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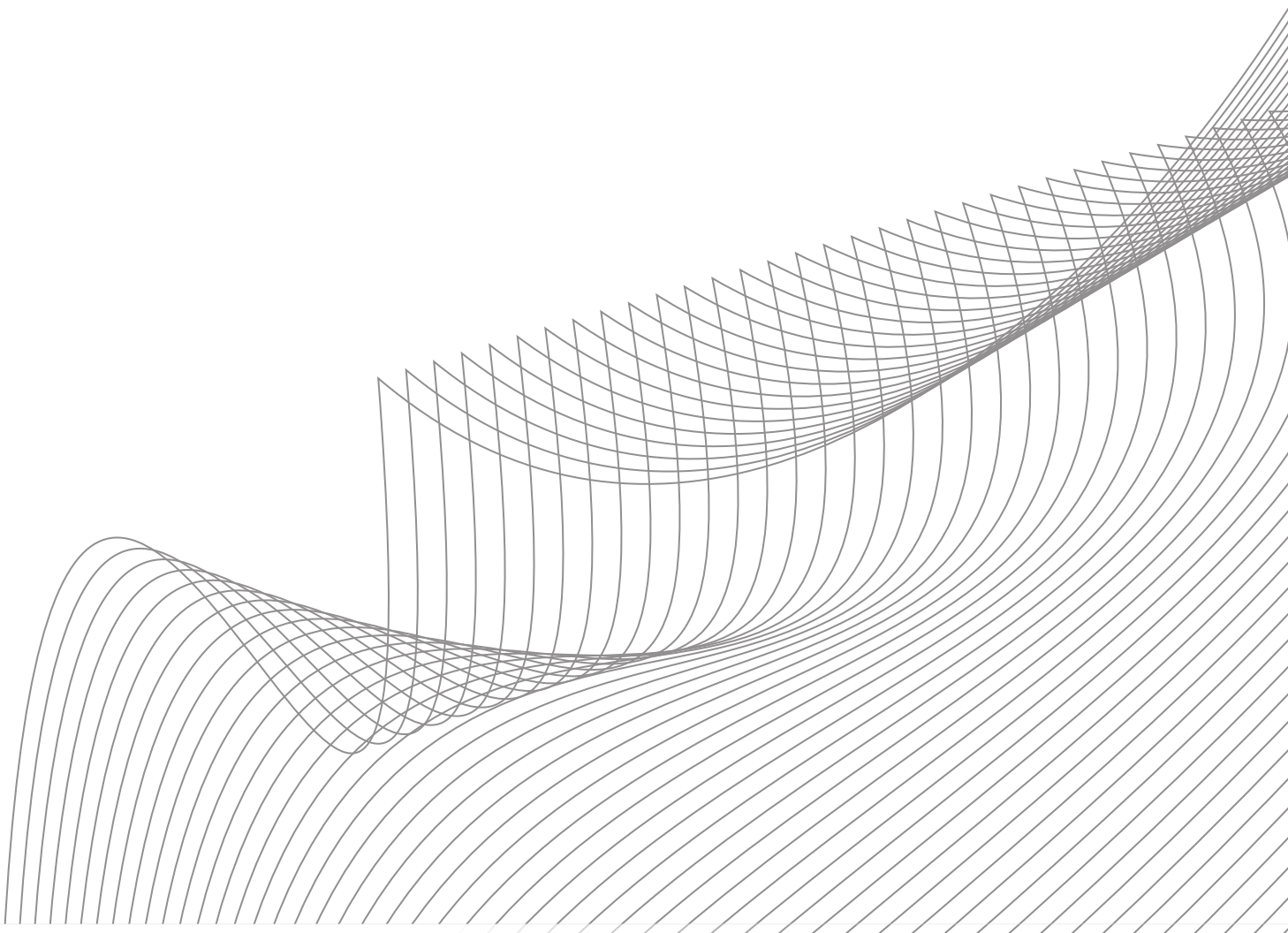
Australian recommendations for the Management of Drug-Resistant Tuberculosis, 2023

Richard Stapledon, Ellen Donnan and the National Tuberculosis Advisory Committee



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Australian recommendations for the management of drug-resistant tuberculosis, 2023

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Summary recommendations

Recent updates in international guidance on the treatment of drug-resistant tuberculosis (DR-TB) in both adults and children reflect significant advances in laboratory diagnostics, strengthened evidence for newer all oral treatment options and an emphasis on patient-centred care and support. The use of injectable agents is no longer recommended in either the shorter or longer course regimens, unless there is no suitable alternative to ensure an effective regimen.[1–8]

The following summary recommendations for the management of DR-TB are based largely on the most up to date World Health Organization (WHO) and ATS/CDC/ERS/IDSA[i] guidance.[1,3–6] Although most of the recommendations are conditional reflecting limited evidence, assessments by WHO guideline development groups comprising international TB experts and results from recent clinical trials (TB PRACTECAL, ZeNix) support the recommended use of the newer drugs and regimens.[1–4,9–11] The implementation of these newer regimens should be subject to expert oversight at the case management level, careful patient selection, a strong emphasis on monitoring for adverse drug effects and close involvement of the patient in the decision-making process.

It is important to acknowledge that this is a rapidly evolving area with further changes to treatment options anticipated in the next few years.

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

Standards of practice and care

The following best practice standards are considered a pre-requisite to the management of DR-TB cases in the Australian context.

1. Management of DR-TB cases should be based on a multi-disciplinary approach led by, or in close consultation with, an expert with DR-TB management experience.

2. Patient care and support measures include:

    a. appropriate counselling and education about the diagnosis and the available treatment options, as well as the importance of regular monitoring to assess drug safety and clinical progress

    b. a mutually agreed approach to supporting and monitoring treatment adherence

    c. adequate social and psychological support

    d. an assessment to evaluate ongoing healthcare needs, after DR-TB treatment completion.

3. Access to state-based TB reference laboratories for drug susceptibility testing (molecular and phenotypic) is essential to ensure the use of an effective regimen.

4. A drug procurement system that provides reliable and prompt access to quality-assured first- and second-line anti-TB drugs, facilitating the uptake of newer WHO endorsed regimens.

5. Access to therapeutic drug monitoring (TDM) to optimise drug exposure, especially to limit linezolid related adverse effects.

6. Participation in routine pharmacovigilance to monitor and inform on drug safety, particularly regarding the newer drugs.

Multidrug-resistant TB treatment regimens

All patients diagnosed with multidrug-resistant tuberculosis (MDR-TB) can now be considered for treatment with an all-oral shorter or longer course regimen.[1] This also applies to those with additional resistance to a fluoroquinolone. The WHO guidance (2022) prioritises the use of a standardised shorter course regimen providing certain criteria are met.

The most up to date options recommended by the WHO (2022) are:

1. 6-month BPaLM regimen (fluoroquinolone susceptible):

- comprises bedaquiline, pretomanid, linezolid (600 mg daily) and moxifloxacin
- is preferred to the 9–11 months shorter course or 18–20 months longer course regimens
- not suitable for those with previous exposure to bedaquiline, pretomanid, or linezolid for greater than one month unless resistance is excluded.

2. 6–9 month BPaL regimen (fluoroquinolone resistant):

- comprises bedaquiline, pretomanid, linezolid (600 mg daily)
- A 9-month regimen can be used if there is a slower, but still favorable, treatment response
- not suitable for those with previous exposure to bedaquiline, pretomanid, or linezolid for greater than one month unless resistance is excluded.

On current evidence, use of the BPaLM and BPaL regimens is limited to patients who:

- are 15 years and older
- do not have severe extra-pulmonary disease (miliary TB, TB meningitis, osteoarticular TB or pericardial TB)
- are not pregnant or breastfeeding
- have not had previous exposure to bedaquiline, pretomanid, or linezolid for greater than one month.

If the above regimens cannot be implemented due to not meeting the above criteria or in full due to adverse effects or drug interactions, a longer all-oral regimen is indicated.

3. 9–11 month all-oral regimen:

Although this standardised shorter course regimen is still a WHO option that can be considered for use, the inclusion of drugs with proven or possible resistance such as isoniazid, ethionamide and pyrazinamide, has raised concerns. The ATS/CDC/ERS/IDSA guideline (2019) did not make a recommendation for or against the use of this regimen.

The regimen comprises

- an initial phase: 4–6 months bedaquiline (6 months), moxifloxacin or levofloxacin, clofazimine, ethionamide (or linezolid 2 months), isoniazid (high dose), ethambutol, pyrazinamide then
- a continuation phase: 5 months moxifloxacin or levofloxacin, clofazimine, ethambutol, pyrazinamide;
- linezolid (600 mg daily) for an initial 2 months can be considered as an alternative to ethionamide for 4 months;
- extension of the initial phase of treatment to 6 months will depend on clinical and bacteriological assessment.

This shorter course all-oral regimen should only be considered in those with:

- confirmed fluoroquinolone susceptibility;
- non-extensive pulmonary disease (no bilateral cavitary or extensive parenchymal disease on chest radiology) or non-severe extra-pulmonary disease (no miliary TB, TB meningitis, osteoarticular TB or pericardial TB);
- for children less than 15 years of age, other extra-pulmonary sites are also excluded (except lymph peripheral nodes or isolated mediastinal mass without compression);
- no additional resistance to other first or second line drugs (other than isoniazid; if a katG mutation is present, high dose isoniazid is unlikely to be of benefit) or previous use of any drugs contained in the regimen for greater than one month.

Note: Ethionamide (or prothionamide) is contra-indicated in pregnancy. This 9–11 month oral regimen should only be considered in pregnancy if ethionamide is replaced with linezolid.

4. All-oral longer course regimen

The use of a longer course individualised regimen should be considered in those with more extensive forms of disease, or if a shorter course regimen cannot be used because eligibility criteria are not met or treatment is failing or drug intolerance issues arise.

The design of the regimen is based on a priority selection of drugs from the new WHO drug groupings (see table 1 below) which should be supported by drug susceptibility testing (DST) and careful pre-treatment evaluation of the patient. Minor differences between the WHO (2019) and ATS/CDC/ERS/IDSA (2019) guidelines include:

- Initial drug selection in fluoroquinolone susceptible cases should include at least 4 drugs from WHO groups A and B, consider 5 (WHO); ATS/CDC/ERS/IDSA advise at least 5 drugs.
- Bedaquiline is usually ceased at 6 months (WHO); but can be considered for use up to 5–7 months post sputum culture conversion (ATS/CDC/ERS/IDSA).
- The continuation phase should comprise at least 3 drugs (WHO); or 4 drugs (ATS/CDC/ERS/IDSA).
- Total duration of treatment should be 18–20 months (or at least 15–17 months post culture conversion) but can be adjusted according to treatment response determined by clinical, bacteriological and radiological parameters (WHO); ATS/CDC/ERS/IDSA suggest 15–21 months post culture conversion to define duration.
- In an MDR-TB case with additional fluoroquinolone resistance (or where one or more group A or B agents cannot be used), prolonged use of bedaquiline should be considered in addition to the selection of a group C agent(s) as prioritised to ensure a 5-drug regimen.
- In a case of XDR-TB, the same approach to drug selection should be followed.

Table 1: WHO drug groupings, 2019[a]

Grouping	Antimicrobials
Group A	Moxifloxacin or levofloxacin, bedaquiline, linezolid
Group B	Clofazimine and cycloserine
Group C	Ethambutol, pyrazinamide, delamanid, amikacin, carbapenem with clavulanic acid (meropenem or imipenem/cilastatin), ethionamide and PAS (para-aminosalicylic acid)

a Source: reference 4.

Children

The same principles that guide regimen design in adults can be used in children.[6,7] However, some key aspects should be noted:

- In young children the diagnosis will often be based on clinical and radiological findings in association with a history of close contact or previous treatment.
- In the event of a clinical diagnosis, the regimen design should be based on the DST result of the likely source case.
- An all-oral regimen should be used – **the use of amikacin should be avoided** unless there is no other reasonable option, due to the potential for a profound impact of hearing loss on a child's language and learning development.
- Bedaquiline and delamanid can be used for all age groups, using WHO recommended age and weight specific dosing.
- Weight should be closely monitored and drug doses adjusted with changes in weight.
- Linezolid use needs careful consideration due to toxicity risk. Shorter durations could be considered dependent on disease severity and fluoroquinolone susceptibility. Close monitoring for bone marrow toxicity, optic neuritis and peripheral neuropathy is essential.
- **Child-friendly dispersible tablet formulations should be used where possible** – the use of adult preparations risks imprecise dosing.

Isoniazid mono-resistance (rifampicin susceptible)

WHO guidance on management of isoniazid resistant but rifampicin susceptible TB has been in place since 2018 and includes the following:

1. A combination of rifampicin, ethambutol, pyrazinamide and levofloxacin or moxifloxacin (levofloxacin preferred) for 6 months.
2. If disease is severe, 9 months is advised.
3. If low-level isoniazid resistance is confirmed, the use of high dose isoniazid can be considered.

The ATS/CDC/ERS/IDSA guidance also suggests that pyrazinamide can be ceased after two months in those with less severe disease.[5]

If a fluoroquinolone cannot be used, the previously recommended combination of rifampicin, ethambutol and pyrazinamide (with or without high dose isoniazid) for 6–9 months is still considered acceptable particularly in less severe disease.[4]

Rifampicin mono-resistance (isoniazid susceptible)

The WHO advise the same treatment for both rifampicin mono-resistant TB (RR-TB) and MDR-TB.[1,3,4] Although isoniazid is a potent bactericidal drug and theoretically still available for treatment, the most recent ATS/CDC/ERS/IDSA guidelines also make no new recommendation for RR-TB that is isoniazid susceptible.

Surgery

In patients with pulmonary DR-TB and a high likelihood of treatment failure or relapse despite optimal drug therapy (e.g. XDR-TB), surgery can be considered as an adjunct to medical treatment using the following criteria:

- a multidisciplinary approach, that includes close consultation with a Thoracic surgeon with experience in lung resection and treating patients with TB, to ensure careful patient selection based on clinical, bacteriologic and radiologic information and advice on optimal timing of the surgery
- disease is largely localised and suitable for resection (wedge resection, segmentectomy or lobectomy)
- where the general health status of the patient and co-morbid conditions favour a positive surgical outcome and longer term survival.

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The National Tuberculosis Advisory Committee (NTAC) and the NTAC Secretariat provided oversight in the development process.

List of abbreviations

Abbreviations	Definition
ADR	adverse drug reaction
BPaLM	bedaquiline, pretomanid, linezolid and moxifloxacin
BPaL	bedaquiline, pretomanid and linezolid
DOT	directly observed treatment
DR-TB	drug-resistant tuberculosis
DST	drug susceptibility testing
Hr-TB	rifampicin-susceptible, isoniazid-resistant TB
MDR-TB	multidrug-resistant tuberculosis
MDR/RR-TB	multidrug- or rifampicin-resistant tuberculosis
MRLN	Australia's Mycobacterium Reference Laboratory Network
MTBC	*Mycobacterium tuberculosis complex*
NTAC	Australia's National Tuberculosis Advisory Committee
Pre XDR-TB	pre-extensively drug-resistant tuberculosis
RR-TB	rifampicin-resistant tuberculosis
SLD	second-line drug
TB	tuberculosis
TDM	therapeutic drug monitoring
WGS	whole genome sequencing
WHO	World Health Organization
XDR-TB	extensively drug resistant tuberculosis

List of first- and second-line drug abbreviations

Abbreviations	Definition
Amk	amikacin
Bdq	bedaquiline
Cfz	clofazimine
Cs	cycloserine
Dlm	delamanid
E	ethambutol
Eto	ethionamide
H	isoniazid
Hh	high dose isoniazid
Ipm-Cln	imipenem-cilastatin
Lfx	levofloxacin
Lzd	linezolid
Mpm	Meropenem
Mfx	moxifloxacin
Pa	pretomanid
Pto	prothionamide
PAS	para-aminosalicylic acid
R	rifampicin
S	streptomycin
Trd	terizidone
Z	pyrazinamide

1. Introduction

The emergence of multidrug-resistant (MDR-) tuberculosis (TB) since the 1990s has posed substantial challenges to TB care and prevention on a global basis. Although Australia has maintained good TB control with low annual rates of MDR-TB, the significant numbers of new arrivals from high TB burden countries means that Australia will continue to be exposed to this issue through the migration of persons already infected with drug-resistant TB strains.

Guidance until 2010 on the construct and duration of treatment regimens for use in MDR-TB cases had largely been based on expert consensus recommendations.[12,13] The key principles were to construct a regimen using a step-wise approach based on treatment history, drug susceptibility testing (DST) and the hierarchy of second line drug groups recommended at the time, using at least four drugs with reasonably certain effectiveness that included as a core a later generation fluoroquinolone and an injectable agent. Treatment durations of 18–24 months have proven problematic due to drug toxicities and unsatisfactory treatment outcomes further aggravated by psycho-social and financial difficulties for the patient.[12,13]

However, over the past decade there have been some important advances reflecting significant changes in available diagnostic and treatment options. The endorsement by the WHO in 2016 of a shorter standardised regimen (9–12 months) known as the 'Bangladesh' regimen was an important initial step forward, particularly in the low and middle income countries, in the effort to overcome some of the patient and health care challenges related to the use of the longer regimens.[14]

The advent of rapid molecular based methods to detect mutations most frequently associated with resistant strains is leading to the more timely detection and implementation of treatment for MDR-TB. Newer drug options such as bedaquiline, delamanid, pretomanid, and linezolid have facilitated a key shift in focus to the use of all-oral shorter and longer course regimens in association with an enhanced approach to patient-centred care and support. Injectable agents have largely been replaced by oral agents in these regimens because of their unacceptable rate of adverse events and administration issues.[1,3–5] Advocacy groups have strongly supported these innovations.

The transition to the new all-oral treatment recommendations was first announced by WHO in 2018 based on work undertaken by Guideline Development Groups (GDGs) using the GRADE* methodology. This approach comprised reviewing individual patient data (IPD) from several thousand records from multiple studies worldwide to assess the relative influence of different treatment combinations to patient outcomes. The relative risks assigned to the various drugs used in MDR-TB treatment regimens were used to form the new tier of drug groupings (Table 1).[4] Subsequent ATS/CDC/ERS/IDSA guidance (2019), using a similar methodology, made recommendations in keeping with those of the WHO but with an emphasis on an individualised approach to regimen design based on DST.[5] This contrasted to the standardised empiric approach of the WHO directed at low-income, high-burden settings where DST data are often limited.

Further key announcements have occurred in relation to the recommendations for use of shorter course MDR-TB treatment regimens. Initially this simply related to modification of the 2016 'Bangladesh' regimen through replacement of the injectable agent amikacin by bedaquiline.[3] In May 2022, a key WHO advisory was issued based on outcomes from the ongoing TB-PRACTECAL and ZeNix studies.[2,9,11] This supported programmatic implementation of the 6-month BPaLM

(bedaquiline, pretomanid, linezolid, moxifloxacin) and BPaL (bedaquiline, pretomanid, linezolid) regimens for treatment of fluoroquinolone susceptible and fluoroquinolone resistant MDR-TB respectively for most patients.

Overall, the key changes in recommendations from guidelines pre-2018 emphasise:

- The need for an enhanced focus on patient-centred care and support measures to help patients better understand their diagnosis and treatment and minimise potential barriers.

- The strong recommendation that an all-oral shorter course regimen be used in preference to an injectable containing one unless there is no alternative.

- Certain drugs from previous groupings are no longer recommended; the injectable agents kanamycin and capreomycin, and amoxicillin/clavulanic acid alone.

This document, which is current as of June 2023, is intended to provide an overview of the current guidance on the management of drug-resistant tuberculosis (DR-TB) based on the most recent evidence. However, it is important to acknowledge that this is a rapidly evolving area and with trials of new regimens and classes of drugs in the pipeline there are likely to be further changes in guidance on the treatment of drug-resistant TB in the next few years.

Definitions

The definition of MDR-TB remains unchanged. However, the WHO definition of XDR-TB was updated, and that of pre-XDR-TB included, following a WHO Expert Consultation meeting in October 2020 to reflect the changes in second line drug groupings (with an all-oral approach to regimen design) and also allow for future changes that may occur to the group A drugs. The revisions came into effect from January 2021.[15] Disease severity is also defined given its importance to regimen selection.

Multi- and extensive drug resistance definitions

MDR-TB: an *M. tuberculosis* strain that is resistant to at least rifampicin and isoniazid.

MDR/RR-TB: either multidrug-resistant TB (MDR-TB) or rifampicin-resistant TB (RR-TB).

Pre-XDR-TB: an *M. tuberculosis* strain that meets the definition of MDR/RR-TB and is also resistant to any fluoroquinolone.

XDR-TB: an *M. tuberculosis* strain that meets the definition of MDR/RR-TB and is also resistant to any fluoroquinolone* and at least one additional Group A drug (Table 1).

Other resistance definitions

Mono-resistance: resistance to one anti-tuberculosis drug.

Poly-resistance: resistance to more than one anti-tuberculosis drug other than both isoniazid and rifampicin.

Disease severity definitions[1]

Extensive pulmonary TB disease: bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged below 15 years, severe disease is usually defined by the presence of cavities or bilateral disease on chest radiography.

Severe extrapulmonary TB: miliary TB, TB meningitis, osteoarticular TB or pericardial TB. In children aged below 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered severe.

DR-TB epidemiology

An understanding of the status of drug resistance in other countries can assist in the design of an effective regimen when rifampicin-resistance has been detected by a molecular test but other genotypic and phenotypic DST results are not yet available.

Globally in 2021, there were an estimated 450,000 MDR/RR-TB cases (95% uncertainty interval [95% UI]: 399,000–501,000). The estimated proportion occurring in new cases was 3.6% (95% UI: 2.7–4.4%) and in previously treated cases 18% (95% UI: 11–26%). In several countries of the former Soviet Union, the proportions have been greater than 20% in new cases and 50% in previously treated cases.[16,17]

The number of incident cases of MDR/RR-TB reported globally in 2021 was 167,000 (including 25,000 pre-XDR or XDR-TB cases), representing 37% of the estimated burden. In the Western Pacific region there were 28,700 laboratory confirmed cases of MDR/RR-TB, representing 41% of the estimated burden of 70,000 (95% CI: 55,000–85,000). The countries with the largest share of cases were India (26%), the Russian Federation (8.5%), and Pakistan (7.9%). India, the country with the highest number of estimated and reported MDR/RR-TB cases, detected pre-XDR/XDR-TB in 18.5% of confirmed MDR/RR-TB cases.[16]

Representative drug resistance surveillance data collected over the fifteen years prior to the 2020 WHO Global Report found that the proportion of MDR/RR-TB cases with resistance to any fluoroquinolone was 20.1% (95% CI: 15.5–25.0%).[17] In 2021, the estimated proportion globally of MDR/RR-TB cases with laboratory detected resistance to a fluoroquinolone was 20% (95% CI: 16–26%). Estimates of isoniazid resistance in 2019 were 13.1% (95% CI: 9.9–16.9%) of new cases and 17.4% (95% CI: 0.5–54%) of previously treated cases. Overall 11% (range: 6.5–15%) of all incident cases of TB had isoniazid-resistant and rifampicin-susceptible TB.[17]

In Australia, the number of cases notified with DR-TB is low; such cases most commonly occur in overseas-born people. The notification data for drug resistance profiles from 2019–2022 are summarised in Table 2 below.[18]

Table 2: Drug resistance profiles among TB cases with DST results available, Australia, 2019–2022

Resistance	2019 (1,123 cases)	2020 (1,118 cases)	2021 (968 cases)	2022 (907 cases)
Any first-line anti-TB drug[a]	11.1% (125)	11.1% (124)	11.3% (109)	12.2% (111)
Mono-resistance to rifampicin	0.3% (3)	0.4% (5)	0.2% (2)	0.2% (2)
Mono-resistance to isoniazid	5.2% (58)	4.3% (48)	5.2% (50)	5.6% (51)
MDR-TB	2.2% (25)	2.1% (23)	2.2% (21)	1.9% (17)
Pre-XDR-TB[b]	0.6% (7)	0.6% (7)	0.3% (3)	0.6% (5)
XDR-TB	0.1% (1) [c]	0% (0) [c]	0% (0) [d]	0% (0) [d]

a Resistance to at least one first-line anti-TB drug: isoniazid, rifampicin, pyrazinamide, and ethambutol.

b Resistance to rifampicin, isoniazid, and any fluroquinolone, OR resistance to rifampicin, isoniazid, and any second-line injectable (amikacin, capreomycin, and kanamycin).

c Resistance to rifampicin, isoniazid, and any fluroquinolone, and to at least one of the three injectable second-line drugs (WHO definition prior to 2021).

d Resistance to isoniazid and rifampicin, and any of the fluoroquinolones, and to at least one additional Group A drug (updated WHO definition from 2021 onwards).

Of the MDR-TB cases reported in 2019–2022 among overseas-born people, the majority were born in India (17 cases), China (13), the Philippines (13), and Vietnam (11). Of the six Australian-born MDR-TB cases notified in the four-year period, none were in Indigenous Australians. Additional resistance to a fluoroquinolone was reported in an average of 21% (range: 12.5–23.3%) of those cases with resistance to both isoniazid and rifampicin for 2019–2022. Extensively drug-resistant TB accounted for only one case over this period.

DR-TB development and transmission

Most cases of TB are fully drug susceptible and treatable with WHO standard first line therapy. If appropriately managed and supervised, this regimen can achieve high cure rates and prevent acquired drug resistance.

Drug-resistant TB may arise through two means:

1. selection for pre-existing resistant bacteria in a person on treatment for drug susceptible or single drug-resistant TB – acquired (secondary) resistance

2. infection occurring in a previously untreated person through direct transmission from an individual with active MDR-TB disease – transmitted (primary) resistance

Acquired drug resistance occurs due to the selection of naturally occurring resistant mutant subpopulations from inadequate drug treatment. Although the probability of spontaneous resistance occurring to both rifampicin and isoniazid is extremely unlikely, several factors can contribute to acquired resistance developing to one or more drugs within a relatively short time-frame:

- use of an inadequate regimen combination
- sub-optimal drug doses
- irregular patient adherence to treatment
- patient pharmaco-kinetic variability
- impaired drug penetration at the site of disease, e.g. cavitary pulmonary TB
- drug malabsorption, e.g. in TB/human immunodeficiency virus (HIV), diabetic cases
- drug quality and supply issues.

Primary drug resistance due to transmission of a drug resistant strain is increasingly recognised as a key contributor to the MDR-TB burden. While most cases in Australia are likely to be primary in nature from drug resistant infection acquired in the country of origin (or possibly local recent transmission from close contact), monitoring for acquired drug resistance is important as it may have implications for the quality of the treatment program.

Laboratory diagnosis of drug-resistant tuberculosis

The early laboratory diagnosis of MDR-TB and the provision of accurate drug susceptibility data are critical to ensuring the use of an effective treatment regimen and a successful treatment outcome, preventing resistance amplification and minimising transmission.

Australia's Mycobacterium Reference Laboratory Network (MRLN) provides phenotypic drug susceptibility testing (DST) on all initial *M. tuberculosis* isolates from new TB patients and in other specific circumstances as outlined in NTAC's TB Laboratory Guidelines.[19] This DST testing is performed by liquid-based systems, such as Mycobacterium Growth Indicator Tubes (MGIT; Becton Dickinson), with the aim of reporting TB DST results within an average of 15–30 days from the time of receipt of the original specimen. This phenotypic testing is complemented by rapid molecular testing when appropriate using: the Xpert® MTB/RIF Ultra assay (Cepheid, Sunnyvale, CA – for detection of *M. tuberculosis* and rifampicin resistance); the Xpert® MTB/XDR assay (for detection of resistance to six drugs); commercial line-probe assays (Hain Lifescience GmbH, Nehren, Germany); and/or Sanger sequencing of known resistance genes.

Phenotypic testing for susceptibility to the new and repurposed agents (e.g. bedaquiline, delamanid, clofazimine, linezolid, pretomanid) has proved challenging for the MRLN laboratories, as it has for international reference laboratories. The challenges have included: access to drug powders and drug-resistant type strains; agreed methodologies and breakpoints for these agents; and involvement in external quality assurance programs (QAPs) that test a laboratory's performance for DST of these agents. One potential solution is the use of commercial broth microdilution assays containing these various agents. Careful adherence to instructions for use, good laboratory work practices and PC3 biocontainment environment are emphasised when dealing with the inoculation and reading of these microtitre plates. Improvements in dilution range, drug preparation, validation of atmospheric condition and quality control also would be required for implementation.

Whole genome sequencing (WGS) for *M. tuberculosis* is now available in all Australian jurisdictions though coverage and turnaround times do vary between states and territories. WGS offers the prospect of compiling detailed genetic information from TB strains to identify genetic markers of resistance and to determine the level of resistance associated with specific mutations.[19] The Communicable Diseases Genomics Network and the Australian Pathogen Genomics Program research project have identified *M. tuberculosis* as a priority organism.[ii] Working groups aim to develop a genomic tool for *in silico* detection of TB drug resistance and to assess the predictive capacity of the tool on a national dataset. In the meantime, phenotypic testing may remain necessary for agents where the molecular mechanism of resistance remains (incompletely) defined.

The MRLN is therefore working with clinical colleagues and bioinformaticians to integrate the phenotypic and genotypic testing methods for TB DST with the aim of optimising their speed and accuracy, which will ultimately benefit patients with DR-TB.

ii https://www.cdgn.org.au/public-health-genomics.

2.Principles of management of MDR-TB

Given the small number of cases of MDR-TB that occur in Australia and the complexities involved, management in terms of best practice should be undertaken using a multi-disciplinary approach by or in close consultation with those with TB expertise. State and territory-based TB Services provide a focal point to undertake this or support Respiratory and Infectious diseases clinicians with experience in TB management.

Key principles in the management of a person with DR-TB include:

- A patient-centred case management approach with appropriate counselling and education about their diagnosis and available treatment options and social support measures.
- An individualised approach to regimen design/drug selection based on international guidance and quality assured drug susceptibility testing (molecular and phenotypic DST) with a strong preference for use of an all-oral standardised shorter course regimen in those who meet the recommended criteria.
- Strategies that support treatment adherence and an agreed approach to administration.
- Routine monitoring of the patient to ensure
    - appropriate adherence to therapy, including the use of direct or video observed therapy
    - early detection and management of adverse events and adverse drug reactions, and
    - an appropriate response to treatment based on clinical, radiological and bacteriological assessments (optimally monthly culture in pulmonary cases).
- Infection control measures to minimise transmission.
- Evaluation of contacts to assess for TB transmission
    - Identify and treat cases of active disease
    - Consider preventive therapy in those with evidence of recent infection taking into account the DST of the source case, e.g. fluoroquinolone in MDR-TB contacts.

Treatment regimen design

The WHO recommends use of all oral regimens for treatment of MDR-TB, either a shorter course standardised regimen, providing certain criteria are met, or a longer duration more individualised regimen, the latter particularly when more extensive disease or resistance is involved.[1]

Previously there had been concerns over the use of the 9–11 month standardised shorter course approach because of the inclusion of some drugs that may be resistant or had been previously used. The addition of the newer drug options such as bedaquiline, linezolid and pretomanid provides the advantage that effective shorter or longer course regimens can be implemented promptly when rifampicin resistance is first detected and likely remain effective even if fluoroquinolone resistance is subsequently detected.

Shorter course MDR-TB treatment

WHO recommendations now preference the use of a standardised all oral shorter course regimen providing certain criteria are met, particularly that fluoroquinolone susceptibility has been confirmed (BPaLM and 9–11 month regimens) and that disease is not extensive or severe in nature.

Six month BPaLM regimen (fluoroquinolone susceptible)

More recently (May 2022), based on outcomes from the TB-PRACTECAL study first reported in October 2021, a WHO advisory was released supporting implementation of the so termed 'BPaLM' regimen.[2] The regimen comprises bedaquiline, pretomanid, linezolid, and moxifloxacin administered over six months.

The multi-country TB-PRACTECAL study is a randomised controlled trial that has been testing the six-month BPaLM regimen against the accepted standard of care (SOC) for the particular country. The findings provided to the WHO indicate that 89% of patients enrolled in the BPaLM arm had been cured versus 52% in the SOC arm. In terms of drug safety, severe adverse events were lower in the BPaLM group (19%) than the SOC group (59%).[9] Although there were initial concerns from animal studies that pretomanid caused testicular atrophy and impaired fertility in male rats, new data suggest this potential effect on human male fertility appears unlikely.[1]

The present level of evidence for the BPaLM regimen is limited to those over 14 years, with no data yet to support its use in pregnancy or severe extra-pulmonary disease such as TB meningitis.[9]

6–9 month BPaL regimen (fluoroquinolone resistance)

The WHO have proposed the BPaL regimen comprising bedaquiline, pretomanid and linezolid (600 mg dose) for use over 6–9 months in MDR-TB patients with additional resistance to a fluoroquinolone. Previous exposure to bedaquiline, linezolid or pretomanid for greater than one month precludes its use unless resistance can be excluded (conditional recommendation, very low certainty in the estimates of effect). Although 90% of people who received the BPaL regimen in the Nix study remained free of TB six months after completing treatment, the high frequency of serious side-effects due to the initial use of linezolid in a 1200 mg daily dose was a major limitation (81% peripheral neuropathy, 48% myelosuppression).[10] Follow-up findings from the ZeNix study looking at the impact of a reduced daily dose (600 mg) of linezolid suggested no significant reduction in efficacy.[11] The six-month duration can be extended to nine months in the event of a slower (but favorable) response to treatment.

As with the BPaLM regimen, use of the BPaL regimen is limited to those over 14 years, and is not yet advised in pregnancy or severe extra-pulmonary disease.

9–11 month all-oral regimen

This regimen was first introduced in 2016 and known as the 'Bangladesh' regimen.[14] The regimen was updated in 2019 with bedaquiline replacing the injectable agent amikacin and further modified in 2022 with the advice from WHO that linezolid (600 mg daily) for an initial two months can be considered in preference to ethionamide (or prothionamide) for four months.[1,3] The latter update was prompted by data from South Africa which found that replacing ethionamide for four months with linezolid (600 mg daily) for two months had similar efficacy.

The regimen is comprised as follows:

- Initial phase (4–6 months): bedaquiline (6 months), moxifloxacin or levofloxacin, linezolid (2 months) or ethionamide (4–6) months, clofazimine, isoniazid (high dose, 10–15 mg/kg/day), pyrazinamide, ethambutol

- Continuation phase (5 months): moxifloxacin or levofloxacin, clofazimine, pyrazinamide, ethambutol

The use of the regimen is contingent on meeting the following criteria:

- excluding resistance to the fluoroquinolone

- no extensive pulmonary or severe extra-pulmonary disease

- unlikely resistance to other drugs except for isoniazid (if a katG mutation is present, high dose isoniazid unlikely to be of benefit)

- no previous exposure to second line agents for more than a month and

- ethionamide (or prothionamide) is contra-indicated in pregnancy. This all-oral regimen should only be considered in pregnancy if ethionamide is replaced with linezolid.

With the introduction of bedaquiline, it is important to be mindful of the 1–2 week period required to achieve a therapeutic drug level and hence the importance of drug susceptibility testing to exclude additional resistance. The early use of linezolid strengthens the regimen. A further issue of which to be mindful is that, if treatment is interrupted for a protracted period particularly in the earlier stages, the long half-life of bedaquiline (6 months) can effectively result in monotherapy with a consequent risk of acquired resistance. This latter concern applies equally in other regimens.

The ATS/CDC/ERS/IDSA guidelines make no definitive recommendation for or against the use of the 9–11 month shorter course regimen.[5] In making this determination they reviewed the impact of applying the eligibility criteria to the individual patient data meta-analysis (IPDMA) data and found only 15% would have qualified for use of this shorter course regimen. Similar findings have been reported elsewhere.[20–22]

In the Australian setting, the shorter course 9–11 month MDR-TB regimen has not been widely adopted and this may reflect some of the concerns regarding its effectiveness, particularly when there is additional resistance (excepting isoniazid).

Recommendations

1. The 6-month BPaLM regimen be considered for use in most new cases of fluoroquinolone susceptible MDR-TB in accordance with WHO guidance 2022

- comprises bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin
- previous exposure to bedaquiline, pretomanid, or linezolid for greater than 1 month precludes use of this regimen unless resistance is excluded.

2. The 6–9 month BPaL regimen be considered for use in cases of fluoroquinolone resistant MDR-TB

- comprises bedaquiline, pretomanid, linezolid (600 mg)
- 9 months can be used if there is a slower but still favorable treatment response
- previous exposure to bedaquiline, pretomanid, or linezolid for greater than 1 month precludes use of this regimen unless resistance is excluded.

3. In cases with extensive pulmonary or severe extra-pulmonary disease, use of a longer course regimen is advised.

Current evidence limits use of the BPaLM and BPaL regimens to patients who are:

- over 14 years
- do not have severe extra-pulmonary disease
- are not pregnant.

4. The shorter course 9–11 month all-oral standardised regimen can be considered as an alternative with linezolid for 2 months replacing ethionamide (or prothionamide) for 4 months providing the following criteria are met:

- fluoroquinolone susceptibility is confirmed
- no severe pulmonary or extra-pulmonary disease
- no additional resistance to other first or second line drugs or previous use for greater than 1 month.

If any of the above regimens cannot be implemented due to not meeting the necessary criteria or in full due to adverse effects or drug interactions, a longer course regimen is indicated.

All-oral longer course regimen

WHO guidance in 2019 regrouped/reordered the second-line drugs recommended for use in MDR-TB cases (Table 3).[4] This reflected a key change in emphasis to the use of an all-oral approach with newer or repurposed drugs based on efficacy evidence and a move away from the longstanding injectable containing regimens because of their unacceptable level of adverse events and associated difficulties in administration over several months. The new guidance also acknowledges the importance of patient preference in this regard.

The ATS/CDC/ERS/IDSA guidelines are in overall agreement with those of the WHO. However, their drug hierarchy in the 'Group C' range is prioritised in a slightly different order, with the injectable agents (amikacin and streptomycin) ranking higher than the remaining oral agents.[5] From a practical perspective, this does not appear to make a significant difference in terms of final selections other than the importance of patient preference. There are also variances between the recommendations in terms of the number of agents to be used in the initial (IP) and continuation (CP) phases, and the use of shorter course regimens. A summary of the variances between these two key international guidelines is set out in Table 4.

Number of drugs

Based on the most recent WHO and ATS/CDC/ERS/IDSA second line drug rankings, in order of priority the fluoroquinolones (levofloxacin or moxifloxacin), bedaquiline, linezolid, clofazimine and cycloserine represent the agents of initial choice. The strength and certainty of evidence for the use of these drugs is represented in Table 5. The WHO advise starting with four effective second-line drugs versus the ATS/CDC/ERS/IDSA's recommendation of five. The difference in the initial number of drugs recommended (and subsequent numbers in the continuation phase) may relate to some variances in the IPDMA data assessed by the respective bodies despite the substantial overlap. The ATS/CDC/ERS/IDSA decision to recommend starting with five effective second-line drugs also takes into account the reasonable likelihood of drug intolerance or toxicity occurring during the initial phase of treatment, especially to linezolid or cycloserine.

If selection of 4–5 second-line drugs from this higher priority set of drugs is not possible, e.g. due to fluoroquinolone resistance, drug toxicity or concern from previous use of a drug, then drugs from the remaining agents should be considered. In contrast to the WHO recommendation, the ATS/CDC/ERS/IDSA 'step 4' indicates the preference for amikacin (or streptomycin) ahead of the remaining oral agents if a more effective or less toxic regimen cannot be developed.[5] This assumes confirmed drug susceptibility and appropriate discussions to determine patient preference.

This overall approach emphasises that an effective regimen requires the use of drugs with a proven or high likelihood of susceptibility. Designing an effective regimen should also consider the bactericidal and sterilising properties of the individual drugs.[23] The final selection will also depend on factors such as medical comorbidities, the potential for drug–drug interactions and patient preference if an injectable agent is to be considered. In the event of central nervous system (CNS) involvement, drug penetration is an important consideration. For example, in terms of the newer all-oral recommendations, while levofloxacin/moxifloxacin, cycloserine and linezolid penetrate the CNS well, information for clofazimine, bedaquiline and delamanid is limited.

Duration

The initial phase of treatment has previously been defined by the duration of use of the injectable agent (≥ 8 months) including time from culture conversion. With the new WHO recommendations, the duration of the initial phase in effect is determined by the current use of bedaquiline for the first six months only. The continuation phase beyond this point is recommended to continue to complete a total treatment period of 18–20 months or at least 15–17 months beyond culture conversion.[1,3]

The ATS/CDC/ERS/IDSA, however, place a continued emphasis on time from culture conversion to determine the duration of the initial phase, recommending 5–7 months from when culture conversion is confirmed. The basis for this determination centres on factors that likely influence patient response to therapy such as disease severity, the pattern of drug resistance and the strength of the regimen. The recommended duration of the 4-drug continuation phase is a cautious 15–21 months from the time to culture conversion, up to 24 months in the pre-XDR and XDR-TB patients.[5]

Recommendations

1. Longer course regimens are recommended in those with more severe or extensive forms of MDR-TB, pre-XDR or XDR-TB (pulmonary and extra-pulmonary)

2. Use an individualised approach based on molecular and phenotypic DST to determine the regimen design

3. Initial drug selection in fluoroquinolone susceptible cases should preferably include all five drugs from groups A&B – moxifloxacin or levofloxacin, bedaquiline, linezolid, clofazimine, cycloserine

4. Bedaquiline use beyond six months can be considered in those with slower but favorable sputum culture conversion (5–7 months post culture conversion)

5. The continuation phase should comprise four drugs

6. Total duration of treatment should be 18–20 months (or at least 15–17 months post culture conversion) but can be adjusted according to treatment response

Pre-XDR and XDR-TB (or where one or more group A or B agents cannot be used):

7. In an MDR-TB case with additional fluoroquinolone resistance and the use of BPaL is excluded, prolonged use of bedaquiline should be considered in addition to the selection of a group C agent(s) as prioritised to ensure a 5-drug regimen. Group C includes ethambutol, pyrazinamide, delamanid, amikacin, carbapenem with clavulanic acid (meropenem or imipenem/cilastatin), ethionamide (or prothionamide) and PAS (para-aminosalicylic acid)

8. In a case of XDR-TB (MDR with additional resistance to two or more group A drugs), the same approach to drug selection should be followed.

Table 3: Revised MDR-TB drug groupings and steps to regimen – WHO guidance 2019[a]

Groups and steps	TB medication
A **Include all three**	Levofloxacin (Lfx) or moxifloxacin (Mfx) Bedaquiline (Bdq) Linezolid (Lzd)
B **Add one or both**	Clofazimine (Cfz) Cycloserine (Cs)
C **Add to complete if drugs from A or B can't be included**	Ethambutol (E) Pyrazinamide (Z) Delamanid (Dlm) Carbapenem with amoxicillin/clavulanic acid (imipenem-cilastatin (Ipm-Cln) or meropenem (Mpm)) Amikacin (Amk) (or streptomycin) Ethionamide (Eto) or prothionamide (Pto) p-aminosalicylic acid (PAS)

a Source: reference 4.

Table 4: Comparison of WHO and ATS/CDC/ERS/IDSA MDR-TB treatment recommendations

Category	WHO[a]	ATS/CDC/ERS/IDSA[a]
Number of effective drugs	At least 4 drugs initial 6 months & 3 drugs after Bdq ceased	At least 5 drugs initial phase & 4 drugs continuation phase
	Conditional rec, very low certainty in the evidence	*Conditional rec, very low certainty in the evidence*
Duration of initial phase	6 months = Bdq cessation	5–7 months after culture conversion
	Use of Bdq can be extended 'off label'	*Conditional rec, very low certainty in the evidence*
Total treatment duration	15–17 months after culture conversion 18–20 months duration	15–21 months after culture conversion
	Conditional rec, very low certainty in the evidence	*Conditional rec, very low certainty in the evidence*
Shorter course regimen for 9–11 months	Acceptable providing certain criteria met in particular exclusion of fluoroquinolone resistance and severe disease	Could not make a recommendation for or against the shorter regimen compared with individualised regimens
Individualised, empiric or standardised regimen	Standardised regimens used empirically with incomplete DST data	Individualised – build a regimen based on DST
Isoniazid resistant TB (rifampicin susceptible)	6REZLfx	6REZLfx 2REZLfx 4RELfx Option to use pyrazinamide for first 2 months only in those with a low burden of infection, hepato-toxicity
Rifampicin resistant TB (Isoniazid susceptible)	Same as for MDR-TB	No new recommendation 2HEZFQN 10-16HEFQN

a E: ethambutol; H: isoniazid; R: rifampicin; Z: pyrazinamide; FQN: fluoroquinolone; Lfx: levofloxacin.

Table 5: WHO and ATS/CDC/ERS/IDSA priority second-line drug selections 2019: comparison between strength of recommendation and level of certainty of evidence

Drug	WHO	ATS/CDC/ERS/IDSA
Moxifloxacin or levofloxacin	Strong recommendation Moderate certainty in the estimates of effect	Strong recommendation Very low certainty in the evidence
Bedaquiline	Strong recommendation Moderate certainty in the estimates of effect	Strong recommendation Very low certainty in the evidence
Linezolid	Strong recommendation Moderate certainty in the estimates of effect	Conditional recommendation Very low certainty in the evidence
Clofazimine	Conditional recommendation Very low certainty in the estimates of effect	Conditional recommendation Very low certainty in the evidence
Cycloserine	Conditional recommendation Very low certainty in the estimates of effect	Conditional recommendation Very low certainty in the evidence

Paediatric considerations

Although treatment principles and recommendations for adults broadly apply to children as well, there are some important differences in approach to diagnosis and treatment that should be considered:

1. Diagnosis is often based on clinical and radiological findings due to:
    a. the often paucibacillary nature of disease in younger children
    b. the lack of adequate diagnostic specimens (pulmonary or extra-pulmonary) to establish microbiological confirmation
2. The need for treatment to be implemented as early as possible using the DST of the likely source case as the basis for regimen selection
3. The same principles that guide regimen design in adults can be used in children
    a. At least four drugs from groups A and B (a fifth drug can be added in severe disease for an initial period, determined by expected bacterial load and clinical response)
    b. Delamanid is prioritised from group C, particularly for use in fluoroquinolone resistant disease
4. **'Injectable free' regimens** should be used in all instances unless no other treatment options are available, as hearing loss in children can result in profound language and learning difficulties.
5. Bedaquiline and delamanid can be used in children of all ages, using age and weight appropriate dosing.[6] Child-friendly formulations are now available.[iii]
6. Linezolid could be used for shorter durations based on disease severity and DST, due to its du-

iii For further information, refer to https://www.who.int/news/item/28-06-2023-who-publishes-information-notes-on-the-use-of-bedaquiline-and-delamanid-in-children-and-adolescents-with-drug-resistant-tuberculosis.

ration dependent toxicity risk. Table 6 provides a suggested approach in accordance with *The Sentinel Project for Pediatric DR-TB (2022 Field Guide)*.[7] Use in children with severe disease and proven or possible fluoroquinolone resistance requires close monitoring for bone marrow toxicity, optic neuritis and peripheral neuropathy.

7. The shorter course BPaLM and BPaL regimens are not currently recommended for use in children under 15 years; more data are awaited on the safety of pretomanid use in children.

8. Children can likely be treated for shorter durations dependent on disease severity:

    a. non-severe pulmonary or peripheral lymph node disease, defined as TB disease involving lymph nodes only or affecting less than one lung lobe without cavitation, can be treated for 6–9 months

    b. those with severe disease (not meeting non-severe criteria above) should be considered for 9–12 months treatment

    c. extra-pulmonary disease other than peripheral lymph node involvement, usually requires 12 months of treatment and specific consideration should be given to cerebral spinal fluid (CSF) drug penetration in children with CNS TB.

9. Child-friendly formulations should be used where possible to try and overcome issues related to manipulation of adult tablets: poor taste, swallowing difficulties and risk of imprecise dosing.[6,7]

Based on guidance from *The Sentinel Project for Pediatric DR-TB (2022 Field Guide)*[7] and aligned with revised WHO recommendations (2022), an overview of suggested treatment options are provided in table 6. These consider disease severity, the fluoroquinolone drug susceptibility status and concern about linezolid toxicity in the regimen design.[7] In all instances, seeking advice from a paediatrician with expertise in the management of DR-TB cases is strongly recommended.

Table 6: Treatment regimen options for children < 15 years of age according to disease severity and fluoroquinolone susceptibility status[a]

	Fluoroquinolone susceptible (or resistance unlikely)	Fluoroquinolone resistant
Non-severe disease – 6–9 months	Bedaquiline-levofloxacin-clofazimine-cycloserine	Bedaquiline-delamanid-clofazimine-cycloserine + linezolid
Severe disease – 9–12 months	Bedaquiline-levofloxacin-clofazimine-cycloserine + linezolid	Bedaquiline-delamanid-clofazimine-cycloserine + linezolid
	Linezolid use can be limited to eight weeks or not used if non-severe disease & risk factors for toxicity	Linezolid duration to be determined by severity of disease, drug resistance profile & risk factors for toxicity

a Bedaquiline and delamanid can be used in children of all ages. Pretomanid is not recommended in those < 15 years of age.

Bedaquiline use for longer than six months and/or in combination with delamanid

With the advent of the new MDR-TB treatment guidance, two important questions arose in the context of additional drug resistance to the fluoroquinolones or in the event of limited suitable drug options such as in an XDR-TB case:

1. the use of bedaquiline for longer than six months

2. the use of bedaquiline and delamanid in combination.

An initial assessment of these questions was addressed in 2020 updates on WHO recommendations based on the available evidence.[24] For both questions, the level of evidence in terms of efficacy and effectiveness was not considered adequate but from the drug safety perspective, there appeared no contra-indication to their prolonged use. Therefore, definitive recommendations to support these propositions are yet to be made but in terms of drug safety if deemed appropriate their use has not been precluded. The importance of regular monitoring for adverse events throughout was stressed.

Bedaquiline appears to have good bactericidal and sterilising activity.[23] Given these qualities and the limited alternative drug options available in cases with pre-XDR and XDR-TB, the extended use of bedaquiline beyond six months as a core drug should be strongly considered. The other important factor to consider relates to the long half-life of bedaquiline (six months). If its use is not continued beyond six months and the continuation regimen is potentially sub-optimal, the low level of persistent bedaquiline may place it at risk of developing resistance.

Delayed culture conversion is another instance where the extended use of bedaquiline should be considered. As noted in the ATS/CDC/ERS/IDSA guidelines, the use of bedaquiline is recommended up to 5–7 months beyond culture conversion.

Rifampicin resistance (isoniazid susceptible)

In patients with rifampicin mono-resistant TB, there has been variation in practice, largely determined by expert opinion and capacity for an individualised DST based regimen. The WHO recommendation is that RR-TB be treated the same as for MDR-TB, although this is often in the setting of limited access to DST for all first-line drugs and hence the rationale to view it as a proxy for MDR-TB. RR-TB is not discussed in the 2019 ATS/ERS/CDC/IDSA guidance. However, the longstanding advice in the USA with the benefit of reliable DST has been to use 12–18 months of isoniazid, ethambutol and a fluoroquinolone, and with pyrazinamide for at least the first two months.

An Australian study highlighted the dilemma of determining an optimal regimen for treatment of RR-TB because of the small case numbers involved and variability of regimen construct; their overall findings did suggest that the use of an isoniazid and ethambutol based first-line regimen with the addition of a fluoroquinolone for at least 12 months can achieve good outcomes.[25] Studies in the pre-rifampicin era showed that isoniazid and ethambutol containing regimens used for at least 18 months had satisfactory treatment success rates.[26]

The six-month BPaLM regimen (WHO), as discussed in the MDR-TB section, provides a new option to consider in preference to a longer course regimen.

Recommendations

Given the recent shift to a shorter treatment regimen for MDR-TB and access to quality assured DST to first line drugs and fluoroquinolones, the following options with priority to the use of a shorter regimen should be considered for use in those with proven rifampicin mono-resistance:

1. the fully oral 6-month BPaLM regimen (criteria for use as per MDR-TB section) or

2. a longer course regimen in those with more severe or extensive disease or do not meet the criteria for use of the shorter course regimen. These include:

    a. the all-oral longer course MDR-TB regimen (WHO) or

    b. a combination of isoniazid, ethambutol, a fluoroquinolone (levofloxacin or moxifloxacin) and pyrazinamide (for at least the first 2 months) for a duration of 12-18 months (existing ATS recommendation). Some Australian jurisdictions recommend pyrazinamide for at least 12 months.

Role of surgery

Although there is limited evidence, expert consensus and reviews support consideration of surgical intervention in combination with adequate medical therapy when the overall clinical assessment is strongly suggestive of treatment failure or a high likelihood of relapse.[29–31] This generally applies to those with more extensive drug resistance and persistent localised disease where the aim of surgery is to reduce the burden of disease and resect foci of disease presumed resistant to therapy. Partial lung resection has been associated with improved treatment success but pneumonectomy a poorer outcome.[30,31]

In patients being considered for surgery based on a high likelihood of treatment failure or relapse the following criteria are suggested:

- a multidisciplinary approach to patient selection undertaken in close consultation with a thoracic surgeon with appropriate TB experience
- disease is largely localised and suitable for resection (wedge resection or lobectomy)
- the patient has pulmonary function assessment to ensure a satisfactory post-surgical lung capacity
- the patient must remain on adequate MDR-TB therapy
- appropriate infection control and prevention measures must be in place to protect those present from aerosolised TB bacilli during the surgical procedures.

Recommendation

In patients with a high likelihood of treatment failure or relapse (e.g. XDR-TB), surgery can be considered as an adjunct to optimal drug therapy using the following criteria:

- a multidisciplinary approach that includes close consultation with a thoracic surgeon with TB experience to ensure careful patient selection
- disease is largely localised and suitable for partial resection (wedge resection, segmentectomy or lobectomy)
- pneumonectomy should be reserved for a major complication e.g. severe haemoptysis.

Special situations

The following special situations that arise in the management of an MDR-TB case are alluded to briefly. In general, it is recommended that because of the complexities involved, cases such as those with HIV co-infection or are pregnant should be jointly managed by clinicians with the relevant expertise.

MDR-TB and HIV Infection

Key issues that arise in the treatment of an HIV positive person diagnosed with MDR-TB include:

- drug-drug interactions, e.g. potential for reduced bedaquiline concentration due to the enzyme inducing effect of efavirenz
- potential for overlapping drug toxicities and adverse effects
- immune reconstitution inflammatory syndrome (IRIS)
- the complexities of treatment and the need for rigorous monitoring, including consideration of therapeutic drug monitoring.

To best manage the patient, close collaboration between the MDR-TB and HIV clinicians will be essential. The WHO recommendation remains that antiretroviral therapy (ARV) is strongly advised for all patients with HIV and drug-resistant tuberculosis requiring treatment, irrespective of CD4 cell count.[1] Further, if ARV is not yet being undertaken, it should be initiated within the first 8 weeks following the start of anti-tuberculosis treatment.

Pregnancy

Overall, the risks from failure to treat the pregnant woman and foetus are significantly greater than risks from treating the MDR-TB disease.

The following are the main areas to consider when a pregnant woman is diagnosed with MDR-TB:

- Most patients should be commenced on treatment as soon as possible
- If MDR-TB is detected in the first trimester and the woman is clinically satisfactory and has minimal disease, then deferring the start of treatment to the second trimester could be considered. However, such a strategy would require close clinical monitoring as TB can accelerate in pregnancy.
- In some cases, termination of pregnancy may need to be considered.
- Amikacin and ethionamide should be avoided due to the potential for causing teratogenic effects.
- Management should be shared between an MDR-TB expert and an obstetrician experienced in the care of high risk pregnancies.

The table set out in Appendix A.4 shows the Federal Drug Administration (FDA) safety categories for each of the MDR drugs.

Central nervous system TB

The drug regimen used to treat CNS TB should be based on drug susceptibility and specific consideration to CSF drug penetration. Moxifloxacin, levofloxacin, linezolid, cycloserine, pyrazinamide, meropenem and ethionamide have good penetration. Amikacin and streptomycin have adequate penetration in the presence of meningeal inflammation. Findings from a small number of studies suggest that bedaquiline and delamanid may achieve sufficient drug concentrations in brain tissue and CSF, but their use in the treatment of TB meningitis remains uncertain pending further studies. Ethambutol and PAS have poor penetration and there is insufficient data regarding clofazimine and pretomanid. Corticosteroids should be considered for use in all cases.[27,32–34]

More detailed information on the management of these special situations and others including in renal and liver disease can be found in the *Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-resistant Tuberculosis*.[27] Attached appendices (Appendix A.5, A.6) also contain tables showing drug options/risks with respect to the care of patients with severe liver or renal dysfunction.

3. Isoniazid resistance

Isoniazid resistance (rifampicin susceptible)

There is concordance between WHO and ATS/CDC/ERS/IDSA recommendations on the treatment of TB cases with proven isoniazid resistance but rifampicin susceptible.[1,5] The only difference is the recommendation in the ATS/CDC/ERS/IDSA guidance that in the more paucibacillary cases particularly those with an increased risk of hepato-toxicity, pyrazinamide could be discontinued after two months.[5] The main question to address is the choice of fluoroquinolone with most preferring levofloxacin because of concern over sub-optimal moxifloxacin blood levels due to its interaction with rifampicin. Levofloxacin also may have less effect on the Q-T interval. If a fluoroquinolone cannot be used, the previously recommended combination of rifampicin, ethambutol and pyrazinamide (with or without high dose isoniazid) for 6–9 months is still considered acceptable particularly in less severe disease.[3]

Recommendation

In those with proven isoniazid mono-resistant TB, a combination of rifampicin, ethambutol, pyrazinamide and levofloxacin or moxifloxacin (levofloxacin preferred) is recommended for 6 months.

- If disease is severe, nine months is advised.
- If isoniazid resistance is low level, high dose isoniazid could be considered for inclusion.
- If disease is non-severe, discontinuing pyrazinamide at two months could be considered particularly in those with increased hepato-toxicity risk.[5]

Isoniazid poly-resistance

There is limited information on the treatment of isoniazid with additional resistance to other first line agents. The regimens set out in table 7 are those suggested in the WHO MDR-TB companion and Curry handbooks and, apart from the recommendation for isoniazid mono-resistance, are based on expert consensus opinion.[27,28] Moxifloxacin or levofloxacin can be used, but the latter is the preferred fluoroquinolone. The BPaLM regimen now provides an additional option to consider.

Table 7: Treatment regimens for isoniazid mono- and poly-resistant TB

Drug resistance pattern[a]	Proposed regimen(s)[a,b]	Duration of treatment
H	R E Z Lfx (or Mfx)	6–9 months
H + E	R Z Lfx (or Mfx)	6–9 months
H + Z	R E Lfx (or Mfx)	9–12 months
H + E + Z	BPaLM R Lfx (or Mfx) Eto Amk (2–3)	6 months 9–12 months

a H: Isoniazid; R: Rifampicin; E: Ethambutol; Z: Pyrazinamide; Eto: Ethionamide; Amk: Amikacin.

b Levofloxacin (Lfx) currently preferred to moxifloxacin (Mfx).

4. Treatment monitoring

Patient safety

Regular clinical and laboratory monitoring of the patient throughout treatment is essential to ensure patient safety through the timely identification and management of adverse drug reactions (ADRs) and drug toxicity. Failure to detect adverse events in a timely manner may result in additional patient suffering and treatment interruptions, the latter a risk for poorer treatment outcomes including further drug resistance. A recommended monitoring schedule and list of the most common ADRs/associated drugs are attached (appendix A.3). Optimally there should also be a data collection system in place to monitor the frequency of these adverse events and subsequent clinical actions including the need to cease a drug or modify the treatment regimen.

Response to treatment

Assessing the patient's response to DR-TB treatment through regular clinical, radiographic and bacteriologic assessments is important to ensure appropriate improvement and if not, detect evidence of treatment failure as early as possible. A suggested monitoring schedule is set out in Appendix A.3.

In pulmonary cases, the WHO recommended standard is monthly cultures for the duration of treatment. Repeat DST is recommended to assess for additional resistance if cultures are still positive at 3–4 months or if following culture conversion to negative, reversion to positive occurs. If cultures are still positive at 4 months, treatment failure should be considered.[5,28]

Therapeutic drug monitoring

While appropriate selection of antimicrobial agents as detailed in this document is critical, individual variation in pharmacokinetics can be significant. Tailoring therapy to optimise effectiveness while limiting toxicity benefits from therapeutic drug monitoring (TDM) of a number of agents.[35] Routine use of TDM can assist in confidence regarding drug absorption and penetration to the site of disease, and dose adjustment may assist in reducing side effects without compromising treatment outcomes.[36] Optimal TDM parameters are not defined for all medications but are expected to become more available during the lifetime of this document.

Access to TDM across Australia is variable, and delays in clinical impact may result from transfer of samples to remote testing facilities or batching of assays. NTAC supports efforts to expand TDM access and encourage more routine use.

Post treatment follow-up

Follow-up at six-monthly intervals for at least two years to assess for relapse is advised. Dependent on the initial severity of disease and resistance pattern, and any complicating issues, further longer-term follow-up may be indicated. It is recommended that an end of treatment functional assessment be conducted. While this may vary in relation to site of disease, with regards to pulmonary disease this assessment should include imaging, respiratory function tests, six-minute walk test, quality of life assessment and consideration of pulmonary rehabilitation.[37]

Patient care and support

There is an increased emphasis on patient-centred case management, to help the patient better understand their diagnosis and participate in their treatment decisions. This treatment partnership approach allows for improved communication to help ensure:

- that adequate information about treatment options and potential benefits and risks is provided;
- that the patient (and family) better understand the diagnosis and treatment and side effects;
- the importance of treatment adherence and agreeing to a suitable approach for treatment administration;
- provision of the support measures for the patient/family that may be required; and
- the most appropriate means of communication and who to report concerns.

Regular interactions with the patient throughout treatment provide valuable opportunities to identify and help address any concerns, e.g. nutritional, psycho-social, financial. This patient-centred support is important to gaining the patient's confidence and trust in the treatment process to help ensure a successful outcome.

5. Public health issues

Infection control

Emphasis should be placed on strict adherence to infection control measures when managing a case of MDR-TB, as there is limited data on the efficacy of treatment of recently acquired latent MDR-TB infection.

Infection control practices and isolation can significantly impact the patient and family and add to the stigma of the patient with MDR-TB. The duration of isolation needs not only to take account of the safety of the public and the patient's family and contacts but should also consider the mental health and morale of the patient.

In those with pulmonary disease, effective treatment rapidly reduces the infectiousness risk. The approach to determining when the patient can be considered safe from a public health perspective should be based on the patient's clinical improvement particularly cough reduction, trend in sputum smear/culture results and continuity of an effective treatment regimen.[38,39]

Management of contacts

Assessment of those exposed to a MDR-TB case needs to consider the probability of recent infection and the subsequent risk for progression to active TB, which is greatly increased in children under 5 years of age and in those who are immunocompromised. The lifetime risk of progression to disease in healthy adults is approximately 10%, with around 50% of disease occurrence happening within the first two years after exposure/infection. However, in young children (< 5 years of age) and

the immunocompromised, the disease risk is far higher (20–50% depending on age and degree of immune compromise) and most disease progression (> 90%) occurs within 12 months of exposure/infection.

The decision as to whether to use preventive treatment in close MDR-TB contacts remains problematic due to insufficient evidence. However, the guidance is now more definitive, with one systematic review estimating a protective effect of 90% when using a fluoroquinolone or fluoroquinolone-based preventive treatment regimen.[40] Several ongoing trials (e.g. the PHOENix, V-QUIN and TB-CHAMP trials) are evaluating DR-TB preventive therapy options.

The new ATS/CDC/ERS/IDSA guidelines support the use of a fluoroquinolone for 6–12 months (with/without a second drug, e.g. ethambutol) based on the DST result of the source case. If a second drug is to be considered, pyrazinamide is not advised.[5] In the event of fluoroquinolone resistance, there is little evidence for use of other agents, although ethambutol and pyrazinamide could be considered if susceptible, or newer drugs like delamanid. In Australia, the use of fluoroquinolone-based treatment for those with evidence of likely recent MDR-TB infection (active disease excluded) is now commonly undertaken and considered reasonable given the benefit:risk ratio.

If a careful observation only approach (clinical and radiologic surveillance) is adopted, a minimum period of two years is advised, although the evidence for what constitutes optimal follow-up in terms of patient benefit and cost is limited.

Active TB should always be excluded before considering preventive treatment, as unintentional treatment of active infection with a single drug risks drug resistance amplification.

Surveillance

The WHO in 2021 aligned treatment outcome definitions for both drug-susceptible and drug-resistant TB to help simplify reporting of TB outcomes.[41] The new definitions are set out in Table 8.

Additional key areas for monitoring in the Australian context include patterns of resistance, regimen implemented (shorter versus longer course), and contact management.

Table 8: New TB treatment outcome definitions for DS-TB and DR-TB (WHO 2021)

Outcome	Definition
Treatment failed	A patient whose treatment regimen needed to be terminated or permanently changed to a new regimen or treatment strategy.
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who completed the recommended treatment with evidence of bacteriological response and no evidence of failure.
Treatment completed	A patient who completed the recommended treatment but whose outcome does not meet the definition for cure or treatment failure.
Treatment success	The sum of cured and treatment completed.
Died	A patient who died before starting treatment or during the course of treatment.
Lost to follow-up	A patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A patient for whom no treatment outcome was assigned.

Drug procurement

Most drugs used for treating MDR-TB are not registered with the Therapeutic Goods Administration (TGA) or listed for this indication on the Pharmaceutical Benefits Scheme. Some repurposed drugs, such as linezolid, are listed for other indications. TB programs and practitioners typically access these medications through use of the TGA Special Access Scheme. Regimens involving medications available for use internationally can be difficult to access in Australia, which at this time include pretomanid and delamanid, as well as paediatric formulations of many MDR-TB medications. As effective and shorter course regimens are developed and become established internationally, it is critical that reliable pathways for access be established and supported across Australia.

Networking

In a low incidence setting such as Australia, overall case numbers for MDR-TB are low. As such, even those with TB expertise may have limited exposure to the care of MDR-TB, particularly to the more problematic cases (e.g. severe XDR-TB). State-based TB reference groups provide an important multidisciplinary forum to discuss and advise on MDR-TB treatment plans, but strengthening connections nationally and with global TB networks would support optimal clinical care in our low incidence setting.

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Appendix A

A.1. Web annexes. In: WHO operational handbook on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. Geneva: World Health Organization; 2022.[32] Available at: https://www.who.int/publications/i/item/9789240065116.

a. Web annex 1. Tuberculosis medicines – information sheets

b. Web annex 2. Management of adverse events in MDR-/RR-TB treatment

A.2. Dosing of medications used in drug-resistant TB regimens (adults and children)

A.3. Recommended monitoring schedule

A.4. MDR drugs in pregnancy

A.5. MDR drugs in liver disease

A.6. MDR drugs in renal disease

Appendix A.2: Dosing of medications used in drug-resistant TB regimens (adults and children < 15 years of age)[a]

Drug	Route	Adult dose[b]		Children < 15 years[c]		Comments
		Mg/kg/day	Daily dose (max)	Available preparations	Dose mg/kg/day	
Levofloxacin	Oral or IV		< 46 kg 750 mg ≥ 46 kg 1000 mg	100 mg scored, dispersible tab 250 mg tab 250 mg tab in 10 ml	15–20 mg/kg	Standard upper daily dose 1500 mg (WHO)
Moxifloxacin	Oral or IV		400 mg	100 mg scored, dispersible tab 400 mg tab 400 mg tab in 10 ml	10–15 mg/kg	High dose 600–800 mg/day
Bedaquiline	Oral		400 mg daily for 14 days then 200 mg 3 times/week	100 mg dispersible tab (100 mg in 10 ml)	Refer WHO weight based schedule by age	Usual duration 6 months Duration can be prolonged in more severe disease
Linezolid	Oral or IV	10–12 mg/kg (IV ≥16 kg)	600 mg	600 mg tab 600 mg in 10 ml 150 mg scored, dispersible tablet	< 16 kg: 15 mg/kg ≥ 16 kg: 10–12 mg/kg	Some studies suggest Vitamin B6 (pyridoxine) may help prevent myelotoxicity (WHO). TDM advised.
Pretomanid	Oral		200 mg			Not presently recommended in children < 14 years or pregnancy
Clofazimine	Oral		100 mg	50 mg and 100 mg cap or tab: can dissolve in water	2–5 mg/kg	
Cycloserine	Oral	10–15 mg/kg	1000 mg	250 mg cap 125 mg minicap	15–20 mg/kg	Vitamin B6 (pyridoxine) should be given
Ethambutol	Oral	15 mg/kg	1200 mg	100 mg scored, dispersible tab 400 mg tab	15–25 mg/kg	Use with care in renal disease. Dose adjustment required
Pyrazinamide	Oral	25–35 mg/kg	2000 mg	150 mg scored, dispersible tablet 500 mg tab	30–40 mg/kg	Significant uncertainty remains about optimal dosing. ATS/CDC/ERS/IDSA recommend 25–40 mg/kg in adults. WHO recommend 25 mg/kg (20–30 mg/kg). WHO weight band dosing in adults ≥ 46 kg ranges 20–35 mg/kg daily.

Drug	Route	Adult dose[b]		Children < 15 years[c]		Comments
		Mg/kg/day	Daily dose (max)	Available preparations	Dose mg/kg/day	
Delamanid	Oral		200 mg	50 mg tab 25 mg dispersible tablet	Refer WHO weight-based schedule by age (Note 1).[c]	
Amikacin (or streptomycin)	IV or IM	15–20 mg/kg 6–7 days per week > 60 years: 10 mg/kg 5–7 times/week or 15 mg/kg 3 times/week	1000 mg		**NOT** recommended for use in children, unless as a last resort	Use with care in people > 60 years or with renal disease. Audiometry and TDM required
Carbapenem (combined with clavulanic acid): **Meropenem** **or** **Imipenem-cilastatin (not for use if < 15 years)**	IV only		(Mpm) 1000 mg 3 times daily (Ipm-Cln) 1000 mg 2 times daily		20–40 mg/kg IV every 8 hours	Clavulanic acid 125 mg to be given one hour before each dose (adults) Children: refer to weight-based dosing in annex 6 in WHO Module 5 (Note 1).[c] Dose adjustments required in renal disease Use meropenem in children < 15 years
Ethio- or prothionamide	Oral	15–20 mg/kg	1000 mg	125 mg scored, dispersible tablet 250 mg tab	15–20 mg/kg	Monitor thyroid function in children and adults if used for > 6 months
PAS	Oral	200 mg/kg	4 g 2–3 times daily (12 g max)	4 g PAS sachet Paediatric dosing spoon available	200–300 mg/kg in two divided doses	Monitor thyroid function in children and adults if used for > 6 months
Isoniazid (high dose)	Oral	10–15 mg/kg	30–45 kg 450 mg daily ≥ 46 kg 600 mg daily	50 mg/5 ml solution 100 mg dispersible tablet 100 mg tablet	15–20 mg/kg	Vitamin B6 (pyridoxine) should always be used especially in children (1–2 mg/kg) and those with medical risk factors eg renal disease, HIV

a Adapted from WHO Operational Guidelines for Drug-resistant TB (2022) and for Children and Adolescents (2021).
b Adult doses can be used in all children 15 years of age and older.
c In children: (1) please refer to WHO operational handbook on tuberculosis. Module 5: management of tuberculosis in children and adolescents (Annex 6) for dosing of children according to weight bands or Module 4: treatment: drug-resistant tuberculosis treatment (Annex); (2) dissolving of crushed adult tablets or capsule contents in 10 ml of water may be required in the absence of child friendly preparations; (3)all child friendly preparations are available via the Global Drug Facility (GDF).

Appendix A.3: Recommended monitoring schedule

Table A.3.1: Clinical assessments

Screening test	Schedule
Clinical evaluation	Inpatient care: daily until tolerating treatment Outpatient care: baseline, weekly until tolerating treatment, and then at least monthly
DOT worker screen	At every DOT encounter for clinical well-being and adverse drug reactions.
Weight / nutrition status	Baseline, then monthly
Visual acuities/colour vision	Baseline, at least monthly (linezolid, ethambutol, isoniazid)
Peripheral neuropathy screen	Each clinical assessment and/or as clinically indicated (linezolid, isoniazid)
Psychological screen – depression, mood changes	Each clinical assessment and/or as clinically indicated (cycloserine, moxifloxacin/levofloxacin)

Table A.3.2: Microbiological assessments

Assessment method	Recommendation
Sputum smear microscopy	Monthly until treatment is completed. (Gene Xpert is **not** recommended for monitoring except when treatment failure is suspected in drug sensitive or H-resistant cases)
Sputum culture	Monthly
Drug susceptibility testing (DST)	Baseline, repeat at 3–4 months if still culture positive or if following culture conversion to negative, reversion to positive occurs.

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Table A.3.3: Routine drug safety monitoring

TB medication	Adverse reactions		Routine monitoring recommended
	Commoner	Less frequent	
Levofloxacin (Lfx)	Gastro-intestinal disturbance Musculoskeletal QTc prolongation (considered less common than Mfx) Hepatic toxicity	Hypoglycaemia Peripheral neuropathy Mood disturbances/anxiety	ECG: baseline, 2 weekly first month and then monthly Electrolytes: at least monthly (K, Ca, Mg) Liver function: at 2 weeks then at least monthly
Moxifloxacin (Mfx)	Gastro-intestinal disturbance Musculoskeletal QT_c prolongation (estimated increase 10–20 msec) Hepatic toxicity	Hypoglycaemia Peripheral neuropathy Mood disturbances/anxiety	ECG: baseline, 2 weekly first month and then monthly Electrolytes: at least monthly (K, Ca, Mg) Liver function: at 2 weeks then at least monthly
Bedaquiline (Bdq)	Nausea, headache Arthralgia QT_c prolongation (10–15 msec increase, maximal week 15)	Hepatic toxicity	ECG: baseline, 2 weekly first month and then monthly Electrolytes: at least monthly (K, Ca, Mg) Liver function: at 2 weeks then at least monthly
Linezolid (Lzd)	Gastro-intestinal disturbance Rash Myelosuppression Peripheral and optic neuropathy	Lactic acidosis Serotonin syndrome	Monitor haemoglobin, platelets, white cell count weekly month 1 and then at least monthly Regular peripheral neuropathy screens Visual acuities and colour vision screens: at least monthly TDM: according to local protocol pH, anion gap and lactate levels in the event of suspected lactic acidosis
Pretomanid (Pa)	Headaches, nausea, contact dermatitis, diarrhoea, dizziness Anaemia QT_c prolongation: average 5 msec increase, not found to have clinical impact.	Hepatic impairment Convulsions Animal studies attributed male reproductive toxicity to Pa. Current evidence does not suggest a risk to male fertility	ECG: baseline, 2 weekly first month and then monthly Electrolytes: at least monthly (K, Ca, Mg) Liver function: at 2 weeks then at least monthly
Clofazimine (Cfz)	Skin, conjunctiva and body fluid discoloration. QT prolongation: 10-20 msec increase. Photosensitivity dermatitis	Abdominal pain	ECG: baseline, 2 weekly first month and then monthly when used with other QT prolonging agents
Cycloserine (Cs)	Psychiatric: depression, psychosis, suicidal ideation CNS toxicity: lethargy, seizures Gastro-intestinal disturbance	Peripheral neuropathy Optic neuritis Rash	Psychiatric screen TDM: peak concentration at 1–2 weeks after starting then as indicated. CNS toxicity is usually associated with a peak level > 35 µg/ml but can occur in the normal range

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TB medication	Adverse reactions		Routine monitoring recommended
	Commoner	Less frequent	
Ethambutol (E)	Gastrointestinal disturbance	Visual acuity and colour vision impairment (optic neuropathy) Liver toxicity rare – generally considered liver safe Rash	Visual acuities, colour vision: baseline, then at least monthly (particularly in those with any renal impairment)
Pyrazinamide (Z)	Asymptomatic hyperuricaemia (expected, treat only if gouty arthritis occurs) Arthralgia Gastrointestinal disturbance	Hepato-toxicity Gout Photosensitive dermatitis Hypersensitivity reactions	Liver function: baseline, at 2 weeks then at least monthly
Delamanid (Dlm)	Gastrointestinal disturbance Insomnia	QT_c prolongation	ECG: baseline, 2 weekly first month and then monthly Electrolytes: at least monthly (K, Ca, Mg) Liver function: at 2 weeks then at least monthly
Amikacin (Am) Streptomycin (S)	Proteinuria Ototoxicity	Electrolyte abnormalities: may result in QT_c prolongation Renal toxicity Peripheral neuropathy Rash	Electrolytes (K, Ca,Mg) and renal function: baseline and at least monthly Audiometry: baseline and at least monthly Regular vestibular clinical assessment TDM: peak and trough blood levels according to local protocol
Imipenem/cilastatin Meropenem/clavulanic acid	Often poorly tolerated Headache, nausea, vomiting, diarrhoea Hepatic toxicity Thrush	Pseudomembranous colitis Rash Fatigue	Electrolytes (K, Ca,Mg) and renal function: at least monthly TDM: peak and trough blood levels according to local protocol
Ethionamide (Eto) (or prothionamide)	Often poorly tolerated Gastro-intestinal disturbance Hepatic toxicity	Psychiatric disturbance Neurotoxicity eg convulsions (beware if also using cycloserine) Hypothyroidism (increased risk when used with PAS)	Liver function: at 2 weeks then at least monthly TSH: baseline and then at least 3 monthly
PAS (Para-aminosalicylic acid)	Often poorly tolerated Gastro-intestinal disturbance Hypothyroidism (increased risk when used with ethionamide)	Hepato-toxicity Nephrotoxicity Coagulopathy (rare) Rash	Complete blood picture monthly Monthly liver function, renal function and electrolytes TSH: at least 3 monthly

Appendix A.4: MDR drugs in pregnancy

Drug	Category[a]	Comment
Moxifloxacin Levofloxacin	C	Use with caution. Studies have not reported an increased risk of major birth defects with other quinolones; however, cartilage damage and arthropathies are reported in immature animals, raising **concern over effects on foetal bone formation.**
Bedaquiline	B	No data available on use of this drug in pregnancy relating to the risk of birth defects, miscarriage or adverse foetal/maternal outcomes.
Pretomanid		Not presently recommended for use in pregnancy
Linezolid	C	No adequate studies of safety in pregnancy .
Clofazimine	C	Infants born with deeply pigmented skin that fades over 1 year.
Cycloserine	C	Animal studies have not shown evidence of teratogenicity. There are no controlled data in human pregnancy.
Amikacin	D	**Avoid use.** Ototoxicity and foetal malformation risk.
Delamanid		Should be avoided until more data is available. Animal studies do not show evidence of teratogenicity
Ethambutol	B	Considered safe for use in pregnancy
Pyrazinamide	C	Safe use in pregnancy supported by most studies.
Prothionamide *Ethionamide*	C	**Avoid use.** Teratogenic effects observed in animal studies. Worsens nausea due to pregnancy

a FDA pregnancy categories: A: human studies show no risk; B: animal studies show no risk, no human studies; C: animal studies show risk, no human studies; D: human studies show risk.

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Appendix A.5: MDR drugs in liver disease

Drug	Hepato-toxicity risk
Moxifloxacin/levofloxacin	Fluoroquinolones are generally considered 'liver friendly' but are occasionally associated with hepato-toxicity.
Bedaquiline	Bedaquiline possibly caused serious liver toxicity in a small number of patients in the Phase 2 studies.[a] **It should be used with caution in those with pre-existing liver disease particularly due to its long half life.**
Pretomanid	**Use with caution in liver disease.** Safety, effectiveness and pharmacokinetics unknown (WHO).
Linezolid	**Prolonged exposure may induce severe hepato-toxicity.**[b] Higher than therapeutic concentrations may occur in cirrhotic patients.[c]
Clofazimine	Minimal hepato-toxicity risk.
Cycloserine	Minimal hepato-toxicity risk.
Amikacin	Minimal hepato-toxicity risk.
Prothionamide/ethionamide	Potentially hepato-toxic but the risk is lower than for the first line drugs.
Pyrazinamide	**Pyrazinamide is the most hepato-toxic TB drug and should NOT be used in those with chronic liver disease.**
High dose isoniazid	High dose isoniazid in those with normal liver function does not appear to increase the risk of hepato-toxicity. **However its use in chronic liver disease has not been studied and is NOT recommended particularly in unstable liver disease.**

a Source: reference 42.
b Source: reference 43.
c Source: reference 44.

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Appendix A.6: MDR drugs in renal disease

Drug	Recommended dose and frequency if creatinine clearance is < 30 ml/min
Moxifloxacin	No dose change needed. 400 mg daily. There may be a higher risk of neurotoxicity and tendonopathy when used in severe renal disease.
Levofloxacin	750–1000 mg per dose **3 times per week**, NOT daily.
Bedaquiline	No dose change needed in mild to moderate renal impairment. **Use with caution in severe renal impairment.**
Pretomanid	**Use with caution in renal disease.** Safety, effectiveness and pharmacokinetics unknown (WHO).
Linezolid	No dose change needed. 600 mg/day. Increased risk of haematological toxicity and peripheral neuropathy.
Clofazimine	No dose change needed. 100 mg/day. Monitor QT_c.
Cycloserine	**AVOID if possible** in severe renal disease as there is a significantly increased risk of neurotoxicity. Dose at 250 mg daily or 500 mg 3 times per week. Always use pyridoxine (vitamin B6) 50 mg to minimise the adverse CNS risk.
Delamanid	No dose change needed in mild to moderate renal impairment. Use with caution in severe renal impairment.
Ethambutol	**AVOID if possible** as main route of clearance is renal. 15–25 mg/kg 3 times weekly, NOT daily. Optic nerve toxicity resulting in vision impairment is a significant concern.
Pyrazinamide	Can be used safely. 25 mg/kg **3 times per week**, NOT daily. Monitor LFTs and uric acid ; reduced uric acid clearance may lead to gout.
Amikacin	**AVOID if possible.** 12-15 mg/kg per dose 2-3 times per week, NOT daily. Strict monitoring of renal function, potassium and audiometry. Increased risk of nephrotoxicity and ototoxicity. Use with the anti-retroviral drug Tenofovir should be avoided as it can cause severe hypokalaemia.
Prothionamide	No dose change needed. 15–20 mg/kg/day in divided doses.