

## CHAPTER 7

# Treatment strategies for MDR-TB

### 7.1 Chapter objectives

Any patient in whom chronic TB or drug-resistant TB is diagnosed requiring treatment with second-line drugs falls under WHO diagnostic Category IV and will need specialized regimens (termed “Category IV regimens” in these guidelines). This chapter provides guidance on the strategy options, including standardized, empirical and individualized approaches, to treat MDR-TB. For a description of drugs, doses and coding of treatment regimens used in these guidelines, see Annexes 1, 2 and 5.

### 7.2 Essential assessments before designing a treatment strategy

Ideally, programmes should design a treatment strategy when both the drug resistance survey data and the availability and use of antituberculosis drugs in the country have been assessed. Programmes that plan to introduce a treatment strategy for drug-resistant TB should be familiar with the prevalence of drug resistance in new patients as well as in different groups of re-treatment cases (failure, relapse, return after default and other cases). It is essential to determine which second-line drugs have been used and the frequency of use in the area served by the DR-TB control programme. Some second-line drugs may have been used only rarely and are likely to be effective in treatment regimens for drug-resistant TB, while others may have been used extensively and are therefore more likely to be ineffective in patients with resistant strains.

### 7.3 Different programme treatment strategies

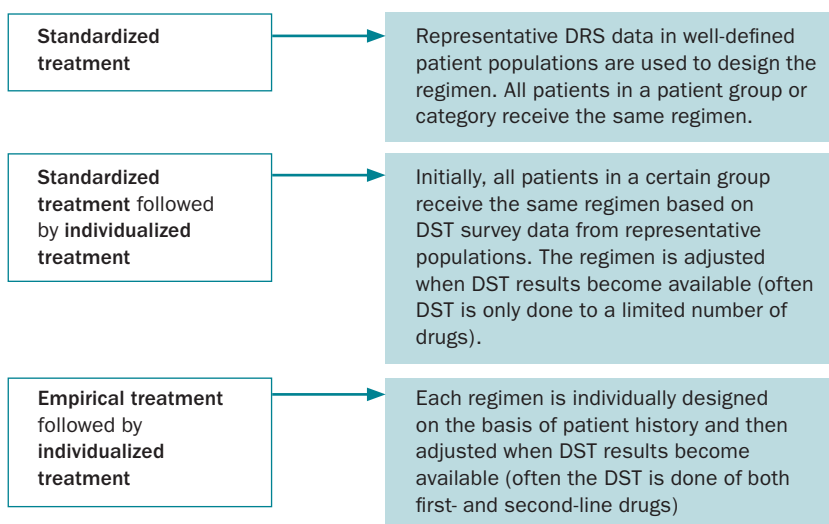
Programmes have different options for treatment strategies. The following are definitions of terms that are often used to describe treatment strategies:

- **Standardized treatment.** Regimens are designed on the basis of representative DRS data of specific treatment categories. However, suspected MDR-TB should always be confirmed by DST results whenever possible. All patients in a defined group or category receive the same treatment regimen (see section 7.7.2 for further details).

- **Empirical treatment.** Each regimen is individually designed on the basis of the previous history of antituberculosis treatment and with the help of representative DRS survey data. Commonly, an empirical treatment is adjusted in each patient when his or her DST results become available (see section 7.7.3 for further details).
- **Individualized treatment.** Each regimen is designed on the basis of previous history of antituberculosis treatment and individual DST results (see section 7.7.3 for further details).

These guidelines recommend using treatment strategies illustrated by Figure 7.1.

**Figure 7.1 Recommended treatment strategies for MDR-TB**



## 7.4 Selecting treatment strategies

Treatment strategies involving standardized Category IV regimens offer several advantages. Standardized regimens are based on representative DRS from patient categories or groups. If DST is not available in the country, a supranational TB reference laboratory can perform it to obtain representative patterns. Standardized regimens may enable more patients to access care, while maintaining cure rates comparable to those obtained with individualized treatment strategies. Other advantages include:

- simpler operational aspects of implementation,
- simpler drug ordering,
- easier training,
- less likelihood of mismanagement,
- less dependence on highly technical laboratories.

Individualized treatment strategies require a high degree of laboratory capacity necessary to perform DST of second-line drugs. One advantage of individualized regimens is that they avoid placing patients on toxic and expensive drugs to which the strain is resistant. Individualized regimens have advantages in settings with high rates of resistance to second-line drugs where it may be difficult to find a standardized regimen that is appropriate for all patients.

A strategy using a combination of standardized and individualized treatment will often be used, as mentioned above. For example, a programme may choose to do DST of H, R, E and S only and place any patients with documented resistance on different standardized regimens based on the pattern of resistance found. Here, the programme is using individualized DST but then applying a set number of standardized regimens. This is the most frequently used strategy in settings where second-line drugs have not been widely used.

## 7.5 Classes of antituberculosis drugs

The classes of antituberculosis drugs have traditionally been divided into first- and second-line drugs, with isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin being the primary first-line drugs. These guidelines often refer to this classification but also use a group system based on efficacy, experience of use and drug class. These groups are referred to in the following sections and are very useful for the design of treatment regimens. The different groups are shown in Table 7.1. For more information on individual drugs, see Annexes 1, 2 and 5.

TABLE 7.1 **Alternative method of grouping antituberculosis drugs**

GROUPING	DRUGS (ABBREVIATION)
<b>Group 1</b> – First-line oral antituberculosis agents	Isoniazid (H); Rifampicin (R); Ethambutol (E); Pyrazinamide (Z)
<b>Group 2</b> – Injectable antituberculosis agents	Streptomycin (S); Kanamycin (Km); Amikacin (Am); Capreomycin (Cm); Viomycin (Vi)
<b>Group 3</b> Fluoroquinolones	Ciprofloxacin (Cfx); Ofloxacin (Ofx); Levofloxacin (Lfx); Moxifloxacin (Mfx); <sup>a</sup> Gatifloxacin (Gfx) <sup>a</sup>
<b>Group 4</b> – Oral bacteriostatic second-line antituberculosis agents	Ethionamide (Eto); Protionamide (Pto); Cycloserine (Cs); Terizidone (Trd) <sup>a</sup> ; <i>P</i> -aminosalicylic acid (PAS); Thioacetazone (Th) <sup>b</sup>
<b>Group 5</b> – Antituberculosis agents with unclear efficacy (not recommended by WHO for routine use in MDR-TB patients)	Clofazimine (Cfz); Amoxicillin/Clavulanate (Amx/Clv); Clarithromycin (Clr); Linezolid (Lzd)

<sup>a</sup> The long-term safety and efficacy for MDR-TB treatment have not yet been fully confirmed and therefore use is not yet recommended for treatment of MDR-TB.

<sup>b</sup> Thioacetazone should be used only in patients documented to be HIV-negative and should usually not be chosen over other drugs listed in Group 4.

## 7.6 Standard code for antituberculosis regimens

There is a standard code for antituberculosis regimens, and each drug has an abbreviation (shown in the list of abbreviations, Table 7.1 and Annex 5). An MDR-TB regimen consists of two phases: the first phase is the period in which the injectable agent is used and the second phase is after it has been stopped. The number shown before each phase stands for phase duration in months and is the minimum amount of time that stage should last. The subscript number after a letter is the number of drug doses per week. If there is no subscript number, treatment is daily (or six times a week). An alternative drug(s) appears as a letter(s) in parentheses. The drugs in the higher groups are written first followed in descending order of potency. An example is given in Box 7.1.

### BOX 7.1

#### Example of standard drug code used to describe a regimen 6Z-Km(Cm)-O<sub>6</sub>x-Eto-C<sub>6</sub>s/12Z-O<sub>6</sub>x-Eto-C<sub>6</sub>s

The initial phase consists of five drugs and lasts for at least 6 months, or 6 months past conversion, depending on country protocol. In this example, the phase without the injectable continues all the oral agents for a minimum of 12 months for a total minimum treatment of at least 18 months. The injectable agent is kanamycin (Km), but there is an option for capreomycin (Cm). Sometimes only the initial treatment is written and the assumption is that either the regimen will be adjusted following DST or the injectable agent will be stopped according to the programme protocol. This type of notation is used without a coefficient, i.e. **Z-Km-O<sub>6</sub>x-Eto-C<sub>6</sub>s**

## 7.7 Regimen design

The following basic principles are involved in any regimen design:

- Regimens should be based on the history of drugs taken by the patient.
- Drugs and regimens commonly used in the country and the prevalence of resistance to first-line and second-line drugs should be taken into consideration when designing a regimen.
- *Regimens should consist of at least four drugs with either certain, or almost certain, effectiveness.* If the evidence about the effectiveness of a drug is unclear, the drug can be included in the regimen but it should not be depended upon for success. Often, more than four drugs may be started if the susceptibility pattern is unknown, if effectiveness is questionable for an agent(s) or if extensive, bilateral pulmonary disease is present.
- Drugs are administered at least six days a week. When possible, pyrazinamide, ethambutol and fluoroquinolones should be given once per day because the high serum levels attained in once-a-day dosing may be more efficacious. Once-a-day dosing is permitted for other second-line drugs,

depending on patient tolerance. However, ethionamide/prothionamide, cycloserine and PAS have traditionally been given in split doses during the day.

- The drug dosage should be determined by body weight. A suggested weight-based dosing scheme is given in Annex 2.
- An injectable agent (an aminoglycoside or capreomycin) is used for a minimum of 6 months (see section 7.6).
- Treatment is for a minimum duration of 18 months beyond conversion (see section 7.8).
- Each dose is given as DOT throughout the treatment. A treatment card is marked for each observed dose.
- DST, when available and from a reliable laboratory, should be used to guide therapy. It should be noted that the full assessment of DST of some first-line and most of the second-line drugs in terms of reliability and clinical value has not been determined. DST does not predict the effectiveness or ineffectiveness of a drug with complete certainty (*I*). Nonetheless, regimens should include at least four drugs that are highly likely to be susceptible, based on DST and/or the drug history of the patient.
- Pyrazinamide can be used for the entire treatment if it is judged to be effective. Many MDR-TB patients have chronically inflamed lungs, which theoretically produce the acidic environment in which pyrazinamide is active.
- Early MDR-TB detection and prompt initiation of treatment are important factors in achieving successful outcomes.

### 7.7.1 Drug selection for the treatment of MDR-TB

Antituberculosis drugs may be placed into five groups, as illustrated in Table 7.1. The order of the five groups is based on potency, evidence of efficacy, experience of use and drug class.

- **Group 1 – First-line oral antituberculosis drugs.** Group 1 drugs are the most potent and best tolerated antituberculosis drugs. They should be used in patients only where there is laboratory evidence or clinical history to suggest their efficacy. Patients who have strains that test resistant to low levels of isoniazid but are susceptible to higher concentrations may benefit from high doses of the drug. However, since the benefit may be small, isoniazid in this situation should not be included as one of the four core drugs. The newer rifamycins should be considered ineffective if results of DST show resistance to rifampicin.

- **Group 2 – Injectable antituberculosis agents.** A Group 2 injectable agent should be given to all patients in whom susceptibility is documented or suspected, according to a hierarchical order based on efficacy, adverse effects and cost. If the strain is susceptible, streptomycin is the usual injectable agent of choice. Kanamycin or amikacin is the logical second choice given the low cost of these drugs and good experience of their use. Amikacin and kanamycin are considered to be very similar and have close to 100% cross-resistance. If an isolate is resistant to both streptomycin and kanamycin, capreomycin should be used. Viomycin is very similar to capreomycin, and these agents also share a high level of cross-resistance.
- **Group 3 – Fluoroquinolones.** A Group 3 drug should be used if the strain is susceptible. Currently, the most potent available fluoroquinolones in descending order based on in vitro activity and animal studies are: moxifloxacin = gatifloxacin > levofloxacin > ofloxacin = ciprofloxacin (2–3). However, the long-term safety of the newer-generation fluoroquinolones has not yet been fully evaluated.
- **Group 4 – Oral bacteriostatic second-line antituberculosis drugs.** Group 4 drugs are added on the basis of estimated susceptibility, drug history, efficacy, adverse effects profile and cost. If only one of these agents is needed, ethionamide/protonamide is often added because of its proven efficacy and low cost. If cost is not a constraint, PAS may be added first because the enteric-coated formulas are relatively well tolerated. If two agents are needed, cycloserine is commonly used in conjunction with ethionamide/protonamide or PAS. Since the combination of ethionamide/protonamide and PAS has a high incidence of gastrointestinal adverse effects, these two agents are commonly used together only when all three Group 4 agents are needed. Ethionamide/protonamide should be started at a low dose (250 mg) for a few days and then gradually increased every 3–5 days until the full dose is reached. Terizidone contains two molecules of cycloserine and can be used instead of cycloserine because its efficacy is assumed to be similar, although there are no direct studies comparing the two. The use of thioacetazone is limited by the development of rashes that are more prevalent in HIV-positive individuals and can result in Stevens-Johnson syndrome and death. In addition, thioacetazone has cross-resistance with the thioamides (ethionamide and protonamide) and is considered a relatively weak antituberculosis agent.
- **Group 5.** The Group 5 drugs are not recommended by WHO for routine use in MDR-TB treatment because their contribution to the efficacy of multidrug regimens is unclear. However, they can be used in cases where adequate regimens are impossible to form with the medicines from Groups 1–4.

### 7.7.2 Standardized treatment regimens

A standardized empirical regimen should be designed for each group through the use of representative DRS data from specific treatment categories. Some groups, such as “relapse” and “return after default”, can often safely use the standard Category II regimens (2HRZES/1HRZE/5HRE), while other groups will need a standardized regimen of second-line drugs. The survey data in each group help to determine the rate of MDR-TB and drug resistance to other antituberculosis drugs such as ethambutol, streptomycin and pyrazinamide. Evaluating the prevalence of resistance to some second-line drugs (kanamycin, capreomycin, fluoroquinolones) in these groups is also recommended and aids design of the regimen, especially in settings with widespread use of second-line drugs.

It is strongly recommended that MDR-TB be confirmed in all patients enrolled on a standardized Category IV regimen. Otherwise, misclassification of patients will either deny isoniazid and rifampicin to patients who would benefit from these drugs, or unnecessarily expose patients to potentially toxic first- or second-line drugs that they do not need. For a standardized regimen that will treat the vast majority of patients with four effective drugs, it is often necessary to use five or six drugs to cover all possible patterns of resistance. In most cases, an injectable agent and a fluoroquinolone form the core of the regimen (see examples provided in Box 7.2).

### 7.7.3 Individualized treatment regimens based on DST

The design of an individualized regimen differs from that of standardized treatment regimens in that it uses the resistance pattern of the infecting strain of the individual patient as another source of data, in addition to the patient’s treatment history and the prevailing resistance patterns in the community. The method for designing the individualized regimen is described in Table 7.2.

The above design is heavily dependent on knowing the results of DST of first-line drugs. If DST results are not known for all the first-line drugs, the choice can be guided by knowledge of prevalence of resistance based on sample surveys, for which the assistance of experts in conducting drug resistance surveys is necessary.

Empirical regimens are commonly used in specific groups of patients while DST is pending. They can be standardized (i.e. all patients from a certain group receive the same regimen until DST results return) or individualized for each patient on the basis of the patient’s treatment history and contact history. Empirical regimens are strongly recommended since most DST methods have a turnaround time of several months. A patient is placed on an empirical regimen while DST results are pending to avoid clinical deterioration and prevent transmission to contacts. There are a few exceptions. It may be convenient to wait for DST results if the laboratory uses a rapid method with a turnaround

**BOX 7.2 EXAMPLES OF HOW TO DESIGN STANDARDIZED REGIMENS**

**Example 1.** Survey data from 93 consecutively enrolled relapse patients from a resource-constrained area show that 11% have MDR-TB. Of these MDR-TB cases, 45% are resistant to ethambutol (E) and 29% are resistant to streptomycin (S). DST to other drugs is unknown; however, there is virtually no use of any of the second-line drugs in the area. What re-treatment strategy is recommended in this group of relapse patients?

**Answer:** Given the relatively low rate of MDR-TB in this group, the following strategy is planned. All relapse patients will be started on the WHO Category II regimen (HRZES). DST of isoniazid (H) and rifampicin (R) will be done at the start of treatment to identify the 11% of MDR-TB patients who will not do well on Category II regimen. Those identified with MDR-TB will be switched to the standardized regimen 8Z-Km-Ofx-Pto-Cs/12Ofx-Pto-Cs. The regimen contains four new drugs rarely used in the area, and is also relatively inexpensive. A small DST survey is planned to document the prevalence of resistance to the regimen's five drugs in 30 relapse patients found to have MDR-TB. If this survey shows high resistance to any of the proposed drugs, redesign of the regimen will be considered. (Note: the regimen proposed in this answer is only one example of a regimen that is considered adequate; many others based on the principles in this chapter would be just as adequate.)

**Example 2.** DST is not available locally in Country X, but survey data from a supranational TB reference laboratory in 82 consecutive patients in whom Category II regimen failed demonstrate resistance to each of the following 11 drugs: H(93%), R(90%), E(56%), Z(38%), S(69%), Km(11%), Cm(8%), Ofx(3%), Eto(18%), Cs(1%) and PAS(3%). What are some of the possible strategies that use a standardized regimen?

**Answer:** Given the high rates of MDR-TB in this group, it is possible that all failures of Category II regimen enter into a standardized regimen with second-line drugs without confirmation of MDR-TB. This should be done only until local laboratory capacity is available; thereafter DST can be performed at the start of the regimen with second-line drugs and adjusted if MDR-TB is not found (this will occur in approximately 10% of patients).

Appropriate standardized regimens include:

- Km-Ofx-Eto-Cs-PAS would place 93% on four or more effective drugs and no patients on two or fewer drugs.
- Z-Km-Ofx-Eto-Cs would place 81% of patients on regimens with four or more effective drugs, and 2.3% on two or fewer drugs.
- Cm-Ofx-Cs-PAS would place 84% of patients on regimens with four or more effective drugs and no patients on two or fewer drugs.

Note that the percentage of effective drug numbers in this example is based on DST and calculated from the data given here (full DST patterns for each of the 82 patients were needed for the calculations).

There are other possible regimens in addition to the three that are listed here. Each regimen must be considered in the context of what the programme can support. Unless excellent patient support is in place, the combination of Eto and PAS in a standardized regimen may cause a high default rate, negating the benefit from the first option. The third option employs the three most expensive antituberculosis agents (Cm, PAS and Cs) making it a costly regimen, yet it uses the lowest quantity of drugs and may have the fewest adverse effects. The second regimen has the disadvantage of placing approximately 2% of the patients on a regimen with only two effective drugs, but would be significantly less toxic and expensive than the other two options.

TABLE 7.2 Individualized regimen design based on DST for first-line drugs

PATTERN OF DRUG RESISTANCE	SUGGESTED REGIMEN (DAILY UNLESS OTHERWISE STATED)	COMMENTS
H-R	Z-E-injectable agent-fluoroquinolone ( $\pm$ one or two Group 4 agents)	One Group 4 agent is sufficient if E and Z susceptibility has been ascertained. Two Group 4 agents should be used in extensive disease, or if the DST result is questionable (i.e. reported susceptibility to E or Z despite a history of these agents being used in a failing regimen).
H-R ( $\pm$ S) and E or Z	Z or E-injectable agent-fluoroquinolone (+ two or more Group 4 agents)	Only use the first-line agents to which the patient's strain is susceptible. Use alternative injectable agent if S resistance is present. More than two Group 4 agents should be used in extensive disease or if resistance to E and Z is present or suspected. Group 5 agents can be considered if an adequate regimen of four drugs cannot be formed based on DST.

H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide; S = streptomycin

time of 1 to 2 weeks. In addition, in a patient with chronic disease treated several times with second-line drugs, waiting for DST results may be prudent even if the turnaround time is several months, as long as the patient is clinically stable and appropriate infection control measures are in place.

Every effort should be made to supplement the patient's memory with objective records from previous health-care providers. A detailed clinical history can help to indicate which drugs are likely to be ineffective. The probability of acquired resistance to a drug increases with the length of time it has been administered. In particular, evidence of clinical or bacteriological treatment failure (positive smears or cultures) during a period of regular drug administration is highly suggestive of drug resistance. If a patient used a drug for longer than one month with persistent positive smears or cultures, the strain should be considered as "probably resistant" to that drug, even if by DST it is reported as susceptible. Resistance can develop in some cases in less than one month (4).

The results of DST should complement rather than invalidate other sources of data about the likely effectiveness of a specific drug. If a history of previous antituberculosis drug use suggests that a drug is likely to be ineffective as a result of resistance, this drug should not be relied upon as one of the four core drugs in the regimen even if the strain is susceptible in the laboratory. However, if the strain is resistant to a drug in the laboratory, but the patient has never taken it and resistance to it is extremely uncommon in the community, this may be a case of a laboratory error or a result of the limited specificity of DST for some second-line drugs.