Another important constraint is the turnaround time necessary for DST. The patient may have already received months of a standard or empirical regimen by the time DST results become available from the laboratory. The possibility of further acquired resistance during this time must be considered. If there is a high probability of acquired resistance to a drug after the specimen for DST was collected, this drug should not be relied on as one of the four drugs in the core regimen.

Some laboratories may report that a strain has a low or intermediate level of resistance to a certain drug. There is very little clinical evidence to support this type of designation, particularly if the patient previously received the drug as part of DOT. Box 7.3 gives three examples of how to design initial individualized regimens.

7.8 Completion administration of the injectable agent (intensive phase)

The recommended duration of administration of the injectable agent, or the intensive phase, is guided by smear and culture conversion. The minimal recommendation is that the injectable agent should be continued for at least 6 months and at least 4 months after the patient first becomes and remains sputum smear- or culture-negative.

The use of an individualized approach that takes account of the results of cultures, smears, X-rays and the patient's clinical status may also help in deciding whether to continue an injectable agent for longer than the recommended period. This would apply particularly in the case of patients for whom the susceptibility pattern is unknown, the effectiveness of a drug(s) is uncertain, or extensive or bilateral pulmonary disease is present.

Intermittent therapy with the injectable agent (three times weekly after an initial period of 2–3 months of daily therapy) can also be considered for patients in whom the injectable agent has been used for a prolonged period and when the risk of toxicity increases.

If the patient has been on an empirical regimen containing five or six drugs, discontinuation of drugs other than the injectable agent can be considered once the DST results are available and provided that the patient continues with at least three of the most potent agents.

7.9 Duration of treatment

The recommended duration of treatment is guided by smear and culture conversion. The minimal recommendation is that treatment should last for at least 18 months after culture conversion. Extension to 24 months may be indicated in patients defined as "chronic cases" (*5*) with extensive pulmonary damage.

BOX 7.3

Examples of how to design initial individualized regimens

Example 1. A patient in whom Categories I and II treatments failed. A review of DST results reveals that the patient's TB infection is resistant to H-R-S and susceptible to all other medications including E-Km-Cm-Ofx-Eto-Cs-PAS; resistance to Z is unknown. The patient has received HRE for 3 months since the date of the DST. What individualized regimen is recommended?

Answer: Since the patient received two courses containing E and Z, and was on functional monotherapy with E for at least 3 months, the utility of these drugs must be questioned despite the DST results. The same drugs can be included in the regimen but they should not be relied on as one of the four core drugs. The injectable choice may depend on the prevalence of resistance in the community, but since this patient never received Km, it may be the first choice in this case:

- Km(Cm)-Ofx-Eto(Pto)-Cs

(Many clinicians will add Z or E to this regimen; others may use PAS instead of Eto or Pto.)

Example 2. A patient in whom Categories I and II treatments failed. A review of DST results reveals that the patient's infection is resistant to H-R-Z-E-S-Km and susceptible to all other medications including Cm-Ofx-Pto-Cs-PAS. The patient has not received any antituberculosis drugs since the date of the DST. What individualized regimen is recommended?

Answer: There are two options in this case:

1. Cm-Ofx-Pto-Cs

Regimen 1 may have the advantage of increased compliance since it requires the minimum amount of drugs and avoids the adverse effects of the combination of PAS and Pto(Eto). However, if one or more of the DST results is wrong (and the reliability of DST of second-line drugs has not been fully determined) the patient may be effectively on a regimen of only two or three drugs. Prevalence of resistance to second-line drugs and their availability in the country can help in the decision.

2. Cm-Ofx-Pto-Cs-PAS

Regimen 2 takes into consideration the uncertainty of DST of second-line drugs. It places the patient on an additional drug as a precaution in case one of the DST results does not reflect the efficacy of any of the drugs tested. Pto and PAS, while difficult to take together, are frequently tolerated by many patients especially with good patient support. A regimen with these five drugs is also preferred if there is extensive damage to the lungs or if susceptibility to any of these drugs is uncertain given a patient's history.

Example 3. A patient in whom a regimen of Z-Km-Ofx-Eto failed remains sputum smear-positive after 8 months of treatment. The DST done from a specimen taken 4 months ago reveals resistance to HRZE-Eto and susceptiblity to Km-Cm-Ofx-Cs-PAS. What individualized treatment regimen is recommended?

Answer: Weak regimens are to be avoided because patients for whom regimens with second-line drugs fail are very difficult to cure. This patient may now be resistant to Ofx and Km. These drugs cannot be relied upon in the regimen but they may be included until new DST results become available. Options for a regimen are limited. The recommended regimen is Cm-Ofx-Cs-PAS. A Group 5 drug may be added until new DST confirms that the patient is susceptible to Ofx.

7.10 Extrapulmonary MDR-TB and MDR-TB treatment

The treatment strategy is the same for patients with pulmonary and extrapulmonary MDR-TB. If the patient has symptoms suggestive of central nervous system involvement and is infected with MDR-TB, the regimen should use drugs that have adequate penetration into the central nervous system (*6–7*). Rifampicin, isoniazid, pyrazinamide, protionamide/ethionamide and cycloserine have good penetration; kanamycin, amikacin and capreomycin penetrate effectively only in the presence of meningeal inflammation; PAS and ethambutol have poor or no penetration.

7.11 Surgery in Category IV treatment

Surgical treatment of TB was common before the advent in the 1950s of highly effective antituberculosis drug combinations. When rifampicin and pyrazinamide were combined with isoniazid in the 1960s and 1970s, short-course chemotherapy became so effective that nearly all patients could be cured without surgery and the indications for surgical intervention, especially in pulmonary TB, declined. Without safe, highly effective short-course chemotherapy, surgical intervention for specific indications may once again be necessary to maximize the likelihood of cure in selected cases.

Surgery for TB requires highly experienced surgeons as well as appropriate pre- and post-operative care, trained support personnel and specialized facilities with availability of safe blood transfusion services. Specialized facilities should also include stringent infection control measures since infectious substances and aerosols are generated in large quantities during surgery and during mechanical ventilation and postoperative pulmonary hygiene manipulations.

The most common operative procedure in patients with pulmonary MDR-TB is surgical resection (taking out part or all of the lung). Surgical resection has been shown to be effective and safe under appropriate surgical conditions (*8*). It is considered to be an adjunct to chemotherapy and appears to be beneficial for patients when skilled thoracic surgeons and excellent postoperative care are available (*9*). Surgery is not indicated in patients with extensive bilateral disease.

Regardless of the specific procedure, surgery should be timed to offer the patient the best possibility of cure with the least morbidity. Thus, the timing of surgery may be earlier in the course of the disease when the patient's risk of morbidity and mortality is lower and when the disease is still localized to one lung or one lung lobe. Generally, at least two months of therapy should be given before surgical resection to decrease the bacterial infection in the surrounding lung tissue. The Category IV regimen should continue according to the local protocol without interruption except for the immediate one or two days during the postoperative period. Doctors and nurses of the surgical departments must be familiar with the drugs used in the Category IV regimens. Even with successful resection, an additional 12–24 months of chemotherapy should be given.

Many programmes will have limited access to surgical treatment. General indications for surgical resection for programmes with limited access to surgery include patients who remain sputum smear-positive, with resistance to a large number of drugs, and have localized pulmonary disease. In programmes with suboptimal surgical facilities and no trained thoracic surgeons, resection is contraindicated as it may lead to increased morbidity or mortality.

7.12 Adjunctive therapies in MDR-TB treatment

In addition to surgery (discussed above), a number of other measures can be used to lessen adverse effects and morbidity as well as improve MDR-TB treatment outcomes.

7.12.1 Nutritional support

In addition to causing malnutrition, MDR-TB can be exacerbated by poor nutritional status, low body mass index and severe anaemia (*10–12*). Without nutritional support, patients can become enmeshed in a vicious cycle of malnutrition and disease, especially those already suffering from baseline hunger. The second-line drugs may also further decrease the appetite, making adequate nutrition a greater challenge. Nutritional support can take the form of providing free staple foods, and whenever possible should include a source of protein.

Vitamin B_6 (pyridoxine) should also be given to all patients receiving cycloserine or terizidone to prevent adverse neurological effects (see Chapter 11). Vitamin (especially vitamin A) and mineral supplements can be given in areas where a high proportion of the patients have deficiencies. If minerals (zinc, iron, calcium, etc.) are given, they should be administered at a different time from the fluoroquinolones, as they can interfere with the absorption of these drugs.

7.12.2 Corticosteroids

The use of corticosteroids in MDR-TB patients can be beneficial in cases of severe respiratory insufficiency and central nervous system involvement (*13–16*). Prednisone is commonly used, starting the dose at approximately 1 mg/kg, with gradual decrease in the daily dose by 10 mg per week when a longer course is indicated. Corticosteroids may also alleviate symptoms in patients with an exacerbation of obstructive pulmonary disease. In these cases, prednisone may be given in a short tapering course over 1–2 weeks, starting at approximately 1 mg/kg and decreasing the dose by 5–10 mg per day. Injectable corticosteroids are often used initially when a more immediate response is needed.

7.13 Conclusion

MDR-TB treatment is a complex health intervention and no single strategy will fit all situations. Epidemiological, financial and operational factors must be taken into consideration in deciding which strategy to use. Table 7.4 provides a summary of the principles of regimen design.

TABLE 7.4 **Summary of general principles for designing a regimen**

BASIC PRINCIPLES	COMMENTS
1. Use at least 4 drugs certain or highly likely to be effective	Effectiveness is supported by a number of factors (the more present the more likely the drug will be effective in the patient): A. DST results show susceptibility. B. No previous history of treatment failure with the drug. C. No known close contacts with resistance to the drug. D. Drug resistance survey indicates resistance is rare in similar patients. E. The drug is not commonly used in the area. If at least 4 drugs are not certain to be effective, use 5–7 drugs depending on the specific drugs and level of uncertainty.
2. Do not use drugs for which resistance crosses over	A. All rifamycins (rifampicin, rifabutin, rifapentene, rifalazil) have high levels of cross-resistance. B. Fluoroquinolones are believed to have variable cross-resistance, with in vitro data showing that some higher-generation fluoroquinolones remain susceptible when lower-generation fluoroquinolones are resistant. In these cases, it is unknown whether the higher-generation fluoroquinolones remain clinically effective. C. Not all aminoglycosides and polypeptides cross-resist; in general, only kanamycin and amikacin fully cross-resist.
3. Eliminate drugs that are not safe in the patient	A. Known severe allergy or unmanageable intolerance. B. High risk of severe adverse effects including renal failure, deafness, hepatitis, depression and/or psychosis. C. Quality of the drug is unknown or questionable.
4. Include drugs from Groups 1–5 in a hierarchical order based on potency	A. Use any Group 1 (oral first-line) drugs that are likely to be effective (see section 1 of this table). B. Use an effective aminoglycoside or polypeptide by injection (Group 2 drugs). C. Use a fluoroquinolone (Group 3). D. Use the remaining Group 4 drugs to make a regimen of at least 4 effective drugs. For regimens with ≤4 effective drugs, add second-line drugs most likely to be effective, to give up to 5–7 drugs in total, on the basis that at least 4 are highly likely to be effective. The number of drugs will depend on the degree of uncertainty. E. Use Group 5 drugs as needed so that at least 4 drugs are likely to be effective.
5. Be prepared to prevent, monitor and manage adverse effects for each of the drugs selected.	A. Ensure laboratory services for haematology, biochemistry, serology and audiometry are available. B. Establish a clinical and laboratory baseline before starting the regimen. C. Initiate treatment gradually for a difficult-to-tolerate drug, split daily doses of Eto/Pto, Cs and PAS. D. Ensure ancillary drugs are available to manage adverse effects. E. Implement DOT for all doses.

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