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# WHO-RECOMMENDED APPROACH ON MULTIDRUG-RESISTANT TUBERCULOSIS: A REVIEW

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**ABSTRACT** TB is the leading cause of death globally, along with HIV/AIDS. Drug-resistant tuberculosis remains a public health concern; in 2020, a total of 157,903 people with drug-resistant tuberculosis were identified and reported globally, a 22% drop from 2019. An estimated 10.6 million people fell ill in 2021. Tuberculosis would once again be the leading cause of death worldwide from single infectious agent, replacing Covid-19. If Isoniazid resistance (Hr) is confirmed before therapy, begin with a TB regimen, including Levofloxacin with or without Isoniazid. Diagnosis of TB should be confirmed using a WHO-recommended rapid molecular diagnostic as the initial test. When bedaquiline and delamanid are administered concurrently, the WHO recommends monitoring baseline and follow-up ECGs, liver function tests, and serum electrolytes. The BPaL regimen is a shorter all-oral therapeutic regimen composed of only three medications: bedaquiline (Bdq), linezolid (Lzd), and pretomanid (Pa). Dosage modifications for Bdq and Pa are not approved or recommended. A full BPaL regimen can be temporarily interrupted for 35 consecutive days. Any missed days are made up by extending the treatment duration by the number of days missed, but this must not be >35 days. The function of pulmonary surgery has been re-evaluated as a method of reducing the amount of lung tissue with interactable pathology and bacterial load. The WHO recommends a conditional recommendation for elective partial lung resection, such as lobectomy or wedge resection, as an adjuvant to treatment. The World Health Organization recommends corticosteroids for patients with TB meningitis and TB pericarditis. WHO suggests the Xpert MTB/RIF test be made available as the initial diagnostic test in HIV-prevalent settings. MDR-TB can be eradicated by strengthening medical systems, adhering to anti-TB agents, avoiding treatment discontinuation after symptomatic recovery, and early diagnosis of patients.

**KEYWORDS**

MDR-TB, tuberculosis, isoniazid-resistance, rifampicin-resistance, BPaL regimen, pulmonary surgery, corticosteroids and HIV-TB coinfection.

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## Introduction

TB is the leading cause of death globally, along with HIV/AIDS. Tuberculosis disproportionately affects the world's poorest and most vulnerable people, exacerbating existing inequities. People with TB experience costs or income loss equal to more than 50% of their income [1]. Tuberculosis often originates in the lungs and can take two forms: primary infection or reactivated infection. In primary infection, the body's immune system suppresses the infection but does not kill the bacilli. They are still alive but inactive and may cause the disease to reactivate. Once reactivated, TB bacilli can spread throughout the body via the lymphatic system and circulation. Initially, tuberculosis generally affects only one lung. Later outbreaks, on the contrary, usually extend to both lungs and may also impair the kidneys, causing pyelonephritis, the adrenal glands, causing Addison's disease, and the membranes surrounding the brain, causing meningitis. Men's testes and women's ovaries may also be affected [2]. TB control and treatment in India is governed by a national programme, the Revised National Tuberculosis Control Plan (RNTCP), established in 1997 [3,4,5]. According to WHO, the most recent data reveals treatment success rates of 86% for TB and 77% for TB living with HIV. Furthermore, drug-resistant tuberculosis remains a public health concern. In 2020, 157,903 people with drug-resistant tuberculosis were identified and reported globally, a 22% drop from 2019. According to the most recent statistics from the World Health Organization, the treatment success rate for MDR-or RR-TB is only 59% [4,5]. An estimated 10.6 million people fell ill in 2021. Tuberculosis would once again be the leading cause of death worldwide from single infectious agent, replacing Covid-19.

- Isoniazid resistance-TB (Hr-TB): Refer to mycobacterium tuberculosis strains resistant to isoniazid yet sensitive to rifampicin.

Hr-TB regimen: 6 (H)-R-E-Z-Lfx

- Rifampicin resistant-TB (RR-TB): refer to patients who have not received treatment with second-line anti-TB drugs in regimens for more than one month and for whom fluoroquinolones have been excluded.

RR-TB regimen: 4-6 months: bedaquiline(6 m)- Lfx-Cfx-Z-E-Hh-Eto/ 5 months: Lfx-Cfz-Z-E

- Longer treatment regimen for MDR and R-RTB (Rifampicin resistant-TB): Refer patients who are ineligible for a shorter all-oral bedaquilne regimen. It is indicated for patients with extensive

tuberculosis, severe forms of extrapulmonary TB, additional resistance to fluoroquinolones and who have been subjected to therapy with second-line TB drugs for more than one month.

longer treatment regimen: 18 Bdq (6m)- Lfx/Mfx-Lzd-Cfz

- All oral BPaL regimen: Refer to patients eligible for this regimen, including MDR-TB with additional resistance to fluoroquinolones. BPaL regimen is used only under operational research conditions. It comprises the novel anti-TB medication Pretomanid, Bedaquiline and Linezolid.

(6-9m)- Bdq-Pa-Lzd

### Approaches to Drug Resistance-TB treatment

An appropriate regimen should be chosen based on the patient's treatment history, drug susceptibility testing, clinical judgement, therapy monitoring, safety and effectiveness, severity, and disease site.

### Treating Isoniazid-Resistant TB (Hr-TB)

Adults, children, adults living with HIV, confirmed Hr-TB without Rifampicin resistance, and Hr-TB diagnosed after starting treatment with 2HREZ/4HR are all eligible for the recommended Hr-TB regimen, which is 6 (H)-R-E-Z-Lfx. If Isoniazid resistance (Hr) is confirmed before therapy, begin with a TB regimen, including levofloxacin with or without Isoniazid, i.e., 6 (H)-R-E-Z-Lfx. If Hr is strongly suspected before treatment and the drug susceptibility test results are pending, the following regimen might be used: 6 (H)-R-E-Z-Lfx. However, if a drug susceptibility test reveals isoniazid susceptibility, the Lfx should be discontinued, and therapy with a first-line regimen of two months of HREZ and four months of HR should be continued [6,7]. It is essential to note that Hr-TB can occasionally be confirmed in individuals after they begin therapy with the 2HREZ/4HR regimen. Despite treatment, this might happen in people who have undiagnosed Hr or later develop (Hr) strains. In this situation, rapid molecular testing for rifampicin resistance (R-RTB) must be performed or repeated before the 6-month course of REZ-Lfx with or without soniazid (H) [4,6,7].

Hr-TB treatment does not include an intensive or continuous phase; instead, this regimen includes daily treatment and adherence to supporting measures such as Directly Observed Treatment (DOT), Social Support, and Digital Technologies. Direct microscopy should be performed at months 2, 5, and 6 since clinical monitoring is critical for determining therapy responses. Culture with smear microscopy to check for emerging resistance, particularly Rifampicin ®. A Drug Susceptibility Test (DST) should be performed [4,6,7].

**Table 1 – Potential medicines and adverse effects to monitor**

| Anti-TB Agent | Adverse events | Management |
|---|---|---|
| Pyrazinamide (Z) When used for a prolonged period | Hepatotoxicity | Frequent monitoring of liver function |
| Ethambutol (E) When used for a prolonged period | Visual disturbances | Test for changes in visual acuity and colour vision |

For patients to be eligible for treatment with the regimen for Hr-TB;

- Isoniazid resistance (Hr) should be confirmed, and Rifampicin resistance should be excluded before treatment starts.
- Sometimes Hr is detected after the patient has started standard 1st line treatment; in this case, 'Rapid Molecular Testing' for rifampicin resistance (RR-TB) must be done or repeated before beginning the regimen for Hr-TB.
- Treatment responses can be monitored by using a sputum examination.
- Regularly monitoring 'Potential Adverse Effects' [4,6,7].

Diagnosis of TB should be confirmed using a WHO-recommended rapid molecular diagnostic as the initial test. When TB is confirmed and susceptible to Rifampicin ®, carry out a test for Isoniazid resistance (Hr) using a line probe assay for 1st line Anti-TB regimens. If rifampicin resistance is excluded and there is a high risk for isoniazid resistance (Hr), a patient could start treatment for Isoniazid Resistant (Hr) TB. Once the drug susceptibility testing (DST) results are obtained, the regimen can be modified as needed [4,8,9].

To prevent treating patients with MDR-TB/RR-TB with an inefficient regimen, rifampicin resistance should be excluded in all patients with isoniazid-resistant TB, using rapid molecular testing (e.g., Xpert MTB/RIF) before levofloxacin is used to avoid treating patients with MDR-TB/RR-TB with an inadequate regimen. When considering the Hr-TB regimen, DST for fluoroquinolones should ideally be performed [4,8,9,10].

Treating MDR-TB and R-RTB with a shorter all-oral bedaquiline-containing treatment regimen.

A shorter all-oral bedaquiline-containing regimen is a standardized regimen of 6–12 months. The first 6 months is the intensive phase, followed by 5 months of the continuation phase for all eligible patients with MDR-TB/RR-TB. The regimen is 4-6 months of Bdq (6 m)-Lfx-Cfz-Z-E-Hh-Eto-5 months of Lfx-Cfz-Z-E [4,11].

### For patients to be eligible for treatment with the regimen;

- Confirmed MDR-TB/ RR-TB without Fluoroquinolones resistance.
- Patients with no exposure to second-line medicines in the regimen for more than 1 month.
- No extensive TB disease or severe form of extrapulmonary TB.
- The patient should not be pregnant.
- Includes children aged six years and older [4].

If the sputum smear culture result is still positive after the fourth month of therapy, the intensive phase is extended for a maximum of 6 months until the smear or culture converts, while the duration of the latter phase stays fixed at 5 months.

The following modifications can be made per WHO guidelines: bedaquiline can be administered for 6 months, Ethionamide (Eto) can be substituted with Prothionamide (Pto), and Moxifloxacin can be used instead of Levofloxacin. A shorter oral treatment regimen is not recommended for children under six, pregnant or lactating women, or patients with severe extrapulmonary TB or extensive TB. The shorter all-oral bedaquiline-containing regimen is a standardized regimen that lasts 9–12 months and begins with seven anti-TB medications. The main eligibility criteria include individuals with proven MDR-/RR-TB and those who have excluded fluoroquinolones [4,11,12].

### Longer treatment regimen for MDR and R-RTB

For the following reasons, switching from the shorter all-oral bedaquiline regimen to a longer treatment regimen could be initiated:

- Lack of treatment response like sputum remains positive after six months of therapy or clinical condition worsens despite treatment.
- Medical conditions such disqualify patients from receiving shorter treatment regimens, such as pregnancy, intolerance or toxicity.
- Treatment interruption is two months or more after being treated for more than one month [4].

The switching could be needed if the actual drug resistance pattern was unknown at the start of treatment or if the patient acquires additional resistance during therapy.

**Table.2. Grouping of medicines for longer treatment regimen [4]**

| Groups and Steps | Anti-TB agents | Characteristics |
|---|---|---|
| Group A Consider all three medicines | Bedaquiline Levofloxacin/ Moxifloxacin Linezolid | Most effective agents Better treatment outcome Reduces the risk of treatment failure/ relapse Reduces the risk of death |
| Group B Add one or both medicines | Cycloserine/ Terizidone Clofazimine | Next most effective agents after group A Some effects on improving treatment outcomes Limited impat on reducing the risk of dying |

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| Group C<br>Add when the agents from groups A and B cannot be used | Ethambutol<br>Pyrazinamide<br>Ethionamide/ Prothionamide<br>P-aminosalicylic acid<br>Amikacin or Streptomycin<br>Delamanid<br>Imipenem-Cilastatin or Meropenum | Less effective agents<br>More toxic<br>Most of the drugs are difficult to administer (parenteral/intramuscular injections)<br>Poor treatment outcomes |

Composition of regimens (stepwise approach): If possible, all three agents of group A drugs and at least one group B drug should be included. If just one or two agents of group A medications are used, a group of B agents must also be included. And if the regimen cannot be composed of drugs from groups A and B, group C drugs are added [4].

For patients to be eligible for longer treatment regimens;

- Patients who are ineligible for the shorter, all-oral bedaquiline therapy regimen.
- Patients with extensive tuberculosis.
- Severe types of extrapulmonary tuberculosis (e.g., milliary TB or TB meningitis).
- Additional resistance, including to fluoroquinolones. More than one month of exposure to second-line medications.
- No response to or relapse on other DR-TB treatments [4].

Anti-TB agents dosage is determined by weight and may not be adjusted for concomitant use of other drugs or co-morbidities. The longer treatment regimen is 18–20 months or 15–17 months after culture conversion, and duration can be modified based on the patient's response to treatment, i.e., treatment of <18 months can be considered in children without extensive disease. When bedaquiline and delamanid are administered concurrently, the WHO recommends monitoring baseline and follow-up ECGs, liver function tests (ALT, AST, bilirubin), and serum electrolytes. In longer treatment regimens, bedaquiline is often administered for 6 months, although administration for more than six months is safe but considered off-label [4,13,14].

Treatment monitoring considerations for longer treatment regimens include; monthly sputum culture and smear microscopy examination, repeat drug-susceptibility testing if no response is suspected, and clinical monitoring parameters like improvement in symptoms, weight gain in children, and improved radiological findings should be monitored. Post-treatment monitoring 6 and 12 months after completion is advised to observe and ensure long-term care [4,13,14].

**Table.3. Drug safety monitoring [4]**

| Anti-TB agents | Monitoring tests |
|---|---|
| Linezolid (Lzd) | Full blood count |
| Ethambutol (E), Linezolid (Lzd) | Peripheral neuropathy of vision |
| Cycloserine (Cs) | Psychiatric assessment |
| Bedaquiline (Bdq), Delamanid (Dlm), Levofloxacin (Lfx), Moxifloxacin (Mfx), Ciprofloxacin (Cfx) | ECG and Electrolyte monitoring |
| Bedaquiline (Bdq), Pyrazinamide (Z) and other medications | Liver function test |
| Second-line injectable drug (SLI) | Audiometry and kidney function test |

### The BPaL treatment regimen

In 2020, the WHO recommended using the BPaL regimen for patients who meet the following criteria:

- Bacteriologically confirmed pulmonary tuberculosis with laboratory-confirmed resistance to rifampicin and fluoroquinolones.
- Patients must be 14 years old or older, weigh ≥35 kg, and provide informed consent for treatment and follow-up.
- Not being pregnant or breastfeeding when treatment begins and being willing to utilise an effective means of contraception [4].

Other eligibility criteria include no known allergies or evidence of resistance to any BPaL regimen, not having previously taken bedaquiline and linezolid or having taken them for less than two weeks, and having no extrapulmonary TB such as TB meningitis, other central nervous system TB, or TB osteomyelitis [14,16].

In terms of composition, the BPaL regimen is a shorter all-oral therapeutic regimen composed of only three medications: bedaquiline (Bdq), linezolid (Lzd), and pretomanid (Pa). Pretomanid is a new nitroimidazole drug that has not before been used in tuberculosis patients. This regimen was approved by the US Food and Drug Administration (FDA) in August 2019 and by the European Medicines Agency (EMA) in March 2020. The World Health Organization now advises that it be used exclusively in the consent of operational research [14,15,16].

**Table.4. BPaL regimen with dosage [4]**

| BPaL Regimen | Dose |
|---|---|
| Bedaquiline (Bdq) | For two weeks, take 400mg once daily, then 200mg thrie weekly |
| Pretomanid (Pa) | 200mg once daily |
| Linezolid (Lzd) | 1200mg once daily (adjustable) |

Dosage modifications for bedaquiline and pretomanid are not approved or recommended, although, after the first month, the linezolid dosage can be modified to 600mg or 300mg. The BPaL regimen lasts six to nine months, whereas the normal treatment time is six months. The duration of BPaL can be extended based on the findings of the sputum culture; for example, if the sputum culture remains positive after four months, the period of BPaL is extended by three months, for a total of nine months. A full BPaL regimen can be temporarily interrupted for 35 consecutive days. Any missed days are made up by extending treatment duration by the number of days missed, but this must not be >35 days [4,14,15,16].

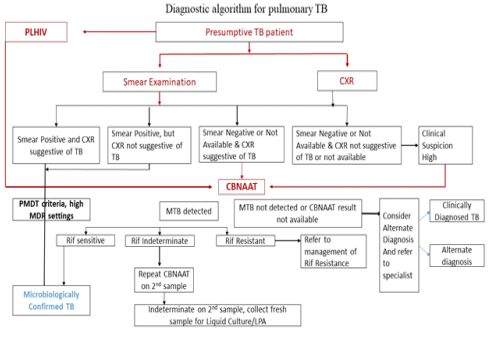
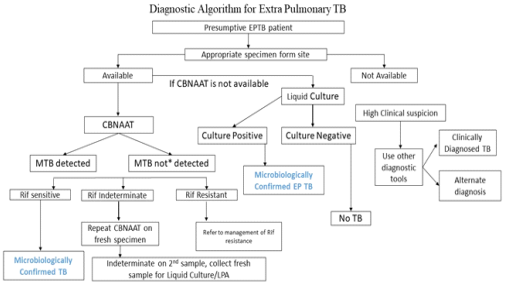



**Fig1:** Diagnostic algorithm for pulmonary TB




**Fig**

**Fig1 and 2;** PLHIV- people living with HIV, CXR- chest X-ray, CBNAT- cartridge based nucleic acid amplification test, PMDT- programmatic management of drug resistant-TB, Rif- rifampicin

### Adjunct therapy for multidrug-resistant and rifampicin resistant-TB

Pulmonary surgery: With the potential of more patients with drug-resistant TB being practically untreatable with present treatments or at risk of catastrophic complications, the function of pulmonary surgery has been re-evaluated as a method of reducing the amount of lung tissue with interactable pathology and bacterial load. For patients with MDR-, RR-, or XDR-TB, the WHO recommendations

contain a conditional recommendation for elective partial lung resection, such as lobectomy or wedge resection, as an adjuvant to treatment. Preoperative workup may include computed tomography, pulmonary function tests, and quantitative lung perfusion or ventilation [17]. Surgery should be considered only when appropriate surgical facilities are available, staffed by skilled and experienced surgeons, anaesthetists, and support staff, and should also provide excellent post-operative care. Resection surgery may increase morbidity or mortality in programs with suboptimal surgical facilities and a lack of adequate training. In conclusion, surgery should only be considered if it can be done safely [4,17,18].

When surgery is indicated, resection surgery is recommended to provide the highest possible cure with the least risk of harm. Surgery should occur early in the course of the disease when the patient's risk of mortality and morbidity is low, such as when the disease is still confined to one lung or lobe. At least two months of chemotherapy is recommended before resection to reduce the risk of bacterial infection in the surrounding lung tissue. Even after successful resection, the total duration of treatment and the course of treatment following culture conversion adhere to WHO guidelines, with no reduction in chemotherapy duration [4,17,18,19].

Use of corticosteroids: Corticosteroids are used to treat severe types of tuberculosis, such as miliary TB, as well as severe TB complications, such as respiratory distress, central nervous system involvement, and pericarditis [20]. Corticosteroids are used to decrease severe adverse effects and improve therapeutic outcomes. The World Health Organization recommends corticosteroids for patients with TB meningitis and TB pericarditis. Patients with TB meningitis should get an initial adjuvant corticosteroid treatment of dexamethasone or prednisolone tapered over a 6-to-8-week period. In individuals with TB pericarditis, initial adjuvant corticosteroid therapy may be considered [4,20,21].

### Management of drug-resistant TB-HIV co-infection

The primary treatment for TB-HIV co-infection is determined based on the type of disease, test findings, and pre-existing comorbidities. According to WHO, all HIV-positive individuals should be screened and tested for tuberculosis (TB), and if positive, they should undergo drug susceptibility testing (DST) for early diagnosis and treatment of drug resistance. WHO suggests the Xpert MTB/RIF test be made available as the initial diagnostic test in HIV-prevalent settings. Treatment with effective antiretroviral medication prolongs and improves the quality of life, sustains and improves immunological function, and lowers mortality in TB-HIV coinfected patients. Given this, it is critical to consider antiretroviral medication's prompt initiation or continuation in any HIV-infected individual [4,22,23].

Antiretroviral medication should be initiated as soon as possible in all TB patients living with HIV, regardless of CD4 cell count or clinical stage. If not already on antiretroviral medication, TB treatment should be initiated initially, followed by antiretroviral therapy as soon as feasible within the first 8 weeks of TB treatment. Within two weeks of initiating TB treatment, antiretroviral therapy should be recommended for HIV-positive patients with severe immunosuppression (CD4 <50 cells/mm3). When administering efavirenz with protease inhibitors, it is necessary to address possible drug-drug interactions between anti-TB drugs and antiretroviral medicines that might impact the clinical treatment of patients with multidrug resistance or rifampicin-resistant TB who are HIV positive [4,22,23].

### Conclusion

Multidrug resistance TB is one of the most critical and complex concerns confronting worldwide TB control programmes. MDR-TB can be eradicated by strengthening medical systems, adhering to anti-TB agents, avoiding treatment discontinuation after symptomatic recovery, and early diagnosis of patients. The global incidence of tuberculosis has dropped in recent years. However, the cumulative reduction in TB incidence rate from 2015 to 2020 was 11%, barely over halfway to the 2020 target. Accelerated action is required to save lives and achieve global treatment objectives for drug-resistant TB.

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