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CLINICAL UPDATE

Diagnosis and management of multidrug resistant tuberculosis

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What you need to know

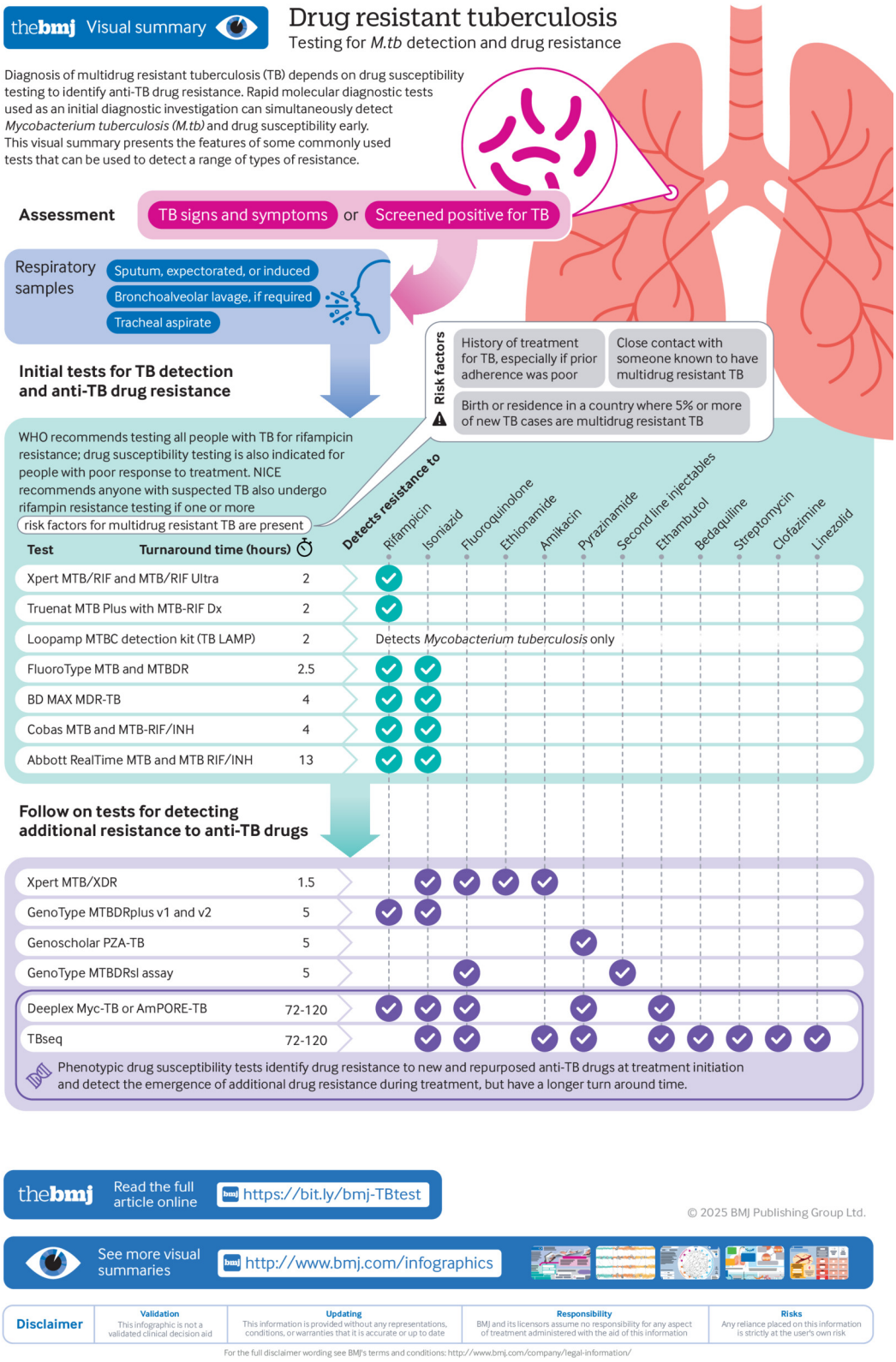
- Universal drug susceptibility testing is key for early diagnosis of drug resistant tuberculosis (TB) and should be offered to all people with bacteriologically confirmed TB; rapid molecular diagnostic tests used as an initial di(eagnostic investigation can simultaneously detect *Mycobacterium tuberculosis* and drug susceptibility early.
- Treatment of people with multidrug resistant TB or rifampicin resistant TB with shorter oral regimens based on bedaquiline results in improved treatment success with better tolerability.
- Conduct monthly clinical and laboratory assessments (including sputum smear and culture) for people who are being treated for multidrug resistant TB or rifampicin resistant TB to monitor the treatment response and promptly detect and address adverse events.
- Refer people for evaluation and initiation of TB preventive treatment if they have been in contact with people with multidrug resistant TB.

A 45 year old man with diabetes mellitus self presents to the TB clinic with productive cough for the past month. The sputum was yellow in colour, copious, and was streaked with blood twice. In that time, he has also hadcontinuousfevers around 38°C, not associated with rigors, and he has lost around 5 kg of weight in the past two months. He reports undergoing treatment for drug sensitive TB three years ago, although he did not take his treatment regularly and did not complete the 6 month course. He lives with his wife and two children, none of whom have had any major respiratory illnesses or have been diagnosed with TB. He works in a garment factory for daily wages, does not drink alcohol, and is a former smoker, having smoked 10 cigarettes per day for 20 years, and quitting three years ago. A cartridge based nucleic acid amplification test of his sputum detected Mycobacterium tuberculosis with rifampicin resistance.A sputum smear for acid fast bacilli showed 3+, and X ray imaging of the chest showed extensive parenchymal infiltrates in bilateral lung fields with cavitations.

Globally, of the 10.8 million people estimated to have tuberculosis (TB) in 2023, 400 000 (3.2%) are estimated to have developed multidrug resistant TB or rifampicin resistant TB.[1] Multidrug resistant TB is associated with worse treatment outcomes, allows further TB transmission, and promotes antimicrobial drug resistance.[1] Since 2010, substantial progress in managing drug resistant TB has been made through increased access to newer molecular World Health Organization (WHO) recommended rapid diagnostic tests.[2] Evolution of various shorter oral regimens consisting of fewer pills, resulting in lesser toxicity, and giving rise to better treatment outcomes has revolutionised treatment of multidrug resistant TB, with treatment success improving from 50% in 2012 to 63% in 2020.[2] However, case detection remains a major challenge: only an estimated 44% of people thought to have multidrug resistant TB or rifampicin resistant TB globally were correctly diagnosed and treated in 2023.[1] Early diagnosis and treatment of drug resistant TB with effective regimens are essential for successful treatment. Monitoring the treatment response, assessing for side effects of anti-TB drugs, and providing person centred care are also vital. Here we describe the latest evidence and guidelines underpinning diagnostic evaluations, treatment, care, and support for adults with pulmonary multidrug resistant TB.

Sources and selection criteria

We conducted a review of the literature to gather the latest evidence, guidelines, and recommendations for the diagnosis and management of multidrug resistant TB. We performed two searches—a more generalized search regarding drug resistant TB, followed by a more focussed search using key words such as “drug resistant tuberculosis”, “multidrug resistant tuberculosis”, “rifampicin resistant tuberculosis”, “risk factors”, “diagnosis”, “diagnostic tests”, “treatment”, “care and support”, “toxicity”, “safety”, and “treatment outcome”. A combination of these words was used to search for articles in PubMed, Google Scholar, and Cochrane databases. We chose articles that were related to multidrug resistant TB. We also identified appropriate articles from the reference lists of the chosen articles.



What is multidrug resistant TB?

Multidrug resistant TB refers to *Mycobacterium tuberculosis* strains that are resistant to both isoniazid and rifampicin (box 1).[6] In contrast, rifampicin resistant tuberculosis refers to *Mycobacterium tuberculosis* strains that are resistant to rifampicin, with or without resistance to other anti-TB drugs.[6] Strains of TB that are sensitive to rifampicin are managed with rifampicin based treatment regimens. Factors that could promote the development of anti-TB drug resistance in mycobacterial strains include treatment interruptions, substandard drugs, interrupted drug supply, and incorrectly prescribed dosage or duration. Malabsorption leading

to suboptimal concentrations or poor drug penetration at target tissue sites despite good adherence can also lead to resistance.[7 8] Individual risk factors for developing multidrug resistant TB relate to the specific strain, the individual patient factors, and the surrounding environment (box 2).

Box 1: Classification of drug resistant tuberculosis

According to WHO, there are five categories of drug resistant TB[3]

- Rifampicin resistant TB: TB bacteria resistant to rifampicin, which could be susceptible or resistant to isoniazid, or resistant to other first line or second line anti-TB drugs
- Rifampicin susceptible, isoniazid resistant TB: TB bacteria resistant to isoniazid but susceptible to rifampicin
- Multidrug resistant TB: TB bacteria resistant to isoniazid and rifampicin
- Preextensively drug resistant TB: TB bacteria resistant to rifampicin (might also be resistant to isoniazid) and at least one fluoroquinolone drug (levofloxacin or moxifloxacin)
- Extensively drug resistant TB: TB bacteria resistant to rifampicin (might also be resistant to isoniazid), at least one fluoroquinolone drug (levofloxacin or moxifloxacin), and resistant to linezolid or bedaquiline (or both).

Resistance can either be primary or secondary.[4 5] Primary drug resistance occurs when someone is infected with a drug resistant *Mycobacterium tuberculosis* strain. Secondary drug resistance occurs when a TB strain acquires resistance conferring mutations to anti-TB drugs while a person is on drug treatment.

Box 2: Risk factors for developing multidrug resistant TB[9 -13]

Agent factors

- Infection with Beijing strain of *Mycobacterium tuberculosis*, a globally significant lineage of the bacteria, which is known to be associated with anti-TB drug resistance[14 15]

Patient factors

- Male sex
- Comorbidities (eg, HIV, concurrent chronic lung disease, diabetes)
- Lifestyle factors (eg, smoking, alcohol consumption)
- History of TB
- Prior TB treatment interruptions
- Previous TB treatment failure
- Failure to respond to first line anti-TB drugs in the current treatment course

Environmental factors

- Living in crowded settings
- Close contact with people with pulmonary drug resistant TB
- Residing in areas with high prevalence of drug resistant TB
- Use of poor quality anti-TB drugs

Clinical presentation

People with pulmonary multidrug resistant TB typically present with symptoms similar to those of drug sensitive TB. Common signs and symptoms include cough, fever, loss of appetite, weight loss, breathlessness, haemoptysis, chest pain, and night sweats (table 1). Longer duration of cough does not increase sensitivity for diagnosis of TB. Systematic reviews underpinning WHO TB screening guidelines found that cough of 2 weeks or more has a sensitivity for TB diagnosis of 0.42 (6737 participants across 40 studies) and a specificity of 0.94 (1 284 181 participants from 40 studies). The presence of any cough has a slightly greater estimated diagnostic sensitivity of 0.51 (2734 participants across 21 studies) with a specificity of 0.88 (768 291 participants across 21 studies). The presence of any of cough, haemoptysis, fever, night sweats, or weight loss had an overall sensitivity of 0.71 for detection of TB (3915 participants across 28 studies), but a reduced specificity of 0.74.[24 25] However, a substantial proportion of people with bacteriologically confirmed TB have no cough at all or are asymptomatic. A meta-analysis of nationally representative surveys conducted between 2007 and 2020 in 12 countries with high incidence of TB (eight in Africa and four in Asia, comprising 602 863 participants in total) found that 39.8% of participants with bacteriologically confirmed TB had reported no cough of any duration (but this figure could be higher), whereas 40.9% reported cough for 2 weeks or more.[26]

Table 1 | Common signs, symptoms, and exposures in pulmonary drug resistant TB

Signs and symptoms	Estimated prevalence (%)
Cough	10-74[16_19]
Fever	15-78[16_19]
Weight loss	23-63[16_19]
Loss of appetite	32-52[17_19]
Breathlessness	18-64[16_18]
Haemoptysis	10-46[16_18]
Chest pain	7-29[16 18]
Contact with people known to have drug resistant TB	2-38[17 20 21]
BMI <18.5	27-84[18 21 22]
History of treatment for TB	42-80[16 20 22 23]

People who present with presumed TB or those already on treatment for drug sensitive TB with persistent or worsening respiratory symptoms, fever, poor weight gain, appearance of new (or deterioration of pre-existing) lesions on chest x ray imaging, and/or persistently positive sputum smears or cultures warrant evaluation for drug resistant TB.

How should I assess for multidrug resistant TB?

Collect a detailed history from people with symptoms suggestive of TB, including respiratory and constitutional symptoms, comorbidities including HIV infection and diabetes, history of TB diagnosis and treatment, TB contact history, high risk occupations, housing conditions, travel history including previous or current

residence in areas where TB is endemic, as well as lifestyle factors such as smoking and alcohol consumption. Complete a detailed, comprehensive physical examination including assessment of nutritional status, involvement of extrapulmonary sites and signs such as icterus or pedal oedema, which could relate to organ dysfunction and lead to drug related toxicities.

Early diagnosis of pulmonary multidrug resistant TB depends on the rapid and accurate detection of *Mycobacterium tuberculosis* in respiratory samples (eg, expectorated or induced sputum, tracheal aspirate, or bronchoalveolar lavage, if required) from people with signs or symptoms of TB or from asymptomatic people who screened positive in community based TB screening or contact tracing programs based on chest x ray imaging, C reactive protein in people living with HIV, or by molecular WHO recommended rapid diagnostic tests.[27] Diagnosis of multidrug resistant TB also depends on drug susceptibility testing to identify anti-TB drug resistance. Nucleic acid amplification tests that simultaneously detect *Mycobacterium tuberculosis* and rifampicin resistance in respiratory samples are the initial diagnostic tests of choice for all people undergoing evaluation for pulmonary TB (table 2),[27 31] largely replacing sputum smear microscopy.

Table 2 | Initial and follow-up diagnostic tests recommended by WHO for *Mycobacterium tuberculosis* detection and drug susceptibility testing[27]

Tests	Turnaround time	Resistance detection
Initial diagnostic test for *Mycobacterium tuberculosis* detection with drug resistance detection		
Low complexity automated nucleic acid amplification (Polymerase chain reaction (PCR) based (genotypic))		
Xpert MTB/RIF and Xpert MTB/RIF Ultra (Cepheid)	2h	Rifampicin
Truenat MTB Plus with MTB-RIF Dx (Molbio)	2h[28]	Rifampicin
Moderate complexity automated nucleic acid amplification (PCR based (genotypic))		
Abbott RealTime MTB and Abbott RealTime MTB RIF/INH (Abbott)	13h[29]	Rifampicin and isoniazid
BD MAX MDR-TB (Becton Dickinson)	4h[29]	Rifampicin and isoniazid
Cobas MTB and Cobas MTB-RIF/INH (Roche)	4h[29]	Rifampicin and isoniazid
FluoroType MTB and FluoroType MTBDR (Hain Lifescience/Bruker)	2.5h[29]	Rifampicin and isoniazid
Low complexity manual nucleic acid amplification (Loop mediated thermal amplification (genotypic))		
Loopamp MTBC detection kit (TB LAMP) (Eiken Chemical)	2h[28]	No
Follow-on test for the detection of additional drug resistance in people with:		
Rifampicin resistant TB		
Low complexity automated nucleic acid amplification (PCR based (genotypic))		
Xpert MTB/XDR (Cepheid)	1.5h	Isoniazid, fluoroquinolone drugs, ethionamide, and amikacin
Targeted next generation sequencing (Genotypic)		
TBseq (Shengting Medical Technology Company)	3-5 days	Isoniazid, fluoroquinolone drugs, bedaquiline, linezolid, clofazimine, pyrazinamide, ethambutol, amikacin and streptomycin
Bacteriologically confirmed TB		
First line probe assay (DNA based reverse hybridisation (genotypic))		
GenoType MTBDRplus v1 and v2 (Hain Lifescience/Bruker)	5h	Rifampicin and isoniazid
Genoscholar NTM+MDRTB II (Nipro)	5h	Rifampicin and isoniazid
Genoscholar PZA-TB (Nipro)	5h	Pyrazinamide
Targeted next generation sequencing (Genotypic)		
Deeplex Myc-TB (GenoScreen/Illumina) AmPORE-TB (Oxford Nanopore Technologies)	3-5 days	Rifampicin, isoniazid, fluoroquinolone drugs, pyrazinamide, and ethambutol
Rifampicin resistant TB or multidrug resistant TB		
Second line probe assay (DNA based reverse hybridisation (genotypic))		
GenoType MTBDRsl assay (Hain Lifescience)	5h[30]	Fluoroquinolone drugs (ofloxacin, levofloxacin, moxifloxacin, and gatifloxacin) and second line injectables (amikacin, kanamycin, and capreomycin)

Of note, chest x ray imaging is not the initial diagnostic test of choice for pulmonary TB, but most clinical guidelines for evaluating respiratory symptoms and possible pulmonary TB recommend it to rule out alternative diagnoses and to estimate the extent of lung involvement. For example, the UK's National Institute for Health and Care Excellence (NICE) TB guideline recommends that evaluation of pulmonary TB includes chest x ray imaging for all age groups and further evaluations if the features in chest x ray imaging are suggestive of TB.[32] Multidrug resistant TB cannot be distinguished from drug sensitive TB on the basis of findings on a chest x ray image, but large lesions, consolidation, and multiple cavitations have been more commonly observed in drug resistant TB compared with drug sensitive TB on chest x ray imaging in small retrospective studies.[33]

WHO recommends universal drug susceptibility testing, which aims to test all people with bacteriologically confirmed TB for rifampicin resistance if this was not done concurrently with Mycobacterium tuberculosis detection. The NICE guideline recommends that anyone with clinically presumed TB should also undergo rifampicin

resistance testing by rapid nucleic acid amplification tests if any one of the following risk factors for multidrug resistant TB is present: previous history of TB treatment, especially with treatment interruptions or poor adherence; contact with a person with multidrug resistant TB; and born or residing in a country in which 5% or more of people with newly diagnosed TB have multidrug resistant TB.[32]

In people with confirmed rifampicin resistant TB, tests for additional resistance to anti-TB drugs including isoniazid and fluoroquinolones are indicated. Low complexity automated nucleic acid amplification tests, line probe assays, and targeted next generation sequencing assays could be used (table 2).[27] For people with bacteriologically confirmed TB who did not have simultaneous drug susceptibility testing for rifampicin and isoniazid, line probe assays and other dedicated drug susceptibility tests could be used as follow-on tests to detect resistance to anti-TB drugs.[27] For people with confirmed multidrug resistant TB or rifampicin resistant TB, second line probe assays could be considered to detect resistance to fluoroquinolones and second line drugs administered by injection.[27] Next generation sequencing assays can detect additional mutations to several anti-TB drugs with a reduced turnaround time and acceptable costs.[34 35] Education about the various diagnostic tests can support people to make informed choices about *Mycobacterium tuberculosis* detection and drug resistance testing.

In the era of molecular WHO recommended rapid diagnostic tests, phenotypic drug susceptibility tests are still important in detecting anti-TB drug resistance. Phenotypic drug susceptibility tests are solid (Lowenstein Jensen media) or liquid (mycobacterial growth indicator tube (MGIT) and BACTEC MGIT 960) culture based methods that identify *Mycobacterium tuberculosis* and provide isolates for line probe assays,[36] but culture based phenotypic drug susceptibility tests have a turnaround time of around 28-42 days. Phenotypic drug susceptibility tests identify resistance to new and repurposed anti-TB drugs at treatment initiation and can detect the emergence of additional drug resistance during treatment. Phenotypic drug susceptibility tests could be useful where genotypic drug susceptibility tests miss novel mutations that confer rifampicin and isoniazid resistance.[27 37]

How is multidrug resistant TB treated?

Since 2013, substantial progress has been achieved in managing drug resistant TB with the development of new drugs and shorter, safe and effective treatment options.[38] Evidence supporting the efficacy of bedaquiline, pretomanid, and linezolid (BPaL) with or without moxifloxacin (BPaLM) regimens has redefined multidrug resistant TB or rifampicin resistant TB treatment. In particular, the Nix-TB and ZeNix trials evaluated different doses of linezolid and durations of use.[39 40] The TB-PRACTECAL trial compared BPaL and additional drugs (clofazimine or moxifloxacin) with standard care.[41] Based on these trials, WHO updated its drug resistant TB treatment guidelines in 2022 to recommend a 6 month oral BPaLM or BPaL regimen for people with either multidrug resistant TB or rifampicin resistant TB (box 3).[1 46] As of April 2025, WHO also recommends a 6 month oral regimen containing bedaquiline, delamanid, linezolid, levofloxacin, and clofazimine (BDLLfxC) that can be given to pregnant or lactating women and others (box 3).[37] Additional treatment regimens include a 9-11 month oral, a modified 9 month oral and a longer 18-20 month regimen (preferably administered orally or by injection) for multidrug resistant TB or rifampicin resistant TB treatment.[37]

Box 3: WHO recommendations for shorter regimens in the management of multidrug resistant TB or rifampicin resistant TB[37]

6 month oral BPaLM or BPaL regimen

BPaLM regimen: Bedaquiline 400 mg once daily (OD) for 2 weeks followed by 200 mg thrice weekly, or bedaquiline 200 mg OD for 8 weeks followed by 100 mg OD. Pretomanid 200 mg OD, linezolid 600 mg OD,* and moxifloxacin 400 mg OD for 26 weeks. No treatment extension is recommended for this regimen.

BPaL regimen: Bedaquiline 400 mg OD for 2 weeks followed by 200 mg thrice weekly, or bedaquiline 200 mg OD for 8 weeks followed by 100 mg OD. Pretomanid 200 mg OD and linezolid 600 mg* OD for 26 weeks. Treatment can be extended to 39 weeks if sputum culture negativity is not achieved or not sustained at treatment week 16 in people with documented resistance.

- Recommended for people:
- with multidrug resistant TB or rifampicin resistant TB (BPaLM) or multidrug resistant TB or rifampicin resistant TB with fluoroquinolone resistance (pre-extensively drug resistant TB) (BPaL)
- with confirmed pulmonary TB and all forms of non-severe extrapulmonary TB
- aged ≥14 years
- Not to be given in people:
- with severe forms of extrapulmonary TB (eg, central nervous system TB, osteoarticular TB, disseminated TB)
- with more than 1 month of previous exposure to bedaquiline, pretomanid or delamanid, or linezolid (unless drug susceptibility testing demonstrates susceptibility)
- with TB strains that are resistant to bedaquiline, pretomanid or delamanid, or linezolid
- aged <14 years
- who are pregnant or lactating
- Evidence
- TB PRACTECAL (2017; 552 people aged 15 years or older in Belarus, South Africa, and Uzbekistan)[42]
  - Treatment success of 89% with BPaLM *v* 77% with BPaL regimen *v* 52% with standard care[3 42]
- ZeNIX TB trial (2017-2019; 181 people (62% male) from aged 14 years or older in South Africa and Georgia, 18 years or older in Moldova and Russia)[43]
  - Fewer side effects and similar efficacy with linezolid 600 mg compared with 1200 mg
- BPaL *v* longer regimen[37]
  - Higher levels of treatment success with BPaL compared with longer regimen (100% *v* 75%)
  - Lower levels of failure and recurrence (0% *v* 6.6%)

6 month oral BDLLfxC regimen

Bedaquiline 400 mg once daily for 2 weeks followed by 200 mg thrice weekly for 22 weeks, or bedaquiline 200 mg OD for 8 weeks followed by 100 mg OD for 16 weeks. Delamanid 100 mg twice daily, linezolid 600 mg OD, levofloxacin OD (750 mg for patients 30-45 kg, 1000 mg for patients ≥46 kg), and clofazimine 100 mg OD for 24 weeks. Treatment can be extended to 39 weeks if sputum culture negativity is not achieved or not sustained at treatment week 16.

In case of unknown fluoroquinolone drug resistance at baseline, start as BDLLfxC. In case of fluoroquinolone drug resistance, discontinue levofloxacin and continue BDLC. In case of fluoroquinolone drug susceptibility, discontinue clofazimine and continue BDLLfx. If drug susceptibility testing results are not available, continue BDLLfxC.

- Recommended for:
- people with multidrug resistant TB, rifampicin resistant TB, or pre-extensively drug resistant TB
- people with confirmed pulmonary TB and non-severe forms of extrapulmonary TB in all age groups
- children and adolescents with higher risk of multidrug resistant TB or rifampicin resistant TB (ie, presence of clinical signs and symptoms and history of contact with a person with multidrug resistant TB or rifampicin resistant TB) but without any bacteriological evidence or resistance patterns
- people who are pregnant or lactating
- Not to be given in people with:
- severe forms of extrapulmonary TB (eg, central nervous system TB, osteoarticular TB, disseminated TB)
- more than 1 month of previous exposure to bedaquiline, delamanid, linezolid, or clofazimine (unless drug susceptibility testing demonstrates susceptibility)
- TB strains that are resistant to bedaquiline, delamanid, or linezolid
- Evidence
- BEAT TB trial (402 participants aged 6 years or older, including pregnant and lactating women in South Africa) compared BDLLfxC with standard of care[37]
  - Lower levels of severe toxicities (34% *v* 38%)
  - Lower pill burden
  - Shorter duration of treatment

9 month all oral regimen

Initial phase (4-6 months): Bedaquiline 400 mg OD for 2 weeks followed by 200 mg thrice weekly for 6 months plus levofloxacin OD (750 mg for patients 30-45 kg, 1000 mg for patients ≥ 46 kg) or moxifloxacin 400 mg OD plus high dose isoniazid (450 mg for patients 30-45 kg, 600 mg for patients ≥ 46 kg) plus ethambutol (800 mg for patients 30-45 kg, 1200 mg for patients 46-69 kg, 1600 mg for patients ≥ 70 kg) plus pyrazinamide OD (1250 mg for patients 30-35 kg, 1500 mg for patients 36-69 kg, 2000 mg for patients ≥70 kg) plus ethionamide[†] OD (500 mg for patients 30-45 kg, 750 mg for patients 46-69 kg, 1000 mg for patients ≥70 kg) plus clofazimine 100 mg OD for 4 months (with the option to extend for two more months in case of sputum smear positivity at the end of month 4).

Continuation phase (5 months): Levofloxacin OD (750 mg for patients 30-45 kg, 1000mg for patients ≥ 46 kg) or moxifloxacin 400 mg OD plus pyrazinamide OD (1250 mg for patients 30-35 kg, 1500 mg for patients 36-69 kg, 2000 mg for patients ≥70 kg) plus ethambutol OD (800 mg for patients 30-45 kg, 1200 mg for patients 46-69 kg, 1600 mg for patients ≥70 kg) plus clofazimine 100 mg OD for 5 months.

- Recommended for:
- people with multidrug resistant TB or rifampicin resistant TB
- people with confirmed pulmonary TB and non-severe forms of extrapulmonary TB in all age groups
- children with higher risk of multidrug resistant TB or rifampicin resistant TB (ie, presence of clinical signs and symptoms and history of contact with a person with multidrug resistant TB or rifampicin resistant TB) but without any bacteriological evidence or resistance patterns
- people who are pregnant or lactating[†]
- Not to be given in people with:
- multidrug resistant TB or rifampicin resistant TB with additional resistance to fluoroquinolone
- severe forms of extrapulmonary TB
- extensive pulmonary TB (extensive parenchymal damage or bilateral cavities in chest x ray)
- previous exposure to bedaquiline, fluoroquinolone, ethionamide, linezolid, and clofazimine for more than one month (unless drug susceptibility testing demonstrates susceptibility)
- resistance to bedaquiline, fluoroquinolone, ethionamide, linezolid, and clofazimine
- Evidence
- Programmatic data from South Africa[44]
  - Treatment success rate of 73% in all oral regimen *v* 60% in 9-12 month regimen with injectable.
  - 9 month regimens with ethionamide for 4 months *v* linezolid for 2 months (64% *v* 66%)[2]

Modified 9 month oral BLMZ, BLLfxCZ, and BDLLfxZ regimen

BLMZ regimen: Bedaquiline 400 mg OD for 2 weeks followed by 200 mg thrice weekly, or bedaquiline 200 mg OD for 8 weeks followed by 100 mg OD plus linezolid 600 mg till 16 weeks followed by 300 mg daily or 600 mg thrice weekly plus moxifloxacin 400 mg OD plus pyrazinamide OD (1250 mg for patients 30-35 kg, 1500 mg for patients 36-70 kg, 2000 mg for patients ≥ 70 kg).

BLLfxCZ regimen: Bedaquiline 400 mg OD for 2 weeks followed by 200 mg thrice weekly, or bedaquiline 200 mg OD for 8 weeks followed by 100 mg OD plus linezolid 600 mg OD till 16 weeks followed by 300 mg OD daily or 600 mg OD thrice weekly plus levofloxacin OD (750 mg 30-45 kg, 1000 mg for patients ≥ 46 kg) plus clofazimine 100 mg OD plus pyrazinamide OD (1250 mg for patients 30-35 kg, 1500 mg for patients 36-69 kg, 2000 mg for patients ≥ 70 kg).

BDLLfxZ regimen: Bedaquiline 400 mg OD for 2 weeks followed by 200 mg thrice weekly, or bedaquiline 200 mg daily for the first 8 weeks followed by 100 mg OD plus delamanid 100 mg twice daily plus linezolid 600 mg OD till 16 weeks followed by 300 mg daily or 600 mg OD thrice weekly plus levofloxacin OD (750 mg for patients 30-45 kg, 1000 mg for patients ≥46 kg) plus pyrazinamide OD (1250 mg for patients 30-35 kg, 1500 mg for patients 36-69 kg, 2000 mg for patients ≥70 kg).

Total duration of treatment is 9 months.

No option of treatment extension.

- Recommended for:
- people with multidrug resistant TB or rifampicin resistant TB
- people with confirmed pulmonary TB and non-severe forms of extrapulmonary TB in all age groups
- children and adolescents with higher risk of multidrug resistant TB or rifampicin resistant TB (ie, presence of clinical signs and symptoms and history of contact with a person with multidrug resistant TB or rifampicin resistant TB) but without any bacteriological evidence or resistance patterns
- people who are pregnant or lactating
- Not to be given in people with:
- people with multidrug resistant TB or rifampicin resistant TB with additional resistance to fluoroquinolone
- severe forms of extrapulmonary TB
- previous exposure to bedaquiline, delamanid (if part of the regimen), linezolid, and clofazimine for more than one month (unless drug susceptibility testing demonstrates susceptibility)
- Evidence
- endTB trial (2017-2024; 754 people aged 15 years or older in Georgia, India, Kazakhstan, Lesotho, Pakistan, Peru, and South Africa)
  - Favourable outcomes (negative culture or no evidence of disease) at 73 weeks after treatment initiation[45]
  - BMLZ, BLLfxCZ, or BDLLfxZ *v* 18-24 month longer regimen: 89 %, 90.4%, or 85.2% *v* 80.7%, respectively

[*] Can be reduced to 300 mg to alleviate linezolid toxicity, if necessary

† 4 months of ethionamide to be replaced with 2 months of linezolid 600 mg daily

In most settings, TB or infectious disease specialists initiate and manage multidrug resistant TB treatment after shared decision making with people diagnosed with multidrug resistant TB about the available treatment options, individual comorbidities, and possible adverse events from drugs. Information about available treatment options and the rationale for recommending a particular regimen or regimen change helps people with multidrug resistant TB or rifampicin resistant TB to fully engage with treatment.

Baseline laboratory investigations can aid in selecting the most appropriate treatment regimen and are useful reference points for monitoring the side effects of anti-TB drugs. Baseline laboratory tests typically include liver function tests, serum electrolytes, a complete blood count, HIV antigen/antibody if HIV status is unknown (also check the CD_4 count in people living with HIV), hepatitis B surface antigen, hepatitis C antibodies, and a pregnancy test for women of reproductive age (if indicated). Depending on the specific treatment regimen, baseline testing might also include thyroid stimulating hormone, uric acid, and electrocardiography.[47] People undergoing testing and treatment for multidrug resistant TB might also benefit from psychosocial assessments to enhance provision of person-centred care and support interventions during treatment.[48 49]

There are nuances to treatment for people in unique or vulnerable populations. All multidrug resistant TB treatment regimens can potentially be used safely in people living with HIV after thoroughly considering drug-drug interactions.[50] Refer people living with HIV who have been diagnosed with multidrug resistant TB or rifampicin resistant TB to specialist care, where available, to consider adjustments to antiretroviral therapy while undergoing treatment for multidrug resistant TB. Refer pregnant or breastfeeding women to obstetric and/or TB specialists for initiation of multidrug resistant TB treatment and its management during pregnancy and for appropriate treatment while breastfeeding.

Some people with multidrug resistant TB will need longer treatment regimens, up to 18-20 months (or 15-17 months after conversion of positive sputum culture to a negative culture result),[2] depending on an individual's response to therapy. Indications for longer treatment regimens for multidrug resistant TB or rifampicin resistant TB are listed in box 4, and WHO provides detailed guidance on extended treatment options.[37] Decisions about longer, individualised courses of treatment are made by TB or infectious disease specialists in many settings and should be based on drug susceptibility testing wherever available, previous anti-TB medication use, drug tolerability, potential drug-drug interactions, and individual preference.[37]

Box 4: Indications for a longer multidrug resistant TB or rifampicin resistant TB treatment regimen[37]

- Extensive drug resistance (box 1)
- Severe forms of extrapulmonary TB (eg, tuberculous meningitis, disseminated TB, pericardial TB, osteoarticular TB)
- Extensive pulmonary TB disease
- Exposure to any of the drugs in a shorter regimen for more than 1 month
- Resistance to drugs in the shorter regimens
- Intolerance to the drugs in a shorter regimen
- Treatment failure or lack of bacteriological conversion or clinical response after taking a 6 or 9 month regimen
- Pregnancy, lactation, or younger age for which a shorter regimen is contraindicated
- BMI <17
- Altered liver function tests suggestive of hepatic inflammation or injury (liver enzymes more than three times the upper normal limit)
- Severe anaemia (haemoglobin <80 g/L) or thrombocytopenia (platelet count $<150\times10^9$/L)
- Severe peripheral neuropathy (grade 3 or 4)

How should I monitor treatment response and adverse events from drugs in people with multidrug resistant TB?

Closely monitor all individuals undergoing treatment for multidrug resistant TB or rifampicin resistant TB to assess the treatment response and detect adverse events from anti-TB drugs. Monthly clinical examination, sputum smear, and culture are recommended for monitoring the response to treatment in all people on treatment, regardless of the regimen they are on or their baseline smear or culture result.[47]

Some guidelines, including the American Thoracic Society, recommend more frequent monitoring until sputum smear conversion, biweekly until culture conversion, and then monthly until treatment completion.[51] Molecular WHO recommended rapid diagnostic tests are not recommended for treatment response monitoring and do not replace sputum smear microscopy and culture for this purpose because they could detect dead *Mycobacterium tuberculosis* as well.[52] Sputum culture is more sensitive than microscopy for monitoring the bacteriological status during treatment (77.9% *v* 68.9%).[53] Limitations of *Mycobacterium tuberculosis* culture include the need for well equipped laboratory facilities and longer turnaround time for results. Sputum microscopy can be performed rapidly with minimal laboratory facilities, but viability of the mycobacteria cannot be confirmed. An individual's ability to produce a good quality sputum sample can also influence smear and culture results.[54]

Chest x ray imaging is indicated at baseline, after the second month of treatment, at the end of treatment, as well as 6 and 12 months post treatment (or when otherwise clinically indicated) to confirm resolution and/or detect the appearance of new or worsening lesions.[47] Respiratory symptoms might persist even after sputum conversion, but improvement is common within 2 months of treatment with an appropriate treatment regimen.[12] Weight gain of more than 5% during the first 3 months of treatment is consistent with a good response.[55 56]

Failure of bacteriological sputum culture conversion (ie, persistent culture positivity) at or after 4 months of treatment or sputum culture reversion (negative to positive culture) during treatment or follow-up warrants drug susceptibility testing by genotypic (Xpert MTB/XDR) or line probe assay as well as phenotypic testing (table 2).[47] Malnutrition (BMI < 18) and culture conversion more than 2 months after treatment initiation are risk factors for unfavourable treatment outcomes, including treatment failure, relapse, and death.[57] Restoration of adequate nutritional status is essential,[58] and hospital stays might be required for people with severe anaemia and malnutrition (haemoglobin <70 g/L, BMI <16 with pedal oedema, mid upper arm circumference <16 cm) to address nutritional status.[48]

Early detection of adverse events from anti-TB drugs

Changes in clinical examination and laboratory evaluations during treatment compared to baseline may reflect drug side effects or toxicity. Older adults, people living with HIV, people with diabetes, and those with renal or hepatic disease, visual impairment, anaemia, or electrocardiogram abnormalities might also need more frequent monitoring for adverse events from drugs.[51]

If poor treatment response or drug toxicities are suspected, involve TB or infectious disease specialists in choosing an alternate regimen. People on BPaLM or BPaL regimens who experience drug reactions to bedaquiline or pretomanid will need to entirely change their treatment regimen to individualised, longer regimens or to BDLLfxC regimens.[47] Both bedaquiline and pretomanid can be hepatotoxic and can prolong the QTc interval; baseline and monthly hepatic enzymes and electrocardiography are recommended for people on regimens that contain bedaquiline and pretomanid.[47] Fluoroquinolones including moxifloxacin or, less frequently, levofloxacin can also occasionally cause QTc prolongation (for which electrocardiography monitoring is also recommended) in addition to blood glucose abnormalities, peripheral neuropathy and tendinitis or tendon rupture.[51] American Thoracic Society guidelines recommend electrocardiogram at 2, 12 and 24 weeks after treatment initiation with BPaL and monthly electrocardiogram for people on the BPaLM treatment regimen.[51] Refer people with HIV, hepatitis B or hepatitis C coinfection, cardiac conditions, renal or hepatic dysfunction, severe anaemia, and all people who experience adverse events or toxicities related to anti-TB drugs to TB or infectious disease specialists to determine the most appropriate treatment regimen. Information about adverse events of anti-TB medicines can be found in the WHO operational handbook on tuberculosis.[47]

Linezolid toxicity for those on regimens that contain linezolid includes myelosuppression (especially anaemia), peripheral neuropathy, and optic neuropathy. In a multicountry study of BPaL treatment with 600 mg linezolid in people with multidrug resistant TB, peripheral neuropathy and anaemia occurred in 32.1% and 24.5% of participants, respectively, most commonly at or within the first 3 months of treatment. Optic neuropathy occurred in 3.8% of participants, mostly after 3 months of treatment.[47 59] Evidence suggests that reducing the dose of linezolid—whether scheduled or in response to adverse events—could reduce toxicity without compromising treatment efficacy.[60 61] Participants in two arms of a multicenter randomized control trial of modified BPaL regimens with structured dose reductions of linezolid at specified time points (n=249/378 participants) had a recurrence-free cure rate of 88% compared with 87% for those with no linezolid dose reduction (n=129/378) at 48 weeks post treatment follow-up.[62] Counsel people on multidrug resistant TB treatment about drug toxicities to prevent harm and because adverse events and disengaging from treatment could result in treatment failure.

Post treatment follow-up

Post treatment follow-up includes clinical evaluation, sputum smear, TB culture, and chest x ray imaging 6 and 12 months after the completion of treatment to identify recurrence early. Most TB recurrences happen within 12 months—especially within the first 6 months—after completing treatment.[62] Almost 90% of individuals with multidrug resistant TB develop post TB lung disease, leading to functional disability.[35] Post TB lung disease comprises a spectrum of post infectious pulmonary sequelae and may be prevented by early diagnosis, treatment initiation, and tailored interventions, but further research is needed in this area.[63]

Care and support for people undergoing treatment for multidrug resistant TB

Fear of testing positive for TB, stigma, apprehensions related to the cost of treatment, frequent clinic visits, and drug toxicities are important deterrents for undergoing diagnostic tests for TB and for completing TB treatment.[64] Health centre accessibility, pill burden, duration of treatment, and misconceptions can also affect adherence to treatment.[65] Provide person centred multidrug resistant TB care that is based on individuals' needs and choices to support individuals and families to overcome unique social, economic, cultural, legal, and psychological barriers they might be facing.[47] Education about TB and adherence to treatment, alongside psychosocial support, improve treatment adherence and outcomes.[66] For example, in a pilot of counselling to improve drug resistant TB treatment among 331 people with drug resistant TB in Papua New Guinea, education by counsellors, including peers, and counselling sessions about TB, TB medications, and adherence to treatment reduced loss to follow-up during treatment from 18% (baseline) to 4% (with interventions).[67] Other measures that could support individuals to complete multidrug resistant TB treatment include material support, such as food, financial assistance or travel support; social connectedness via support groups and other kinds of companionship; tailored treatment support in which health workers or trained lay supporters help an individual to take TB medications; and various digital tools such as SMS medication reminders, event monitoring devices, or video-observed treatment.[47] It might not be possible or appropriate to provide care in the community or at home for people with extensive disease, serious comorbidities and/or with treatment adherence difficulties.

How can multidrug resistant TB be prevented?

TB is a notifiable disease in many countries, requiring physicians to report a detected case to the public health system in accordance with local requirements and procedures.

Transmission of drug resistant TB—like drug sensitive TB—is widely reported and is closely linked to social determinants of health such as overcrowded housing, income insecurity, gender, and absence of social protection that make certain populations more vulnerable to TB risk factors (including HIV infection, tobacco and alcohol use, and undernutrition), TB exposure, and previous TB treatment failure.[1 68] Rapid diagnosis and timely initiation of effective TB treatment, appropriate ventilation, use of N-95 masks, and good hand hygiene (especially in hospital settings, contact screening, and preventive treatment in exposed contacts) prevents the transmission of drug resistant TB.[69]

Refer close contacts of individuals with multidrug resistant TB or rifampicin resistant TB in whom TB disease is not detected to specialist services for consideration of TB preventive treatment.[47]

Education into practice

- Think about the last time you talked to patients about treatment adherence, pill burden, and adverse events from drugs for a given treatment course. What are the most common barriers to treatment adherence?
- What initial assessments are appropriate for people with respiratory symptoms concerning for TB?
- How often do you offer advice about treatment adherence to people being treated for TB?
- How would you discuss the possible adverse events from drugs with people diagnosed with multidrug resistant TB at the time of treatment initiation and during follow-up?

Questions for future research

- What is the optimal frequency of treatment monitoring for people taking anti-TB drugs that have cardiotoxic side effects such as bedaquiline, delamanid, clofazimine, and moxifloxacin?
- What is the optimal frequency of treatment monitoring in people taking anti-TB drugs like linezolid that could cause haematological adverse events such as bone marrow suppression?
- What are the factors at baseline or after 2 months of multidrug resistant TB treatment that might predict the overall treatment response and that could guide the duration of multidrug resistant TB treatment?
- Which other treatment regimens might be constituted with pretomanid in addition to BPaLM or BPaL?
- Which health service delivery and health system elements comprise effective pathways for detecting and escalating care in people experiencing adverse events while on treatment for drug resistant TB?
- Does earlier treatment initiation for multidrug resistant TB prevent post TB lung disease and which other interventions could curtail its development?

How patients were involved in the creation of this article

The author Paran Sarimita Winarni is a drug resistant TB survivor and TB activist. Her experiences and suggestions about the importance of person centred care, nutrition in TB management, training, and involvement of community volunteers in treatment supervision and monitoring of adverse events helped to strengthen the care and support section of this manuscript.

Additional educational resources

- WHO consolidated guidelines on tuberculosis. Module 4: treatment and care. Geneva: World Health Organization 2025 (https://iris.who.int/bitstream/handle/10665/380799/9789240107243-eng.pdf?sequence=1). Evidence based recommendations for the management of drug resistant TB.
- WHO consolidated guidelines on tuberculosis. Module 3: diagnosis. Geneva: World Health Organization 2025 (https://www.who.int/publications/i/item/9789240089488). Recommendations for rapid diagnosis of TB.
- Dheda K, Mirzayev F, Cirillo DM, et al. Multidrug-resistant tuberculosis. *Nat Rev Dis Primers* 2024;10:22 (https://www.nature.com/articles/s41572-024-00504-2). Detailed review of multidrug resistant TB including epidemiology, pathogenesis, transmission, diagnosis, management, and prevention.
- WHO operational handbook on tuberculosis. Module 4: treatment and care. Geneva: World Health organization; 2025 (https://iris.who.int/bitstream/handle/10665/381095/9789240108141-eng.pdf?sequence=1). Practical guidance for drug sensitive and drug resistant TB treatment, care, and support.

Information resources for people with lived experience

- Capacity-building of affected communities for accelerated response to drug-resistant tuberculosis in the South-East Asia Region. New Delhi: World Health Organization, Regional Office for South-East Asia; 2018 (https://cdn.who.int/media/docs/default-source/documents/tuberculosis/tb_module_final-(1)88d7d0b6-1d4e-4163-afcc-ff32a0e72bc8.pdf?sfvrsn=39a8a558_1&download=true). Training module on drug resistant TB for affected communities and community based organizations.
- DR-TB drugs under the microscope 2022. 8th Edition. Pricing and patent landscape of medicines for adults and children (https://msfaccess.org/sites/default/files/2023-02/TB_MSF-AC_Issue-Brief_UTM2022_ENG_10.2.2023.pdf). Information on newer drug resistant TB drugs, pricing, and accessibility.
- Guidance on social protection for people affected by tuberculosis. Geneva: World Health Organization and the International Labour Organization, 2024 (https://iris.who.int/bitstream/handle/10665/376542/9789240089327-eng.pdf?sequence=1). Guidance for people centered care and support for people affected by TB.
- A patient-centered approach to TB care. World Health Organization (https://iris.who.int/bitstream/handle/10665/272467/WHO-CDS-TB-2018.13-eng.pdf). Details of a person centered approach to TB care.

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