
	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>