4. STANDARDIZED TREATMENT REGIMENS

4.1 Objectives of chapter

This chapter describes the recommended standardized treatment regimens for the different categories of tuberculosis cases.

4.2 Aims of treatment

The aims of treatment of tuberculosis are:

- to cure the patient of TB;
- to prevent death from active TB or its late effects;
- to prevent relapse of TB;
- to decrease transmission of TB to others;
- to prevent the development of acquired drug resistance.

It is vital to achieve these aims while preventing the selection of resistant bacilli in infectious patients.

4.3 Essential antituberculosis drugs

There are three main properties of antituberculosis drugs: bactericidal activity, sterilizing activity and the ability to prevent resistance. The essential antituberculosis drugs possess these properties to different extents. Isoniazid and rifampicin are the most powerful bactericidal drugs, active against all populations of TB bacilli. Rifampicin is the most potent sterilizing drug available. Pyrazinamide and streptomycin are also bactericidal against certain populations of TB bacilli. Pyrazinamide is only active in an acid environment. Streptomycin is bactericidal against rapidly multiplying TB bacilli. Ethambutol and thiocetazone are used in association with more powerful drugs to prevent the emergence of resistant bacilli.

Table 4.1 shows the essential antituberculosis drugs and their recommended dosage (range in parentheses).

Table 4.1 **Essential antituberculosis drugs**

Essential drug (abbreviation)	**Recommended dosage (dose range) in mg/kg**	
	Daily	**3 times weekly[a]**
isoniazid (H)	5 (4–6)	10 (8–12)
rifampicin (R)	10 (8–12)	10 (8–12)
pyrazinamide (Z)	25 (20–30)	35 (30–40)
streptomycin (S)	15 (12–18)	15 (12–18)
ethambutol (E)	15 (15–20)	30 (20–35)
thioacetazone[b] (T)	2.5	Not applicable

[a] WHO does not recommend twice-weekly regimens. If a patient receiving a twice-weekly regimen misses a dose of tablets, this missed dose represents a larger fraction of the total number of treatment doses than if the patient were receiving a thrice-weekly or daily regimen. There is therefore an increased risk of treatment failure. Moreover, HIV-positive patients receiving therapy with twice-weekly doses or less are at increased risk of failure or relapse with acquired rifampicin-resistant TB.

[b] WHO discourages the use of thioacetazone because of the risk of severe toxicity, in particular in HIV-infected individuals. It should be replaced by ethambutol, especially in areas where HIV infection is common. Thioacetazone may be used in combination with isoniazid in the continuation phase in areas with low prevalence of HIV infection when financial circumstances preclude the use of ethambutol.

Annex 2 provides information on the recommended dosage and common adverse events of essential antituberculosis drugs. The WHO recommended formulations of antituberculosis drugs and fixed-dose combinations (FDCs) of drugs appear in the WHO Essential Drugs List (EDL). The available formulations and combinations of antituberculosis drugs within each country should conform to this List.

Fixed-dose combination tablets

Tablets of fixed-dose drug combinations have several advantages over individual drugs. First, prescription errors are likely to be less frequent because dosage recommendations are more straightforward and adjustment of dosage according to patient weight is easier. Second, the number of tablets to ingest is smaller and may thus encourage patient adherence. Third, if treatment is not observed, patients cannot be selective in the choice of drugs to ingest.

Fixed-dose combinations of drugs also have disadvantages. First, if prescription errors do occur, excess dosage (risk of toxicity) or sub-inhibitory concentrations of all drugs (favouring development of drug resistance) may result. Second, health care workers may be tempted to evade directly observed therapy, erroneously believing that adherence is automatically guaranteed. Third, poor rifampicin bioavailability has been found for some FDCs, particularly in combinations of 3- and 4-drugs. Quality assurance is therefore essential. Finally, using FDCs does not obviate the need for separate drugs for a minority of cases that develop drug toxicity.

WHO strongly recommends the use of fixed-dose combination tablets for the treatment of TB. The recommended formulations currently available are shown in Table 4.2.

Table 4.2 **WHO recommended formulations of essential antituberculosis drugs**[a]

Separate drugs

Drug	Dose form	Strength
isoniazid	tablet	100 mg, 300 mg
rifampicin	tablet or capsule	150 mg, 300 mg
pyrazinamide	tablet	400 mg
ethambutol	tablet	100 mg, 400 mg
streptomycin	powder for injection in vial	1 g

Fixed-dose combinations of drugs

Drug	Dose form	Strength for daily use	Strength for use 3 times weekly
isoniazid + rifampicin	tablet	75 mg +150 mg 150 mg +300 mg	150 mg + 150 mg
	tablet or pack of granules[b]	30 mg + 60 mg	60 mg + 60 mg
isoniazid + ethambutol	tablet	150 mg + 400 mg	-
isoniazid + thioacetazone	tablet	100 mg + 50 mg 300 mg + 150 mg	-
isoniazid + rifampicin + pyrazinamide	tablet	75 mg + 150 mg + 400 mg	150 mg + 150 mg + 500mg
	tablet or pack of granules[b]	30 mg + 60 mg + 150 mg	-
isoniazid + rifampicin + pyrazinamide + ethambutol	tablet	75 mg + 150 mg + 400 mg + 275 mg	-

[a] From Essential drugs: WHO Model List (revised December 1999). In: *WHO drug information*, 1999, 13(4):249–262.

[b] For paediatric use.

Intermittent use

Isoniazid, rifampicin, pyrazinamide and ethambutol may be as efficacious when given three times weekly as when given daily. Thioacetazone is the only antituberculosis drug ineffective when given intermittently.

Thrice-weekly drug intake facilitates observation, reduces costs and inconvenience for the patient because of fewer visits, and liberates staff for patient retrieval on alternate days. Fully intermittent regimens are used in the two largest TB programmes (China and India) with high levels of effectiveness under programme conditions.

It should be noted that intermittent initial phase therapy is not recommended when the continuation phase of isoniazid and ethambutol is used.

Standardized regimens

The choice by each country of a limited number of standardized regimens should be based on the availability of financial resources, efficacy, effectiveness and applicability in the current health system network, and population distribution and mobility. Standardized regimens have the following advantages over individualized prescription of drugs:

- reduces errors in prescription thereby reducing the risk of development of drug resistance
- facilitates estimates of drug needs, purchasing, distribution and monitoring
- facilitates staff training
- reduces costs
- facilitates regular drug supply when patients move from one area to another.

To facilitate procurement, distribution and administration of treatment to patients, daily dosage may be standardized for 3- or 4- body weight bands – for instance, 30–39, 40–54, 55–70 and over 70 kg (*see Annex 4*) – or a single dosage for most patients with additional rifampicin for patients over 60 kg and individual calculation for children, as in India.

4.4 Recommended standardized treatment regimens

New cases

Treatment regimens have an initial (or intensive) phase lasting two months and a continuation phase usually lasting four or six months. During the initial phase, normally consisting of isoniazid, rifampicin, pyrazinamide and ethambutol, the tubercle bacilli are killed rapidly. Infectious patients quickly become non-infectious (within approximately two weeks). Symptoms abate. The vast majority of patients with sputum smear-positive TB become smear-negative within two months. During the continuation phase, fewer drugs are necessary but for a longer time. The sterilizing effect of the drugs eliminates the remaining bacilli and prevents subsequent relapse.

Patients with a large bacillary load (smear-positive pulmonary TB and many HIV-infected patients with smear-negative pulmonary TB) have an increased risk of selecting resistant bacilli because a large population of bacilli develops spontaneous resistance to a single drug. Short-course chemotherapy regimens, consisting of 4 drugs during the initial phase and 2 drugs during the continuation phase, reduce this risk. Such regimens are highly effective in

patients with susceptible bacilli, and almost as effective in patients with initially isoniazid-resistant organisms.

Patients negative for HIV, with smear-negative pulmonary or extrapulmonary TB that is fully drug-susceptible, have little risk of selecting resistant bacilli because their lesions generally harbour fewer bacilli. However, since initial resistance to isoniazid is common in many areas, and HIV testing of tuberculosis patients is not routinely practised, it is now recommended that ethambutol be included as a fourth drug during the initial phase of treatment for most patients with smear-negative and extrapulmonary TB. Ethambutol may be omitted for patients with non-cavitary, smear-negative pulmonary TB who are known to be HIV-negative, patients known to be infected with fully drug-susceptible bacilli, and young children with primary TB.

Re-treatment cases

Previously treated TB patients include those patients treated as new cases for more than one month who are now smear- or culture-positive (failure, relapse, return after default). Re-treatment cases have a higher likelihood of drug resistance, which may have been acquired through inadequate prior chemotherapy. Adherent patients who fail initial treatment are at high risk of having MDR TB.

The standard re-treatment regimen consists of 5 drugs in the initial phase and 3 drugs in the continuation phase. The patient receives 3 drugs throughout the treatment: RHE. This standardized regimen can cure patients excreting bacilli still fully sensitive to the drugs and those excreting bacilli resistant to isoniazid and/or streptomycin. Under proper case management conditions, MDR-TB cases are those most at risk of failure in the re-treatment regimen.

When program conditions permit the use of alternate treatment regimens, the standard retreatment regimen should not be used for failure cases at high risk of MDR TB (see Section 4.8).

4.5 Rationale for prioritizing TB diagnostic categories

From a public health perspective, the highest priority of an NTP is the identification and cure of infectious TB cases, i.e. patients with sputum smear-positive pulmonary TB. In settings of resource constraint, the rational allocation of resources is necessary to prioritize diagnostic categories according to the impact and cost-effectiveness of treatment for each category. Diagnostic categories are therefore ranked from I (highest priority) to IV (lowest priority).

The new WHO recommendations for TB treatment regimens appropriate to the different diagnostic categories (shown in Table 4.3) reflect developments in drug formulations and advances in understanding the response to TB treatment in HIV-infected persons. For example, the benefits of using a single regimen with 4 drugs in the initial phase of treatment for all new patients may outweigh the disadvantages (including over-treatment of many patients with non-severe smear-negative and extrapulmonary TB).

4.6 Standard code for TB treatment regimens

Treatment regimens for TB have a standard code. Each antituberculosis drug has an abbreviation (shown in Table 4.1).

A TB treatment regimen consists of two phases: an initial phase and a continuation phase. The number before a phase is the duration of that phase in months. Letters in parentheses indicate fixed-dose combinations of those drugs. A number in subscript (e.g. $_3$) after a letter or letters in parentheses indicates the number of doses of that drug per week. If there is no subscript number, treatment is daily (or 6 times weekly, excluding for instance Sundays). Examples are shown below. An alternative drug (or drugs) appears as a letter (or letters) in square brackets [example not shown].

Examples

2 (HRZE)/4 $(HR)_3$
The **initial phase** is 2 **(HRZE)**. The duration of the phase is 2 months. Drug treatment is daily, with isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) in fixed-dose combination.
The **continuation phase** is **4 $(HR)_3$**. The duration is 4 months, with isoniazid and rifampicin, in fixed-dose combination, 3 times per week.

2 (HR)ZE/6 (HE)
The **initial phase** is **2 (HR)ZE.** The duration of the phase is 2 months. Drug treatment is daily, with isoniazid (H) and rifampicin (R) in fixed-dose combination, plus pyrazinamide (Z) and ethambutol (E).
The **continuation phase** is **6 (HE).** The duration of the phase is 6 months. Drug treatment is daily, with isoniazid (H) and ethambutol (E) in fixed-dose combination.

4.7 Recommended treatment regimens for TB diagnostic categories

There are several possible regimens. The regimens recommended in each country's NTP depend on that country's budget, access of patients to PHC services, qualifications of health staff at peripheral level and current best medical practice. The regimen recommended for each patient depends on the diagnostic category for each patient. Table 4.3 and section 4.8 show alternative regimens for each diagnostic category, which can be used under various circumstances and in certain sub-populations. National TB programmes should decide the most appropriate regimens to be followed at national level.

Table 4.2 shows the recommended formulations of essential antituberculosis drugs. Tables 1 to 4 in Annex 4 show the number of tablets by weight band appropriate for most TB patients.

4.8 Considerations for the continuation phase in new patients (Category I and III)

National TB programmes should choose one of the continuation phase regimens listed below. To facilitate training, drug procurement and supply, and drug administration and to minimize errors in prescription, national recommendations should be as simple as possible and avoid multiple alternatives. The options are:

- **4 HR** daily or three times weekly, given under direct observation, is the preferred continuation phase regimen. The primary advantage of this regimen is the low rate of treatment failure and relapse for both HIV negative and HIV infected patients with fully drug-susceptible TB and those with initial isoniazid resistance. The use of HR requires patient oriented measures to ensure adherence to treatment including wider community

and/or family participation in treatment observation, support and health education for the patients and their families, and in some settings the use of incentives and enablers. Disadvantages of this regimen include the possibility of the development of rifampicin-resistant disease in patients with initial isoniazid resistance and drug-drug interactions with some antiretroviral drugs used for HIV-infected patients

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  - Daily treatment may be especially appropriate if the patient is hospitalised, or the observer is nearby (neighbour) or at the patient's home (for example mother to small child). ***The use of FDCs is highly recommended.***
  - Three times weekly therapy always requires direct observation. Its effectiveness is similar to that of daily therapy. Thrice weekly treatment allows the treatment observer to dedicate alternative days to find and recover patients who interrupted treatment. ***The use of FDCs is highly recommended..***

- **6 HE**[1] daily, self-administered treatment, with drug provided every two weeks to one month is an acceptable option that should be used when adherence to treatment with HR cannot be assured, e.g., for mobile populations and patients with very limited access to health services. It may be especially appropriate for countries with limited PHC access that are unable to organize a system of direct observation through health facilities, community health workers or volunteers. For HIV-infected patients, any antiretroviral drug combination may be given concomitantly with this regimen. Although drug costs for this regimen are essentially equivalent to that of 4HR, the costs of supervision are much less. In addition, not using rifampicin in the continuation phase may reduce acquired resistance to this drug. However, there is no assurance that the patient is taking all the drugs and treatment interruption is noted only when the patient does not return to collect drugs. Moreover, results from an international multicenter randomised clinical trial found that the combined rate of treatment failure and relapse for this regimen is significantly higher than that for the 6-month regimen with rifampicin throughout (11% vs. 5%). While less effective than HR, the HE regimen is expected to cure the large majority of adherent patients, and its use may help preserve the effectiveness of a rifampicin-based retreatment regimen for patients who fail or relapse. This regimen should be administered daily throughout treatment. ***The use of FDCs is highly recommended.***

4.9 Considerations for the choice of regimen for cases who fail Category I regimen

In most settings treatment failures of the Category I regimen have a higher probability of being multidrug-resistant, particularly if the whole treatment was directly observed and included rifampicin in the continuation phase. The Category II regimen has poor results in MDR-TB cases (less than 50% cure rate) and may result in amplification of drug-resistance.

For this reason, countries with a high proportion of MDR-TB among failures of the Category I regimen should consider to treat such failures with a Category IV regimen. However, it needs to be stressed that the introduction of these regimens for failures of the Category I regimen requires either individualized susceptibility testing (DST) or representative drug-resistance surveillance (DRS) data in the patient category concerned. Culture and DST

[1] Some countries still use HT (isoniazid/thioacetazone) instead of HE. Although WHO discourages the use of thioacetazone due to the risk of toxicity, it may be continued in countries where HIV infection is uncommon.

should be quality assured and all programmatic conditions for the introduction of a DOTS-plus component within the regular DOTS-programme should be met (see chapter 5). In principle, Category IV regimens should only be introduced in well performing DOTS programmes and be tailored to the local situation (drug-resistance patterns, history of drug-use in the country, human and financial resources).

The use of Category IV regimens for failures of the Category I regimen is not recommended in settings where relevant programmatic and DRS data are lacking, nor in programmes where most of the failures to the Category I regimen are due to poor programme performance. In these situations the standard Category II regimen should be applied until sufficient resources are available, the programme is strengthened, and the conditions listed above are met. At the same time, these programs should work toward meeting the conditions required to eliminate the routine use of the Category II regimen in failure cases with moderate to high rates of MDR-TB.

Table 4.3 Recommended treatment regimens for each diagnostic category

TB diagnostic category	TB patients	TB treatment regimens[i]	
		Initial phase	**Continuation phase**
I	New smear-positive patients; new smear-negative PTB with extensive parenchymal involvement; concomitant HIV disease or severe forms of extra-pulmonary TB[ii]	**Preferred** 2 HRZE[iii]	**Preferred** 4 HR $4\ (HR)_3$
		Optional $2\ (HRZE)_3$ or 2 HRZE[iv]	**Optional** $4\ (HR)_3$ or 6 HE[v]
II	Previously treated sputum smear-positive PTB: - relapse; - treatment after default	**Preferred** 2 HRZES / 1 HRZE[vi]	**Preferred** 5 HRE[vi]
		Optional $2\ (HRZES)_3/1\ HRZE_3$	**Optional** $5\ (HRE)_3$
	- treatment failure of Category I[vii] in settings with: - adequate program performance; - representative DRS data showing high rates of MDR TB and/or capacity for DST of cases, and - availability of Category IV regimens	specially designed standardized or individualized regimens are often needed for these patients. (See Section 4.9 and Chapter 5)	
	in settings where - representative DRS data show low rates of MDR TB or individualized DST shows drug-susceptible disease or in settings of - poor program performance, - absence of representative DRS data, - insufficient resources to implement Category IV treatment	**Preferred** 2 HRZES / 1 HRZE	**Preferred** 5 HRE[vi]
		Optional $2\ (HRZES)_3/1\ HRZE_3$	**Optional** $5\ (HRE)_3$

III	New smear-negative PTB (other than in category I) and less severe forms of extra-pulmonary TB	**Preferred** 2 HRZE[viii]	**Preferred** 4 HR $4(HR)_3$
		Optional $2(HRZE)_3$ or 2 HRZE	**Optional** $4(HR)_3$ or 6 HE
IV	Chronic (still sputum-positive after supervised re-treatment); proven or suspected MDR TB cases[ix]	Specially designed standardized or individualized regimens	

[i] Numbers preceding regimens indicate length of treatment (months). Subscripts following regimens indicate frequency of administration (days per week). When no subscripts are given, the regimen is daily. Direct observation of drug intake is always required during the initial phase of treatment and strongly recommended when rifampicin is used in the continuation phase and required when treatment is given intermittently. FDCs are highly recommended for use in both the initial and continuation phases of treatment.

[ii] Severe forms of extrapulmonary TB are listed elsewhere (Section 3.5.3).

[iii] Streptomycin may be used instead of ethambutol. In tuberculous meningitis ethambutol should be replaced by streptomycin

[iv] Intermittent initial phase therapy is not recommended when the continuation phase of isoniazid and ethambutol is used.

[v] This regimen may be considered in situations where the preferred regimen cannot be applied as recommended. However, it is associated with a higher rate of treatment failure and relapse compared with the 4HR continuation phase regimen (see Section 4.8). Intermittent initial phase treatment is not recommended when followed by the 6HE continuation phase regimen.

[vi] Daily treatment is preferred. However, thrice weekly treatment during the continuation phase or during both phases is an acceptable option.

[vii] Treatment failures may be at increased risk of MDR TB, particularly if rifampicin was used in the continuation phase (See Section 4.9). Drug susceptibility testing is recommended for these cases if available. Treatment failures with known or suspected MDR TB should be treated with a Category IV regimen (See Chapter 5).

[viii] Ethambutol in the initial phase may be omitted for patients with limited, non-cavitary, smear-negative pulmonary TB who are known to be HIV-negative, patients with less severe forms of extrapulmonary TB, and young children with primary TB.

[ix] Drug susceptibility testing is recommended for patients who are contacts of MDR TB patients.