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## Treatment of Drug-Resistant Tuberculosis

Sundari R. Mase, MD, MPH<sup>a</sup>, Terence Chorba, MD, DSc<sup>b,\*</sup>

<sup>a</sup>World Health Organization, Southeast Asian Regional Office, World Health House, Indraprastha Estate, Mahatma Gandhi Marg, New Delhi 110 002, India;

<sup>b</sup>Field Services Branch, Division of Tuberculosis Elimination, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, 1600 Clifton Road NE (MS: US 12-4), Atlanta, GA 30329, USA

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## INTRODUCTION

### Background

The development of drug-resistant (DR) tuberculosis (TB) has become an increasing concern over the past few decades as the result of numerous factors, including widespread inappropriate or ineffectual use of antimicrobials to treat TB in the absence of drug-susceptibility testing (DST), lack of adequate uptake of systematic approaches to the treatment of drug-susceptible (DS) TB and DR-TB, introduction of human immunodeficiency virus (HIV) into areas with preexisting DR-TB, provider error, poor adherence to treatment, lack of availability of effective drugs, and transmission of DR strains.<sup>1</sup> The World Health Organization (WHO) has estimated that annually there are over half a million new cases of rifampicin-resistant (RR) and multidrug-resistant (MDR) TB; that is, disease caused by *Mycobacterium tuberculosis* with resistance to isoniazid and rifampin. Globally, 156,000 persons with MDR-TB or RR-TB began treatment in 2018, but the latest data show that only 56% completed treatment successfully.<sup>2</sup> Such poor treatment completion rates are the result of treatment for a longer duration with second-line anti-TB drugs (SLDs), which are less effective and have greater toxicity than the 4 drugs most commonly used to treat DS-TB. However, treatment performance has been shown to be much better when regimens are designed carefully and ensure good retention, under both trial and programmatic conditions.<sup>3,4</sup>

\*Corresponding author. TLC2@CDC.GOV.

#### SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ccm.2019.08.002>.

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## Definitions

There are many forms of DR-TB (Box 1). Definitions for extensively DR (XDR) TB and pre-XDR-TB need to be modified as all-oral regimens become standard of care.

## Guidelines Development

The treatment and management of DR-TB has evolved significantly in the past decade with the advent of rapid molecular diagnostic tests, new and repurposed drugs, results based on individual patient data meta-analysis (IPD-MA),<sup>5-12</sup> and a strategy to decentralize patient care in line with a patient-centered approach, including in high burden settings.<sup>13</sup> The WHO has recently published an evidence-based update to its MDR-TB treatment guidelines,<sup>14</sup> introducing new regimens, enhanced monitoring strategies, and a feasible implementation plan, based on an IPD-MA of data from recently completed phase III trials of delamanid and a shorter MDR-TB regimen; an IPD-MA with more than 13,100 records from patients treated with longer MDR-TB regimens in 40 countries; another IPD-MA with more than 2600 records from patients treated with the 9-month to 12-month shorter MDR-TB regimens from 15 countries; and pharmacokinetic and safety data from trials of bedaquiline and delamanid in patients less than or equal to 18 years old.<sup>14</sup> These guidelines are intended to be applicable in low-resource countries. The American Thoracic Society (ATS), the Centers for Disease Control and Prevention (CDC), the European Respiratory Society (ERS), and the Infectious Disease Society of America (IDSA) are also collaborating to develop guidelines for low-incidence, high-resource countries, which they will publish in 2019, using published IPD-MA data from more than 12,000 patients treated with MDR-TB regimens from 25 countries in 50 studies.<sup>8</sup> At the time of the writing of this article, those guidelines have not been finalized, but will be based principally on a published IPD-MA<sup>8</sup> and will be intended for settings in which mycobacterial cultures, phenotypic and molecular DST, and radiographic resources are readily available.

## New Recommendations from the World Health Organization (2019)

The new WHO recommendations are a departure from previous approaches to treat MDR-TB/RR-TB in several regards:

- Injectables are no longer considered priority medicines when designing longer MDR-TB regimens. Kanamycin and capreomycin are no longer recommended.
- Oral regimens are preferred for most patients.
- Fluoroquinolones (levofloxacin or moxifloxacin), bedaquiline, and linezolid are strongly recommended for all longer regimens (unless contraindicated), with other medicines ranked by a relative balance of benefits to harms.
- Most regimens should include at least 4 drugs that are likely to be effective in the first 6 months, and 3 drugs thereafter.
- The total duration of longer MDR-TB regimens should be 18 to 20 months, modified depending on patient response.
- A standardized, shorter MDR-TB regimen may be offered to eligible patients who agree to a briefer treatment (9–12 months) if they are cognizant that this

may be less effective than an individualized longer regimen and of the inconvenience/risks associated with the daily injectable agent needed for 4 to 6 months.

- It is strongly recommended that MDR-TB regimens should be monitored with cultures rather than merely with sputum microscopy, and it is preferred that cultures are performed monthly to diagnose treatment failure, relapse, or unidentified/acquired drug resistance in a timely fashion.
- Bedaquiline may be given to children greater than or equal to 6 years old and delamanid to those greater than or equal to 3 years old.
- Regimens that vary substantially from the recommended composition and duration can be explored under operational research conditions.
- Patient-centered support for medication adherence (including the use of digital technologies where feasible) and active TB drug-safety monitoring and management (aDSM) are essential for anyone starting an MDR-TB regimen.

### Key Principles/Best Practices

Several best-practices statements can readily be derived for diagnosing, treating, monitoring, and providing case management for DR-TB, based on expert opinion and on the IPD-MAs that have served as the basis for development of the 2019 WHO guidelines<sup>14</sup>:

- Treatment should follow evidence-based up-to-date guidelines of WHO or of other organizations with similar levels of expertise.
- Diagnosis, treatment, and management strategies differ depending on the epidemiology of TB, programmatic resources, and characteristics of different patient populations.
- Treatment and management of DR-TB or cases in which drug intolerance may complicate care should be done in consultation with an expert in the management of these complex cases.
- Quality-assured laboratory testing, including culture and DST, should be available for optimal patient care.
- Choice of drugs should be informed by quality-assured laboratory testing, including culture and DST, with avoidance of drugs to which there is documented resistance (individualized treatment).
- If possible, testing for rapid detection for molecular evidence of drug resistance in conjunction with growth-based DST should be performed when DR-TB is suspected, whether such suspicion has an epidemiologic or clinical basis.
- In using a longer treatment regimen, 5 drugs may be used rather than 4 drugs for the first 6 months of treatment (when using bedaquiline or in the initiation phase if an injectable agent is used) and 4 drugs rather than 3 drugs after 6 months (or during the continuation phase if an injectable agent is used) if it is deemed medically necessary and if resources allow.

- Treatment choice and duration should be determined in conjunction with the strength of the drugs used for treatment, extent and severity of disease, and the treatment response as shown bacteriologically, clinically, and radiographically. Where possible, monthly cultures should be obtained during treatment. Weight should be monitored monthly.
- Never add a single drug to a failing regimen (as manifested by persistent culture positivity, or clinical or radiographic deterioration).
- If a shorter MDR-TB regimen (9–12 months) is to be implemented, it should be in countries where a longer regimen (18–20 months) is not feasible.
- An uninterrupted supply of quality-assured drugs should be ensured.
- Active pharmacovigilance for serious adverse events (SAEs) and passive pharmacovigilance for adverse drug reactions (ADRs) are crucial. 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. Collection of detailed data on SAEs may help patients and programs to improve performance.
- Treatment adherence should be ensured through directly observed therapy (DOT) or supported using information communication technology (ICT)-based adherence strategies.<sup>15</sup>
- A patient-centered approach with case management strategies (incentives and enablers) should be used, with attention to the social, cultural, and environmental aspects of care, treatment of comorbid conditions such as HIV, malnutrition, diabetes, smoking and alcoholism, and palliative care if needed.
- Posttreatment monitoring should be performed at regular intervals (eg, every 6 months) for 1 to 2 years to evaluate for relapse or recurrence.
- DR-TB contacts should be evaluated to exclude TB disease and offered treatment of latent TB infection (LTBI) tailored to the susceptibility pattern of the source-case isolates whenever possible.

For use of rapid molecular diagnostic tests, see Michelle K. Haas and Robert W. Belknap's article, "Diagnostic Tests for Latent Tuberculosis Infection," in this issue. For treatment of HIV, see the article in this issue on treatment of HIV.

## CLASSIFICATION OF DRUGS

In 2018, WHO revised the classification of anti-TB drugs based on a recent IPD-MA analyzing the relative risk of treatment failure or relapse versus treatment success, death versus treatment success, and the SAEs for each individual drug.<sup>5,8,10</sup> This classification (Table 1) is used to devise the longer-treatment WHO regimen (lasting for a total treatment duration of 20 months), because the standardized shorter treatment regimen (lasting 12

months or less) is composed of a fixed regimen of drugs that cannot be substituted unless done in a research mode.<sup>14</sup>

The key recommendations in the new WHO reclassification scheme for anti-TB drugs are as follows:

- Fluoroquinolones (levofloxacin and moxifloxacin), bedaquiline, and linezolid (group A) were considered highly effective and are strongly recommended to be included in an MDR-TB regimen unless contraindicated.
- Clofazimine and either cycloserine or terizidone (group B) are conditionally recommended as second-choice drugs.
- Drugs are in group C ranked by the balance of benefit to harm and can be considered when group A or B drugs are not available to build an adequate multidrug regimen.
- Injectable agents, amikacin and streptomycin, have been downgraded to group C and are not included if an adequate regimen can be built without them. Kanamycin and capreomycin are no longer recommended for use.
- Gatifloxacin and thioacetazone are either not available or not being used, and therefore are not included in the recommendations.
- High-dose isoniazid may have a role when there is confirmed isoniazid susceptibility or when only an inhA mutation is detected in longer MDR regimens and is a standard drug in the shorter MDR regimen.
- Clavulanic acid (only available in the combination amoxicillin-clavulanic acid form [Augmentin]) should only be given with a carbapenem (eg, meropenem) and should not be individually counted as an anti-TB drug.
- There is no recommendation for the use of 4-thioureidoiminomethyl pyridinium perchlorat interferon-gamma, or sutezolid and no evidence that they increase likelihood of cure.
- Bedaquiline can be given to children greater than or equal to 6 years of age.
- Delamanid can be given to children greater than or equal to 3 years of age.
- There is no recommendation for giving bedaquiline and delamanid together.
- Bedaquiline and delamanid should be given for 6 months and, if extended, would be considered off-label use.
- Pyrazinamide should only be counted in the regimen if susceptibility is shown.
- Amikacin and streptomycin should only be used if susceptibility is confirmed (phenotypic conformation for streptomycin) and if high-quality audiology monitoring is available.

These results reflect analyses from 3 IPD-MA cohorts.<sup>14</sup> ATS/CDC/ERS/IDSA guidelines are being developed using data from a single IPD-MA<sup>8</sup> with a patient cohort (overlapping,

but not identical) similar to that of one of the cohorts used in developing the WHO guidelines.<sup>14</sup>

The results of the IPD-MA used in developing the ATS/CDC/ERS/IDSA guidelines differed from that used in developing the WHO treatment guidelines in the following ways:

1. Amikacin and streptomycin showed better effectiveness if susceptibility was confirmed.
2. Treatment outcomes were significantly worse for patients treated with drugs for which there was documented resistance.
3. Fewer data were available on bedaquiline, resulting in a less pronounced effect of bedaquiline on treatment outcome.

In turn, these findings and other differences, such as the availability of rapid molecular testing for the detection of drug resistance, phenotypic DST for additional SLD, and therapeutic drug monitoring, may lead to some differences in recommendations in treatment approaches for low-incidence settings.

## BUILDING A TREATMENT REGIMEN

MDR-TB/XDR-TB should always be treated with a multidrug regimen consisting of drugs to which the patient's isolate is susceptible, excluding all drugs to which the isolate shows resistance. If DST is not available or an empiric DR-TB regimen must be started before DST results are available, the regimen should consist of drugs that are highly likely to be susceptible or effective, based on previous treatment history, pattern of resistance of the presumed source case, potential for cross-resistance with drugs for which DST is available (see Table 9), and patterns of resistance found from national or regional drug-resistance surveys (DRSs) that tend to indicate the local effectiveness of different drugs. In addition, when only rapid molecular testing for rifampin resistance is available (eg, Xpert MTB/RIF assay, Cepheid, Sunnyvale, CA),<sup>16</sup> RR-TB should be treated as if it were MDR-TB.<sup>14</sup> However, in the United States and other low-prevalence countries, false resistance is common with Xpert MTB/RIF assay (low PPV); in such settings, sequencing is recommended to confirm *rpoB* mutation and assess for potential mutations conferring isoniazid resistance to diagnose MDR-TB.

When treated with an inadequate treatment regimen, DR mutant strains of *M tuberculosis* in the bacterial population are favored, leading to treatment failure, relapse, further acquired drug resistance, and potentially death. According to the new 2019 updated WHO DR-TB guidelines, a longer MDR-TB regimen can be used for MDR/RR-TB, lasts for at least 18 months, and can be either standardized or individualized. A shorter MDR-TB regimen can be used for MDR/RR-TB, is largely standardized, and is given for 9 to 12 months (Fig. 1 shows the choice of longer vs shorter regimens).

### Longer Treatment Regimen

According to the new WHO guidelines, a longer treatment regimen (preferably all oral) should be designed using the following principles.

## Recommendations

- Recommendation 1: if an injectable agent is used, the duration of the intensive phase should be 6 to 7 months (Box 2).
- Recommendation 2: a total duration of 18 to 20 months is recommended.
- Recommendation 3: treatment duration of 15 to 17 months after culture conversion is recommended.
- Other recommendations:
  - All 3 group A drugs and at least 1 group B drug should be included for a total of at least 4 drugs given for 6 months until bedaquiline is stopped and a total of at least 3 drugs for the remainder of the treatment duration (Table 2).
  - If 1 or 2 group A drugs cannot be included, the remaining group A drugs, both group B drugs and group C drugs (if needed) should be added (in order of ranking) to achieve at least 4 drugs at start of treatment.
  - If 1 or 2 group A drugs cannot be included and 1 or both group B drugs cannot be included, group C drugs should be added (in order of ranking) to achieve at least 4 drugs at start of treatment.
  - If 2 agents are likely to be stopped before the end of treatment (eg, bedaquiline at 6 months and linezolid because of toxicity), 5 agents may be given at start of treatment to ensure that 3 agents can be given for the duration of treatment.
  - Duration of treatment depends on the drugs used in the regimen and may be decreased or extended depending on the patient's response to treatment.

## Implementation considerations

- When there is additional resistance to simple MDR-TB, a longer regimen may be preferable to a shorter regimen.
- An all-oral regimen should be the preferred choice for most patients.
- Ideally, all drugs used in a regimen should have confirmed susceptibility.
- Ideally, all patients with RR-TB should have DST to isoniazid to exclude non-MDR RR-TB or polydrug-resistant (PDR) TB.
- Ideally, all patients with MDR-TB should have DST to a fluoroquinolone, and, if an injectable is to be used, DST to second-line injectable (SLI) agents.
- Ideally, DST for bedaquiline, delamanid, linezolid, and pyrazinamide should be performed.



- Ideally, patients should have molecular testing for inhA and katG mutations to look for ethionamide/low-dose isoniazid resistance and high-dose isoniazid resistance respectively.
- DST to other SLDs should be obtained where available and quality assured.
- When DST is not available, selection of drugs should be based on DST pattern of presumed source case, treatment history, cross-resistance between drugs, and surveillance data from national or regional DRS.
- Although the GenoType MTBDR<sub>s</sub> (Hain Life-science GmbH, Nehren, Germany) assay, the only rapid commercial test for detection of resistance to the principal SLDs, may correlate well with phenotypic resistance to ofloxacin and levofloxacin, moxifloxacin resistance is best confirmed through phenotypic testing.
- When there is uncertainty about the efficacy of a particular drug, it can be included as part of the regimen, but not included numerically as one of the effective drugs.
- Five drugs rather than 4 may be started with initial treatment if:
  - Two of the 4 drugs are likely to be stopped before completion of treatment.
  - There is a question as to the efficacy of 1 or more drugs because of lack of quality DST and high level of resistance to that drug, or 1 of the drugs in the regimen shows cross-resistance with another drug for which there is known or suspected resistance.
  - The regimen is unlikely to be successful based on a factor such as the extent of resistance.
  - All 3 group A drugs are not used.

### **Clinical strategy to build an individualized treatment regimen**

#### **Principles**

- Build a regimen using greater than or equal to 4 drugs to which the isolate is susceptible (or has low likelihood of resistance), preferably with drugs that have not been used to treat the patient previously.
- Choice of drugs depends on DST, previous treatment history, the pattern of resistance of the presumed source case, patterns of resistance found from national or regional DRS capacity to appropriately monitor for significant adverse effects, patient comorbidities and preferences/values (choices therefore subject to program and patient safety limitations).
- In children with TB disease who are contacts of infectious MDR-TB source cases, the source case's isolate DST result should be used if no isolate is obtained from the child.



- TB expert medical consultation is recommended.

### Shorter Regimen

Per WHO guidelines, if a shorter treatment regimen is implemented, it should be designed using the following principles.

#### Recommendations

- The shorter regimen consists of 4 to 6 months of moxifloxacin, amikacin, ethionamide, clofazimine, high-dose isoniazid, pyrazinamide, and ethambutol (depending on smear conversion at 4 months), followed by 5 months of moxifloxacin, clofazimine, pyrazinamide, and ethambutol.
- The shorter regimen may be considered for patients who desire a shorter duration of treatment despite the use of an injectable agent and who do not have the exclusion criteria noted in Box 3.
- Patients should only be started on the shorter regimen if they have confirmed susceptibility to fluoroquinolones and SLI agents by molecular or phenotypic DST.
- Ideally, patients should have molecular testing for inhA and katG mutations to look for ethionamide/low-dose isoniazid resistance and high-dose isoniazid resistance respectively; if both mutations are present, a longer MDR-TB regimen should be considered.
- Ideally, patients should also have phenotypic DST to pyrazinamide before starting the shorter regimen, but this should not preclude the use of the regimen if needed.

#### Implementation considerations

- Patients eligible for shorter regimens may still opt for a longer regimen if they want to avoid SLI agents on the understanding that they need a much more protracted course of medication.
- Kanamycin should be replaced by amikacin.
- If any drug in the regimen or essential monitoring (especially audiometry) are unavailable, a longer regimen should be used.
- If an all-oral shorter regimen (eg, replacing kanamycin with bedaquiline) is implemented, this should be done in an operational research mode because there are no data on an all-oral shorter regimen.
- If DRS results show high levels of resistance to any drug in the shorter regimen, especially ethionamide, fluoroquinolone, or pyrazinamide, a longer regimen should be considered.
- The shorter regimen should be given by DOT or an information and ICT-based adherence method.<sup>18</sup>

### Rifampin-Resistant Tuberculosis (Isoniazid Susceptible)

In cases with rifampin resistance in which susceptibility to isoniazid is confirmed:

#### Recommendations

- Expert opinion customarily holds that a longer or shorter MDR-TB regimen may be used with the addition of high-dose isoniazid if there is no DST for ethambutol and/or pyrazinamide and if there is a high level of baseline resistance to either drug based on surveillance data.
- If DST to all first-line drugs and fluoroquinolones is available, please refer to Table 3 for a DST-driven treatment regimen.

#### Implementation considerations

- The regimen used for RR-TB depends on the availability to perform molecular or phenotypic DST to the other first-line drugs and fluoroquinolones, and the availability of quality-assured drugs in country.
- Wherever possible, molecular or phenotypic DST should be performed for isoniazid to confirm lack of MDR-TB.

### Isoniazid-Resistant Tuberculosis (Rifampin Susceptible)

In cases with isoniazid-resistant TB in which susceptibility to rifampin is confirmed:

#### Recommendations

- Treatment with rifampin, ethambutol, pyrazinamide, and levofloxacin recommended for a duration of 6 months.<sup>14</sup>
- The 4-drug HREZ fixed-dose combination (FDC) with isoniazid, rifampin, ethambutol, and pyrazinamide may be used (because there is no approved rifampin-ethambutol-pyrazinamide FDC available) to limit the need for using single drugs.
- Drug susceptibility to fluoroquinolones should preferably be confirmed ahead of start of treatment.
- It is generally not recommended to add streptomycin or other injectable agents to the treatment regimen.

#### Implementation considerations

- If isoniazid resistance is confirmed before start of treatment, follow the recommendations outlined earlier.
- If isoniazid resistance is suspected (based on source-case isolate), start isoniazid, rifampin, ethambutol, and pyrazinamide empirically, and add a fluoroquinolone only after RR-TB has been reliably excluded; if isoniazid susceptibility is confirmed, change to standard 4-drug regimen for DS-TB.

- If isoniazid resistance is confirmed after treatment start (either because of unidentified resistance at treatment start or acquired resistance), exclude rifampin resistance immediately through molecular testing and, if rifampin susceptible, change regimen to rifampin, ethambutol, pyrazinamide, and a fluoroquinolone for 6 months; if rifampin resistance is found, start treatment of MDR-TB.
- If isoniazid resistance is diagnosed 4 to 5 months after treatment start, treatment should be based on patient's clinical, bacteriologic, and radiographic response and further DST results.
- Ideally, fluoroquinolone resistance should be excluded before starting this regimen using a line probe assay to detect resistance to SLDs, especially in countries with high levels of fluoroquinolone resistance based on DRS.
- Levofloxacin is the recommended fluoroquinolone based on its safety profile and fewer drug-drug interactions, particularly with antiretrovirals.
- Moxifloxacin should be considered if only levofloxacin or low-level moxifloxacin resistance is confirmed (moxifloxacin less than or equal to 1.0 µg/mL Lowenstein-Jensen; less than or equal to 0.5 µg/mL Middlebrook 7H10/7H11; 0.25 µg/mL BACTEC MGIT).<sup>19</sup>
- A fluoroquinolone should be used unless any of the following are present:
  - Resistance to rifampin cannot be excluded (ie, unknown susceptibility to rifampin; indeterminate/error results on GeneXpert MTB/RIF).
  - Known or suspected resistance to levofloxacin; moxifloxacin may be considered (discussed earlier).
  - Known intolerance to fluoroquinolones.
  - Known or suspected risk for prolonged QT interval, or high risk for or known aortic aneurysm.<sup>20</sup>
  - In pregnancy or during breastfeeding (not an absolute contraindication).
- If a fluoroquinolone cannot be used, isoniazid, rifampin, ethambutol, and pyrazinamide can be given for 6 months.
- The duration of treatment can be extended based on delayed clinical, bacteriologic, and radiographic response.
- The addition of isoniazid is based on FDC use and there are no data on added efficacy; if there are side effects attributed to isoniazid, single drugs (rifampin, ethambutol, pyrazinamide, fluoroquinolone) should be used.
- Streptomycin or other injectable agents can be added to the regimen in certain exceptional circumstances (see Table 3).
- If DST to all first-line drugs and fluoroquinolones is available, please refer to Table 3.

## Polydrug Resistance (Isoniazid Susceptible)

**Recommendations**—For patients with PDR-TB for whom DST to all first-line drugs and fluoroquinolones is available, treatment decisions must be guided largely by expert opinion, rather than through recommendations developed through the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology<sup>21,22</sup> because of the paucity of available data to inform such a process. Table 3 shows adapted and updated recommendations for individualized treatment (primarily based on expert opinion) from the Curry International Tuberculosis Center DR-TB Survival Guide.<sup>17</sup>

### Implementation considerations

- These recommendations are primarily applicable when DST is available for all first-line drugs and fluoroquinolones.
- As with MDR-TB, for RR-TB (isoniazid susceptible) with or without additional resistance, clinicians and patients may prefer an all-oral MDR-TB regimen, incorporating bedaquiline, rather than an injectable-containing regimen.
- In countries or settings where DST to ethambutol and pyrazinamide are not available:
  - Treat RR-TB as if it were MDR-TB, and
  - Treat any isoniazid-resistant TB per WHO guidelines as set out in relation to treatment of isoniazid-resistant TB.

## TREATMENT IN SPECIAL SITUATIONS

### Extrapulmonary Tuberculosis

- The longer MDR-TB regimen may be given in extrapulmonary TB; TB meningitis should be treated with a regimen of drugs that achieve effective drug levels in the central nervous system (CNS) (Table 4) and should be directed by DST.
- In culture-negative extrapulmonary TB or when culture conversion cannot be shown because of inability to obtain a specimen, a total duration of treatment of 18 to 20 months is recommended; if an injectable agent is used, it should be given for 6 to 7 months based on clinical response.
- The shorter regimen should be avoided in patents with disseminated or CNS disease and in persons living with HIV.
- There is no difference in other regimens for other forms of DR-TB specific to extrapulmonary TB.
- Monthly cultures may not be possible in extrapulmonary TB; therefore, monitoring for response to therapy may be based on clinical and/or radiographic response.

## Pregnancy

There is a paucity of data on the treatment of DR-TB in pregnancy. Untreated MDR-TB during pregnancy can be associated with adverse maternal and fetal outcomes.

- The benefits of treatment of DR-TB to mother, child, and the community outweigh the harms.
- An all-oral individualized longer regimen is preferable in order to avoid drugs that may be teratogenic (Table 5).
- The shorter regimen should be avoided in pregnancy.
- Patients on treatment of DR-TB should be counseled to avoid pregnancy and a birth control method should be recommended; oral contraceptives should be avoided as the method for birth control if rifampin is to be used in the regimen, because of drug-drug interactions rendering oral contraceptive pills less effective.

## Children

There is a paucity of data on the treatment of DR-TB in children, so many of the recommendations made for adults have been extrapolated to children.<sup>10</sup>

- The longer oral MDR-TB regimen is recommended in children. Injectable agents are used only when other drugs cannot be used because of resistance or toxicity.
- Injectable agents are avoided whenever possible because of the adverse side effect of hearing loss, painful injections, and because children often have paucibacillary disease.
- Given that children are often culture negative, a total treatment duration of 18 to 20 months should be given with a low threshold to decrease the duration in the case of children with less extensive or severe disease.
- A shorter MDR-TB regimen may be given in children, although avoiding the injectable agent may be factored into the decision between the longer and the shorter regimens.
- Gastric aspirates should be obtained for diagnosis and follow-up in young children who cannot produce sputa.
- Child-friendly formulations should be given whenever possible, and breaking of adult-sized pills should be minimized because the efficacy of drugs may be affected by altering the physical properties of the drug.

## Comorbid Conditions

The treatment of DR-TB in the setting of comorbid conditions such as diabetes mellitus, tobacco use, alcoholism, and drug use is similar to the treatment of DS-TB in these settings except for the need for dose adjustment of SLDs in the case of renal or hepatic insufficiency. An expert in the management of DR-TB should be consulted in these circumstances.

## TREATMENT OF DRUG-RESISTANT TUBERCULOSIS CONTACTS

The treatment of DR-TB contacts seems to have some efficacy in preventing progression to TB disease.<sup>27–29</sup> DR-TB contacts should be evaluated to exclude TB disease and offered treatment of LTBI tailored to the susceptibility pattern of the source-case isolates whenever possible. Table 6 shows the treatment patterns for appropriate drug choices in this setting.<sup>17</sup>

There are currently 3 ongoing randomized controlled trials evaluating the efficacy of treating contacts of persons with MDR-TB/XDR-TB.<sup>30,31</sup> Close contacts to patients with DR-TB may be considered for prophylactic treatment using the principles set out in Box 4:

## MONITORING AND EVALUATION

### Response to Treatment

- Patients being treated for DR-TB should be closely monitored for treatment failure, acquired drug resistance, loss to follow-up, and potential ADRs.
- Patients should be followed at regular intervals clinically, radiographically (if pulmonary disease), and bacteriologically.
- Monthly cultures should be obtained throughout the treatment duration, and, if still positive at 3 to 4 months,<sup>14,32</sup> or reverts to positive after conversion, DST should be obtained right away to exclude acquired resistance.
- When feasible, an end-of-treatment culture should be obtained to show and document treatment cure.
- Patients should be monitored posttreatment completion at regular intervals for 1 to 2 years for relapse.

### Adverse Drug Reaction Monitoring

One of the biggest obstacles to successful completion of treatment and cure is unrecognized/unmanaged or mismanaged ADRs. Early detection and appropriate management of ADRs minimize treatment interruptions, loss to follow-up, and poor treatment outcomes such as treatment failure, relapse, and acquired drug resistance.

- Per WHO, TB programs need to have comprehensive pharmacovigilance programs in place with aDSM to ensure early detection, timely reporting, and appropriate management of ADRs and SAEs, as the standard of care for all patients on any MDR regimen.<sup>33</sup>
- Training and education of field staff is necessary for proper management of ADRs.
- A list of common ADRs and associated TB drugs is provided in Table 7.
- Routine monitoring for ADRs and SAEs should be performed while patient is on treatment (see Table 7; Table 8).

- Note that intolerance to 1 drug in a drug class does not automatically imply intolerance to all drugs in the drug class (eg, rifabutin may be tolerated when rifampin is not).

## ADDITIONAL CONSIDERATIONS

### Selection of Drugs

The following principles apply when building a DR-TB treatment regimen:

- Cross-resistance: avoid using drugs that have known cross-resistance to other drugs to which the isolate shows resistance (eg, isoniazid and ethionamide) (Table 9).
- Avoid previously used drugs (based on history): avoid using drugs that the patient has taken for greater than or equal to 1 month previously unless DST shows the drug organism to be fully susceptible to the drug.
- Consider side effects: chose drugs that will not potentiate or worsen underlying illnesses or symptoms (eg, cycloserine if the patient has underlying mental illness).
- Drug-drug interactions: avoid drugs that have known interactions with other drugs that the patient is taking (eg, bedaquiline and efavirenz).

### Administration of Medications

Adherence to the complete DR-TB treatment regimen for the full duration is crucial for relapse free cure. Minimizing treatment interruptions caused by ADRs/SAEs and loss to follow-up requires patient education, good case management, active pharmacovigilance, adherence strategies, and a patient-centered approach to care.

- Dose escalation: one of the measures that may minimize side effects such as nausea and vomiting is the dose escalation method when beginning DR-TB drugs such as ethionamide, *para*-aminosalicylic acid, and cycloserine (Fig. 2). Escalating the dose of drugs over a week allows the patient to get used to the drug and mitigate side effects.
- Adherence measures/patient-centered approach: a patient-centered approach considers the values and preferences of the patient during treatment. It is the approach that is likely to result in the most humane and effective treatment strategy to ensure cure and other good outcomes.<sup>13</sup>
  - Ideally medication should be given once daily via DOT.
  - Twice-daily dosing is generally discouraged because of the challenge posed for full adherence.
- Intermittent dosing is not advised except in the case of an injectable agent that can be decreased in frequency of dosing to twice or thrice weekly after sputum culture conversion has occurred, generally after 2 to 3 months of therapy, to minimize the potential for toxicity.



- Intermittent dosing may be required with clofazimine in children (see online Table).<sup>35</sup>
- Palliative care: when there is no treatment option available because of extensive resistance and disease, the patient must receive palliative measures such as pain management and management of dyspnea to provide the most humane care possible. It is also necessary to follow infection control practices to minimize transmission of DR-TB to family members and the community.

## THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring (TDM), or the measurement of serum levels of drugs, can be an important test to check for treatment adherence (confirming ingestion of TB drugs), for adequate dosing of TB drugs, and to maximize efficacy and minimize toxicity of TB drugs.<sup>36</sup>

- A quality-assured laboratory is required for TDM.
- A pharmacology specialist is required for performing TDM and interpreting the results.
- TDM may be helpful in the following situations:
  - For dosage of toxic drugs like amikacin, linezolid, cycloserine.
  - In renal insufficiency, diabetes mellitus, HIV infection, and other comorbid conditions that may affect the absorption or excretion of drugs.
  - For patients with evidence of treatment failure or relapse while on an appropriate treatment regimen.
  - When patients have few effective drugs in the treatment regimen based on DST results.
  - When drug-drug interactions are likely.

## SURGERY

Patients with extensive resistance, extensive disease, or localized disease may benefit from surgical resection in addition to treatment<sup>37</sup> with a DR-TB treatment regimen, especially when there is a high risk of relapse or treatment failure with chemotherapy alone.

- Patients should have preoperative evaluation to determine that they are good surgical candidates, to ensure that they will have adequate lung capacity after surgery, and to ensure that they are not at risk for pulmonary hypertension after surgery.
- Lobectomy or wedge resection is the procedure of choice.
- Surgery should be performed by a surgeon with expertise in TB surgery.

- Proper infection control mechanisms should be in place during surgery (ultraviolet light, personal protective equipment).
- An appropriate treatment regimen should be given in conjunction with surgery, because surgery alone is not curative.

## DRUG DOSAGES

In the recent updated WHO DR-TB guidelines, adult and pediatric drug dosages have been revised. The revised dosages may be found in online Table.<sup>35</sup>

## WORLD HEALTH ORGANIZATION TREATMENT OUTCOMES

A recent publication from the Global TB Network<sup>38</sup> suggests several proposed revisions to the current WHO definitions of TB treatment outcomes to address some of the recent changes in treatment regimens (eg, all-oral regimens) and evolution in programmatic definitions for treatment outcomes. Table 10 highlights current WHO treatment outcome definitions.<sup>14</sup>

## RESEARCH PRIORITIES

Like numerous other pathogens, *M tuberculosis* complex has a remarkable ability to evolve and adapt to the presence of antimicrobials, developing virulence or resistance to commonly used drugs and rendering them ineffective. From programmatic and clinical perspectives, there are several areas in which research will continue to be needed for addressing drug resistance of TB. From a programmatic perspective, it is important that strategies are developed to improve appropriate antimicrobial use and ways of achieving adherence. From a clinical perspective, it is important that clinical trials are conducted to validate use of existing and new drugs and regimens and improve on the methods for conducting surveillance and monitoring of drug resistance. Over the past decade, the products of several comprehensive efforts to identify research priorities for TB have been published.<sup>39–41</sup> These areas of research include:

- Randomized controlled trials, including new drugs and shorter all-oral regimens.
- Studies to include children, pregnant women, extrapulmonary disease, persons living with HIV, patients with other comorbid conditions.
- Pharmacokinetic studies to determine optimal dosing and safety of drugs.
- Documentation of ADRs and SAEs through programmatic pharmacovigilance.
- Shorter MDR-TB regimens and their use in subgroups such as children, pregnant women, and patients with extrapulmonary disease.
- Optimal duration of the longer MDR-TB regimen.
- Predictors and biomarkers of treatment failure and relapse.
- Studies on optimal methods to achieve patient adherence.
- Optimal duration of posttreatment monitoring for relapse.

- Optimal regimen and duration of treatment of MDR-TB contacts.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## APPENDIX 1:: RESOURCES FOR THE MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS

1. Four regionally assigned CDC-supported TB Centers of Excellence (COEs), formerly known as Regional Training and Medical Consultation Centers. The TB COEs support domestic TB prevention and control efforts by increasing knowledge, skills, and abilities through communication, education, and training activities, and by improving evidence-based TB clinical practices and patient care through the provision of expert medical consultation (<https://npin.cdc.gov/featured-partner/tb-regional-training-and-medical-consultation-centers-rtmccs><https://sntc.medicine.ufl.edu/rtmccproducts.aspx>).
  - a. Curry International Tuberculosis Center, part of the University of California at San Francisco (<https://www.currytbcenter.ucsf.edu/>)
  - b. Global Tuberculosis Institute at Rutgers, the State University of New Jersey (<http://globaltb.njms.rutgers.edu/>)
  - c. Heartland National Tuberculosis Center in San Antonio, part of the University of Texas Health Science Center at Tyler (<https://www.heartlandntbc.org/>)
  - d. Southeastern National Tuberculosis Center at the University of Florida in Gainesville, Florida (<https://sntc.medicine.ufl.edu/home/index#/>)
2. Curry International Tuberculosis Center Drug-Resistant TB Survival Guide <https://www.currytbcenter.ucsf.edu/products/view/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition>
3. European Respiratory Society Consultation service (<http://www.waidid.org/site/clinicalIntro>)
4. CA State MDR-TB Consultation Service (<https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/TBCB-MDR-Fact-Sheet.pdf>)

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**Box 1****Drug-resistant tuberculosis definitions**

- Monodrug-resistant TB: TB caused by organisms that show resistance to a single anti-TB drug (eg, isoniazid, rifampin, ethambutol, or pyrazinamide).
- Isoniazid-resistant TB: TB caused by organisms that show resistance to isoniazid (rifampin susceptible).
- Rifampin-resistant TB (RR-TB): TB caused by organisms that show resistance to rifampin, but may be susceptible to isoniazid, or resistant to isoniazid (ie, MDR-TB), or resistant to other first-line TB medicines (polydrug resistant) or second-line TB medicines (eg, 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 rifampin.
- MDR-TB: TB caused by organisms that show resistance to at least isoniazid and rifampin.
- Preextensively drug-resistant TB (pre-XDR-TB): TB caused by organisms that show multidrug resistance, and resistance to any fluoroquinolone or a second-line injectable (SLI) agent (ie, amikacin, kanamycin, or capreomycin).
- Extensively DR TB (XDR-TB): TB caused by organisms that show multidrug resistance, and resistance to any fluoroquinolone and at least 1 of the SLI agents.
- Primary or newly diagnosed DR-TB: DR-TB in a person who has previously received no or less than 1 month of anti-TB treatment (ATT).
- Acquired or previously treated DR-TB: TB in a person who has previously received at least 1 month of ATT.



**Box 2****Duration of treatment of longer multidrug-resistant tuberculosis regimen  
(refer to recommendations 1–3, given earlier, in building a treatment  
regimen)**

- When an injectable agent<sup>a</sup> is used, all 3 recommendations apply for duration of treatment.
- When an all-oral regimen is used, recommendations 2 and 3 apply for duration of treatment.
- With extrapulmonary disease, only recommendation 3 applies for the duration of treatment.
- Changes to the recommended duration of treatment should be tailored to the patient's bacteriologic, clinical, and radiographic response.

<sup>a</sup> Injectable agent here does not refer to meropenem and imipenem-cilastatin; this term is used to refer to amikacin or streptomycin (kanamycin and capreomycin are no longer recommended).

**Box 3****Exclusion criteria for the shorter regimen**

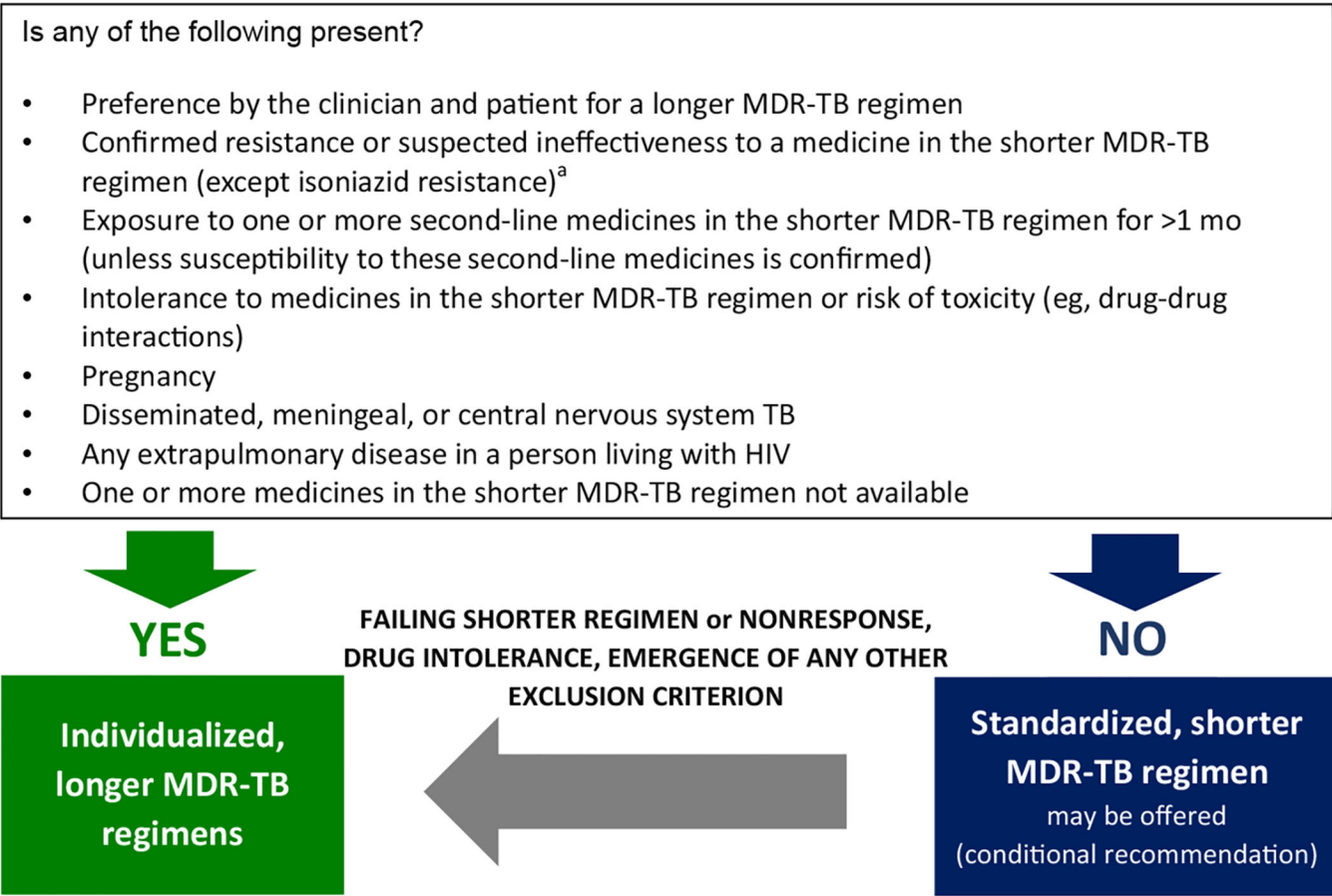
- Resistance to or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance)
- Exposure to 1 or more second-line medicines in the regimen for greater than 1 month (unless susceptibility to these second-line medicines is confirmed)
- Intolerance to any medicine in the shorter MDR-TB regimen or risk of toxicity from a medicine in the shorter regimen (eg, drug-drug interactions)
- Pregnancy
- Disseminated, meningeal, or central nervous system TB
- Any extrapulmonary disease in patients with HIV

**Box 4****Principles for the treatment of drug-resistant tuberculosis contacts**

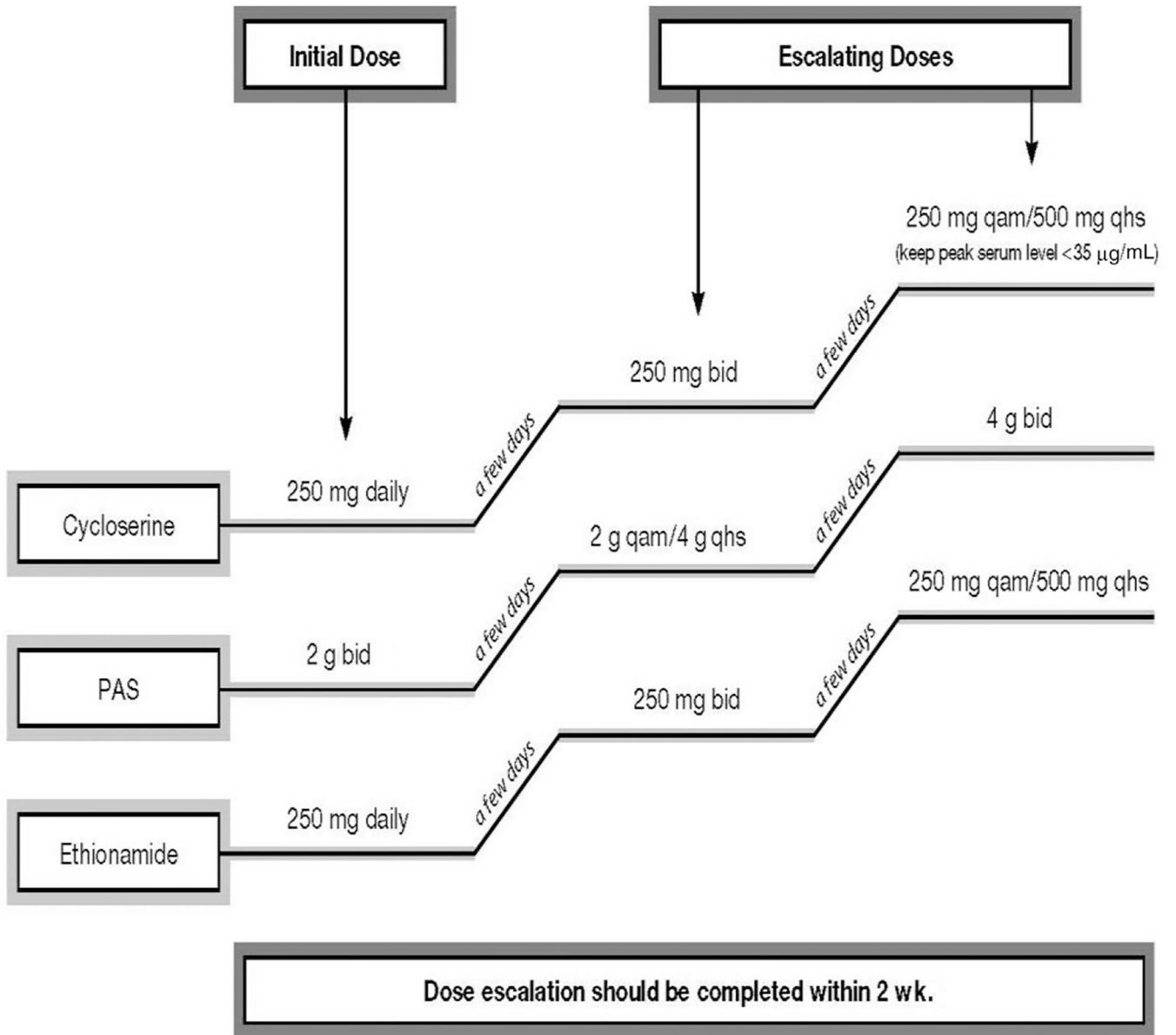
- Contacts to DR-TB should have a positive test for LTBI and have TB disease excluded before receiving treatment of presumed MDR LTBI.
- Treatment with 1 to 2 drugs to which the presumed source-case isolate shows susceptibility may be given for a period of 6 to 12 months (see Table 6).
- For isoniazid-resistant or PDR-TB (rifampin susceptible), rifampin may be given for a period of 4 months.
- For RR-TB or PDR-TB (isoniazid susceptible), isoniazid may be given for 6 to 9 months.
- For MDR-TB, 6 to 12 months of treatment can be given with a fluoroquinolone alone or with a second drug, based on source-case isolate DST.
- When 2 drugs are used, based on evidence of increased toxicity, ADR, and discontinuations, expert opinion is that pyrazinamide should not be routinely used as the second drug.
- In lieu of fluoroquinolone-based treatment, there are few data for the use of other second-line medications and, because of toxicity, they are not recommended by experts.
- For contacts to fluoroquinolone-resistant, pre-XDR-TB, pyrazinamide and ethambutol may be an effective option, if source-case isolate DST shows susceptibility to these drugs.
- For contacts to fluoroquinolone-resistant, pre-XDR-TB with resistance to all first-line drugs, consider ethionamide/p-aminosalicylic acid or the newer drugs bedaquiline or delamanid. Studies are underway with delamanid.
- In children, TB drugs are generally better tolerated, and levofloxacin is preferred because of the availability of an oral suspension formulation.

**KEY POINTS**

- A patient-centered approach with case management strategies should be used in the care of drug-resistant (DR) tuberculosis (TB) with attention to patient preferences; social, cultural, and environmental aspects of care; comorbid conditions, adherence strategies, patient monitoring for clinical response and safety, and the need for palliative care.
- There are 2 World Health Organization–recommended treatment options for multidrug-resistant (MDR) or extensively DR (XDR) TB that can be decided on based on extent of resistance, availability of drug susceptibility testing (DST) results, and patient preference:
  - a. If the clinician and patient opt for an individualized, longer treatment regimen, MDR-TB/XDR-TB should be treated with at least 4 drugs for the first 6 months, followed by 3 drugs for a total duration of 18 to 20 months depending on extent and severity of disease; drug history; and clinical, bacteriologic, and radiographic response.
  - b. If none of the exclusion criteria for the standardized shorter regimen are met and the clinician and patient opt for this regimen, MDR-TB/XDR-TB should be treated for 9 to 12 months with the standardized medications and duration of treatment specified in the shorter regimen.
- The choice of drugs for the treatment of DR-TB should be guided by known effectiveness of given drugs, propensity for adverse drug reactions/drug-drug interactions, and DST, excluding all drugs to which the isolate shows resistance. If DST is only partially available or not available, or if an empiric DR-TB regimen must be started before DST results are available, the regimen should consist of drugs that are highly likely to be susceptible, based on previous treatment history, pattern of resistance of the presumed source case, and patterns of resistance found from national or regional drug-resistance surveys.
- An all-oral treatment regimen including new and repurposed drugs is the preferable strategy for most patients; injectable agents should be avoided whenever possible, especially in children.
- Expert consultation from a recognized DR-TB expert should be sought whenever possible in the treatment of patients with MDR-TB/XDR-TB or patients in whom issues of drug resistance or drug intolerance may complicate care.



**Fig. 1.** Criteria to decide when the shorter MDR-TB regimen may be offered.<sup>14 a</sup> Strains from patients with MDR-TB/RR-TB should ideally be tested for resistance to fluoroquinolones and other regimen components regardless of the type of MDR-TB treatment regimen offered. (From the WHO treatment guidelines for DR-TB: 2019 update. <https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/>.)



**Fig. 2.** Dose escalation. The patient is begun on a low starting dose and the dose is increased every few days until the targeted dose is reached. The dose escalation should be completed within 2 weeks. Some patients will tolerate consolidation of cycloserine to once-daily dosing, which can enhance adherence. bid, twice daily; PAS, *para*-aminosalicylic acid; qam, every morning; qhs, at hour of sleep. (From the Curry International TB Center DR TB survival guide.<sup>17</sup> [http://www.currytbcenter.ucsf.edu/products/view/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition.](http://www.currytbcenter.ucsf.edu/products/view/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition))

**Table 1**  
Grouping of medicines recommended for use in longer multidrug-resistant tuberculosis regimens

Groups and Steps	Medicine	Acronym
Group A: include all 3 medicines	Levofloxacin, or	Lfx
	Moxifloxacin	Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
	Clofazimine	Cfz
Group B: add 1 or both medicines	Cycloserine, or	Cs
	Terizidone	Trd
	Ethambutol	E
Group C: add to complete the regimen and when medicines from groups A and B cannot be used	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem-cilastatin, or	Imp-Cln
	Meropenem	Mpm
	Amikacin, or	Am
	Streptomycin	S
	Ethionamide, or	Eto
	Prothionamide	Pto
	<i>para</i> -Aminosalicylic acid	PAS

From the WHO treatment guidelines for DR-TB: 2019 update. <https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/>.



Stepwise algorithm for building a multidrug-resistant/extensively drug-resistant tuberculosis treatment regimen

Table 2

Step 1: choose all 3 group A drugs (if possible)	Levofloxacin/moxifloxacin, bedaquiline, linezolid
Step 2: choose both of these prioritized drugs	Clofazimine Cycloserine/terizidone
Step 3: if a regimen cannot be assembled with 4 effective oral drugs, and the isolate is likely susceptible, add group C drugs in the order of ranking until a regimen with 4 drugs can be constructed	Ethambutol Delamanid Pyrazinamide Imipenem/cilastatin or meropenem/clavulanate Amikacin (or streptomycin) Ethionamide or prothionamide <i>para</i> -aminosalicylic acid
Step 4: if needed, and the isolate is susceptible, may use the following drug	High-dose isoniazid
The following drugs are no longer recommended for inclusion in DR-TB regimens	Capreomycin and kanamycin Amoxicillin/clavulanate (when used without a carbapenem) Azithromycin and clarithromycin Azithromycin and clarithromycin
The following drugs have no data for or against use	Perchlorone, interferon-gamma, or sutezolid

Adapted and updated from the Curry International Tuberculosis Center DR-TB Survival Guide. <sup>17</sup> <http://www.currytbcenter.ucsf.edu/products/view/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition>.

**Table 3** Treatment regimens for the management of mono-resistant and poly-resistant tuberculosis pattern of drug resistance

Pattern of Drug Resistance	Suggested Regimen	Minimum Duration of Treatment (mo)	Comments
Isoniazid (±reptomycin)	Rifampin, pyrazinamide, ethambutol, and fluoroquinolone	6–9	Levofloxacin or moxifloxacin may be used. Consider high-dose isoniazid if inhA mutation
Isoniazid and ethambutol	Rifampin, pyrazinamide, and fluoroquinolone	6–9	A longer duration of treatment should be used for patients with extensive disease. Consider high-dose isoniazid if inhA mutation
Isoniazid and pyrazinamide	Rifampin, ethambutol, and fluoroquinolone	9–12	A longer duration of treatment should be used for patients with extensive disease. Consider high-dose isoniazid if inhA mutation
Isoniazid, ethambutol, pyrazinamide (±streptomycin)	Rifampin, fluoroquinolone, plus 1–2 oral second-line agents (linezolid, cycloserine)	9–12	A longer duration of treatment should be used for patients with extensive disease. An injectable may strengthen the regimen for patients with extensive disease
Rifampin	Isoniazid, ethambutol, fluoroquinolone, plus at least 2 mo of pyrazinamide Or a fully oral MDR-TB regimen per WHO guidelines (see text)	12–18	A longer duration of treatment should be used for patients with extensive disease. An injectable drug may strengthen the regimen for patients with extensive disease. For additional options, see text
Rifampin and ethambutol (±streptomycin)	Isoniazid, pyrazinamide, fluoroquinolone, plus an injectable agent for at least the first 2–3 mo Or a fully oral MDR-TB regimen per WHO guidelines	18	A longer course (6 mo) of the injectable may strengthen the regimen for patients with extensive disease
Rifampin and pyrazinamide (±streptomycin)	Isoniazid, ethambutol, fluoroquinolone, plus an injectable agent for at least the first 2–3 mo Or a fully oral MDR-TB regimen per WHO guidelines	18	A longer course (6 mo) of the injectable may strengthen the regimen for patients with extensive disease
Pyrazinamide	Isoniazid, rifampin	9	Most commonly seen in <i>Mycobacterium bovis</i> infections

Adapted and updated from the Curry International Tuberculosis Center DR-TB Survival Guide.<sup>17</sup> <http://www.currytbcenter.ucsf.edu/products/view/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition>.

**Table 4**  
Central nervous system (blood-brain barrier) penetration of antituberculosis drugs<sup>23–25</sup>

Drug	CNS Penetration	Notes
Fluoroquinolones (moxifloxacin, levofloxacin)	Good	—
Ethionamide/prothionamide	Good	—
Cycloserine/terizidone	Good	—
Clofazimine	No data	—
Imipenem/cilastatin Meropenem	Poor	Imipenem/cilastatin more likely to cause seizures in children than meropenem
Linezolid	Good	—
High-dose isoniazid	Moderate	Need high dose to be 15–18 mg/kg
Pyrazinamide	Moderate	—
<i>para</i> -Aminosalicylic acid	Negligible	Use is not advised
Ethambutol	Negligible	Use is not advised
Amikacin/streptomycin	Negligible	Only in the presence of meningeal inflammation; in general, use is not advised
Bedaquiline	No data	—
Delamanid	No data	—

Table 5

Teratogenicity of antituberculosis drugs<sup>26</sup>

Drug	FDA Category/Teratogenicity	Notes
Isoniazid	C/Safe	—
Rifampin	Safe	—
Fluoroquinolones (levofloxacin, moxifloxacin)	Possible	Arthropathy in puppy models, but wide use in humans shows no negative effect
Ethionamide/prothionamide	Possible	Associated with congenital defects
Clofazimine	No data	—
Cycloserine/terizidone	Unlikely	Animal models show no toxicity
Imipenem-clastatin Meropenem	No data	—
Linezolid	Possible	High dose has shown toxicity in animal models
High-dose isoniazid	No data	—
Pyrazinamide	No data	—
<i>para</i> -Aminosalicylic acid	Unlikely	Animal models show no toxicity
Ethambutol	Safe	—
Amikacin/streptomycin	Documented	Eighth nerve toxicity
Bedaquiline	No data	—
Delamanid	No data	—

Abbreviation: FDA, US Food and Drug Administration.

Adapted from Table 1 in Gupta A, et al. Toward earlier inclusion of pregnant and postpartum women in tuberculosis drug trials: Consensus statements from an international expert panel. *Clinical Infectious Diseases* 2016;62:762–769.

Treatment of latent tuberculosis infection in contacts of patients with drug-resistant tuberculosis, according to susceptibility pattern of the source-case isolates

**Table 6**

<b>Resistance Pattern</b>	<b>LTBI Treatment Options</b>
Isoniazid (rifampin susceptible)	Rifampin 4 mo (adults and children)
Isoniazid, rifampin, ethambutol	Fluoroquinolone, fluoroquinolone + ethambutol
Isoniazid and rifampin, pyrazinamide	Fluoroquinolone, fluoroquinolone + ethionamide
Isoniazid and rifampin, ethambutol, pyrazinamide	Fluoroquinolone, fluoroquinolone + ethambutol
Isoniazid and rifampin, ethambutol, pyrazinamide, ± injectable	Fluoroquinolone, fluoroquinolone + ethionamide
Isoniazid and rifampin, ethambutol, pyrazinamide, injectable, ethionamide	Fluoroquinolone, fluoroquinolone + cycloserine
Isoniazid and rifampin, ethambutol, pyrazinamide, fluoroquinolone	No treatment, clinical monitoring (in select cases, cycloserine + <i>para</i> -aminosalicylic acid, <i>para</i> -aminosalicylic acid + ethionamide, or ethionamide + cycloserine may be considered)

From Curry International Tuberculosis Center DR-TB Survival Guide. 17 <http://www.currytbcenter.ucsf.edu/products/view/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition>.

**Table 7**

Common adverse drug reactions (ADRs) and associated antituberculosis drugs

ADR	Drug	Management <sup>b</sup>
Nausea/vomiting/gastritis	Ethionamide/prothionamide, linezolid, <i>para</i> -aminosalicylic acid, pyrazinamide, fluoroquinolones, bedaquiline, clofazimine, delamanid, imipenem-cilastatin, meropenem	Antiemetics; drug ramping; twice-daily dosing
Hepatotoxicity	Isoniazid, rifampin, ethionamide/prothionamide, bedaquiline, moxifloxacin, <i>para</i> -aminosalicylic acid	See DR-TB survival guide <sup>17</sup> . Stop drugs when liver function tests of normal or >3× upper limit of normal if symptoms present
Diarrhea	<i>para</i> -Aminosalicylic acid, linezolid	Antidiarrheals; drug ramping
CNS side effects	Cycloserine, terizidone, ethionamide/prothionamide, high-dose moxifloxacin	Pyridoxine; psychiatric evaluation
Peripheral neuropathy	Linezolid, isoniazid	Pyridoxine
Bone marrow suppression	Rifampin, linezolid, high-dose isoniazid	Granulocyte-macrophage colony-stimulating factor; erythropoietin
Electrolyte imbalance	Amikacin, streptomycin	Electrolyte replenishment
Renal toxicity	Amikacin, streptomycin	Drug holiday <sup>a</sup>
Eighth nerve toxicity	Amikacin, streptomycin	Drug holiday <sup>a</sup>
Visual toxicity	Ethambutol, linezolid, ethionamide (rare), rifabutin (uveitis)	Stop drug
Rash	Any drug	Topical steroid; oral antihistamine; hospitalization if severe with involvement of mucous membranes (Stevens-Johnson syndrome)
Skin discoloration	Clofazimine	Reversible
Hypothyroidism	<i>para</i> -Aminosalicylic acid, ethionamide/prothionamide	Reversible
Cardiac (QT-interval prolongation)	Bedaquiline, delamanid, fluoroquinolones, clofazimine	Depends on extent of prolongation
Arthralgias/myalgias	Pyrazinamide, bedaquiline fluoroquinolones	Exclude gout, symptomatic management
Tendon rupture/aortic aneurysm rupture	Fluoroquinolones	Stop drug

<sup>a</sup>Stopping the offending drug for a short while (<1 week) to evaluate for resolution or improvement of ADR, with low threshold to withdraw offending drug if ADR recurs.

<sup>b</sup>For detailed management of ADRs, see Curry International Tuberculosis Center DR-TB Survival Guide. <sup>17</sup> (<http://www.currytbcenter.ucsf.edu/products/view/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition>).

**Table 8**

Monitoring schedule for common adverse drug reactions

<b>Test</b>	<b>Frequency</b>	<b>Drug</b>
Complete blood count	Baseline and monthly	Rifampin, linezolid
Electrolytes, blood urea nitrogen, creatinine	Baseline and monthly	Amikacin, streptomycin
Liver function tests	Baseline and monthly	Isoniazid, rifampin, pyrazinamide, ethionamide/prothionamide, <i>para</i> -aminosalicylic acid, moxifloxacin, bedaquiline
Audiogram	Baseline and monthly	Amikacin, streptomycin
Electrocardiogram	Daily for 2 wk, then monthly	Bedaquiline, delamanid, linezolid, combinations of QT interval-prolonging drugs
Mini mental status examination	Weekly	Cycloserine, terizidone
Neuroexamination	Weekly	Isoniazid, linezolid
Eye examination	Monthly	Ethambutol, linezolid
Skin examination	Monthly	Clofazimine
Thyroid-stimulating hormone	Monthly	<i>para</i> -Aminosalicylic acid, ethionamide



**Table 9**

Cross-resistance between recommended antituberculosis drugs

<b>Drug</b>	<b>Cross-Resistance</b>	<b>Comments</b>
Isoniazid	Ethionamide	Cross-resistance to ethionamide is common (up to 70%) when there is low-level resistance to isoniazid caused by a mutation in inhA promoter region
Rifampin	Rifamycins	Cross-resistance among the rifamycin class of drugs is typical
Ethambutol	None	—
Pyrazinamide	None	—
Cycloserine	Terizidone	—
<i>para</i> -Aminosalicylic acid	None	—
Ethionamide	Isoniazid	Low-level cross-resistance to isoniazid may occur because of mutation in inhA promoter region
Clofazimine	Bedaquiline	Cross-resistance has been shown in both directions through efflux-based resistance
Linezolid	None	—
Bedaquiline	Clofazimine	Cross-resistance has been shown in both directions through efflux-based resistance
Delamanid	None	—
Fluoroquinolones	Other fluoroquinolones	Data suggest that moxifloxacin may continue to show some activity despite resistance to ofloxacin or levofloxacin <sup>34</sup>

From the Curry International TB Center DR TB survival guide.<sup>17</sup> <http://www.currytbcenter.ucsf.edu/products/view/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition>.

**Table 10**

Outcomes for patients with rifampin-resistant/multidrug-resistant/extensively drug-resistant tuberculosis treated using second-line treatment

Treatment Outcome	Current WHO Definition
Cured	Treatment completed as recommended by the national policy without evidence of failure, and 3 or more consecutive cultures taken at least 30 d apart are negative after the intensive phase <sup>a</sup>
Completed	Treatment completed as recommended by the national policy without evidence of failure, but no record that 3 or more consecutive cultures taken at least 30 d apart are negative after the intensive phase <sup>a</sup>
Treatment failure (RR-TB/MDR-TB/XDR-TB)	<p>Treatment terminated or need for permanent regimen change of at least 2 anti-TB drugs because of:</p> <ul style="list-style-type: none"> <li>• Lack of conversion<sup>b</sup> by the end of the intensive phase<sup>a</sup>, or</li> <li>• Bacteriologic reversion<sup>b</sup> in the continuation phase after conversion<sup>b</sup> to negative, or</li> <li>• Evidence of additional acquired resistance to fluoroquinolones or SLI drugs, or</li> <li>• ADRs</li> </ul>
Died	A patient who dies for any reason during the course of treatment
Lost to follow-up	A patient whose treatment was interrupted for 2 consecutive months or more
Not evaluated	A patient for whom no treatment outcome is assigned (this includes cases transferred out to another treatment unit and whose treatment outcome is unknown)
Treatment success	The sum of cured and treatment completed

<sup>a</sup>For treatment failed, lack of conversion by the end of the intensive phase implies that the patient does not convert within the maximum duration of intensive phase applied by the program. If no maximum duration is defined, an 8-month cutoff is proposed. For regimens without a clear distinction between intensive and continuation phases, a cutoff 8 months after the start of treatment is suggested to determine when the criteria for cured, treatment completed, and treatment failed start to apply.

<sup>b</sup>The terms conversion and reversion of culture as used here are defined as follows. Conversion (to negative) means that culture is considered to have converted to negative when 2 consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion. Reversion (to positive) means that culture is considered to have reverted to positive when, after an initial conversion, 2 consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining treatment failed, reversion is considered only when it occurs in the continuation phase.

From the WHO Definitions and Reporting Framework for Tuberculosis, 2013 revision. <https://www.who.int/tb/publications/definitions/en/>.