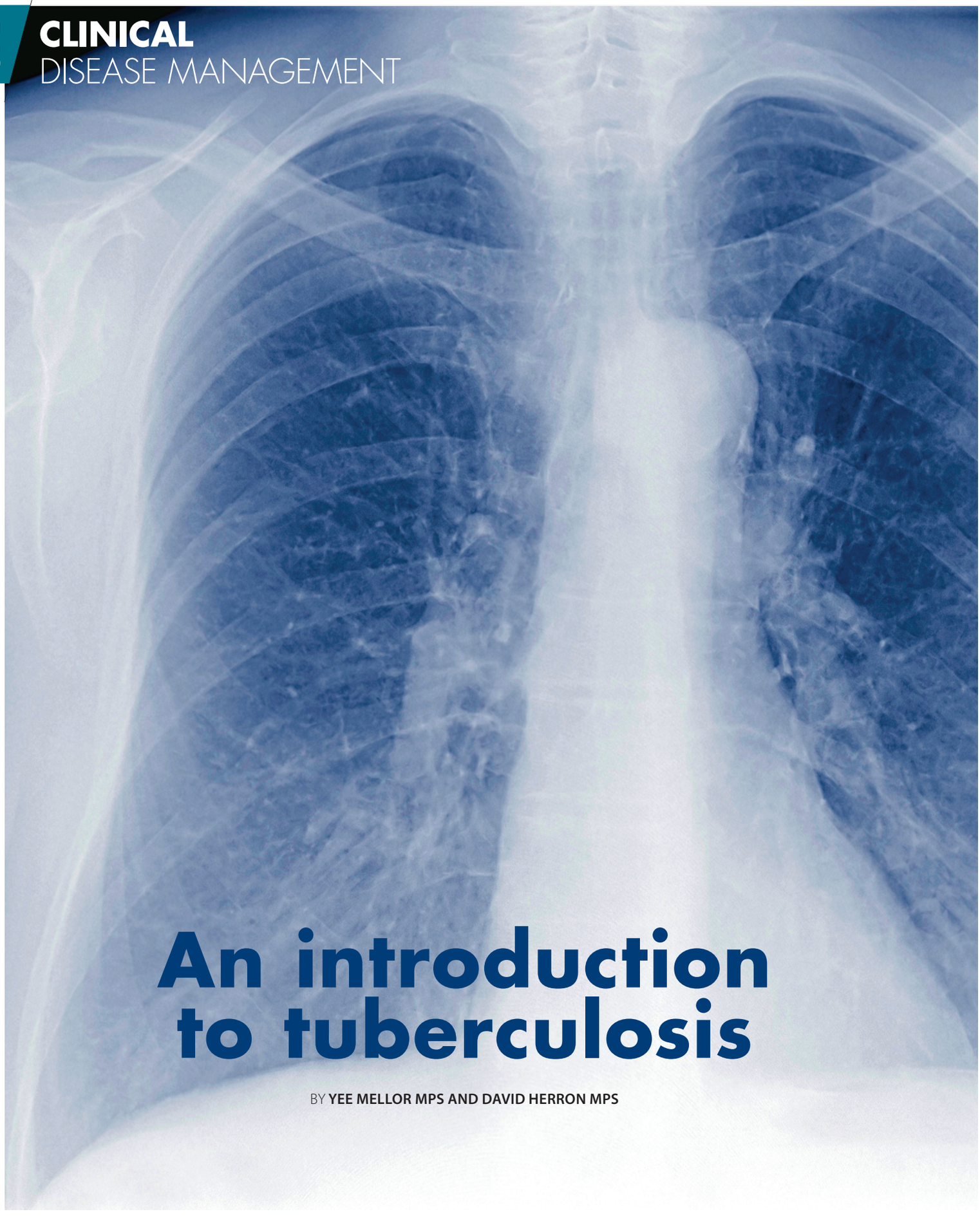

# An introduction to tuberculosis

BY **YEE MELLOR MPS AND DAVID HERRON MPS**

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## LEARNING OBJECTIVES

**AFTER READING THIS ARTICLE, PHARMACISTS SHOULD BE ABLE TO:**

- Explain the infectibility of tuberculosis.
- Differentiate between latent tuberculosis and active tuberculosis infection.
- Summarise current treatment regimens for latent and active tuberculosis infections.
- Recognise the common adverse effects, precautions and counselling points for therapeutic agents used in the treatment of tuberculosis.

**Competency standards addressed (2016):** 1.1, 1.3, 1.5, 2.3, 2.4, 3.1

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## Overview

Tuesday 24 March is the World Health Organization's World Tuberculosis Day. The goal is to end the global epidemic by 2035.[1]

Tuberculosis (TB) is one of the top 10 causes of death worldwide; one third of the world population is believed to be affected.[2,3] *Mycobacterium tuberculosis* is the most common causative organism. Mycobacterium africanum and Mycobacterium canetti cause rare cases of TB in Africa.[3,4] DNA analysis indicates that the *M. tuberculosis* complex emerged approximately 70,000 years ago and accompanied migration out of Africa, expanding as a result of increasing population density in the Neolithic period.[5] Between the 17th and 19th centuries, TB killed 1 in 5 adults in North America and Europe. In the developing world today, it is a cause of both high morbidity and mortality.[5] In the World Health Organization's 2018 Global Tuberculosis Report, it was identified as 'the leading cause [of death] from a single infectious agent.'[6]

## Transmission of TB

TB is an airborne pathogen that predominantly affects the lungs.[4] Transmission is mainly by inhalation of infectious droplets.[7] This is usually through prolonged sharing of airspace with an infected person.[7] The incubation period can vary between 2–10 weeks.[3,8] Risk of transmission is greatest in the interval prior to diagnosis.[8] Once infected, active TB only occurs in 5–10% of those that are immunocompetent.[8]

Where TB is fully drug-susceptible, 2 weeks of standard daily treatment may render the patient noninfectious.[9] Zoonotic tuberculosis (*Mycobacterium bovis*) from cattle and their food products is rare (1.4% of cases overall); the primary reservoir is humans.[3,10] *Mycobacterium microti* (rodents) and *Mycobacterium pinnipedii* (seals) have also been reported to cause zoonotic TB in humans.[3]

## TB in Australia

TB is uncommon in Australia. Effective TB control has resulted in stable and low TB incidence rates since 1985. Incidence reduction, however, has not been achieved even though risk factors (e.g. poverty, poor TB practices, political instability and HIV disease) found in other parts of the world do not contribute to the epidemiology of TB in Australia.[11]

In Australia, TB is a notifiable disease.[1] Notification requirements ensure that diseases such as TB can be monitored and controlled.[12] Incidence has been approximated to be 5.7 per 100 000 population.[1] Multi-drug resistant TB accounts for approximately 1–2% of notifications per year.[1] Eighty-six per cent of notifications are from Australia's overseas-born population; Aboriginal and Torres Strait Islanders have TB rates 6 times higher than the Australian-born non-Indigenous population.[1]

The most commonly reported risk factor overall (in the Australian-born non-Indigenous and overseas-born population) was past travel to or residence in a high-risk country (see »


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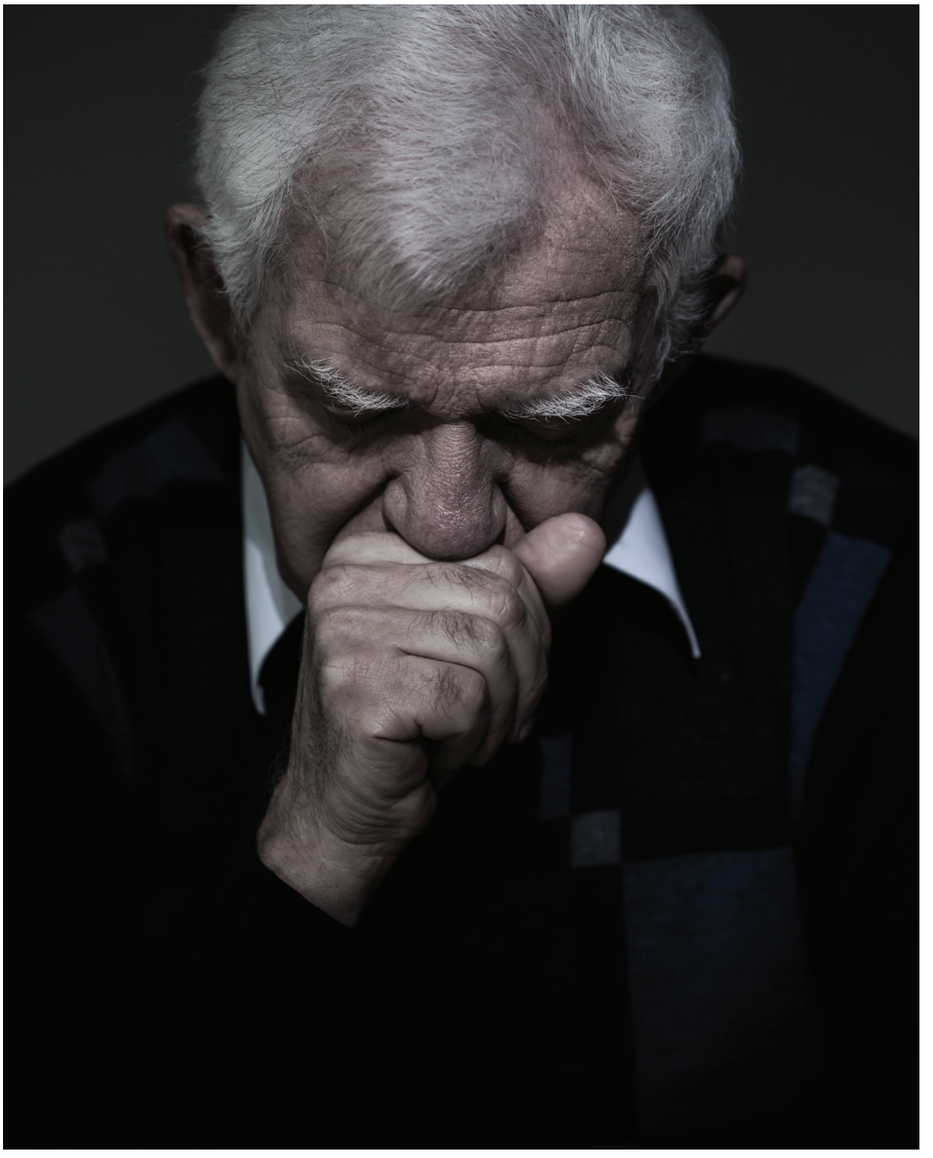


**BOX 1 – RISK FACTORS FOR TB IN AUSTRALIA**

- Past travel to or residence in a high-risk country
- Household or close contact with TB
- Homelessness
- Residence in a correctional facility
- Previously untreated TB
- Current/previous employment in healthcare
- Current immunosuppressive therapy
- Employment in an institution
- Residence in an aged care facility
- Australian-born child with one or more parent born in a high-risk country

**TB = tuberculosis**
***References:*** *Dept of Health*[1]

**BOX 2 – SYMPTOMS OF TB**

- Cough that lasts ≥3 weeks
- Chest pain
- Haemoptysis
- Fatigue (or weakness)
- Anorexia
- Weight loss
- Fever and chills
- Night sweats

***References:*** *CDC*[17]

country (see **Box 1**). In the Australian-born Indigenous population, the most reported risk factor was household or close contact with TB.[1] In Australia, epidemiological evidence of low local transmission and TB notification rates suggests that the majority of active disease is a result of reactivation of latent infection.[13]

Latent TB is the persistence of viable *M. tuberculosis* without associated signs and symptoms, or active disease.[14] It is an infection that has been contained but not eliminated by the host immune system, having the potential to develop into active disease, years or decades after initial infection (see **Figure 1**).[13] People with latent TB are not infectious.[15]

The current Strategic Plan for Control of TB in Australia aims to reduce overall TB occurrence to meet pre-elimination targets by 2035 in the entire Australian population. TB elimination is defined as <1 case per million population.[11]

TB is the most common presenting illness in people living with HIV worldwide and is the leading cause of mortality. In Australia, however, HIV-associated TB occurs at low rates and is mainly found in the overseas-born population.[16] In the setting of HIV, clinical manifestation of TB depends on degree of immunodeficiency. Progression of TB can be more rapid and reflective of a subacute rather than chronic illness.[16]

Multidrug-resistant TB is uncommon in Australia, found in approximately 1–3% of those diagnosed with TB.[9]

## Diagnosis of TB

A diagnosis of TB should be considered in high-risk patient groups and those that present with an undiagnosed febrile or wasting condition, or a persistent cough (symptoms of TB are listed in **Box 2**).[9,17] Chest X-ray and sputum microscopy (acid fast Ziehl-Neelsen stain) form the initial investigation for pulmonary TB.[9] Confirmation of diagnosis and drug resistance is from sputum culture and susceptibility testing.[9]

Extrapulmonary TB is diagnosed via direct sampling of the likely affected organ system.[9]

## Prevention and control of TB in Australia

Early diagnosis and treatment (including treatment of latent TB) is the most effective way to prevent the transmission of TB.[8] Border screening in the form of pre- and post-migration screening is undertaken by the Department of Immigration and Citizenship.[8] Vaccination with Bacille Calmette-Guerin is only recommended in specific high risk groups in Australia due to its low overall efficacy.[8] It is, however, effective in reducing disseminated disease and TB meningitis in children under 5 years from countries with a high prevalence of TB.

In Australia, suspected or confirmed pulmonary TB patients admitted to hospital are isolated in negative pressure rooms, with droplet precautions, until discharge criteria are met (reduction/absence of cough, reduced smear burden or negative smear, assured treatment and appropriate discharge plan).[8]

## Treatment of TB

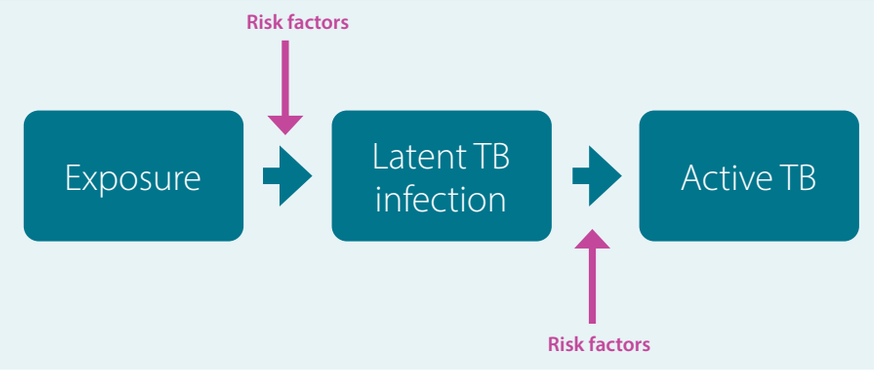
*M. tuberculosis* is an aerobic, acid fast bacilli with low cell wall permeability, this confers an intrinsic resistance to antibiotics.[18,19] Empirical treatment of TB involves multidrug regimens to cover any pre-existing drug resistance and to prevent emerging resistance.[9]

In those with fully drug-susceptible TB, there is a 98% initial cure rate and under 1% 5–year relapse rate when treated with pharmacotherapy.[9] This involves a four-drug, 6-month treatment regimen (see **Table 1**).[9] Treatment with isoniazid and rifampicin is usually for a 6-month period; pyrazinamide and ethambutol is indicated in the first two months.

Ethambutol should be continued until susceptibility to isoniazid and rifampicin can be confirmed – even if this is beyond 2 months. However, once susceptibility has been confirmed, ethambutol can be ceased before 2 months of therapy has been reached. Pyrazinamide should only be discontinued after at least 2 months of treatment and susceptibility to isoniazid and rifampicin have been confirmed.[9]

An intermittent, 3–times weekly dosing regimen can also be used to treat pulmonary TB, however it should only be used under the advice of a TB specialist and only when the daily TB regimen has been used for the first 2 months (further information is available in eTG).[9]

**FIGURE 1 – Progression of TB**




TB = tuberculosis
Risk factors = HIV infection, contact with an infectious person, anti-tumour necrosis factor treatment, dialysis, organ/haematologic transplantation, silicosis, prison, immigrant from high TB-burden countries, homelessness, illicit drug use
***Reference:*** *WHO*[14]

**TABLE 1 – Oral treatment regimen for fully drug-susceptible TB**

| ADULTS | CHILDREN<14 YEARS OLD | TREATMENT DURATION |
|---|---|---|
| **Ethambutol 15 mg/kg up to 1,200 mg daily** | **Child <14 years** 20 mg/kg up to 1,200 mg once daily | 2 months |
| **Pyrazinamide 25 mg/kg up to 2,000 mg** | **Child <14 years** 35 mg/kg up to 2,000 mg once daily | 2 months |
| **Isoniazid 10 mg/kg up to 300 mg daily** | Isoniazid 10 mg/kg up to 300 mg once daily | 6 months |
| **Rifampicin 10 mg/kg up to 600 mg daily** | **Child <14 years (>50 kg)** 600 mg once daily<br>**Child <14years (<50 kg)** 15 mg/kg up to 450 mg once daily | 6 months |
| ***Pyridoxine 25 mg with each dose of isoniazid** | **Child** *Pyridoxine 6.25–12.5 mg with each dose of isoniazid | Duration of isoniazid treatment |

* For patients at high risk of peripheral neuropathy
***Reference:*** *eTG*[9]

## Mechanism of action

Isoniazid may disrupt the mycobacterial cell wall by inhibiting the synthesis of mycolic acids. It is both bactericidal (against actively dividing *M. tuberculosis*) and bacteriostatic (against resting bacteria). It is also a weak monoamine oxidase inhibitor (MAOI).[20]

The rifamycins (rifampicin and rifapentine) inhibit RNA polymerase. It is bactericidal against rapidly dividing *M. tuberculosis*.[21]

Ethambutol may disrupt the cell wall by inhibiting the incorporation of mycolic acid. It is bacteriostatic against *M. tuberculosis*.[22]

Pyrazinamide is bacteriacidal against *M. tuberculosis* in acid pH.[23]

Pyridoxine is a coenzyme in numerous reactions and is used to prevent peripheral neuropathy in those at high risk of developing the condition as a result of pharmcotherapy.[24]

## Treatment of latent TB

Completing a course of treatment for latent TB can prevent disease progression and the possibility of later infection (see **Figure 1**, previous page).[14] Treatment regimen (see **Table 2**) is dependent on: drug availability, duration of therapy, likelihood of drug resistance, potential for hepatotoxicity from isoniazid and drug interactions with rifamycins.

Treatment options for TB in the HIV-infected population are the same as those for the general population.[16]

Treatment for multidrug-resistant TB can be found in the *WHO consolidated guidelines on drug-resistant tuberculosis treatment* 2019.[25]

## Directly observed therapy

Directly observed therapy (DOT) is supervised TB treatment to minimise drug resistance and to ensure successful treatment completion.[3,8] Prior to commencement of therapy, patients should have an assessment to determine likely adherence and evaluate the requirement for DOT. In certain situations DOT is mandatory (e.g. retreatment or drug resistance).[3,8]

## Conclusion

TB can be fatal if not treated appropriately.[16] Compliance is important for curative intent and prevention of resistance.[16] Treatment of latent TB prevents reactivation and therefore later transmission of TB. Pharmacists can counsel patients/consumers on the nature of TB infections and the importance of compliance in addition to medicines counselling (see **Table 3**). The curability and preventability of TB and the consequences of non-compliance should also be emphasised. Resources, including multilingual resources can be found at the BetterHealth Channel and local jurisdictional TB units.[8,25] »

## TABLE 2 – Oral treatment regimens for latent TB

| ADULTS | CHILDREN | | TREATMENT DURATION |
|---|---|---|---|
| **Isoniazid 10 mg/kg up to 300 mg daily** | Isoniazid 10 mg/kg up to 300 mg once daily | | 6 months<br>***OR*** 9 months |
| **Rifampicin 10 mg/kg up to 600 mg daily** | **Child <14 years (>50 kg)**<br>rifampicin 600 mg once daily | **Child <14 years (<50 kg)**<br>rifampicin 15 mg/kg up to 450 mg once daily | 4 months |
| **Rifampicin 10 mg/kg up to 600 mg daily**<br>***PLUS***<br>**Isoniazid 10g/kg up to 300 mg daily** | **Child<14 years (>50 kg)**<br>Rifampicin 600 mg once daily<br>***PLUS***<br>Isoniazid 10g/kg up to 300 mg once daily | **Child <14 years (<50 mg)**<br>Rifampicin 15 mg/kg up to 450 mg once daily<br>***PLUS***<br>Isoniazid 10g/kg up to 300 mg once daily | 3 months |
| **Rifapentine 900 mg weekly**<br>***PLUS***<br>**Isoniazid 15 mg/kg up to 900 mg weekly** | **Child ≥12 years (>50 kg)**<br>Rifapentine 900 mg once weekly<br>**Child ≥12 years (32.1–50 kg)**<br>Rifapentine 750 mg once weekly<br>**Child 2–11 years (10–14 kg)**<br>Rifapentine 300 mg once weekly<br>**Child 2–11 years (14.1–25 kg)**<br>Rifapentine 450 mg once weekly<br>**Child 2–11 years (25.1–32 kg)**<br>Rifapentine 600 mg once weekly | **Child 2–11 years (32.1–50 kg)**<br>Rifapentine 750 mg once weekly<br>**Child 2–11 years (>50 kg)**<br>Rifapentine 900 mg once weekly<br>***PLUS***<br>**Child≥12 years**<br>Isoniazid 15 mg/kg up to 900 mg once weekly<br>**Child 2–11 years**<br>Isoniazid 25 mg/kg up to 900 mg once weekly | 3 months |
| ***Pyridoxine 25 mg with each dose of isoniazid** | **Child** *Pyridoxine 6.25–12.5 mg with each dose of isoniazid | | Duration of isoniazid therapy |

*For patients at high risk of peripheral neuropathy
***Reference:*** *eTG*[9]

## TABLE 3 – Common adverse effects, precautions and counselling points

| THERAPEUTIC AGENT | COMMON ADVERSE EFFECTS (>1%) | PRECAUTIONS | SELECTED COUNSELLING POINTS |
|---|---|---|---|
| **Isoniazid** | Nausea, rash, fever, peripheral neuritis, ↑aminotransferases, hepatitis, acne, fatigue, ↓alertness, ↑antinuclear antibodies | Epilepsy, CNS toxicity with cycloserine, ↑risk of peripheral neuropathy (malnutrition, diabetes, HIV infection, alcoholism)* | Best absorbed when taken on an empty stomach. Tyramine or histamine rich foods can cause tachycardia, postural hypotension, flushing, itch, headache or sweating – avoid if affected |
| **Rifampicin** | GI symptoms (nausea, vomiting, cramps), rash, ↑ LFTs, orange-red colouration of body fluids# | Contraindicated in jaundice, may worsen hepatic impairment, ↑ risk of hepatotoxicity in combination with hepatotoxic drugs (e.g. isoniazid), ↓ effectiveness of the pill | Best absorbed when taken at least half an hour before food. Take it regularly (allergy is more likely with intermittent dosing). Inform prescriber if: rash, fever and swollen glands, loss of appetite, nausea, vomiting, unusual tiredness, jaundice, dark urine or pale faeces |
| **Rifapentine**[27] | Endocrine and metabolic disturbance, haematologic reactions, genitourinary symptoms, GI, CV, CNS, respiratory and ophthalmic symptoms, rash, ↑ LFTs, neuromuscular and skeletal symptoms, orange-red discolouration of body fluids# | Use with caution in hepatic impairment. Not recommended for use in patients with porphyria | Best absorbed with meals – high fat meals increase absorption |
| **Ethambutol** | Optic neuritis | Contraindicated in optic neuritis. May cause changes in vision. May precipitate gout | Vision may be affected (e.g. clarity and colour). Cease and inform prescriber of any changes to eyesight |
| **Pyrazinamide** | Hyperuricaemia, polyarthralgia, nausea | Contraindicated in acute gout and significant liver disease | Cease and inform prescriber if: continuous nausea, vomiting, unusual tiredness, yellowing of the skin or whites of eyes, dark urine or pale faeces |
| **Pyridoxine** | None listed | None listed | Avoid unnecessary use. Prolonged high doses may be toxic and cause peripheral neuropathy |

*use pyridoxine 25mg daily as prophylaxis, #can stain soft contact lenses, **UTI**=urinary tract infection, **GI**=gastrointestinal, **CV**=cardiovascular, **CNS**=central nervous system
***References:*** *MH,*[20-24] *BetterHealth*[26]

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Photography: Damien Pleming

## KEY POINTS

- **Tuberculosis is an airborne pathogen that predominantly affects the lungs.**
- **It is important to treat both latent and active tuberculosis, treatment guidelines and regimens differ.**
- **The adverse reactions of tuberculosis medicines can be diverse.**
- **Absorption of the medicines used in the treatment of tuberculosis can be affected by food, counselling by pharmacists is important.**

Up to **1.5 CPD CREDIT** Group 2

## Assessment questions

**Each question has only one correct answer.**

### 1 Which of the following statements about the transmission of tuberculosis is CORRECT?

A) Mycobacterium tuberculosis is an airborne pathogen that is transmitted by inhalation of infectious droplets. Cross infection between humans and animals is common.
B) Mycobacterium tuberculosis is an airborne pathogen that is transmitted by inhalation of infectious droplets and can cause both latent and active tuberculosis infections.
C) Mycobacterium tuberculosis is an airborne pathogen that is transmitted by inhalation of infectious droplets that is responsible for zoonotic tuberculosis.
D) Mycobacterium tuberculosis is an airborne pathogen that is transmitted by inhalation of infectious droplets that causes zoonotic tuberculosis from cattle.

### 2 Which of the following statements on the importance of treating latent tuberculosis is CORRECT?

A) To prevent the transmission of tuberculosis to other people.
B) To control symptoms of active tuberculosis.
C) To prevent progression to active tuberculosis.
D) To prevent multi-drug resistant tuberculosis.

### 3 Which of the following statements on the standard recommended treatment regimens for fully drug susceptible active tuberculosis is CORRECT?

A) 2 months of ethambutol and pyrazinamide in combination with 6 months of isoniazid and rifampicin with or without pyridoxine.
B) 6 months of ethambutol and pyrazinamide in combination with 2 months of isoniazid and rifampicin with or without pyridoxine.
C) 6 or 9 months of rifampicin.
D) 4 months of isoniazid with or without pyridoxine.

### 4 Adrian comes into the pharmacy and asks for a lens cleaner for his soft contact lenses. He has been told by a friend that they may help with the pinkish discoloration he has noticed on his lenses. During your conversation with Adrian he tells you that he is new to wearing contact lenses and has been told by a friend that this is not normal. Adrian has recently been commenced on a treatment regimen for latent tuberculosis. Which of the following statements is CORRECT?

A) Isoniazid can affect the colour of bodily fluids which can stain soft contact lenses.
B) Pyrazinamide can affect the colour of bodily fluids which can satin soft contact lenses.
C) Rifampicin can affect the colour of bodily fluids which can stain soft contact lenses.
D) Ethambutol can affect the colour of bodily fluids which can stain soft contact lenses.