Communicable Diseases Intelligence

2026 • Volume 50 • cdc.gov.au/cdi • Epub date: 16.11.2026 • doi.org/10.33321/cdi.2026.50.067

National position statement: diagnosis and treatment of tuberculosis infection

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Australian Centre for Disease Control

Communicable Diseases Intelligence

Communicable Diseases Intelligence (CDI) is a peer-reviewed scientific journal published by the Australian Centre for Disease Control.

The journal aims to disseminate information on the epidemiology, surveillance, prevention and control of communicable diseases of relevance to Australia and the near region.

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ISSN: 2209-6051 Online

This journal is indexed by Index Medicus and Medline.

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Acknowledgement

NTAC is a subcommittee of the Communicable Diseases Network Australia (CDNA). CDNA is a subcommittee of the Australian Health Protection Committee (AHPC).

Revision history

Version	Publication date	Revised by	Comments
2 – National position statement: diagnosis and treatment of tuberculosis infection	16 November 2026	NTAC, Australian CDC & CDNA	Endorsed by the CDNA on 30 March 2026 Endorsed by the AHPC on 8 September 2026
1 – National position statement for the management of latent tuberculosis infection	1 September 2017	NTAC	Endorsed by the CDNA on 22 June 2016

Background

It is estimated that nearly one-quarter of the global population has been infected with *Mycobacterium tuberculosis* (Mtb), with the highest prevalence of tuberculosis (TB) infection in countries/regions with the highest prevalence of active disease.[1] The host immune system often succeeds in containing the initial (or primary) infection with Mtb, but may fail to eliminate the pathogen. The persistence of viable organisms explains the potential for the development of active disease occurring years or even decades after initial infection. This entity where there is TB infection (TBI) but without symptoms or signs of TB disease is traditionally referred to as latent tuberculosis infection (LTBI) and is characterised only by a state of persistent immune response to Mtb antigens. A persistent immune response doesn't necessarily imply that viable organisms persist in the subject showing a positive test. There are no commercially available diagnostics tests to determine whether viable bacilli are present or not, or to determine likelihood of progression to TB disease in those considered TB infected, although this is an area of active global research. In keeping with World Health Organization (WHO) terminology, this position paper will refer to TBI to describe the entity previously referred to as LTBI; however, the descriptor of 'latent TB' or similar alternatives such as 'dormant TB' or 'sleeping TB' may be useful when discussing with patients.

It is now recognised that there is a spectrum of stepwise progression between TBI with dormant but viable bacilli through to incipient TB, subclinical TB (commonly referred to as asymptomatic TB) and finally to TB disease with clinical symptoms and signs.[2] Progression through these stages is not necessarily one way and a TB infected individual may move between states. Incipient TB implies there are slow and or intermittently dividing bacilli, but there are no commercial assays available or other investigations which can distinguish incipient TB from TBI with true dormancy. At this point in time, considerations for investigation and management of TBI also apply to incipient TB. It is very important that microbiological and radiological investigations are employed to exclude subclinical TB and TB disease, both of which should be treated with a TB disease treatment regimen, before management of TBI is undertaken.

In Australia, nearly 90% of notified active TB cases are in persons born overseas, typically in a country with high TB incidence.[3] Most active cases result from reactivation of latent infection acquired prior to migration.[4,5] Nonetheless, TB transmission in Australia still occurs within households; in migrant groups; amongst socially disadvantaged groups (e.g. homeless people); in healthcare facilities; and within some Aboriginal and Torres Strait Islander communities. Consistent with Australia's support of global TB elimination efforts[6] is the prevention of progression of TBI to active disease by appropriate use of antimicrobial TB preventive therapy (TPT) targeting those most at risk.[7]

It is generally stated that of those with TBI, there is a lifetime risk of 5–10% for development of active TB disease. This estimate varies significantly for individuals and may be as high as almost 15% where infection is recently acquired.[8] The risk is higher if the host is immune suppressed through disease, e.g. human immunodeficiency virus (HIV) infection or diabetes mellitus; medical therapies, such as corticosteroids / anti-tumor necrosis factor (anti-TNF) inhibitors; or environmental factors, e.g. smoking or indoor smoke inhalation.

Individuals with TBI may reduce their risk of progression to active TB disease substantially (60–90% risk reduction) by completing a TPT course. The diagnosis and treatment of TBI represents an important opportunity for intervention by jurisdictional TB control programs.

How to diagnose TB infection?

Testing for TBI should be undertaken where there is a reasonable likelihood of prior TB exposure (see 'Who to test' below).

Two types of tests are currently in use for the diagnosis of TBI in Australia: the tuberculin skin test (TST) and interferon-gamma release assay (IGRA). Both TST and IGRA are indirect tests, demonstrating immune sensitisation to Mtb antigens. They cannot, therefore, distinguish between elimination and persistence of Mtb following primary infection. There is also the potential for test failure in the setting of impaired host immunity. Neither test can distinguish between recent and distant infection, nor reliably predict who will progress to active disease. It generally takes 8–12 weeks, following initial infection, to reliably produce a positive test result in most subjects, a timepoint commonly known as 'break of contact' in the context of contact tracing and testing following exposure to a known index case.

The TST, also known as the Mantoux test, requires the administration of an intradermal antigen injection with subsequent induration, or no induration, recorded and interpreted by an experienced observer. An IGRA test requires phlebotomy and the assay is performed in a recognised pathology laboratory.

Both TST and IGRA are acceptable for the diagnosis of TBI. This is consistent with published WHO guidelines[9] on testing in high income, low prevalence countries. Further clarity may be provided by the use of both tests in some circumstances. For further information please refer to the following National Tuberculosis Advisory Committee (NTAC) document: *Position statement on interferon-γ release assays in the detection of latent tuberculosis infection*.[10]

The principal advantage of IGRA over TST is in terms of specificity. Unlike TST, the test outcome is unaffected by previous testing; by bacille Calmette-Guérin (BCG) vaccination (typically high coverage in at risk populations); or by exposure to non-tuberculous mycobacteria (NTM) except M. *marinum*, M. *szulgai* and M. *kansasii*. A 'lost to follow up' outcome may be reduced with IGRA testing, as only a single visit for phlebotomy is required, whereas TST requires two patient visits (to administer and read). Additional advantages of IGRA testing are less subjective interpretation and capacity for higher throughput testing. IGRA testing, however, has requirement for blood processing within specified timeframes and exceeding these time frames leads to inaccurate results. TST does provide more interactive time with TB knowledgeable staff. These pros and cons need to be considered carefully when testing for TBI in different settings, especially in rural and remote (including island) communities.

Although earlier studies suggested higher rates of indeterminant results with IGRA testing in young children, more recent experience is that IGRA tests are an acceptable alternative to TST without further qualification, including in children under the age of 2 years.[11] Not all staff involved in TBI diagnosis will feel competent in drawing blood in children < 5 years or < 2 years of age. Performing TST on individual children < 5 years of age may be preferable, or when considering (e.g.) community screening or extensive contact tracing that may include a large number in the < 5 year old category.

Although not currently available in Australia, other tests based on similar principles (gamma interferon release or skin test reactivity) are endorsed by the WHO, including intradermal skin tests using recombinant antigens akin to the antigens used in IGRA testing.[9] As such, these newer generation skin tests should also be unaffected by prior BCG administration.

Interpretation of the TST is contextual, as outlined in Table 1. Jurisdictional interpretation guidelines should be followed if these are at variance with Table 1.

It is important to note that where the risk and consequence of infection is very high, it may be appropriate in the context of contact management to treat presumptively prior to confirming TBI. For example, HIV-infected and pre-school age (< 5 years of age) contacts of an infectious case may have indeterminant or false negative results for TBI but remain at risk for meningitis and disseminated infection.[12]

Table 1: Tuberculin skin test (TST) interpretation

Measured induration	Consistent with past TBI[a]	Comments[a]
≥ 15 mm	In all persons	
≥ 10 mm but < 15 mm	Persons with a history of close contact or an abnormal chest radiograph (calcified nodules, upper lobe fibrosis)	
≥ 5 mm	Those age <5 years with high pre-test probability AND increased risk of progression to active disease	In immune suppressed persons or young children, a supplementary IGRA test may also be performed: a significant result of either TST or IGRA would be a prompt for treatment
	Immune suppressed persons	

a TBI: tuberculosis infection; IGRA: interferon-gamma release assay.

Table 2: Interpretation of interferon-gamma release assay (IGRA) tests using Quantiferon Gold Plus[a]

Results[b]	Interpretation[c]	Comments[d]
TB antigen 1 and/or TB antigen 2 > 0.35 IU	Consistent with previous infection with Mtb complex	Some clinicians may be more likely to consider a false positive result where the values are very close to the cut off
TB antigen 1 and 2 < 0.35 IU	No evidence of past infection with Mtb complex	A negative result does not exclude TBI nor TB disease
Indeterminant	Unable to interpret	Usually caused by inadequate response in the mitogen control
Invalid	Unable to interpret	Excessive gamma interferon release detected in absence of any immune stimulation

a Quantiferon Gold Plus (QIAGEN) assay is the only IGRA test in common usage in Australia at time of writing. The T-Spot.TB test (ELISpot technology) by Oxford Immunotec/Revvity may be available in some centres.

b TB: tuberculosis; IU: international units.

c Mtb: *Mycobacterium tuberculosis*.

d TBI: tuberculosis infection.

Who to test?

Resources should focus on at-risk persons and groups who would benefit from treatment. As such it is important to identify individuals and populations in Australia who are most likely to have been infected with Mtb complex and to further risk stratify to determine, where possible, the likelihood of progression to TB disease (including asymptomatic TB) and the degree of severity of disease based on comorbid risk factors.

Those at greater risk of having acquired TBI include:

1. *close household or other close contacts (including in congregate settings) of a known index case(s) with pulmonary TB*. Acid fast smear positive pulmonary TB cases are more likely to transmit TB, but all forms of pulmonary TB may transmit to others. Laryngeal TB is also considered to be highly infectious. While extrapulmonary TB is not usually considered transmissible, it is prudent to test other family members for TBI as risk factors for exposure are often shared, or such investigations may identify an unsuspected primary case;
2. *Aboriginal and Torres Strait Islander people*, who have a significantly greater incidence of TB disease, and by inference TBI, compared to Australian-born non-Indigenous people. This incidence may vary geographically but is highest in communities with recent TB cases, including recognised outbreaks. High degrees of mobility, often over great geographical distance, needs to be considered in any epidemiological assessment;
3. *persons who have lived in high burden TB countries and have migrated to Australia to live, work or study*. Australian incidence of TB is highest in this diverse group of people and accounts for the greatest burden of both TB disease and TBI.[3,13] Unique to the Torres Strait, cross border movement of people between Queensland and South Fly District Papua New Guinea also accounts for variable numbers of TB cases diagnosed in that region of Australia; and
4. *healthcare workers*, who are more likely to have had contact with TB patients (in or outside of Australia) or exposure to Mtb through laboratory, radiological or mortuary work.[14]

It should be acknowledged that anyone can 'get TB', but environmental risk factors and social determinants of health have pivotal influence on TB acquisition and/or progression to active disease. Such factors may be common to TB acquired within Australia or overseas, and include:

- poverty and overcrowded living conditions;
- malnutrition;
- diabetes mellitus;
- tobacco smoking and poor indoor air quality;
- inhalational drug use;
- silica exposure sufficient to cause pulmonary silicosis;
- alcohol abuse; and
- incarceration.

Additional risk factors for progression from TBI to active TB (TB disease and asymptomatic TB) are outlined in Table 3.

It follows that NTAC recommends testing for TBI in people who have one or more risk factors for acquisition of TBI, with or without heightened risk of progression to TB disease. NTAC acknowledges that implementing these recommendations may require an increase in resources. Jurisdictions should prioritise efforts aiming to prevent active TB in those most at risk of TB disease, and especially those at risk of more severe disease presentations.

Table 3: Risk factors for tuberculosis (TB) progression and impact on severity of illness

Circumstance or comorbidity increasing progression[a]	Impact on severity of disease following progression[b]
Infection likely to be recently acquired (especially in the preceding two years)	No additional impact on severity of disease
Abnormal CXR with fibrotic change consistent with past TB and without history of treatment	No additional impact on severity of disease
Child less than 5 years of age	Disseminated disease and meningitis more likely, especially if age < 2 years
HIV infection	Severity can be substantial in absence of effective ART if immune compromised; disseminated disease more likely
Certain malignancies (head and neck, lung, haematological)	Unknown whether severity increased
Solid organ and bone marrow transplantation	Increased severity of disease; disseminated disease more likely
Previous gastrectomy/jejuno-ileal bypass	Unknown whether severity increased
Other immunosuppressive therapy, including long-term oral corticosteroids (prednisolone ≥ 15 mg/day or equivalent for greater than one month)	Increased severity of disease; disseminated disease more likely
Chronic kidney disease (stage V)	Unknown whether severity increased

a CXR: chest radiograph; HIV: human immunodeficiency virus.

b ART: antiretroviral therapy.

As nearly 90% of active TB cases in Australia are in those born overseas, TBI detection in this diverse group needs to be optimised to benefit individuals and communities, and to contribute broadly to TB elimination. Such strategies begin prior to migration. Where the country of origin is considered to have high TB burden, the Australian Government requires TBI testing of those intending to work, study or train within healthcare (including age and disability care) while in Australia. In addition, TBI screening is conducted in pre-migration settings for children from high TB burden countries, of ages 2 years and above but under 11 years old, who are entering Australia on provisional or permanent visas. TBI screening in children serves as an initial assessment for TB, reducing the need for chest x-rays for all children under 11 years of age.

Irrespective of age, any migration applicant who is a known close household contact of a TB case is also prioritised for TB and TBI screening. Those found to have TBI, but with exclusion of active disease, are offered TBI treatment. Following migration, each Australian jurisdiction should have a strategy aimed at diagnosis and preventative treatment for at-risk migrants.

'High TB incidence' is generally considered to be at least ≥ 40 active cases per 100,000 population per year. A threshold of 40 per 100,000 population aligns with current policy for TBI testing of healthcare worker visa applicants and for testing prior to BCG vaccination.

Acknowledging many years of disproportionately high rates of TB in Aboriginal and Torres Strait Islander people, as well as in the context of recently recognised TB outbreaks in some Indigenous communities, testing for TBI is recommended where people are members of, or closely connected to, communities with documented recent TB outbreaks; have identified contact with a past pulmonary TB case; or where sporadic TB cases have been known to occur recently. The connectiveness between family and community may span across significant geographic distance and this should be considered in assessing 'who to test' in Aboriginal and Torres Strait Islander people.

In the context of co-morbid disease or immunosuppressive therapy:

- all people living with HIV should have a test for TBI which should be repeated if more recent contact with TB is likely; and
- all efforts should be made to diagnose TBI prior to introduction of immune suppressant drugs if clinically appropriate (e.g. before organ transplants or TNF inhibitor therapy).

Age itself is not a contraindication to treatment for TBI and thus is not a contraindication for testing for TBI.

Healthcare workers who have lived or worked in countries of high TB incidence should be prioritised, noting the additional possible consequence of transmission to vulnerable people in healthcare facilities should progression to active disease occur.

Detection and treatment of TBI is an important aspect of contact management. Considering the broader public health goal of TB elimination, implementation of strategies to detect and treat TBI in migrants from high incidence countries is also essential.

Estimating risk of TB disease using on-line tools

Clinicians may find online calculators useful in estimating risk of progression from TBI to TB disease. Risk of adverse drug effects may also be calculated. This information can be presented to patients to aid understanding of their risk of TB disease and to assess risk of harm and benefit of preventative therapy. NTAC has not performed an assessment of these tools and as such does not formally endorse them; however, useful tools include The Online TST/IGRA Interpreter[i] and PERISKOPE-TB.[ii] While these tools have used data from many countries, including Australia, recommendations are general and the extent that data from Aboriginal and Torres Strait Islander people, or people from specific ethnicities, have informed the online tools is not clear.

i Version 3: tstin3d.com; version 4: tstin4d.com.

ii www.periskope.org/tb/.

Treatment of TB infection

A diagnosis of TBI requires ensuring that active disease is excluded. This also applies to subclinical TB where symptoms and signs may be absent or unrecognised. Prior to initiation of TBI treatment, patients should have a chest x-ray (CXR) performed; should always have sputum collected for testing if symptoms or CXR findings are present (induced if necessary) and cultured for TB where feasible; and should be reviewed by a clinician with experience in the diagnosis and management of TB. Assessment also includes clinical consideration and examination to rule out extrapulmonary TB, e.g. including lymph nodal examination.

Unlike treatment for active and subclinical (asymptomatic) disease where combination therapy is required, TBI can be treated with single agent therapy, although combination regimens of two drugs may permit shortening of the preventative regimen. Monotherapy can be used for TBI as bacillary replication is very low or absent, such that the risk of emergent drug resistance is extremely low. Drug-resistant TB despite a course of preventative therapy is more likely to arise from initial infection with a drug-resistant strain or new infection, rather than emerging because of preventative therapy.

NTAC endorses a number of regimens which are also recommended by the WHO. A choice of regimen allows tailoring to specific patient needs. The conclusion from clinical trials, and many years of experience for some regimens, is that there is mostly equivalent efficacy between regimens. Factors to consider include:

- Duration of regimen: a patient-centric approach favours a shorter regimen where possible. Besides patient preference, shorter regimens may be a better option in remote settings or where access to a healthcare facility is difficult.
- Co-morbid conditions and possible drug-drug interactions: rifamycins commonly interact with other agents metabolised by the hepatic cytochrome P450 system (for example warfarin or hormonal contraception) and many anti-TB agents may be poorly metabolised in the presence of advanced liver disease.
- Known antimicrobial agent allergies.
- Frequency of administration: a weekly regimen is more suited to directly observed therapy and is less intrusive for patients, compared to daily administration, and offers advantages where adherence may be potentially a problem.
- Availability: only isoniazid is listed on the Australian Pharmaceutical Benefits Scheme. Other possible agents may not be registered with the Therapeutics Good Administration or not approved for prolonged use for this indication. For regimens other than isoniazid monotherapy, access to agents for treating TBI is generally provided by the public sector directly, or as coordinated by jurisdictional TB programmes and public hospitals.
- Fixed dose combination (FDC) tablets are generally preferred by patients and usually decrease pill burden. However, all FDCs noted below are not registered on the Australian Register of Therapeutic Goods (ARTG) but must be procured by one or more jurisdictions.
- Therapy for TBI usually assumes no antimicrobial resistance unless an index case is known and drug resistance identified. Of note, for these cases WHO has recently endorsed a regimen of 6 months daily levofloxacin for prevention of multidrug-resistant TB in contacts.[15]

The combination of rifampicin and pyrazinamide should not be used for treatment of TBI as the risk of liver toxicity is significant. Table 4 summarises regimens and weight based dosing for adolescents and adults, and also contains recommendations for monitoring for adverse effects. Table 5 summarises regimens and weight based dosing for children.

Table 4: Agents used for treatment of tuberculosis (TB) infection in adults and adolescents[a]

Antimicrobial agent(s)	Weight based dosing[b]	Maximal dose	Duration	Important adverse effects (AE)[c,d]
Isoniazid (6-9H)	5 mg/kg/day	300 mg	6 or 9 months	Age related drug induced hepatitis (note mild transient rise in transaminases is common), peripheral neuropathy. Other possible AE include optic neuropathy, CNS changes, seizures, drug induced lupus, diarrhoea, DRESS or hypersensitivity reactions including rash, arthralgia
Rifampicin (4R)	10 mg/kg/day	600 mg	4 months	Orange staining of urine and other body fluids Rash and pruritis, hypersensitivity reactions, hepatotoxicity, GI upset, thrombocytopenia, haemolytic anaemia
Isoniazid/rifapentine Weekly (3HP)	Tablets or FDC	900 mg/900 mg WEEKLY	3 months	As for isoniazid and rifampicin. Note: a flu-like syndrome can be caused by intermittent rifamycin dosing
Isoniazid/rifapentine daily (≥ 13 years of age) (1HP)	Tablets	300 mg/600 mg DAILY	1 month	As above
Levofloxacin	< 50 kg body weight: 500 mg ≥ 50 kg body weight: 750 mg	750 mg	6 months	Nausea, diarrhoea and bloating Headache, dizziness, insomnia, or tremulousness Tendonitis and rare tendon rupture (increased risk > 60 years old or with corticosteroid use), arthralgias QTc prolongation (risk is lower than for moxifloxacin) Hypoglycaemia Hypersensitivity Antibiotic-associated diarrhea or *Clostridium difficile* colitis Aortic aneurysm and aortic dissection (older age, peripheral vascular disease, prior aneurysm increase risk)
Moxifloxacin	Tablet 400 mg for body weight ≥ 30kg	400 mg	6 months	As for levofloxacin Rarely hepatotoxicity

a World Health Organization (WHO) dosing recommendations are available: https://tbksp.who.int/en/node/3053.

b FDC: fixed-dose combination.

c Curry International Tuberculosis Center: Chapter 5: Medication fact sheets. Available at: https://www.currytbcenter.ucsf.edu/products/page/chapter-5-medication-fact-sheets.

d CNS: central nervous system; DRESS: drug reaction with eosinophilia and systemic symptoms; GI: gastrointestinal; QTc: corrected QT interval.

Table 5: Agents used for treatment of tuberculosis (TB) infection in children

Antimicrobial agent(s)	Weight based dosing[a]	Usual maximal dose	Duration
Isoniazid	10 mg/kg (< 10 years)	300 mg	6 or 9 months
Rifampicin	15 mg/kg (< 10 years)	600 mg	4 months
Isoniazid / rifapentine FDC[b]	See weight based table[a]	Isoniazid 700 mg / rifapentine 750 mg per WEEK (or 5 tabs FDC[b] per WEEK isoniazid 150 mg / rifapentine 150 mg)	3 months
Levofloxacin	15–20 mg/kg	1.0 g	6 months
Moxifloxacin	10–15 mg/kg	400 mg	6 months

a Reference 14.

b FDC: fixed-dose combination.

Rifampicin

Daily rifampicin for four months is demonstrated to be non-inferior to nine months of isoniazid (9H) in a large randomised clinical trial.[16] Adverse events were also significantly less, including less hepatotoxicity which, when present, was not age-related for rifampicin. The most common form of drug resistance in general is resistance to isoniazid. Rifampicin as preventative therapy offers some advantage where knowledge of a defined index case with documented drug susceptibility is lacking. The main drawback is the potential for drug-drug interactions, including hormonal contraception and a number of agents metabolised by the hepatic cytochrome P450 system. A careful medication history should be taken and interactions checked, preferably using an online tool. Barrier contraception should be used by women of childbearing age taking rifampicin (or rifapentine), rather than reliance on hormonal contraception.

Isoniazid

This is the most widely used and evidence-based regimen, although there is continuing debate as to the most appropriate duration of treatment. A risk reduction in excess of 90% can be achieved after 12 months of daily self-administration, but field effectiveness is compromised by declining adherence and increasing risk of adverse effects.[17] Extrapolation from trial data had suggested that treatment for nine months is optimal,[18] but subsequent meta-analyses concluded that there is no statistically significant benefit in continuing beyond six months unless there are fibrotic lesions greater than 2 cm^2 evident on CXR.[17,19] There are no head-to-head studies of six versus nine months isoniazid (INH), and therefore 6–9 months of therapy is considered adequate in existing international guidelines.

There is evidence of an extremely durable treatment response in a low-prevalence setting.[20] The principal safety concern has been the hepatotoxic potential of this drug.[21] There is a small increased risk in hepatotoxicity after the age of 35 years, which is somewhat greater after age 50 years. More recent data has shown very low rates of significant hepatitis, perhaps as a result of better patient selection and treatment monitoring.[22]

Co-administration with pyridoxine (vitamin B6) is not mandatory, but should be administered if the subject is malnourished or develops early symptoms of peripheral neuropathy. A review of over-the-counter supplements should be made to ensure total dose of pyridoxine does not exceed 100 mg daily, noting diverse supplements may contain variable doses of pyridoxine.

Rifampicin-isoniazid

This combination has been shown to have an equivalent efficacy and safety profile to isoniazid.[23] Daily treatment for three months is recommended as an alternative to isoniazid monotherapy.[24] The regimen is commonly used in children and is also useful when completion of preventative therapy is considered time-sensitive, e.g. pending organ transplantation. Although not registered on the ARTG, a FDC tablet including dispersible formulation for children can be procured by jurisdictional TB programmes from offshore sources such as the Global Drug Facility.

Isoniazid-rifapentine

Rifapentine is a potent, long-acting rifamycin. An open-label study of weekly, directly observed therapy (DOT) with this combination (3HP) for 12 weeks showed non-inferiority to nine months of daily, self-administered isoniazid.[25] It also appears to be efficacious and well-tolerated in HIV-infected adults.[26] This regimen is recommended by the WHO and can be used in adults and children of all ages.[14] It is also endorsed by the United States (US) Centres for Disease Control and Prevention.[27] It is not currently registered for use in Australia but may be available via special procurement as implemented by some jurisdictional TB programmes. While there are no head-to-head trials against 3HP, one month of daily isoniazid and rifapentine (1HP) is also endorsed by WHO as an efficacious regimen.[14] Experience with 1HP in Australia is limited. In fixed dose formulation, 3HP offers the most patient-centric regimen with minimal pill burden, suitability for patient adherence support (including DOT), and practicality where access to a healthcare facility is difficult. For these reasons the regimen may be advantageous in remote settings, including Aboriginal and Torres Strait Islander communities. Precautions regarding possible failure of hormonal contraception whilst taking a rifapentine should be heeded.

Levofloxacin and moxifloxacin

Recent clinical trials conducted in Vietnam[28] and South Africa,[29] together with a meta-analysis of data from these two trials,[30] provide evidence that six months of daily levofloxacin is effective in preventing progression to multi-drug resistant tuberculosis (MDR-TB) disease in adult and children household contacts of an index case. The meta-analysis concludes that the overall effect is a 60% relative reduction in TB incidence. The regimen was well tolerated and there was no signal for cardiac toxicity, noting the propensity of fluoroquinolones in general to prolong the QT interval. While these trials assessed only levofloxacin, NTAC considers moxifloxacin to have equivalence in this setting; choice of agent should consider availability, concurrent medications, and cardiac comorbidity, recognising that risk of QTc prolongation is higher for moxifloxacin compared to levofloxacin. Variable tablet strength availability and palatability may favour levofloxacin for use in children, although no formulation of levofloxacin is currently listed on the ARTG.

Summary of NTAC recommendations for treatment of TB infection

- Daily rifampicin for four months can be used in all patients with TBI unless there are significant drug-drug interactions, other contraindications, or the index case is known to have rifampicin resistant or multidrug resistant (RR/MDR)- TB.
- Daily isoniazid for at least six months remains a sound choice and preferred when rifampicin is not suitable. The risk of hepatotoxicity, while low, does increase with adult age. Nine months' duration may be preferred in some scenarios.
- Rifampicin-isoniazid for three months is an acceptable alternative, especially when treating TBI in children or when treatment completion is time-sensitive.
- Weekly isoniazid-rifapentine, as fixed-dose combination tablets, may be the most patient-centric regimen; this is effective, but may be limited by availability. Rifamycin drug interactions must still be considered.

Monitoring

Baseline liver function tests, electrolytes and full blood examination should be performed. Routine monitoring of liver function is not necessary in those under 35 years of age without risk factors (regular alcohol consumption, pre-existing liver function abnormalities). Otherwise, these should be checked monthly for a minimum of three months if on an isoniazid containing regimen. Transaminases in excess of 5 × the upper limit of normal (ULN), according to the local laboratory reference range, should prompt cessation of treatment, with a lower cut-off of 3 × ULN if symptoms are present. It should be noted that mild rises in alanine aminotransferase (ALT) / aspartate aminotransferase (AST), viz. 10–20%, are common on isoniazid.[31]

All patients should be educated about symptoms of hepatitis and should be advised to stop treatment, pending assessment by a doctor, if they are concerned. Patients should be advised to report promptly any symptoms of peripheral neuropathy, and should always be asked about any such symptoms during episodes of clinical contact. Mild symptoms may be ameliorated by oral pyridoxine administration, if not already prescribed.

If using a fluoroquinolone for preventative therapy, an electrocardiogram (ECG) should be performed at baseline and following one month of therapy (earlier if symptoms such as palpitations are reported). However, ECG monitoring may be considered non-mandatory where levofloxacin is used without other recognised risk factors for congenital or acquired QTc prolongation, including the presence of other pharmacological agents known to prolong the QTc interval. In general, a corrected QT interval Fredericia method (QTcF) is considered prolonged if > 450 msec in males and > 470 msec in females. A QTcF > 500 msec is potentially dangerous. Recommendations on how to calculate a corrected QT interval and recommendations on how to manage can be found online from the Tuberculosis Data, Impact Assessment and Communications Hub (TBDIAH).[iii] Cardiology advice should be considered where QTcF is > 500 msec, if a patient is symptomatic, or where alternative methods of QT correction are used, and interpretation is uncertain.

Ongoing monitoring monthly may be appropriate if there has been a significant rise in QTc or if there is underlying cardiac disease. Potential of other co-administered medications for QT prolongation should also be considered.

iii https://www.tbdiah.org/resources/publications/guide-for-qtc-monitoring-and-management-of-drug-resistant-tb-patients-with-qt-prolonging-agents/.

Follow up after treatment of TB infection

At or near the completion of therapy, it is important to advise that, while treatment is highly effective, it is not 100% protective and does not protect against new acquisition of TBI. The patient should be re-educated regarding symptoms of tuberculosis and advised to present for assessment should these occur.

There is no role for repeating TST or IGRA as a 'test of cure'. Repeat CXR is not required, unless needed for clearance or if new signs or symptoms direct further investigations.

Inquiring about the health of other family members and close contacts at this time can aid in identifying TB early in those at increased risk.

Acknowledgments

The authors would like to acknowledge Dr David Stocks for his writing of the previous version of this position statement and the contributions from the National Tuberculosis Advisory Committee (NTAC) members past and present (in alphabetical order): Dr Simone Barry, Dr Megan Campbell, Ms Ellen Donnan, Dr Vikas Goyal, Dr Alison Keed, Dr Vicki Krause, Dr Alison Ratcliff, Professor Vitali Sintchenko, Dr Marianne Turner, Dr Justin Waring and the NTAC Secretariat from the Australian Centre for Disease Control.

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