CHAPTER 5: TREATMENT OF CASES WITH DRUG-RESISTANT TUBERCULOSIS (DR-TB)

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SUMMARY OF RECOMMENDATIONS

- For patients with clinically suspected TB, the treating physician should request rapid diagnostic nucleic acid amplification (GeneXpert MTB/Rif Ultra assay) tests for rifampicin resistance on primary specimens.
- In patients with MDR/RR-TB, the 6-9 month all oral regimen BPaLM should be prioritised where possible, as recommended by the WHO.
- For people with pre-XDR-TB, moxifloxacin should be dropped from the regimen (BPaL)
- Drug susceptibility testing (DST) for fluoroquinolones is essential in people with MDR/RR-TB.
- Longer treatment regimens are still recommended for CNS-TB (Table 5.2). Treatment of MDR/RR-TB meningitis is best guided by DST of the infecting strain and by knowledge of the properties of TB medicines that cross the blood–brain barrier.
- All patients diagnosed with TB should receive directly observed therapy (DOTS) or video observed therapy (VOTS) especially in the early stages of treatment. Where resources are scarce priority for DOT/VOT should be given to those patients with drug resistant TB and/or those patients whose medical or social circumstances indicate that treatment adherence may be problematic.

5.1 Introduction

Tuberculosis (TB) strains with drug resistance (DR-TB) are more difficult to treat than drug-susceptible ones and threaten global progress towards the targets set by the End TB Strategy of the World Health Organization (WHO). There is thus a critical need for evidence-based policy recommendations on the treatment and care of patients with DR-TB, based on the most recent and comprehensive evidence available.

5.2 Definitions of Drug resistance

Monodrug-resistant (mono-resistant) TB: TB caused by organisms that show resistance to a single anti-TB drug (e.g., isoniazid, rifampicin, ethambutol, or pyrazinamide).

Isoniazid-resistant TB: TB caused by *Mycobacterium tuberculosis (M. tuberculosis)* strains that show resistance to isoniazid (rifampicin susceptible).

Rifampicin-resistant TB (RR-TB): TB caused by organisms that show resistance to rifampicin, but may be susceptible to isoniazid, or resistant to isoniazid (i.e., MDR-TB), or resistant to other first-line TB medicines (polydrug resistant) or second-line TB medicines (e.g., extensively drug-resistant TB [XDR-TB]).

Polydrug-resistant TB (PDR-TB): TB caused by organisms that show resistance to more than 1 anti-TB drug, but not including both isoniazid and rifampicin.

Multidrug resistant TB (MDR-TB): TB caused by *M. tuberculosis* strains with resistance to rifampicin and Isonaizid.

Pre-XDR-TB: TB caused by *Mycobacterium tuberculosis (M. tuberculosis)* strains that fulfil the definition of multidrug resistant and rifampicin-resistant TB (MDR/RR-TB) and which are also resistant to any fluoroquinolone.

Extensively drug-resistant TB (XDR-TB): TB caused by *M. tuberculosis* complex that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (levofloxacin or moxifloxacin) and to at least one other “Group A” drug (bedaquiline or linezolid).

5.3 Treatment of Mono-resistant TB

5.3.1 Isoniazid mono-resistance

OPTION 1: Daily rifampicin (RIF), ethambutol (EMB), pyrazinamide (PZA) plus a later-generation fluoroquinolone for 6 months (Preferred) (1, 2). See Table 5.1.

- If a patient was initiated on a standard 4-drug regimen, isoniazid (INH) can be replaced by the fluoroquinolone once resistance is documented, and RIF, EMB, and PZA continued, beginning the 6-month duration with the start of the fluoroquinolone. Levofloxacin (LFX) may be preferred over moxifloxacin (MFX) (due to drug-drug interactions with RIF).
- Confirm fluoroquinolone susceptibility with growth-based drug-susceptibility testing (DST, available, use molecular DST to provide more rapid results).
- In select situations, the duration of PZA may be reduced to 2 months (lower disease burden or increased risk of PZA toxicity).

OPTION 2: Daily RIF, EMB, PZA for 6 months. (1, 2). See Table 5.1

Table 5.1: Treatment regimens for isoniazid-resistant TB (Adopted from Curry guidelines) (2)

Pattern of resistance	Suggested regimen	Minimum duration of treatment	Comments
INH	RIF, later-generation fluoroquinolone, EMB and PZA (2-6 months)	6 months	A shorter duration of PZA (2 months) should be considered in selected situations (e.g., non-cavitary and lower-burden disease or toxicity for PZA).
INH and EMB*	RIF, later-generation fluoroquinolone and PZA (2-6 months)	6-9 months	The longer duration of treatment should be used for patients with extensive disease. With this resistance pattern there is a risk for acquired RIF-resistance when HRZE (RIPE) is used initially pending DST results.
INH and PZA*	RIF, later-generation fluoroquinolone and EMB	9-12 months	The longer duration of treatment should be used for patients with extensive disease (and some experts consider substituting LZD for EMB).
INH, EMB and PZA*	RIF, later-generation fluoroquinolone and LZD	9-12 months	An additional drug may strengthen the regimen for patients with extensive disease and consider the longer duration of treatment
INH and FQ*	RIF, EMB, PZA	6-9 months	LZD may strengthen the regimen for patients with extensive disease and consider the longer duration of treatment

5.3.2 Rifampicin mono-resistance

RIF mono-resistance is uncommon but increasing in some areas of the world. The loss of RIF from the treatment regimen has, to date, required a longer duration of therapy, but shifting expert practice includes consideration for the new shorter (6-month) BPaL and BPaLM regimens (2) (see section 5.3.3 below).

5.3.3 Isolated resistance to EMB, PZA, or SM

Isolated resistance to EMB, PZA, or SM will have little impact on the efficacy of the treatment regimen (2).

- Loss of EMB or SM from the regimen will not decrease the efficacy or change the treatment duration.

- Loss of PZA from the regimen, however, requires prolonging the duration of therapy with INH and RIF by 3 months, for a total of 9 months of therapy.
- Most PZA mono-resistant isolates are due to *Mycobacterium* (*M.) bovis.*

5.4 Multi-drug-resistant TB

In 2018, the World Health Organization (WHO) published new treatment guidelines, relying on a large-scale meta-analysis (3), which revolutionized the traditional hierarchy of anti-TB drugs (4). In those guidelines, newer and repurposed drugs, such as bedaquiline and linezolid, were recommended for all MDR TB patients in addition to fluoroquinolones; second line injectables would be reserved for cases where no other options are available.

Apart from ranking by balance of effectiveness and harms, choice is also determined by a preference for composition of agents; the results of drug-susceptibility testing (DST); the reliability of existing DST methods; population drug resistance levels; history of previous use of the medicine in a patient; drug tolerability; and potential drug-drug interactions.

5.4.1 Diagnosis

For patients with clinically suspected TB, the treating physician should request rapid diagnostic nucleic acid amplification (GeneXpert MTB/Rif Ultra assay) tests for rifampicin resistance on primary specimens. Where the result of the GeneXpert MTB/Rif Ultra assay demonstrated rifampicin resistance, the healthcare professional should seek specialist advice. This includes the National advisory service for multidrug resistant TB, provided by St James's Hospital.

5.4.2 Antibiotic regimens for MDR-TB

The composition of MDR-TB regimens should be guided by the selection of individual medicines considered to be effective and also by a need to combine sufficient medicines to maximise the likelihood of relapse-free cure without increasing toxicity. Regimens may be of standardized (fixed) composition or may be individualized to patient needs. For medicines recommended for use in longer MDR-TB regimens, please see Table 5.2.

Active pharmacovigilance for serious adverse events (SAEs) and passive pharmacovigilance for adverse drug reactions (ADRs) are crucial (5). At each patient contact while on treatment, patients should be asked about possible ADRs, with attention to identification of toxicities or

other evidence of issues in tolerability of the anti-TB drugs and any ADRs or SAEs should be reported immediately. All ADRs merit investigation and early action to limit harms (5).

Table 5.2: Grouping of medicines recommended for use in longer MDR-TB regimens

Groups and steps	Medicine and abbreviation	
Group A: Include all three medicines	Levofloxacin *or* Moxifloxacin	Lfx Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B: Add one or both medicines	Clofazimine	Cfz
	Cycloserine *or* Terizidone	Trd
Group C Add to complete the regimen, and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem–cilastatin *or* Meropenem	Ipm–Cln Mpm
	amikacin (*or* streptomycin)	Am (S)
	ethionamide *or* prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

5.4.2.1 BPaLM/BPaL and BDLLfxC

In a 2022 update, WHO guidelines recommended the addition and prioritisation of a new all-oral 6-month regimen (6, 7).

- For people with **MDR/RR-TB,** the regimen comprises: bedaquiline (B), pretomanid (Pa), linezolid (L) and moxifloxacin (M), and is referred to as **BPaLM**.
- For people who have **pre-XDR-TB**, the regimen can be used without moxifloxacin (**BPaL**).

The WHO decision to recommend this regimen was based on evidence from a randomized controlled trial: TB-PRACTECAL (8). This trial showed much-improved treatment success rates with the 6-month BPaLM regimen (89%) compared with previous standard-of-care regimens (52%), as well as lower levels of treatment failure, death and loss to follow-up. A second trial, called ZeNiX-TB (9), randomized people with RR-TB to receive regimens of bedaquiline, pretomanid and daily linezolid at four different dosing schedules. Data from this trial as well as TB-PRACTECAL suggested that a linezolid dose of 600 mg maintains high efficacy but leads to fewer adverse events.

BPaL/BPaLM may be used in the following situations:

a. People with MDR/RR-TB or with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB).
b. People with confirmed pulmonary TB and all forms of extrapulmonary TB except for TB involving the CNS (see Section 5.4.4), osteoarticular and disseminated TB.
c. Adults and adolescents aged 14 years and older.
d. All people regardless of HIV status.
e. Patients with less than 1-month previous exposure to bedaquiline, linezolid, pretomanid or delamanid. When exposure is greater than 1 month, these patients may still receive these regimens if resistance to the specific medicines with such exposure has been ruled out.

There are some limitations to the use of the BPaLM/BPaL regimen:

- The lack of safety data on pretomanid in children aged under 14 years means that the recommendation currently applies only to adults and adolescents aged 14 years and above.
- Although the recommendation applies to all people, regardless of HIV status, some caution is needed when enrolling patients with CD4 counts lower than 100 cells/mm3.
- The safety of pretomanid during pregnancy and breastfeeding is also unclear, and other treatment options should be used for pregnant and breastfeeding women.
- The BPaLM/BPaL regimen is suitable for most forms of TB but is not recommended for extrapulmonary TB involving the central nervous system (CNS), or osteoarticular and disseminated (miliary) TB.

BDLLfxC regimen (bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine):

A 2024 rapid communication from the WHO Guideline Development group concluded that this 6-month regimen may be used in MDR/RR-TB patients without prior exposure to these medicines (defined as > 1-month exposure) in place of the previously recommended 9-month or longer (≥18 months) regimens (10). It is recommended for some patient groups unsuited to BPaL.

The regimen may be used without either levofloxacin or clofazimine depending on fluoroquinolone DST results - BDLLfxC can be initiated without delay in case of unknown FQ-resistance at time of diagnosis of RR-TB. BDLLfx is continued for FQ-sensitive TB; BDLC for FQ-resistant TB. The available evidence included children, adolescents, pregnant and breastfeeding women, flagging the possible use of the regimen in these population groups

The new BDLLfxC regimen can expand the use of the 6-month regimens to additional patient groups, like children, adolescents, and pregnant women, who could not benefit from the currently recommended BPaLM 7 BPaLM/BPaL regimen.

5.4.3 Drug-susceptibility testing

Drug susceptibility testing (DST) for fluoroquinolones is essential in people with MDR or RR-TB, and although it should not delay initiation of treatment, results of the test should guide the decision on whether fluoroquinolones can be retained or should be dropped from the regimens.

5.4.4 Regimens for drug-resistant CNS-TB

Longer treatment regimens are still recommended for CNS TB.

Treatment of MDR/RR-TB meningitis is best guided by DST of the infecting strain and by knowledge of the properties of TB medicines that cross the blood–brain barrier. Levofloxacin and moxifloxacin penetrate the CNS well, as do ethionamide or prothionamide, cycloserine or terizidone, linezolid and imipenem–cilastatin (11,12). High-dose isoniazid and pyrazinamide can also reach therapeutic levels in the cerebrospinal fluid, and they may be useful if the strains are susceptible. There is limited data on CNS penetration of clofazimine, bedaquiline or delamanid (13).

5.4.5 Directly or video observed therapy (DOTS/VOTS)

All patients diagnosed with TB should receive directly observed therapy (DOTS) or video observed therapy (VOTS) especially in the early stages of treatment. Where resources are scarce priority for DOT/VOT should be given to those patients with drug resistant TB and/or those patients whose medical or social circumstances indicate that treatment adherence may be problematic. Providing DOT for a full course of treatment associated with a higher treatment success rate in MDR-TB patients (14). For populations such as Travellers, Roma, refugees, and asylum seekers, additional barriers exist, including housing instability and limited access to digital tools. Alternative solutions, such as the use of community healthcare workers or mobile healthcare services, may be needed to ensure that these groups can comply with the requirements of DOTS or VOTS, taking into account their specific living conditions.

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