Chapter 25

TREATMENT OF MYCOBACTERIAL INFECTIONS

MYCOBACTERIUM TUBERCULOSIS COMPLEX

THE GOALS OF TUBERCULOSIS (TB) DRUG TREATMENT ARE

- To cure the patient of TB
- To prevent death from both active TB and its late effects
- To prevent TB relapse and recurrent disease
- To prevent the development of drug resistance
- To reduce the risk of TB transmission to others

PRINCIPLES OF TREATMENT ARE

- Standardised combination therapy is used
- TB drug-susceptibility testing is essential to guide appropriate therapy
- Short-course therapy – typically six months is advised for drug-sensitive TB
- Drug-resistant TB requires prolonged therapy
- Directly observed treatment (DOT) is advocated – essential for facilitating adherence and preventing the development of drug-resistance
- Ambulatory care should be provided
- Admit for clinical indications/patients that require injectable medication
- Treatment interruption – if treatment is interrupted for less than a month continue treatment and add missed doses at the end of the treatment phase (extend the intensive or continuation phase by the number of days that the patient did not take treatment).

In cases where patients are started on treatment in the absence of laboratory evidence (only clinical and radiological suspicion and no molecular or culture evidence), it is essential that the same clinician(s) who initiated this treatment follow up and re-evaluate the case. Adequate dosing and adherence to short-course TB therapy is essential to treat TB infections and prevent the development of resistance. Doses should be adjusted at end of the intensive phase when the patient's weight is likely to have changed.

IMPORTANT MANAGEMENT POINTS TO ADDRESS WHEN A DIAGNOSIS OF TB HAS BEEN MADE

- Exclude HIV infection
- If HIV-infected, start antiretroviral therapy (see latest recommendations for timing of ART in patients with TB)
- Ask about other children or adults in the household and screen them for TB
- Notify health authorities for recording in the TB register

- Record the diagnosis in the 'Road to Health' card (children)
- Consider referral for nutritional support
- Provide psychosocial support to the child/parents/guardian/patient.

FIRST-LINE TB TREATMENT REGIMENS

Standardised treatment regimens with fixed-dose drug combinations are used as first-line TB treatment. First-line treatment regimens are used to treat drug-sensitive TB and it is essential that, where possible, laboratory confirmation of drug susceptibility is available before starting first-line treatment.

The regimens consist of an intensive phase lasting two months and a continuation phase lasting four months. During the intensive phase, four drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) are used to rapidly kill tubercle bacilli. In the continuation phase, two drugs (isoniazid, rifampicin) are used over a period of four months. The sterilising effect of these drugs eliminates the remaining bacilli and prevents subsequent relapse.

There are now three first-line treatment regimens recommended in South Africa. Regimen 2, the re-treatment regimen, with the addition of streptomycin and a duration of eight months, has fallen away due to the widespread availability of genotypic drug-susceptibility results (GeneXpert PCR and HAIN line probe assays) to confirm or exclude TB drug-susceptibility.

The three first-line regimes for drug-sensitive TB that are currently in use are:

- Regimen 1: Regimen for new and previously treated adults and children > 8 years / > 30 kg.
- Regimen 3A: Regimen for children < 8 years old and < 30 kg with uncomplicated TB disease.
- Regimen 3B: Regimen for children < 8 years and < 30 kg with complicated TB disease

REGIMEN 1: NEW AND PREVIOUSLY TREATED ADULTS AND CHILDREN > 8 YEARS/ > 30 KG

A 'new' case is defined as a patient who has never been treated for TB in the past, or who has taken TB drugs for less than four weeks. A 'previously treated' case refers to a patient who has received TB treatment for four weeks or more in the past.

RECOMMENDED DRUGS AND DOSES FOR ADULTS AND CHILDREN > 8 YRS/ > 30 KG

TB DRUG	MODE OF ACTION	POTENCY	DAILY DOSE (MG/KG)	DOSE RANGE (MG/KG)
Rifampicin (R)	bactericidal	high	10	8–12
Isoniazid (H)	bactericidal	high	5	4–6
Pyrazinamide (Z)	bactericidal	low	25	20 – 30
Ethambutol (E)	bacteriostatic	low	15	15 – 20

NOTE

Fixed-dose combination tablets available for adults and children > 8 yrs/ >30 kg:
Intensive phase: RHZE (150, 75, 400, 275 mg)
Continuation phase: RH (150, 75 mg) and RH (300, 150 mg)

FIXED-DOSE COMBINATION REGIMEN FOR ADULTS AND CHILDREN > 8 YRS/ > 30 KG

	INITIAL PHASE (7 DAYS A WEEK FOR 2 MONTHS)	CONTINUATION PHASE (7 DAYS A WEEK FOR 4 MONTHS)	
BODY WEIGHT (KG)	RHZE (150, 75, 400, 275 MG)	RH (150, 75 MG)	RH (300, 150 MGM)
30–37 kg	2 tablets	2 tablets	
38–54 kg	3 tablets	3 tablets	
55–70 kg	4 tablets		2 tablets
>70 kg	5 tablets		2 tablets

REGIMEN 3A: CHILDREN < 8 YEARS OLD AND < 30 KG WITH UNCOMPLICATED TB DISEASE

This regimen is recommended for the treatment of uncomplicated TB disease. This includes low bacillary load TB disease such as PTB with minimal lung parenchyma involvement, intrathoracic disease (mediastinal/hilar lymph node involvement), TB lymphadenitis and TB pleural effusion.

DRUG	DAILY DOSE (MG/KG)	MAXIMUM DAILY DOSE
Isoniazid (H)	10 -15	300 mg
Rifampicin (R)	10–20	600 mg
Pyrazinamide (P)	30–40	2 g
Ethambutol (E)	15–25	1200 mg

FIXED-DOSE COMBINATION REGIMEN FOR CHILDREN < 8 YEARS OLD AND < 30 KG WITH UNCOMPLICATED TB DISEASE

BODY WEIGHT KG	INTENSIVE PHASE (7 DAYS A WEEK FOR 2 MONTHS)			CONTINUATION PHASE (7 DAYS A WEEK FOR 4 MONTHS)
	RIFAMPICIN/ISONIAZID 60/60 MG TABLETS	PYRAZINAMIDE 150 MG* OR 150 MG/ 3 ML	PYRAZINAMIDE 500 MG TABLETS	RIFAMPICIN/ISONIAZID 60/60 MG TABLETS
2–2.9 kg		1.5 mL	Expert consult	
3–3.9 kg		2.5 mL		
4–5.9 kg	1	3 mL		1
6–7.9 kg	1			1
8–11.9 kg	2			2
12–14.9 kg	3		1	3
15–19.9 kg	3		1	3
20–24.9 kg	4		1	4
25–29.9 kg	5		2	5

*Pyrazinamide: For each dose dissolve 150 mg dispersible (1 tablet) in 3 mL of water to prepare a concentration of 50 mg/mL (150 mg/3mL). Only Pyrazinamide 150 mg or 500 mg tablets may be given at a time depending on availability but not both.

REGIMEN 3B: CHILDREN < 8 YEARS OLD AND < 30 KG WITH COMPLICATED TB DISEASE

This regimen is recommended for the treatment of complicated TB disease. This includes severe forms of TB such as TB pericarditis, abdominal TB, osteo-articular TB and high bacillary load pulmonary TB (smear positive disease, extensive parenchymal involvement on chest x-ray, cavities on chest x-ray). The continuation phase may be prolonged to seven months in slow responders and children who are HIV-infected.

FIXED-DOSE COMBINATION REGIMEN FOR CHILDREN < 8 YEARS OLD AND < 30 KG WITH COMPLICATED TB DISEASE

BODY WEIGHT KG	INTENSIVE PHASE 2 MONTHS				CONTINUATION PHASE 4 MONTHS
	RIFAMPICIN/ ISONIAZID 60/60 MG TABLET(S)	PYRAZINAMIDE 500 MG	PYRAZINAMIDE 150 MG* OR 150 MG/3ML	ETHAMBUTOL 400 MG TABLET OR 400 MG/8 ML **SOLUTION	RIFAMPICIN/ ISONIAZID 60/60 MG TABLET(S)
2–2.9 kg		Expert consult	1.5 mL	1 mL	
3–3.9 kg			2.5 mL	1.5 mL	
4–5.9 kg	1		3 mL	2 mL	1
6–7.9 kg	1			3 mL	1
8–11.9 kg	2			tablet	2
12–14.9 kg	3	1		tablet	3
15–19.9 kg	3	1		1 tablet	3
20–24.9 kg	4	1		1 tablet	4
25–29.9 kg	5	2		1 tablets	5

*Pyrazinamide: For each dose dissolve 150 mg dispersible (1 tablet) in 3 mL of water to prepare a concentration of 50 mg/mL (150 mg/3 mL). Only Pyrazinamide 150 mg or 500 mg tablets may be given at a time depending on availability but not both.

**For each dose, crush 400 mg (1 tablet) to a fine powder and dissolve in 8 mL of water to prepare a concentration of 400 mg/8 mL. Discard unused solution.

EXTRAPULMONARY TUBERCULOSIS

The principles of treating extrapulmonary tuberculosis (EPTB) are the same as for managing pulmonary TB (PTB). For most forms of extrapulmonary tuberculosis (EPTB: lymph node, pleural, genitourinary, etc.) patients can be treated with the standard short-course therapy (i.e. six months).

In some forms of severe or complicated disease such as military TB, TB meningitis, tuberculoma and TB of bones/joints, a longer duration of treatment may be warranted (nine to 12 months guided by clinical response). The intensive phase remains two months and the continuation phase is prolonged accordingly.

ADJUNCTIVE TREATMENT

Pyridoxine (vitamin B6) 25 mg daily is recommended for all adult patients started on TB treatment to prevent INH-associated peripheral neuropathy. The dose can be increased from 50–75 mg if symptoms develop while on treatment (maximum dose 200 mg) until symptoms subside, and then reduced gradually to 25 mg daily. Pyridoxine may be added to the treatment of children who are malnourished or HIV-infected. For children older than five years, give 25 mg daily, and for children younger than 5 years, give 12.5 mg daily.

Corticosteroids is recommended for treatment of tuberculous pericarditis and tuberculous meningitis – give high dose (prednisone 1–2 mg/kg/day) for two to four weeks and then taper off gradually over three to four weeks. Corticosteroids (prednisone 1–2 mg/kg/day for two weeks

and taper off over two weeks) are also recommended in patients on ART who develop TB-IRIS (immune reconstitution inflammatory syndrome) and those with massive lymph node enlargement with pressure effects.

BASELINE SCREENING

PRE-THERAPY SCREENING SHOULD INCLUDE

- HIV ELISA: HIV testing and antiretroviral therapy for HIV-infected patients is essential for all patients with TB
- Baseline weight
- Liver function tests (LFTs) including ALT, AST, total bilirubin and alkaline phosphatase
- Hepatitis B and C serology: since co-infection with hepatitis B and C increases the risk of hepatic toxicity with anti-TB treatment
- Full blood count
- Serum creatinine
- Uric acid: hyperuricaemia is a frequent adverse effect of pyrazinamide

Repeated LFTs are not necessary in patients with normal baseline LFTs. However, they should be repeated in the following settings:

- Abnormal baseline results
- A drug-induced hepatitis is suspected
- Co-existing liver disease, e.g. hepatitis B or C infection, alcohol abuse

MONITORING RESPONSE TO THERAPY

Response to treatment should be assessed clinically and bacteriologically (microscopy for acid-fast bacilli +/– culture). PCR testing should not be used to monitor response to treatment as TB DNA from dead bacilli can be detected for several weeks or months after starting TB treatment giving positive TB PCR results.

All patients diagnosed with PCR/GeneXpert must have a baseline sputum smear result and followed up accordingly.

- Patients with smear-positive PTB are monitored by TB microscopy
- Patients with smear-negative PTB are monitored by TB microscopy and culture
- Patients with EPTB and those without bacteriological confirmation are monitored clinically and radiologically as indicated

Sputum AFB and TB cultures should be requested at the time of completion of the intensive phase of treatment (specimen to be collected a week before the end of week eight) in order to determine smear conversion or identify patients at risk of treatment failure, relapse and drug resistance.

Culture and susceptibility testing should be performed on all patients who are AFB/culture positive at eight weeks, in addition to checking for treatment compliance and evaluating clinically.

The last bacteriological examination should be done towards the end of the maintenance phase (a week before the end of 24 weeks) to determine the final outcome of treatment.

Note: Patients must be weighed at all visits and drug doses adjusted as their weight increases. Failure to adjust the dose can result in treatment failure and the development of TB drug-resistance.

ANTI-TB DRUG RELATED HEPATOTOXICITY

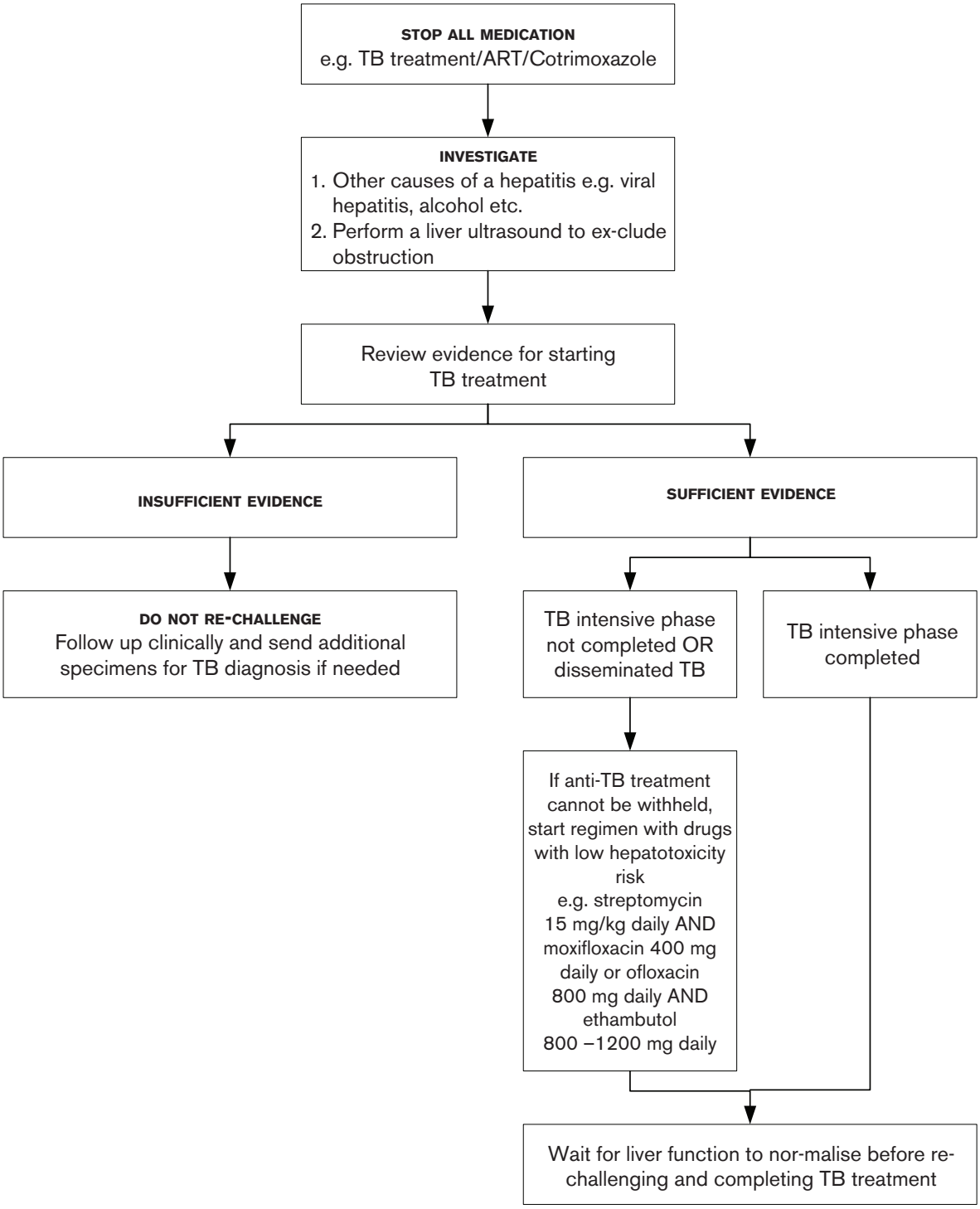
Antituberculous drugs can cause a drug-induced hepatitis. Isoniazid and pyrazinamide are more likely to cause a hepatitis followed by rifampicin. Ethambutol is rarely responsible. Older patients and patients with HIV, alcoholism, malnutrition and chronic hepatitis B or C are at higher risk of developing TB drug-induced hepatitis. Drug-induced hepatitis occurs most commonly in the first two months of treatment, but may occur later. Before starting TB treatment, a baseline ALT should be performed to assess changes once TB treatment is started.

Symptoms of hepatitis include anorexia, nausea, vomiting, fatigue, mild fever, tender hepatomegaly, jaundice and dark urine. Liver function tests should be performed should any suspicious symptoms develop. Patients who develop hepatitis on TB treatment require a full evaluation to determine the cause and severity of the hepatitis.

Case definitions for drug-induced hepatitis, requiring the discontinuation of any hepatotoxic drugs are:

- In symptomatic patients an increase in ALT $\geq$ 3 x the upper limit of normal (ULN)
- In asymptomatic patients an increase in ALT $\geq$ 5 x the upper limit of normal (ULN)

MANAGING HEPATOTOXICITY



REINITIATING ANTI-TB DRUGS

If the patient can be re-challenged, then follow the procedure below once asymptomatic, ALT < 100 μL and conjugated bilirubin is normal. Use full doses according to the patient's weight. Stop the liver friendly TB regimen if used before re-challenging.

DAY	PROCEDURE
D1	Start rifampicin 10 mg/kg/day (max 600 mg/day)
D3	Do ALT on day three and check for any hepatitis symptoms
D4-6	If ALT is normal and the patient asymptomatic, add isoniazid 5 mg/kg/day (max. 300 mg/day)
D7	Do ALT
D8-10	If ALT is normal and the patient asymptomatic, add ethambutol 15 mg/kg/day
D10	Do ALT and if normal consider pyrazinamide 25 mg/kg/day (if in the intensive phase of treatment)
D10-40	Repeat ALT weekly for a month

Construct a new TB regimen using the guidelines for patients who cannot tolerate first-line drugs below. Restart antiretrovirals in HIV-infected patients and reintroduce cotrimoxazole, where needed, when LFTs are acceptable. Dapsone can be used as an alternative if cotrimoxazole is not tolerated.

DO NOT RE-CHALLENGE

- If a patient has fulminant hepatitis with liver failure. Use a liver friendly second-line regimen for 18–24 months with drugs such as moxifloxacin, ethambutol, ethionamide and streptomycin (for two months). Consult an infectious disease expert.
- Do not re-challenge with a drug to which the patients TB is resistant.
- Do not re-challenge with PZA if there was severe liver injury.

TREATMENT OF PATIENTS WHO CANNOT TOLERATE FIRST-LINE DRUGS

INTOLERANCE TO	SUGGESTED REGIMEN
Isoniazid	Moxifloxacin, rifampicin and ethambutol for 12 months Pyrizinamide can be added in the intensive phase
Rifampicin	Moxifloxacin, isoniazid, ethambutol for 18 months Pyrizinamide or streptomycin can be added in the intensive phase
Isoniazid and rifampicin	Moxifloxacin, streptomycin and ethambutol for 18 months
Pyrazinamide	Isoniazid, rifampicin, ethambutol for nine months

TREATMENT OF DRUG-RESISTANT TUBERCULOSIS

Mono-drug-resistant tuberculosis refers to resistance to only one of the first-line agents, i.e. isoniazid or rifampicin or pyrazinamide or ethambutol.

Multi-drug-resistant tuberculosis (MDR-TB) refers to *M. tuberculosis* complex that is resistant to both isoniazid and rifampicin.

Poly-drug-resistance refers to resistance to two or more first-line drugs other than isoniazid and rifampicin.

Extensively drug-resistant tuberculosis (XDR-TB) refers to *M. tuberculosis* complex that is resistant to at least isoniazid, rifampicin, the fluoroquinolones, and at least one of three injectable second-line drugs (amikacin, capreomycin or kanamycin).

Treatment of drug-resistant infections should be extended beyond the standard six months. Second-line anti-tuberculous agents are used for MDR-TB and third-line drugs may have to be used for XDR-TB. Treatment of patients infected with mono- or poly-resistant strains using standardised short-course therapy has been associated with increased risk of treatment failure and further acquired resistance including the development of MDR-TB. The design of regimens for mono- and poly-resistant cases of TB requires experience; personnel who are trained in treating drug-resistant TB and under supervision of the provincial DR-TB clinical review committees. Expert opinion should always be obtained when treating patients with drug-resistant TB.

NOTE

All patients with confirmed DR-TB (XDR, MDR, poly- and mono-drug resistant tuberculosis) must be referred to specialist TB referral centres.

ISONIAZID MONO-RESISTANCE

Treatment of isoniazid mono-resistance has not been evaluated rigorously in randomised controlled trials. Treatment approaches are thus based on expert opinion informed by retrospective or single-arm studies. In general, such strains should be treated with rifampicin, pyrazinamide and ethambutol for six to nine months. Addition of a quinolone may strengthen the regimen for patients with extensive disease. In the setting of low-level resistance to isoniazid (inhA mutations), some experts favour continuation of isoniazid for a duration of six to nine months at maximal doses. The duration of treatment for all these regimens should be guided by clinical and bacteriological response.

RIFAMPICIN MONO-RESISTANCE

Experience has shown that not treating *M. tuberculosis* with rifampicin resistance adequately, leads to poorer outcomes. Treat with a standardised MDR-TB regimen plus isoniazid for a duration of 18 months after culture conversion.

MULTI-DRUG-RESISTANT TUBERCULOSIS

The standardised MDR-TB guideline consists of an intensive phase of at least six months with a five drug regimen followed by a continuation phase of 18 months with four drugs.

Intensive phase: injectable amikacin or kanamycin or capreomycin, oral moxifloxacin, ethionamide/prothionamide, pyrazinamide, cycloserine or terizidone (at least 6 x per week).

Continuation phase: excludes the injectable amikacin or kanamycin (at least 6 x per week).

EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS

The treatment of XDR tuberculosis should include agents to which the organism is susceptible to, based on laboratory drug susceptibility testing. Treatment should be given for at least 18–24 months after culture conversion.

XDR tuberculosis requires individualised treatment given the inability of standardised regimens to accurately address both first-line and second-line treatment resistance.

Any first-line agent to which the isolate is susceptible and any appropriate second-line drugs should be used to achieve a regimen with a minimum of four to five effective drugs.

SECOND-LINE DRUGS FOR TREATING DR-TB (ADULTS)

DRUG	AVERAGE DAILY DOSE	MINIMUM DAILY DOSE	MAXIMUM DAILY DOSE
Streptomycin	15 mg/kg	750 mg	1000 mg
Kanamycin	15 mg/kg	750 mg	1000 mg
Amikacin	15 mg/kg/	750 mg	1000 mg
Capreomycin	15 mg/kg	750 mg	1000 mg
Ethionamide	15–20 mg/kg	500 mg	750 mg
Prothionamide	15–20 mg/kg	500 mg	750 mg
Pyrizinamide	20–30 mg/kg	1200 mg	1600 mg
Levofloxacin	7.5–10 mg/kg	750 mg	1000 mg
Moxifloxacin	400 mg	400 mg	400 mg
Ethambutol	15–20 mg/kg	1000 mg	1200 mg
Terizidone	15–20 mg/kg	500 mg	750 mg
Cycloserine	10–20 mg/kg	500 mg	750 mg
PAS	150 mg/kg	8 g	12 g

THIRD-LINE DRUGS

Sometimes referred to as repurposed drugs: linezolid, clofazimine, thiocetazone, macrolides, imipenem and amoxicillin-clavulanate. These drugs are not specifically developed for TB but have shown efficacy in treating TB. None of these drugs are recommended for routine treatment of MDR-TB or drug-sensitive TB. They can be used, in consultation with a clinician with experience in managing drug-resistant TB, when there is difficulty in designing a treatment regimen from first- and second-line drugs.

NEW ANTI-TB DRUGS

Bedaquiline is a new anti-tuberculous drug. It was approved for use in 2014 by the Medicines Control Council (MCC) of South Africa for the National TB Program (NTP) to treat XDR TB or pre-XDR TB patients defined as MDR-TB with additional resistance to either a fluoroquinolone or second-line injectable agent. It is used in combination with at least three anti-TB drugs to which the isolate is still susceptible to. Although a bedaquiline containing regimen is associated earlier culture conversion and higher cure rates, registration trials in the U.S.A. noted unexplained deaths in this arm hence the FDA approval which came with a black box warning. In S.A. it is used under strict control. National bedaquiline clinical access program (Ndjeka, *et al.* 2015) reported good outcomes. ECG monitoring for prolonged QT-intervals is required.

Delanamid is not yet routinely available in SA. However, restricted access authorised through an international committee is possible. Specialist MDR/XDR TB treatment facilities should be consulted.

MONITORING OF TREATMENT OF DRUG-RESISTANT TUBERCULOSIS

Sputum specimens are taken every month for TB smear microscopy and culture. TB culture conversion occurs when the patient has two consecutive negative TB culture results on sputum taken 30 days apart. The duration of intensive phase (injectable phase) is guided by culture conversion together with clinical response and chest X-ray findings. For patients who have extrapulmonary TB, monitoring is largely clinical and imaging where appropriate.

TUBERCULOSIS IN CHILDREN

Infants and children less than five years old are predisposed to developing disseminated and meningeal TB. Children with TB are generally not infectious and do not need to be isolated or excluded from school (paucibacillary disease), unless they have upper lobe infiltration and cavity formation with sputum production or miliary disease. Standard short-course therapy can be used for children with pulmonary TB. Refer to the section: 'first-line TB treatment regimens' in this chapter.

TUBERCULOSIS IN PREGNANCY AND BREASTFEEDING

- Isoniazid, rifampicin and ethambutol all cross the placenta and do not have teratogenic effects. Pyrazinamide is probably safe in pregnancy and is recommended by the WHO during pregnancy. If pyrazinamide is not included in the initial regimen, the minimum duration of therapy is nine months.
- Breastfeeding should be encouraged, since the small concentrations of the drugs in breast milk do not produce toxicity in the infant.
- Babies who are being breastfed by mothers taking isoniazid should be given 5 mg pyridoxine daily (crush the 25 mg pyridoxine tablet in 5 mL of water, and give 1 mL per day).
- If the mother is infectious (both smear-positive and smear-negative/culture positive PTB), a surgical mask must be used to protect the child from infection.

TUBERCULOSIS AND HIV INFECTION

- Management of tuberculosis in patients with HIV infection is complex. However, therapy for susceptible TB is as effective in HIV-infected patients as it is in the general population, and thus most patients can be treated with the standard six-month regimen.
- Appropriate HIV management of co-infected patients is essential. Remember to check CD4 count, request a RPR, perform a PAP smear, assess clinically and counsel for sexually transmitted diseases and counsel on the use of contraception. All HIV-TB co-infected patients require antiretroviral therapy.
- It should be noted that rifampicin is a strong inducer of hepatic cytochrome p450 enzymes and has significant drug interactions with antiretroviral drugs, especially the protease inhibitors and the non-nucleoside reverse transcriptase inhibitors (NNRTIs).
- Rifabutin is an alternative to rifampicin – it is a less potent cytochrome p450 inducer, and can be given if available, at a reduced dose of 150 mg orally daily, in an antiretroviral (ART) regimen which includes protease inhibitors. The concentrations of rifabutin may be reduced by the concomitant administration of efavirenz, and therefore rifampicin is preferred in an ART regimen which includes efavirenz.
- Immune reconstitution syndrome (IRIS), whose clinical manifestations include new or expanding lymph and worsening pulmonary infiltrates, may occur within the first few weeks of ART being administered together with anti-tuberculous therapy, especially in those with low CD4 cell counts. To reduce the risk of IRIS and drug interactions, the following is recommended with regard to initiating ART in HIV-infected patients with TB:

TB with a CD4 count < 50 cells/ μL: ART should be started within two weeks of starting TB treatment once the patient's symptoms are improving and TB treatment is tolerated.

TB with a CD4 count > 50 cells/ μL: ART should be started within two to eight weeks of starting TB treatment.

TB meningitis: ART should be started four to eight weeks following the start of TB treatment.

TREATMENT OF LATENT TB INFECTION

Individuals with a positive Mantoux skin test or TB-specific interferon-gamma release assay (T-spot-TB or Quantiferon), but no evidence of active TB, may have latent tuberculous infection. After active TB has been excluded, individuals with a positive Mantoux skin test or a TB-specific interferon-gamma release assay, may be considered for 'prophylaxis' to prevent active TB from developing. These include:

- Patients with HIV infection
- Patients with underlying medical conditions such as diabetes and chronic renal failure
- Children < 5 years of age who are close contacts of a patient with smear-positive pulmonary TB

Treatment of such cases is with a single drug such as isoniazid, given daily for six to nine months or a combination of isoniazid and rifampicin for three months.

NON-TUBERCULOUS MYCOBACTERIUM SPECIES

- Non-tuberculous *Mycobacterium* (NTM) species are environmental organisms that occasionally cause respiratory, cutaneous or disseminated disease.
- Distinguishing between colonisation, specimen contamination and infection is not always easy. When NTM species are isolated from a sterile site, e.g. blood, bone marrow, lymph node tissue, etc., it is usually indicative of NTM disease. However, when these mycobacteria are isolated from non-sterile sites, e.g. sputum, bronchoalveolar lavage, the diagnosis is less straightforward and may require additional clinical, laboratory and radiological evidence of disease.

MYCOBACTERIUM AVIUM COMPLEX

Mycobacterium avium complex (MAC) consists of two species: *Mycobacterium avium* and *Mycobacterium intracellulare.* MAC infections typically occur in patients with some form of cellular immunodeficiency (e.g. HIV infection, especially if the CD4 count is less than 50–100 cells/μL). Isolation in healthy, immunocompetent patients is most likely not significant and may represent colonisation. Infection is usually disseminated and presents with fever, night sweats, weight loss, wasting, abdominal pain, diarrhoea, hepatosplenomegaly, intra-abdominal lymphadenopathy, an elevated alkaline phosphatase level and anaemia. Localised disease is rare, but may involve the lungs, soft tissues, skin, bones, lymph nodes and the CNS.

TREATMENT: MYCOBACTERIUM AVIUM COMPLEX

MAC infections are treated with combination therapy

Clarithromycin 500 mg orally 12 hourly (the preferred drug) OR azithromycin 500 mg orally once daily

AND

Ethambutol 15 mg/kg orally once daily

A third drug such as rifabutin 300 mg orally once daily may also be added (adjust as needed for drug-drug interactions)

MYCOBACTERIUM ULCERANS

Mycobacterium ulcerans infection causes chronic, necrotising skin lesions which usually present as an ulcer. Surgical debridement of necrotic tissue is the mainstay of treatment. Treatment with rifampicin 600 mg orally once daily and clarithromycin 500 mg orally 12 hourly for eight weeks may reduce the extent of debridement required and is the best antibiotic choice for controlling complications.

MYCOBACTERIUM MARINUM

Mycobacterium marinum causes infection after injuries associated with water or aquatic animals (fish-tank or swimming-pool granuloma). It causes localised papular or nodular skin lesions and soft tissue infection. Lesions should be surgically excised. Antibiotics should be used if the lesion is not completely excised or for severe cases. A combination of clarithromycin 500 mg orally 12 hourly or rifampicin 600 mg orally once daily and ethambutol 25 mg/kg orally once daily should be used.

MYCOBACTERIUM CHELONAE, MYCOBACTERIUM ABSCESSUS AND MYCOBACTERIUM FORTUITUM

These rapidly growing mycobacteria are uncommon causes of lung disease. They are usually contaminants or colonisers, especially in respiratory specimens from non-immunocompromised patients and therefore need not be treated, especially if the CXR is normal. In patients infected with HIV, especially if the CD4 count is less than 100 cells/μL, or patients with cystic fibrosis, malignancy, etc., repeated isolation of the rapidly growing mycobacteria from multiple respiratory samples, may suggest that it may be pathogenic and treatment should be considered if no other cause for the lung pathology can be found.

The isolation of any of these rapidly growing mycobacteria from sterile sites such as bone marrow and blood or from a skin biopsy is considered diagnostic. These mycobacteria are typically resistant to the anti-tuberculous agents. Surgical excision of infected areas is an important adjunct to antibiotic therapy. Patients should be referred to an Infectious Disease physician for further management.

TREATMENT: MYCOBACTERIUM ABSCESSUS, MYCOBACTERIUM CHELONAE

Cutaneous infection	Clarithromycin 500 mg PO 12 hourly for 6 months
Disseminated disease	Two or three IV drugs: options include amikacin 10–15 mg/kg IV once daily and cefoxitin up to 12 g daily in divided doses and imipenem 500 mg 6–12 hourly. Treatment is for six months
Pulmonary disease	Two or three IV drugs as above. No antibiotic regimens based on *in vitro* susceptibilities have been shown to produce long-term sputum conversion for patients with *Mycobacterium abscessus* lung disease. The goal of 12 months of negative sputum cultures while on therapy may be reasonable, but there is no medication strategy to reliably achieve this goal Other drugs to consider: ciprofloxacin, doxycycline, tobramycin and cotrimoxazole Inducible clarithromycin resistance has been described

TREATMENT: MYCOBACTERIUM FORTUITUM

Amikacin and cefoxitin and probenecid for two to six weeks then oral cotrimoxazole or doxycycline for two to six months

MYCOBACTERIUM GORDONAE

M. gordonae is one of the least pathogenic mycobacteria. It is usually a contaminant or coloniser, especially in respiratory specimens of non-immunocompromised patients and therefore need not be treated.

In patients infected with HIV, especially those with the CD4 counts less than 100 cells/μL, repeated isolation of *M. gordonae* from multiple respiratory specimens may suggest that it is pathogenic and treatment should be considered if no other cause for the lung abnormalities can be found. Please consult an Infectious Diseases physician if treatment is considered.

MYCOBACTERIUM KANSASII

The isolation of *Mycobacterium kansasii* from respiratory tract specimens is significant, especially in immunocompromised patients such as HIV-infected patients, as well as patients with pneumoconiosis and those with chronic obstructive lung disease.

The most common presentation of *M. kansasii* is a chronic pulmonary infection that resembles tuberculosis clinically, radiologically and histologically. Little evidence exists for person-to-person transmission. Sensitivity testing is generally not recommended.

TREATMENT: MYCOBACTERIUM KANSASII

At least three drugs should be used: isoniazid 300 mg PO once daily **AND** rifampicin 600 mg PO once daily **AND** ethambutol (25 mg/kg PO for two months then 15 mg/kg PO once daily)

Pyrazinamide should not be used due to intrinsic resistance

Treatment duration is 18 months

REFERENCE

Ndjeka N, Conradie F, Schnippel K, Hughes J, Bantubani N, Ferreira H, Maartens G, Mametja D, Meintjes G, Padanilam X, Variava E, Pym A & Pillay Y. 2015. Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis. *International Journal of Tuberculosis and Lung Disease*, Vol. 19(8): 979-985.