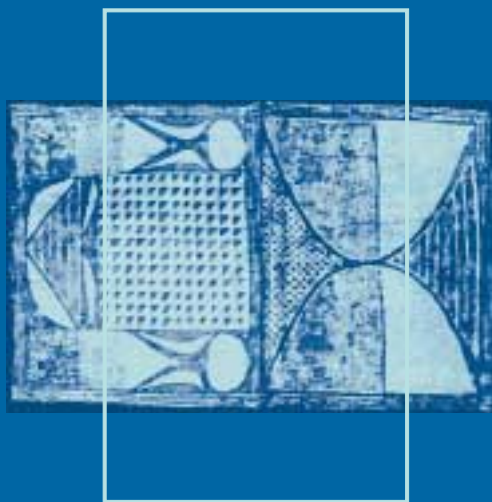


# TREATMENT *of* TUBERCULOSIS



## GUIDELINES *for* NATIONAL PROGRAMMES



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# **TREATMENT OF TUBERCULOSIS: GUIDELINES FOR NATIONAL PROGRAMMES**

**SECOND EDITION 1997**



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# TREATMENT OF TUBERCULOSIS: GUIDELINES FOR NATIONAL PROGRAMMES

SECOND EDITION 1997

*Writing committee:*

**DERMOT MAHER**

**PIERRE CHAULET**

**SERGIO SPINACI**

**ANTHONY HARRIES**

*for the Global Tuberculosis Programme  
World Health Organization  
Geneva, Switzerland*

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## PREFACE

The World Health Organization's Global Tuberculosis Programme (GTB) has prepared this first revision of "Treatment of Tuberculosis: Guidelines for National Programmes", with the help of experts world-wide. The aim is to give practical guidance to national TB programmes (NTPs) in the effective management of TB control. The principles of TB control, as set out in the first edition of "Treatment of Tuberculosis: Guidelines for National Programmes" in 1993, remain the same. The purpose of this revision is to update the guidelines in the light of the experience gained since the first edition in assisting NTPs. This book is for use in any country in which there are high TB incidence populations. Since 95% of the global TB burden is in low and middle-income countries, the main use of this book will be in these countries.

The most cost-effective public health measure to control TB is the identification and cure of the infectious cases, i.e. patients with smear-positive pulmonary TB. However, NTPs provide for the identification and cure of all patients with TB. These guidelines cover the treatment of patients with smear-positive pulmonary TB, smear-negative pulmonary TB, and extra-pulmonary TB.

The treatment of TB is the cornerstone of any NTP. The modern strategy of TB treatment is based on standardised short-course chemotherapy regimens, applied under proper case management conditions. Standardised treatment is a component of the TB control policy package, set out in the WHO document "Framework for effective tuberculosis control". The WHO recommended TB control strategy is known by the brand name "DOTS". The whole policy package is necessary to ensure the success of the treatment strategy. The emphasis is on placing the patient at the centre of TB control activities.

The DOTS strategy provides the TB patient with all the necessary requirements for cure. The focus of these revised guidelines is on the technical and managerial aspects of treatment.

The objectives of the revised guidelines are the following:

- to describe briefly the global TB burden and the framework for effective TB control;
- to describe standardised treatment regimens according to TB case definitions and categories;
- to describe the monitoring of individual patients and how to ensure their adherence to treatment;
- to describe the special considerations in treating HIV-infected TB patients;
- to provide information on anti-TB drug supply in the context of national pharmaceutical policies and essential drug programmes.

These guidelines are primarily for TB programme managers, policy makers in Ministries of Health, NGOs and donor agencies, but clinical health workers and teachers and students in medical and nursing schools will also find them useful.



## FOREWORD

There will be a warm welcome for this second edition of the Guidelines. The first edition in 1993 was most valuable and has been extensively used. Since its publication much more experience of National Tuberculosis Control Programmes in a wide variety of countries has accumulated. It is appropriate therefore that the Guidelines should be reviewed.

The initial approach to that review was to explore whether the previous recommendations could be simplified. After wide consultation it became clear that there were considerable variations between countries both in circumstances and in resources. It was therefore decided that the Guidelines should have some degree of flexibility. For several aspects of a control programme there should be reliable alternatives. Each national programme can choose the treatment regimens and modes of application most appropriate to its own circumstances.

One of the important activities of a national tuberculosis programme is finding solutions to problems. For example, how can a programme in a country with limited resources implement directly observed treatment in a rural area with poor infrastructure? It is essential to evaluate proposed methods of implementing directly observed treatment. Wider adoption of a particular proposed method depends on proven success of that method in carefully identified demonstration sites.

The key treatment principle of direct observation of treatment remains the same whichever method of implementation is chosen. For all smear-positive cases, directly observed treatment is always recommended in the initial phase of treatment and when the continuation phase contains rifampicin. The results of this approach are the following: high sputum smear conversion rates at the end of the initial phase; high cure rates; decreased prevalence of chronic excretors of tubercle bacilli; decreased transmission of infection; prevention of drug-resistance.

The writers of the Guidelines are to be congratulated on their success on presenting the key principles with clarity and relative simplicity. The text presents much practical advice based on experience in many different national programmes. It takes into account the tragic impact of the HIV pandemic on the individual patient, on the epidemiology of tuberculosis and on the necessary modification of programmes.

With the global explosion of HIV, and in some countries much ill-informed and chaotic treatment of tuberculosis, the world is threatened with an untreatable epidemic of multi-drug resistant tuberculosis. The only way to prevent it is to ensure that the principles outlined in this booklet are universally applied, both in government programmes and in private practice. We must all make every effort to ensure that this vital objective is indeed achieved. Time is not on our side. The need is urgent. These Guidelines must have the widest possible distribution.

SIR JOHN CROFTON

*Professor Emeritus of Respiratory Diseases  
and Tuberculosis, University of Edinburgh, Scotland*

KAREL STYBLO

*Former Scientific Director of the International Union Against  
Tuberculosis and Lung Disease, The Hague, The Netherlands*



## LIST OF ABBREVIATIONS

AIDS	<i>Acquired Immunodeficiency Syndrome</i>
CIF	<i>Cost-Insurance-Freight</i>
EDL	<i>Essential Drugs List</i>
FDC	<i>Fixed Dose Combination</i>
FIFO	<i>First In, First Out</i>
FOB	<i>Free On Board</i>
GMP	<i>Good Manufacturing Practices</i>
GTB	<i>Global Tuberculosis Programme</i>
HIV	<i>Human Immunodeficiency Virus</i>
INNs	<i>International Non-proprietary Names</i>
IUATLD	<i>International Union Against Tuberculosis and Lung Disease</i>
NGO	<i>Non-Governmental Organization</i>
NTP	<i>National Tuberculosis Programme</i>
PHC	<i>Primary Health Care</i>
PTB	<i>Pulmonary Tuberculosis</i>
SCC	<i>Short-Course Chemotherapy</i>
STDs	<i>Sexually Transmitted Diseases</i>
TAI	<i>Treatment After Interruption</i>
TB	<i>Tuberculosis</i>
TB/HIV	<i>TB and HIV co-infection</i>
UNICEF	<i>United Nations Children's Fund</i>
WHO	<i>World Health Organization</i>



## 1 INTRODUCTION

### 1.1 Global epidemiology and burden of disease

About one third of the world's population is infected by *Mycobacterium tuberculosis*. World-wide in 1995 there were about nine million new cases of TB with three million deaths. *M. tuberculosis* kills more people than any other single infectious agent. Deaths from TB comprise 25% of all avoidable deaths in developing countries. 95% of TB cases and 98% of TB deaths are in developing countries. 75% of TB cases in developing countries are in the economically productive age group (15-50 years).

### 1.2 Reasons for global TB burden

The main reasons for the increasing global TB burden are the following:

- poverty and the widening gap between rich and poor in various populations, e.g. developing countries, inner city populations in developed countries;
- neglect (inadequate case detection, diagnosis and cure);
- changing demography (increasing world population and changing age structure);
- the impact of the HIV pandemic.

### 1.3 Failure of global TB control efforts so far

Despite the discovery of the TB bacillus in 1882, and of anti-TB drugs since 1944, efforts to control TB globally have so far failed. The main reasons for failure include the following:

- inadequate political commitment and funding;
- inadequate organisation of services;
- inadequate case management (failure to cure cases that were diagnosed);
- over-reliance on BCG.

### 1.4 Global TB control is possible through the DOTS strategy

Global TB control is possible despite the above problems. Good tools exist for diagnosis (sputum smear microscopy) and therapy (short-course chemotherapy). The WHO TB control policy package represents an organisational framework for the effective utilisation of these tools in identifying and curing patients. Many countries have achieved high cure rates using the DOTS strategy. By 1995, about 80 countries had adopted, or begun to adopt, the DOTS strategy. Since properly applied anti-TB chemotherapy is effective in curing the infectious cases and interrupting the chain of transmission, the best prevention of TB is the cure of the infectious cases. The World Bank recognises the DOTS strategy as one of the

most cost-effective of all health interventions and recommends that effective TB treatment should be a part of the essential clinical services package available in Primary Health Care (PHC).

Governments have the responsibility of ensuring the provision of effective TB control through the DOTS strategy.

### 1.5 The consequences of failure to implement effective NTPs

The consequences of failure to implement effective NTPs include the following:

- the TB case load will continue to increase;
- the number of deaths from TB globally each year will continue to increase from the three million currently estimated;
- multi-drug resistant TB will increase considerably world-wide;
- a currently treatable epidemic will become an untreatable epidemic;
- reliable information on TB, including case-finding and cure rates, will be lacking.

Political commitment to fund and implement effective NTPs is necessary to promote global TB control and avoid the consequences of failure.

### Suggestions for Further Reading

*TB - A Global Emergency. WHO report on the tuberculosis epidemic, 1994. WHO/TB/94.177*

*Stop TB at the source. WHO report on the tuberculosis epidemic, 1995. WHO/TB/95.183*

*Groups at risk. WHO report on the tuberculosis epidemic, 1996. WHO/TB96.198*

*Framework for effective tuberculosis control.  
WHO Global Tuberculosis Programme, 1994. WHO/TB/94.179*

*The World Bank. Investing in Health: World Development Report 1993.  
New York, NY. Oxford University Press, 1993.*

## STRATEGY AND FRAMEWORK FOR EFFECTIVE TUBERCULOSIS CONTROL

### 2.1 Objectives of chapter

This chapter describes the WHO recommended DOTS strategy and the framework for effective TB control.

### 2.2 Background

WHO has declared that TB is a global emergency because TB is out of control in many parts of the world. TB programmes in many developing countries have failed in the past to control TB, because they have not cured enough TB patients, particularly the infectious (smear-positive) patients. The main reasons for this are the following:

- reliance on special TB care facilities which have failed to ensure directly observed treatment and which have not been accessible for many patients;
- use of inadequate treatment regimens and failure to use standardised treatment regimens;
- lack of an information management system for the rigorous evaluation of treatment outcomes of TB patients.

WHO has adopted a new strategy and framework for effective TB control in response to this global emergency. “DOTS” is the brand name of the WHO recommended TB control strategy. It is vital for successful TB control for health care workers to treat TB patients within this framework in a National TB Programme (NTP).

The organisational principles of this strategy are the following:

- availability of a decentralised diagnostic and treatment network based on existing health facilities and integrated with PHC;
- good programme management based on accountability and supervision of health care workers;
- an in-built evaluation system for case-finding of new cases and relapses and for full cohort analysis of treatment outcomes.

The WHO framework for effective TB control consists of the following:

- Overall objectives of TB control.
- Strategy for TB control.
- Targets for TB control.
- TB control policy package.
- Key operations of a NTP.
- Indicators to measure progress in TB control.

### 2.3 Overall objectives of TB control

- To reduce mortality, morbidity and disease transmission.
- To prevent the development of drug resistance.

### 2.4 Strategy for TB control

To provide standardised short-course chemotherapy (SCC) under direct observation at least during the initial phase of treatment to, at least, all identified smear-positive TB cases (the sources of infection).

### 2.5 Targets for TB control

- To cure 85% of detected new cases of sputum smear-positive TB.  
NTPs which achieve at least an 85% cure rate in patients with sputum smear-positive pulmonary TB have the following impact on TB:
  - TB prevalence and the rate of TB transmission both decrease immediately;
  - TB incidence decreases gradually;
  - there is less acquired drug resistance (which makes future treatment of TB easier and more affordable).
- NTPs with low cure rates have the following impact on TB:
  - there are more cases of sputum smear-positive treatment failure;
  - acquired drug-resistance increases.
- To detect 70% of existing cases of sputum smear-positive TB.

It is important to expand case-finding only when a National Tuberculosis Programme has achieved a high cure rate throughout the country.

AN EFFECTIVE NTP HAS A HIGH CURE RATE, A LOW LEVEL OF ACQUIRED DRUG RESISTANCE, AND ULTIMATELY A HIGH CASE DETECTION RATE.

### 2.6 TB control policy package

The success of the DOTS strategy depends on the implementation of a five-point package:

- government commitment to a National Tuberculosis Programme;
- case detection through case-finding by sputum smear microscopy examination of TB suspects in general health services;
- standardised short-course chemotherapy to, at least, all smear-positive TB cases under proper case management conditions;
- regular, uninterrupted supply of all essential anti-TB drugs;
- monitoring system for programme supervision and evaluation.

## 2.7 Key NTP features

- NTP has a central unit.
- NTP manual available at district level.
- A recording and reporting system using standardised registers.
- A training programme covering all aspects of the policy package.
- Nation-wide network of microscopy services in close contact with PHC services and subject to regular quality control.
- Treatment services within the PHC system, with priority for directly observed short-course chemotherapy.
- Regular supply of drugs and diagnostic materials.
- Plan of supervision.
- A project development plan, with budget details, funding sources, and responsibilities.

## 2.8 Indicators to measure NTP progress in TB control

- NTP manual (reflects government commitment).
- The number of administrative areas in the country which are implementing the new TB control strategy.
- The cure rate.
- The case detection rate.

### Suggestions for Further Reading

*TB - A Global Emergency. WHO report on the TB epidemic, 1994. WHO/TB/94.177*

*Stop TB at the source. WHO report on the TB epidemic, 1995. WHO/TB/95.183*

*Framework for effective tuberculosis control. WHO Tuberculosis Programme, 1994. WHO/TB/94.179*



## 3 CASE DEFINITIONS

### 3.1 Objectives of chapter

The diagnosis of TB refers to the recognition of an active case, i.e. a patient with symptomatic disease due to lesions caused by *M. tuberculosis*. Beyond making the diagnosis of TB, it is also necessary to define the type of TB case, i.e. to make a case definition. This applies to all TB patients, adults and children. This chapter explains the purpose, importance, determinants and uses of case definitions.

### 3.2 Why case definitions?

The box shows the four purposes of making case definitions.

- for proper patient registration and case notification
- to evaluate the trend in the proportions of new smear-positive cases and smear-positive relapse and other retreatment cases
- to allocate cases to standardised treatment categories
- for cohort analysis

### 3.3 Why match treatment to standardised category?

The box shows the three reasons for matching treatment to standardised category.

- to prioritise resource allocation to the treatment of sputum smear-positive cases
- to avoid under-treatment of sputum smear-positive cases and therefore to prevent acquired resistance
- to increase cost-effective use of resources and to minimise side-effects for patients by avoiding unnecessary over-treatment

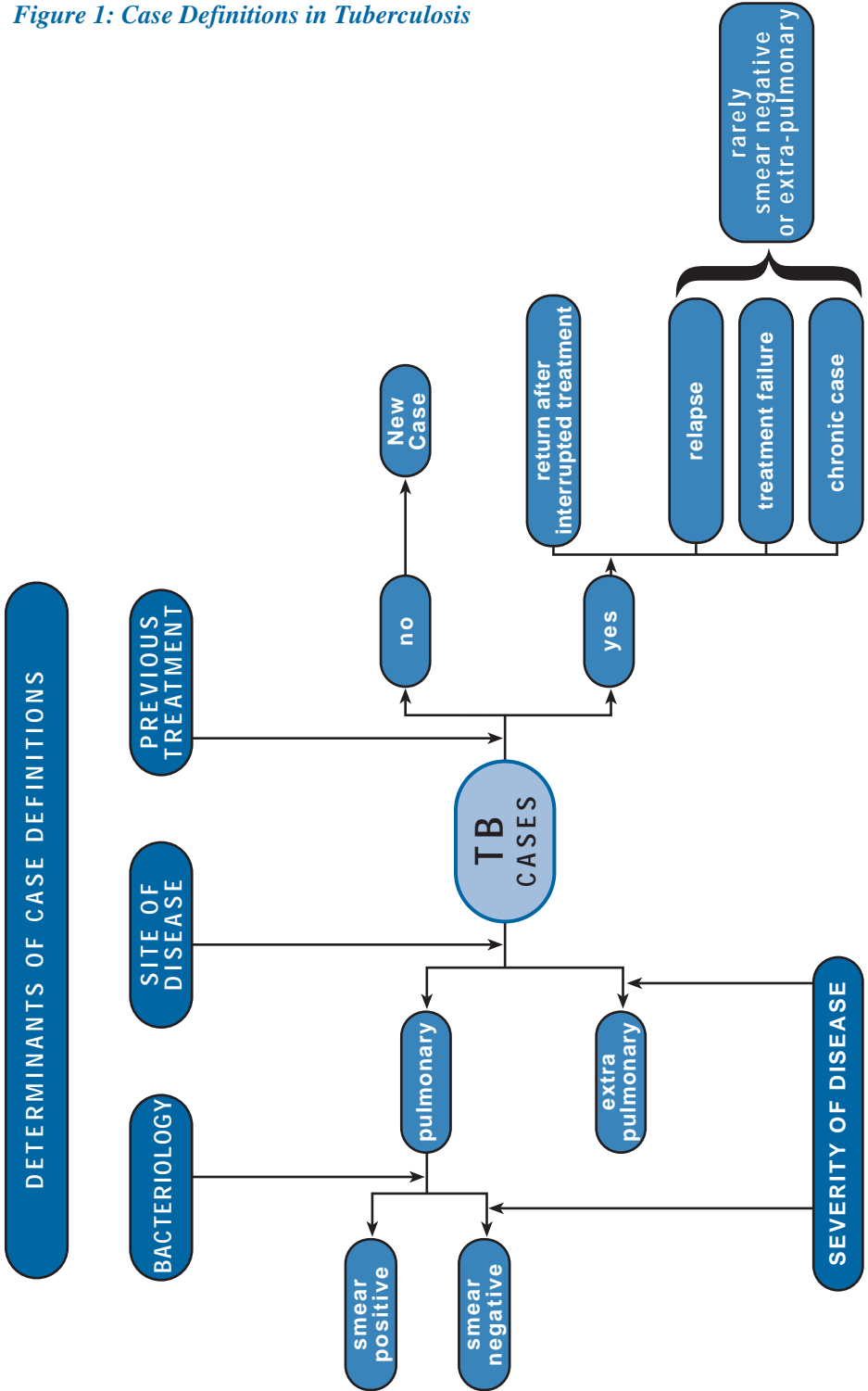
### 3.4 What determines case definitions?

The box shows the four determinants of case definition.

- site of TB disease
- severity of TB disease
- bacteriology (result of sputum smear)
- history of previous treatment of TB

*Figure 1 summarises the determinants of case definitions.*

Figure 1: Case Definitions in Tuberculosis



### 3.5 Determinants of case definitions

#### 1 Site of TB disease: pulmonary or extrapulmonary

In general, recommended treatment regimens are similar irrespective of site (although, for example, some authorities recommend a prolonged continuation phase for tuberculous meningitis). The importance of defining site is for recording and reporting purposes.

Note:

- Pulmonary TB refers to disease involving the lung parenchyma. Therefore tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extra-pulmonary TB.
- A patient with both pulmonary and extra-pulmonary TB constitutes a case of pulmonary TB.
- The case definition of an extra-pulmonary case with several sites affected depends on the site representing the most severe form of disease.

#### 2 Severity of TB disease

Bacillary load, extent of disease and anatomical site are considerations in determining TB disease severity and therefore the appropriate treatment. Involvement of an anatomical site results in classification as severe disease if there is either a significant acute threat to life (e.g. pericardial TB) or a risk of subsequent severe handicap (e.g. spinal TB), or both (e.g. meningeal TB).

The following forms of extra-pulmonary TB are classified as severe: meningitis, miliary, pericarditis, peritonitis, bilateral or extensive pleural effusion, spinal, intestinal, genito-urinary.

The following forms of extra-pulmonary TB are classified as less severe: lymph node, pleural effusion (unilateral), bone (excluding spine), peripheral joint, skin.

#### 3 Bacteriology (result of sputum smear)

The importance of defining the smear result in pulmonary cases is for the following:

- the identification of smear-positive cases (because they are the most infectious cases and they have an increased mortality);
- recording and reporting (smear-positive cases are the only cases for which bacteriological monitoring of cure is available).

The flow chart in Annex 1 shows the recommended diagnostic approach in pulmonary TB suspects.

***Smear-positive pulmonary TB***

**EITHER:** a patient with at least two sputum specimens positive for acid-fast bacilli by microscopy;

**OR:** a patient with at least one sputum specimen positive for acid-fast bacilli by microscopy and radiographic abnormalities consistent with pulmonary TB; and a decision by a physician to treat with a full curative course of anti-TB chemotherapy;

**OR:** a patient with at least one sputum specimen positive for acid-fast bacilli by microscopy, which is culture positive for *M. tuberculosis*.

Under programme conditions, when microscopy laboratory services are available and diagnostic criteria are properly applied, pulmonary TB smear-positive cases represent at least 65% of the total of pulmonary TB cases in adults, and 50% or more of all TB cases. Note that these proportions may be lower in high HIV incidence populations.

***Smear-negative pulmonary TB***

**EITHER:** a patient who fulfills all the following criteria:

- two sets (taken at least 2 weeks apart) of at least two sputum specimens negative for acid-fast bacilli on microscopy;
- radiographic abnormalities consistent with pulmonary TB and a lack of clinical response despite one week of a broad-spectrum antibiotic;
- a decision by a physician to treat with a full curative course of anti-TB chemotherapy;

**OR:** a patient who fulfills all the following criteria:

- severely ill;
- at least two sputum specimens negative for acid-fast bacilli by microscopy;
- radiographic abnormalities consistent with extensive pulmonary TB (interstitial or miliary);
- a decision by a physician to treat with a full curative course of anti-TB chemotherapy;

**OR:** a patient whose initial sputum smears were negative, who had sputum sent for culture initially, and whose subsequent sputum culture result is positive.

**N.B.** It is apparent from the above definitions that in the absence of culture, standard chest radiography is necessary to document cases of smear-negative pulmonary TB. Fluoroscopy examination results are not acceptable as documented evidence of pulmonary TB.

**4 History of previous treatment: treatment after interruption (default), treatment failure, relapse**

It is important for the following purposes to define a case according to whether or not the patient has previously received anti-TB treatment:

- the identification of patients at increased risk of acquired drug resistance and the prescription of appropriate treatment;
- epidemiological monitoring.

### 3.6 Case definitions

#### *New case*

A patient who has never had treatment for TB or who has taken anti-tuberculosis drugs for less than four weeks.

#### *Relapse*

A patient who has been declared cured of any form of TB in the past by a physician, after one full course of chemotherapy, and has become sputum smear-positive.

#### *Treatment failure*

A patient who, while on treatment, remained or became again smear-positive five months or later after commencing treatment. It is also a patient who was initially smear-negative before starting treatment and became smear-positive after the second month of treatment.

#### *Treatment after interruption (TAI) (previously known as return after default)*

A patient who interrupts treatment for two months or more, and returns to the health service with smear-positive sputum (sometimes smear-negative but still with active TB as judged on clinical and radiological assessment).

#### *Chronic case*

A patient who remained or became again smear-positive after completing a fully supervised re-treatment regimen.

Note:

- Although smear-negative pulmonary cases and extra-pulmonary cases may also be treatment failures, relapses or chronic cases, this should be a rare event (supported by pathological or bacteriological evidence).

#### ***Importance of case definitions for registration, notification, and treatment categories***

Case definitions are used for 3 purposes: registration of cases, notification (quarterly reports) and determination of treatment categories.

#### **REGISTRATION OF CASES**

On diagnosis, every TB patient is registered in the district TB register under one of the following 6 categories:

- new (smear positive, smear negative and extra-pulmonary)
- relapse
- failure
- treatment after interruption (default)
- transfer in (from another district)
- other (e.g. chronic cases)

**NOTIFICATION OF CASES**

The district TB officer notifies cases to the provincial/regional TB co-ordinator by quarterly reports, prepared from the district TB register, on the following patient categories:

- new (smear positive, smear negative and extra-pulmonary)
- relapse

**TREATMENT CATEGORIES**

For each TB patient, the recommended regimen depends on the treatment category (I, II, III or IV) determined by the case definition.

**SUMMARY OF USES OF CASE DEFINITIONS**

Table 1 shows case definitions used for registration (R), notification(N) and treatment (T) categories.

*Table 1. Summary of uses of case definitions*

*Explanation of contents of table:*

√ indicates use of case definitions for registration (R) and notification (N).

I, II, III, IV indicate the treatment category, or categories, appropriate to the case definitions.

	PTB SMEAR POS NEW	PTB SMEAR POS RELAPSE	PTB SMEAR NEG NEW	EXTRA PTB NEW	TAI	TREATMENT FAILURE	CHRONIC CASE
<b>R</b>	√	√	√	√	√	√	√
<b>N</b>	√	√	√	√			
<b>T</b>	I	II	III (I) (severe)	III (I) (severe)	II <sup>a</sup> I <sup>b</sup> III <sup>c</sup>	II	IV

<sup>a</sup> A patient with pulmonary TB who received treatment for more than one month, interrupted treatment, and then on return has a positive smear, receives category II treatment.

<sup>b</sup> A patient who started on Category I treatment, interrupted treatment, and then on return has a negative smear, continues on Category I treatment.

<sup>c</sup> A patient who started on Category III treatment, interrupted treatment, and then on return has a negative smear, continues Category III treatment.

**Suggestions for Further Reading**

*International Union Against Tuberculosis and Lung Disease.  
Tuberculosis Guide for Low Income Countries. Fourth edition, 1996.*

*Managing TB at District Level. A Training Course.  
WHO Global Tuberculosis Programme, Geneva, 1992. WHO/TB/96.211*

## 4 STANDARDISED TREATMENT REGIMENS

### 4.1 Objectives of chapter

This chapter describes the recommended standardised treatment regimens for the different categories of TB cases.

### 4.2 Aims of treatment

The aims of treatment of TB are the following:

- 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.

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

### 4.3 The essential anti-TB drugs

There are three main properties of anti-TB drugs: bactericidal ability, sterilizing ability and the ability to prevent resistance. The anti-TB drugs possess these properties to different extents. Isoniazid and rifampicin are the most powerful bactericidal drugs, active against all populations of TB bacilli. Pyrazinamide and streptomycin are also bactericidal against certain populations of TB bacilli. Pyrazinamide is active in an acid environment against TB bacilli inside macrophages. Streptomycin is active against rapidly multiplying extracellular TB bacilli. Ethambutol and thioacetazone are bacteriostatic drugs used in association with more powerful bactericidal drugs to prevent the emergence of resistant bacilli.

*Table 2 shows the essential anti-TB drugs, their mode of action and recommended dose (range in parenthesis).*

**Table 2. The essential anti-TB drugs**

ESSENTIAL ANTI-TB DRUG (ABBREVIATION)	MODE OF ACTION	RECOMMENDED DOSE (MG/KG)		
		DAILY	INTERMITTENT	
			3x/WK	2x/WK <sup>a</sup>
isoniazid (H)	bactericidal	5 (4-6)	10 (8-12)	15 (13-17)
rifampicin (R)	bactericidal	10 (8-12)	10 (8-12)	10 (8-12)
pyrazinamide (Z)	bactericidal	25 (20-30)	35 (30-40)	50 (40-60)
streptomycin (S)	bactericidal	15 (12-18)	15 (12-18)	15 (12-18)
ethambutol (E)	bacteriostatic	15 (15-20)	30 (25-35)	45 (40-50)
thioacetazone (T)	bacteriostatic	2.5	not applicable	

<sup>a</sup> WHO does not generally recommend twice weekly regimens. If a patient receiving a twice weekly regimen misses a dose of tablets, this missed dose represents a bigger fraction of the total number of treatment doses than if the patient were receiving a thrice weekly or daily regimen. There is therefore a bigger risk of treatment failure.

Annex 2 provides information on the recommended dosages and common side effects of these drugs.

**N.B.** WHO recommended formulations of anti-TB drugs appear in the WHO Essential Drugs List (EDL). The available formulations and combinations of anti-TB drugs within each country should conform to the EDL.

#### INTERMITTENT USE

Isoniazid, rifampicin, pyrazinamide and streptomycin are all as efficacious when given intermittently (2 or 3 times per week) as when given daily. Ethambutol is usually only given intermittently when also given with rifampicin. Thioacetazone is the only anti-TB drug not effective when given intermittently (2 or 3 times per week).

#### 4.4 Rationale for recommended standardised treatment regimens

##### *New cases*

Treatment regimens have an initial (intensive) phase lasting 2 months and a continuation phase usually lasting 4-6 months. During the initial phase, consisting usually of 4 drugs, there is rapid killing of tubercle bacilli. Infectious patients become non-infectious within about 2 weeks. Symptoms improve. The vast majority of patients with sputum smear-positive TB become smear-negative within 2 months. In the continuation phase fewer drugs are necessary but for a longer time. The sterilizing effect of the drugs eliminates remaining bacilli and prevents subsequent relapse.

In patients with smear positive pulmonary TB, there is a risk of selecting resistant bacilli, since these patients harbour and excrete a large number of bacilli. Short-course chemotherapy regimens consisting of 4 drugs during the initial phase, and 2 drugs during the continuation phase, reduce this risk of selecting resistant bacilli. These regimens are practically as effective in patients with initially resistant organisms as in those with sensitive organisms.

In patients with smear negative pulmonary or extra-pulmonary TB there is little risk of selecting resistant bacilli since these patients harbour fewer bacilli in their lesions. Short-course chemotherapy regimens with three drugs during the initial phase, and two drugs in the continuation phase, are of proven efficacy.

##### *Re-treatment cases*

Previously treated patients may have acquired drug resistance. They are more likely than new patients to harbour and excrete bacilli resistant to at least isoniazid. The re-treatment regimen consists of initially 5 drugs, with 3 drugs in the continuation phase. The patient receives at least 2 drugs in the initial phase which are still effective. This reduces the risk of selecting further resistant bacilli.

#### 4.5 Rationale for prioritization of patient treatment categories

From the public health perspective the highest TB control programme priority is the identification and cure of the infectious cases, i.e. those patients with sputum smear-positive pulmonary TB. In settings of resource constraint, it is necessary for rational resource allocation to prioritise TB treatment categories according to the cost-effectiveness of treatment of each category. Treatment categories are therefore ranked from I (highest priority) to IV (lowest priority).

#### 4.6 Standard code for TB treatment regimens

There is a standard code for TB treatment regimens. Each anti-TB drug has an abbreviation (shown in Table 2). A regimen consists of 2 phases. The number before a phase is the duration of that phase in months. A number in subscript (e.g. 3) after a letter is the number of doses of that drug per week. If there is no number in subscript after a letter, then treatment with that drug is daily. An alternative drug (or drugs) appears as a letter (or letters) in brackets.

**EXAMPLES:****2 HRZE / 6 HE**

This is a common regimen.

The **initial phase** is **2 HRZE**. The duration of the phase is 2 months.

Drug treatment is daily (no subscript number, e.g. <sub>3</sub> after the letters), with isoniazid (H), rifampicin (R), 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).

**2 H<sub>3</sub>R<sub>3</sub>Z<sub>3</sub>E<sub>3</sub> / 4 H<sub>3</sub>R<sub>3</sub>**

In some countries, resources are available to provide rifampicin in the continuation phase as well as in the initial phase.

The **initial phase** is **2H<sub>3</sub>R<sub>3</sub>Z<sub>3</sub>E<sub>3</sub>**. The duration of the phase is 2 months.

Drug treatment is 3 times per week (subscript number <sub>3</sub> after the letters).

The **continuation phase** is **4 H<sub>3</sub>R<sub>3</sub>**. The duration is 4 months, with isoniazid and rifampicin three times per week (subscript number <sub>3</sub> after the letters).

**4.7****Recommended treatment regimens for different treatment categories**

There are several different possible regimens. The regimens recommended in each country's NTP depend on that country's budget, health coverage by PHC services, and qualifications of health staff at peripheral level. For each patient, the regimen recommended depends on the patient treatment category. Table 3 shows possible alternative regimens for each treatment category that can be used under various circumstances and in certain sub-populations. **Follow the regimens recommended by your NTP in your country, shown in your NTP manual.**

**Table 3. Possible alternative treatment regimens for each treatment category**

TB TREATMENT CATEGORY	TB PATIENTS	ALTERNATIVE TB TREATMENT REGIMENS	
		INITIAL PHASE (DAILY OR 3 TIMES PER WEEK)	CONTINUATION PHASE
I	New smear-positive PTB; new smear-negative PTB with extensive parenchymal involvement; new cases of severe forms of extra-pulmonary TB.	2 EHRZ (SHRZ) 2 EHRZ (SHRZ) 2 EHRZ (SHRZ)	6 HE 4 HR 4 H <sub>3</sub> R <sub>3</sub>
II	Sputum smear-positive: relapse; treatment failure; treatment after interruption.	2 SHRZE/1 HRZE 2 SHRZE/1 HRZE	5 H <sub>3</sub> R <sub>3</sub> E <sub>3</sub> 5 HRE
III	New smear-negative PTB (other than in Category 1); new less severe forms of extra-pulmonary TB.	2 HRZ 2 HRZ 2 HRZ	6 HE 4 HR 4 H <sub>3</sub> R <sub>3</sub>
IV	Chronic case (still sputum-positive after supervised re-treatment)	NOT APPLICABLE (Refer to WHO guidelines for use of second-line drugs in specialized centres)	

**N.B.** Some authorities recommend a 7 month continuation phase with daily isoniazid and rifampicin (7 HR) for Category 1 patients with the following forms of TB: TB meningitis, miliary TB, spinal TB with neurological signs.

*Table 2 on page 26 and Tables 11-12 in Annex 3 show, for the currently recommended treatment regimens, the drug doses which are appropriate for most patients with TB.*

## 4.8 Treatment regimens in special situations

### *Treatment for pregnant women*

It is important to ask a woman before she starts anti-TB chemotherapy if she is pregnant. Most anti-TB drugs are safe for use in pregnant women. The exception is streptomycin which is ototoxic to the fetus, should not be used in pregnancy, and can be replaced by ethambutol. It is important to explain to a pregnant woman that successful treatment of TB with the recommended standardised regimen is important for a successful outcome of pregnancy.

### *Treatment for breastfeeding women*

A woman who is breastfeeding and has TB should receive a full course of anti-TB chemotherapy. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to her baby. All the anti-TB drugs are compatible with breastfeeding and a woman taking them can safely continue to breastfeed her baby. The mother and baby should stay together and the baby should continue to breastfeed in the normal way. The baby should receive isoniazid prophylaxis and BCG immunisation.

### *Treatment for women taking the oral contraceptive pill*

Rifampicin interacts with the oral contraceptive pill, with a risk of decreased protective efficacy against pregnancy. A woman who usually takes the oral contraceptive pill may choose between the following two options while receiving treatment with rifampicin. Following consultation with a physician, she could take an oral contraceptive pill containing a higher dose of oestrogen (50mcg). Alternatively she could use another form of contraception.

### *Treatment for patients with liver disorders*

The patients with the following conditions can receive the usual short-course chemotherapy regimens provided that there is no clinical evidence of chronic liver disease: hepatitis virus carriage, a past history of acute hepatitis, excessive alcohol consumption.

### *Established chronic liver disease*

Isoniazid plus rifampicin plus one or two non-hepatotoxic drugs such as streptomycin and ethambutol can be used for a total treatment duration of eight months. An alternative regimen is streptomycin plus isoniazid plus ethambutol in the initial phase followed by isoniazid and ethambutol in the continuation phase, with a total treatment duration of 12 months. Patients with liver disease should not receive pyrazinamide. Therefore recommended regimens are the following: 2 SHRE/6 HR or 2 SHE/10 HE.

### *Acute hepatitis (e.g. acute viral hepatitis)*

It is a rare eventuality that a patient has TB and also at the same time acute hepatitis unrelated to TB or anti-TB treatment. Clinical judgement is necessary. In some cases it is possible to defer TB treatment until the acute hepatitis has resolved. In other cases when it is necessary to treat TB during acute hepatitis,

the combination of streptomycin and ethambutol up to a maximum duration of 3 months is the safest option until the hepatitis has resolved. The patient can then receive a continuation phase of 6 months isoniazid and rifampicin (6 HR).

### *Treatment of patients with renal failure*

Isoniazid, rifampicin and pyrazinamide are either eliminated almost entirely by biliary excretion or metabolized into non-toxic compounds. These drugs can, therefore, be given in normal dosage to patients with renal failure. In severe renal failure, patients should receive pyridoxine with isoniazid in order to prevent peripheral neuropathy. Streptomycin and ethambutol are excreted by the kidney. Where facilities are available to monitor renal function closely it may be possible to give streptomycin and ethambutol in reduced doses. Thioacetazone is excreted partially in the urine, but since the margin is too narrow between a therapeutic and a toxic dose, patients in renal failure should not receive this drug.

The safest regimen to be administered in patients with renal failure is as follows: 2 HRZ/6 HR.

### **Suggestions for Further Reading**

*Crofton J, Horne N, Miller F. Clinical Tuberculosis. Macmillan Education Limited. 1992.*

*WHO, 1995. Essential Drugs. WHO Model List: revised in December 1995.  
WHO Drug Information, Vol. 9, No. 4, 223-234.*

*Crofton J, Chaulet P, Maher D. Guidelines for the management of drug-resistant tuberculosis. WHO Global Tuberculosis Programme, Geneva, 1997. WHO/TB/96.210 (Rev. 1).*



## 5 MONITORING THE PATIENT

### 5.1 Objectives of chapter

The objectives of this chapter are to provide clear guidelines on the following:

- how to monitor and record the response to treatment, especially in sputum smear-positive TB patients;
- how to monitor and manage drug-induced toxicity.

### MONITORING THE TREATMENT RESPONSE

### 5.2 Monitoring the treatment response

Patients with sputum smear-positive pulmonary TB should be monitored by sputum smear examination. This is the only group of TB patients for whom bacteriological monitoring is possible. It is unnecessary and wasteful of resources to monitor the patient by chest radiography. For patients with sputum smear-negative pulmonary TB and extra-pulmonary TB, clinical monitoring is the usual way of assessing response to treatment. Under programme conditions in high TB incidence countries, routine monitoring by sputum culture is not feasible or recommended. Where facilities are available, culture surveys can be useful as part of quality control of diagnosis by smear microscopy.

### 5.3 New sputum smear-positive pulmonary TB patients (Category I)

The treatment response should be monitored by sputum smear examination. In general, two sputum specimens should be collected for smear examination at each follow-up sputum check.

Table 4 shows when sputum smears should be performed in the six month and eight month treatment regimens. Negative sputum smears at the times shown in Table 4 indicate good treatment progress, which encourages the patient and the health worker responsible for supervising the treatment.

**Table 4. Monitoring by sputum smear examination of patients with new smear-positive pulmonary TB**

SPUTUM SMEAR EXAMINATION	TREATMENT REGIMENS	
	SIX MONTH REGIMEN	EIGHT MONTH REGIMEN
At end of initial phase	End of second month	End of second month
In continuation phase	End of fourth month	End of fifth month
At end of treatment	In the sixth month	In the eighth month

At the end of the second month of treatment most patients will have a negative sputum smear. Such patients will then start the continuation phase of treatment. If a patient has a positive sputum smear at this time, this may indicate one of the following:

- most frequently, that the initial phase of therapy was poorly supervised and patient adherence was poor;
- sometimes, that there is a slow rate of progress with sputum smear conversion, e.g. if a patient had extensive cavitation and an initial heavy bacillary load;
- rarely, that the patient may have drug-resistant TB which does not respond to first line treatment.

Whatever the reason, if the sputum smears are positive at the end of the second month, the initial phase is prolonged for a third month. The patient then starts the continuation phase. If the sputum smears are still positive at the end of the 5th month, this constitutes treatment failure. The patient is re-registered as a treatment failure and starts a full course of the re-treatment regimen as a Category II patient.

In most high TB prevalence countries, susceptibility testing should be reserved for surveillance of drug resistance. Access to culture facilities and the reliability of susceptibility testing are usually inadequate for the utilisation of susceptibility test results in patient management.

In some settings where culture facilities are accessible and susceptibility test results are reliable, susceptibility testing may be useful in cases of treatment failure or relapse, or in chronic cases.

#### 5.4 Previously treated sputum smear-positive patients (Category II)

Sputum smear examination is performed at the end of the initial phase of treatment (at the end of the third month), during the continuation phase of treatment (at the end of the fifth month) and at the end of treatment (at the end of the eighth month). If the patient is sputum smear-positive at the end of the third month, the initial phase of treatment with four drugs is extended by another month and sputum smears examined again at the end of the fourth month. If the patient still has positive smears at the end of the fourth month, where possible sputum is sent to the laboratory for culture and sensitivity, and the patient then starts the continuation phase. If the culture and sensitivity results subsequently show resistance to 2 or more of the 3 drugs employed in the continuation phase, then the patient should be referred to a specialized centre for consideration of treatment with second-line anti-TB drugs. Where there are no facilities for culture and sensitivity testing, the patient continues treatment right until the end of the re-treatment regimen.

#### 5.5 New sputum smear-negative pulmonary TB patients (usually Category III)

It is important to check sputum smears at the end of the second month in case of the following 2 possibilities: an error at the time of initial diagnosis (i.e. a true smear-positive patient was misdiagnosed as smear-negative); non-adherence to

treatment. A patient who was initially diagnosed as sputum smear-negative and treated as a category III patient, and who has a positive sputum smear at the end of the second month, should then be re-registered as sputum smear-positive and start a full course of treatment as a Category II patient.

## RECORDING THE TREATMENT RESPONSE

### 5.6 Recording standardised treatment outcomes

At the end of the treatment course in each individual patient with sputum smear-positive pulmonary TB, the District TB Officer records the treatment outcome in the District TB Register. Table 5 shows the standardised definitions of treatment outcomes.

*Table 5. Recording treatment outcome in smear-positive TB patients*

Cure	Patient who is smear-negative at, or one month prior to, the completion of treatment and on at least one previous occasion
Treatment completed	Patient who has completed treatment but without proof of cure
Treatment failure	Patient who remains or becomes again smear-positive at five months or later during treatment
Died	Patient who dies for any reason during the course of treatment
Treatment interrupted (default)	Patient whose treatment was interrupted for 2 months or more
Transfer out	Patient who has been transferred to another reporting unit and for whom the treatment outcome is not known

Note:

- Sputum smear-positive patients who are identified in the sputum laboratory register but have never appeared for registration or treatment must be registered in the District TB Register and should be classified as treatment interrupted (defaulters) in the treatment outcome (“default before starting treatment”).
- Patients wrongly diagnosed as having TB should be erased from the District TB Register and therefore not included in treatment outcome analysis.
- In smear-negative pulmonary TB and extra-pulmonary TB patients, cure and treatment failure cannot be assessed because these outcome indicators depend on sputum smear examination. However, outcome indicators such as treatment completion, death, default and transfer out should be recorded for these patients in the District TB Register.

### 5.7 Cohort analysis of treatment outcome in smear-positive pulmonary TB patients

The District TB Officer should perform cohort analysis of treatment outcome every quarter-year and at the end of every year. A cohort of TB patients consists of all those sputum smear-positive pulmonary TB patients registered during a certain time which is usually a quarter of a year (i.e. 1 January to 31 March, 1 April to 30 June, 1 July to 30 September, and 1 October to 31 December). New and previously treated patients form separate cohorts. Evaluation of the end of treatment (6 or 8 months) outcome takes place about three months after all patients in the cohort would have completed their course of treatment.

District quarterly reports on treatment outcome are forwarded to the Region. The Regional TB Officer verifies that district reports are correct, complete and consistent, compiles cohort analysis reports on all sputum smear-positive patients in the region, and submits the report to the Central Unit of the National TB Control Programme (NTP). The NTP compiles cohort analysis reports on all smear-positive TB patients registered nationally. Cohort analysis is the key management tool used to evaluate the effectiveness of TB control programme delivery. It enables the identification of problems, so that the NTP can institute appropriate action to overcome them and improve programme performance.

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## MONITORING AND MANAGING DRUG TOXICITY

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### 5.8 Monitoring of TB patients for significant adverse effects of anti-TB drugs

Most TB patients complete their treatment without any significant adverse effects of drugs. However, a few patients do develop adverse effects and therefore clinical monitoring of all TB patients for adverse effects is important during treatment. Routine laboratory monitoring is not necessary.

Health personnel can monitor adverse effects of drugs in the following two ways. First, they can teach patients how to recognise symptoms of common adverse effects and to report if they develop such symptoms. Second, they can specifically ask about symptoms when patients report to collect drugs.

### 5.9 Prevention of adverse effects of drugs

Health personnel can prevent some drug-induced side effects, for example isoniazid-induced peripheral neuropathy. This usually presents as burning sensation of the feet and occurs more commonly in pregnant women and in people with the following conditions: HIV infection, alcohol abuse, malnutrition, diabetes, chronic liver disease. These patients should receive preventive treatment with pyridoxine 10 mg daily along with their anti-TB drugs.

### 5.10 Adverse effects of anti-TB drugs

The adverse effects of individual anti-TB drugs are shown in Annex 2. Table 6 shows a symptom-based approach to adverse effects. Adverse effects are classified as minor or major. In general, a patient who develops minor adverse effects should continue the anti-TB treatment, usually at the same dose but sometimes at a reduced dose. The patient also receives symptomatic treatment. If a patient develops a major side effect, the treatment or the offending drug is stopped. Further management depends on the nature of the adverse reaction and is shown in Table 6. Patients with major adverse reactions should be managed in a district or central hospital.

**Table 6. Symptom-based approach to adverse effects of TB drugs**

SIDE EFFECTS	DRUG(S) PROBABLY RESPONSIBLE	MANAGEMENT
<b>Minor</b>		<b>Continue anti-TB drugs, check drug doses</b>
Anorexia, nausea, abdominal pain	Rifampicin	Give drugs last thing at night
Joint pains	Pyrazinamide	Aspirin
Burning sensation in the feet	Isoniazid	Pyridoxine 100 mg daily
Orange/red urine	Rifampicin	Reassurance
<b>Major</b>		<b>Stop responsible drug(s)</b>
Itching of skin, skin rash	Thioacetazone (Streptomycin)	Stop anti-TB drugs, see below
Deafness (no wax on auroscopy)	Streptomycin	Stop streptomycin, use ethambutol
Dizziness (vertigo and nystagmus)	Streptomycin	Stop streptomycin, use ethambutol
Jaundice (other causes excluded)	Most anti-TB drugs (especially isoniazid, pyrazinamide and rifampicin)	Stop anti-TB drugs, see below
Vomiting and confusion (suspect drug-induced acute liver failure)	Most anti-TB drugs	Stop anti-TB drugs. Urgent liver function tests and prothrombin time
Visual impairment (other causes excluded)	Ethambutol	Stop ethambutol
Shock, purpura, acute renal failure	Rifampicin	Stop rifampicin

### 5.11 Management of a cutaneous reaction

The approach depends on whether or not the patient is receiving thioacetazone.

*Treatment regimen includes thioacetazone.*

If a patient develops itching, with or without a rash, and there is no other obvious cause (e.g. scabies), it is essential to stop anti-TB drugs at once. Treatment is only restarted once the skin reaction has completely resolved. The patient will need intravenous fluids, and possibly steroids, if the rash is severe, or if there is mucosal involvement or hypotension. A patient must never receive thioacetazone again after any thioacetazone reaction.

*Treatment regimen does not include thioacetazone*

If a patient develops itching, and there is no obvious cause (e.g. scabies), the recommended approach is to try symptomatic treatment with anti-histamines, continue anti-TB treatment, and observe the patient closely. However, if a skin rash develops then all anti-TB drugs must be stopped. Once the reaction has resolved, anti-TB drugs are re-introduced. The problem is how to re-introduce TB treatment when the particular anti-TB drug responsible for the reaction is not known. Table 7 shows the standard approach to re-introducing anti-TB drugs after a drug reaction.

**Table 7. Re-introduction of anti-TB drugs following drug reaction**

DRUGS (IN SEQUENCE)	LIKELIHOOD OF CAUSING A REACTION	CHALLENGE DOSES		
		DAY 1	DAY 2	DAY 3
Isoniazid	least likely	50mg	300mg	300mg
Rifampicin	↓	75mg	300mg	Full dose
Pyrazinamide		250mg	1 gram	Full dose
Ethambutol		100mg	500mg	Full dose
Streptomycin		125mg	500mg	Full dose
		most likely		

If the initial cutaneous reaction was severe, smaller initial challenge doses should be given (approximately one tenth of the doses shown for day 1).

The idea of drug challenging is to identify the drug responsible for the reaction. Drug challenge starts with the anti-TB drug least likely to be responsible for the reaction (i.e. isoniazid). The idea of starting with a small challenge dose is that if a reaction occurs to a small challenge dose, it will not be such a bad reaction as to a full dose. The dose is gradually increased over 3 days. The procedure is repeated, adding in one drug at a time. A reaction after adding in a particular drug identifies that drug as the one responsible for the reaction. There is no evidence that this challenge process gives rise to drug resistance.

If the drug responsible for the reaction is pyrazinamide, ethambutol, or streptomycin, anti-TB treatment is resumed without the offending drug. If possible, the offending drug is replaced with another drug. It may be necessary to extend the treatment regimen. The start of the resumed regimen is then considered as a new start of treatment. This prolongs the total time of TB treatment, but decreases the risk of recurrence.

Occasionally, patients develop hypersensitivity to the 2 most potent anti-TB drugs, isoniazid and rifampicin. These drugs form the cornerstone of short-course chemotherapy. If an HIV-negative patient has had a reaction (but not a severe reaction) to isoniazid or rifampicin, it may be possible to desensitise the patient to the drug. However, HIV-infected TB patients must never undergo desensitisation because of the high risk of serious toxicity. Desensitisation procedures are complex. Patients should only undergo desensitisation in specialized centres. It is important to remember that the desensitisation process does give rise to the risk of resistance. Therefore, a patient who is undergoing desensitisation should, if possible, receive 2 anti-TB drugs which the patient has not had before. The reader is referred to “Clinical Tuberculosis” by Crofton, Horne and Miller, 1992, for details.

### 5.12 Management of drug-induced hepatitis

Most anti-TB drugs can damage the liver. Isoniazid, pyrazinamide and rifampicin are most commonly responsible. Ethambutol is rarely responsible. When a patient develops hepatitis during anti-TB treatment, the cause may be the anti-TB treatment or another cause. It is important to rule out other possible causes before deciding that the hepatitis is drug-induced. If the diagnosis is drug-induced hepatitis, stop the anti-TB drugs. After the hepatitis has resolved, the same regimen can often be re-introduced. If drug-induced hepatitis has been severe, then it is advisable to avoid pyrazinamide and also rifampicin. A suggested regimen in such patients is a two month initial phase of daily streptomycin, isoniazid and ethambutol followed by a 10 month continuation phase of isoniazid and ethambutol (2 SHE/10 HE).

A severely ill TB patient with drug-induced hepatitis may die without anti-TB drugs. In this case, treat the patient with 2 of the least hepatotoxic drugs, streptomycin and ethambutol. After the hepatitis has resolved, re-start usual anti-TB treatment.

### Suggestions for Further Reading

*Crofton J, Horne N, Miller F. Clinical Tuberculosis.  
Macmillan Education Limited, 1992.*



## 6 ADHERENCE TO TREATMENT

### 6.1 Objectives of chapter

The public health priority of a National Tuberculosis Programme is to cure smear-positive cases, while avoiding drug resistance. Ensuring adherence to treatment is necessary to achieve this priority, and also to ensure the cure of a patient with any form of TB. This chapter gives recommendations on how to ensure treatment adherence.

### 6.2 Ensuring patient compliance versus defaulter tracing

Patients' compliance is a key factor in treatment success. In many countries, a significant proportion of patients stop treatment before the end, for various reasons. The premature interruption of treatment represents a problem for patients, those who care for them, and those responsible for TB programmes.

Promoting adherence by directly observing treatment is much more important than expending resources on defaulter tracing. When patients receive self-administered treatment, defaulter tracing is difficult and often unproductive, especially in low-income countries.

It is vital for health staff and community workers to be polite and considerate to the patient's needs at every contact with the patient.

### 6.3 Directly observed treatment: questions and answers

#### 6.3.1 *What is directly observed treatment?*

Directly observed treatment is one element of the DOTS strategy, i.e. the WHO recommended policy package for TB control. Direct observation of treatment means that a supervisor watches the patient swallowing the tablets. This ensures that a TB patient takes the right drugs, in the right doses, at the right intervals. In many countries, supervisors have observed patients' treatment in in-patient settings in hospitals or in sanatoria. Supervisors have also directly observed treatment in out-patient settings. The supervisor may be a health worker or a trained and supervised community member. There may be an incentive of some sort for these community members. The NTP trains and monitors the community supervisors who directly observe treatment. There must be a clearly defined line of accountability from NTP staff to general health services staff and the supervisor who directly observes treatment. It is important to ensure confidentiality and that direct observation of treatment is acceptable to the patient.

#### 6.3.2 *Why is it necessary to observe treatment directly?*

Many patients receiving self-administered treatment will not adhere to treatment. It is impossible to predict who will or will not comply, therefore directly observed treatment is necessary at least in the initial phase to ensure adherence. If a TB patient misses one attendance to receive treatment, it is necessary to find that patient and continue treatment.

### 6.3.3 *Is there an alternative to the direct observation of treatment?*

The only proven way of ensuring adherence and achieving WHO global targets is through direct observation of treatment. In some settings in some countries, other ways of closely supervising treatment have been tried. No developing country has so far demonstrated country-wide application of ways of supervising self-administered treatment under programme conditions, with success rates equalling those when treatment is directly observed.

### 6.3.4 *When is direct observation of treatment necessary?*

Direct observation of treatment is always recommended in the following cases:

- two months initial phase of treatment for all new smear-positive cases;
- four months continuation phase of rifampicin-containing (intermittent and daily<sup>1</sup>) regimens, for all new smear-positive cases;
- throughout the whole retreatment regimen.

Since it is not always possible to directly observe the treatment of all patients throughout the whole treatment, it is therefore necessary to supervise treatment as closely as possible in other situations:

- initial and continuation phases of treatment for smear-negative pulmonary TB and extra-pulmonary cases;
- six months non-rifampicin-containing continuation phase of treatment for smear-positive cases.

### 6.3.5 *How to ensure that direct observation of treatment fits patients' needs?*

A TB patient who has to go far for treatment is less likely to adhere to treatment. One of the aims of a TB programme is to organise TB services so that the patient has TB treatment as close to home (or sometimes the workplace) as possible. A TB programme brings TB treatment to TB patients close to where they live, by integrating TB services with general health services.

Many TB patients live close to a health facility (e.g. health centre, district hospital). For these patients, the supervisor who directly observes treatment will therefore be one of the health staff in the health facility. Some TB patients live far away from a health facility. For these patients, the supervisor will be a health outreach worker or a trained local community member. Collaboration with other programmes allows the identification of staff from these other programmes, e.g. leprosy control programme, who may supervise direct observation of treatment. Some areas have HIV/AIDS community care schemes. The HIV/AIDS home care providers with suitable training and monitoring can supervise direct observation of treatment.

<sup>1</sup> There is an exception to the recommendation of direct observation of treatment for the continuation phase of a daily rifampicin-containing regimen. In low-incidence countries (TB incidence rate less than 10 per 100,000), close supervision of self-administered treatment using fixed dose combinations is recommended provided that programmes demonstrate high (85%) sputum conversion and cure rates.

### 6.3.6 *How to facilitate the direct observation of treatment?*

- The aim is maximised ambulatory treatment with treatment as close to the patient's home (or sometimes the workplace) as possible. Where possible, general health services staff should directly observe treatment. When this is not possible, community supervisors can directly observe treatment.
- Where possible, use fixed drug combinations (see Annex 3) and blister packs to help reduce risk of wrong use of tablets.
- The use of fixed dose combinations and blister packs is mandatory when doses are not directly observed.
- Consider incentives for staff and patients, bearing in mind the advantages and disadvantages of incentive schemes.

### 6.3.7 *How to ensure the direct observation of treatment in different settings?*

The way of ensuring direct observation of treatment depends on the setting, facilities, resources and environment. There must therefore be flexibility in ensuring the direct observation of treatment, with adaptation in different districts and countries. Table 8 shows examples of methods of ensuring direct observation of treatment adapted to local circumstances.

For any chosen method of supervision and administration of treatment, a programme must show high sputum smear conversion and cure rates, under routine conditions in rural and urban areas on a large and representative sample. If evaluation of the method of supervision and administration of the regimen showed that the method failed, the method should be altered and tested in regional and national demonstration and training districts.

Within a country, a district or region which demonstrates a successful method of ensuring direct observation of treatment can be a model for other districts or regions. A country which demonstrates successful direct observation of treatment may be a model for neighbouring countries in the same region.

## 6.4 **Interrupted treatment (default): what to do?**

The direct observation of treatment, adapted to patients' needs and to the working conditions of health care workers, is certainly the best method of avoiding treatment interruption. However, even with direct observation of treatment, and also during the continuation phase of treatment which is often self-administered, there may be treatment interruptions.

### 6.4.1 *Preventive measures to decrease the duration of treatment interruption*

At the time of registration of a tuberculosis patient starting treatment, it is important to set aside enough time to meet with the patient, and preferably also with the patient's relative(s), since this is an important opportunity to advise and counsel the patient. During this meeting, it is vital to record the patient's details, address and several other addresses (e.g. partner/spouse, parents, work place,

place of study) in order to be sure to be able to contact the patient. Also, it is important to identify potential problems which the patient may face during the initial phase of treatment.

A new meeting with the patient at the end of the initial phase of treatment enables confirmation or correction of contact addresses. The patient can inform the health worker about plans (work, family, moving house) for the following months of the continuation phase of treatment. In some countries, a visit to the patient's home during the two months' initial phase of treatment allows verification of the patient's exact address, while at the same time providing an opportunity to arrange for screening of household contacts, especially children under the age of 5 years.

#### 6.4.2 *Corrective measures to decrease the duration of treatment interruption*

When a patient doesn't keep an arranged appointment to receive treatment, it is necessary to find the patient, using the contact addresses previously obtained and appropriate means of tracing the patient according to each local context. In order to take appropriate action, it is important in the following week to find out the cause of the patient's absence (e.g. death, accident, other intermittent illness, change of address on account of work or family reasons).

**Table 8. Examples of methods of ensuring direct observation of treatment adapted to local circumstances**

SETTING	LOCATION	METHODS OF ENSURING DIRECT OBSERVATION OF TREATMENT
Rural nomads living in an area with a poor health infrastructure	North-East Province, Kenya	Prolonged intensive phase of treatment in "manyattas" (villages)
Urban, close-knit families	Guinea, West Africa	Role of extended family
Rural villages	Hlabisa, South Africa, KwaZulu/Natal	Community supervisors, e.g. store-keepers
Inner-city deprivation with marginalised groups, e.g. alcoholics, drug users, homeless	New York City, U.S.A.	Outreach health workers
Rural, good district hospitals	Malawi, Africa	Hospitalisation in intensive phase
Rural, good primary health care infrastructure	China	Village health workers, incentive scheme
Urban, accessible health facilities	Tanzania	Ambulatory attendance at health facilities

## 7 HIV INFECTION AND TUBERCULOSIS

### 7.1 Objectives of chapter

This chapter briefly sets out the epidemiology of the TB/HIV co-epidemic and describes the implications of the co-epidemic for the treatment of TB.

### 7.2 Epidemiology of TB/HIV co-epidemic

The HIV epidemic has increased the burden of TB, especially in populations where the prevalence of TB infection is high among young adults. It is estimated that world-wide nearly two billion people are infected with *M. tuberculosis*, 16 million are HIV infected and five to six million are dually infected with *M. tuberculosis* and HIV. 70% of TB/HIV dually infected people live in sub-Saharan Africa and 20% in Asia. HIV is the most powerful factor known to increase the risk of progression of TB infection to disease: for a person dually infected with HIV and *M. tuberculosis*, the lifetime risk of developing TB is about 50%.

In several countries in sub-Saharan Africa, 30% to 70% of TB patients are HIV-positive. In some countries the incidence of TB has more than doubled during the last 10 years. This has placed an enormous burden on their general health services, particularly hospitals.

### 7.3 Patterns of HIV-related TB

As HIV infection progresses, CD4 lymphocytes decline in number and function. The immune system is less able to prevent the growth and local spread of *M. tuberculosis*. Disseminated and extra-pulmonary disease is more common.

#### *Pulmonary TB*

Even in HIV-infected patients, pulmonary TB is still the commonest form of TB. The presentation depends on the degree of immunosuppression. The table below shows how the clinical picture, sputum smear result and chest X-ray appearance often differ in early and late HIV infection.

**Table 9. How pulmonary TB differs in early and late HIV infection**

FEATURES OF PULMONARY TB	STAGE OF HIV INFECTION	
	EARLY	LATE
clinical picture	often resembles post-primary pulmonary TB	often resembles primary pulmonary TB
sputum smear result	often positive	often negative
chest X-ray appearance	often cavities	often infiltrates with no cavities

There has been an increase in reported case rates of smear-negative pulmonary TB in association with the TB/HIV co-epidemic. There is a lack of a widely available “gold standard” diagnostic test for smear-negative pulmonary TB. It is often difficult to distinguish other HIV-related pulmonary diseases from pulmonary TB. The extent of over-diagnosis of smear-negative pulmonary TB is therefore uncertain. It is important to follow recommended diagnostic guidelines as closely as possible in order to diagnose smear-negative pulmonary TB as accurately as possible.

### ***Extra-pulmonary TB***

The commonest forms are the following: lymphadenopathy, pleural effusion, pericardial disease, miliary disease, meningitis.

### ***HIV-related TB in children***

As in adults, the natural history of TB in a child infected with HIV depends on the stage of HIV disease. Early in HIV infection, when immunity is good, the signs of TB are similar to those in a child without HIV infection. As HIV infection progresses and immunity declines, dissemination of TB becomes more common. Tuberculous meningitis, miliary TB, and widespread tuberculous lymphadenopathy occur.

## **7.4 Anti-TB treatment in HIV-infected TB patients**

The same criteria determine treatment categories for TB patients irrespective of HIV status. Generally, anti-TB chemotherapy is the same for HIV-infected as for non-HIV-infected TB patients, with the exception of the use of thioacetazone. Thioacetazone is associated with a high risk of severe, and sometimes fatal, skin reaction in HIV-infected individuals. Ethambutol should therefore be used instead of thioacetazone in patients with known or suspected HIV infection.

It is recognised that some countries do not have the resources to substitute ethambutol for thioacetazone. On individual and public health grounds, the most effective treatment available in some countries may still include thioacetazone. Where it is not possible to avoid the use of thioacetazone, it is essential to warn patients about the risk of severe skin reactions. It is essential to advise the patient to stop thioacetazone at once and report to a health unit if itching or a skin reaction occurs.

Streptomycin remains a useful drug in some countries provided that there is the capability to ensure sterilisation of needles and syringes. Some countries with a high HIV prevalence may not be able to ensure sterilisation of needles and syringes and should therefore not use streptomycin.

## **7.5 Response of HIV-infected TB patients to anti-TB treatment**

### ***Case fatality***

The case fatality of TB/HIV patients 1 year after starting TB treatment is about 20%. This case fatality is greater than that in HIV-negative TB patients. The excess deaths in TB/HIV patients during and after treatment are partly due to TB

itself and partly due to other HIV-related problems. Case fatality is less in TB/HIV patients treated with SCC than with the old standard regimen (1 SHT or SHE / 11 HT or HE). This is partly because SCC is a more effective anti-TB treatment. Also, rifampicin has broad-spectrum antimicrobial activity as well as anti-TB activity. This may decrease deaths due to HIV-related bacterial infections during anti-TB treatment.

### ***Response in survivors***

Several studies have assessed the clinical, radiological, and microbiological response to SCC in HIV-positive and HIV-negative TB patients. Excluding patients who died, response rates were similar in HIV-positive and HIV-negative TB patients.

### ***Recurrence of TB after completing anti-TB treatment***

The recurrence rate is similar in HIV-positive and HIV-negative TB patients who complete SCC. The recurrence rate is higher in HIV-positive than in HIV-negative TB patients treated with the old standard treatment regimens.

## **7.6 Consequences of HIV for TB control**

The consequences include the following:

- over-diagnosis of sputum smear-negative PTB
- under-diagnosis of sputum smear-positive PTB
- inadequate supervision of anti-TB chemotherapy
- low cure rates
- high case fatality rates during treatment
- high default rates because of adverse drug reactions
- high rates of TB recurrence
- increased emergence of drug resistance

## **7.7 Response of National TB Programmes to the TB/HIV epidemic**

The impact of HIV exposes any weaknesses in NTPs. The HIV epidemic heightens the need to focus on the identification and cure of infectious TB patients. The principles of TB control are the same even when there are many TB/HIV patients. However, in populations where TB/HIV is common, health services struggle to cope with the large and rising numbers of TB patients.

The TB/HIV epidemic necessitates the following responses:

- strengthening of NTPs (structures and activities) and decentralisation of treatment activities;
- strengthening of co-ordination and collaboration between NTPs, HIV/AIDS/STD services and general health services;

- reinforcing diagnostic criteria for pulmonary and extra-pulmonary TB;
- searching for local solutions in certain settings where there has been the biggest increase in TB burden, e.g. large cities.

### 7.8 HIV counselling and testing of individual TB patients

The link between HIV and TB is well known to many members of the public. A patient who has TB may therefore be well aware of the possibility of also having HIV infection. It is important to offer counselling and voluntary HIV testing, if available, to TB patients on account of the following possible benefits:

- patients may want the chance to know their HIV status;
- better diagnosis and management of other HIV-related illnesses;
- avoidance of drugs associated with a high risk of side-effects;
- increased condom use and decreased HIV transmission.

A policy of compulsory HIV testing (even if this were legal) of TB patients would be counter-productive. This type of policy would have the following results:

- patients deterred from seeking care;
- decreased case-finding in at-risk groups;
- reduced credibility of health services.

Confidential counselling is essential before and after HIV antibody testing. The patient gives explicit informed consent to have the test, i.e. the patient understands what the test involves and the implications of testing. The counsellor provides support. Counselling is a dialogue between patient and counsellor.

### 7.9 Co-ordinated care of TB patients.

NTP staff and general health service staff need to be aware of other HIV-related diseases that TB/HIV patients may have as well as TB. Co-ordination of care in different settings and at different levels promotes continuity of care for TB/HIV patients. Sometimes patients know they are HIV-positive and later on develop TB. More often, patients only find out they are HIV-positive after developing TB. In either case, the TB control programme needs to co-ordinate closely with other services providing support and care for HIV-positive individuals. The clinician who treats the TB/HIV patient is in a key position to refer the patient to appropriate services for counselling, support, and care of the patient and the family.

#### Suggestions for Further Reading

*Harries AD, Maher D. TB/HIV: A Clinical Manual.  
World Health Organisation Global Tuberculosis Programme, 1996.*

## ANTI-TUBERCULOSIS DRUG SUPPLY AND USE

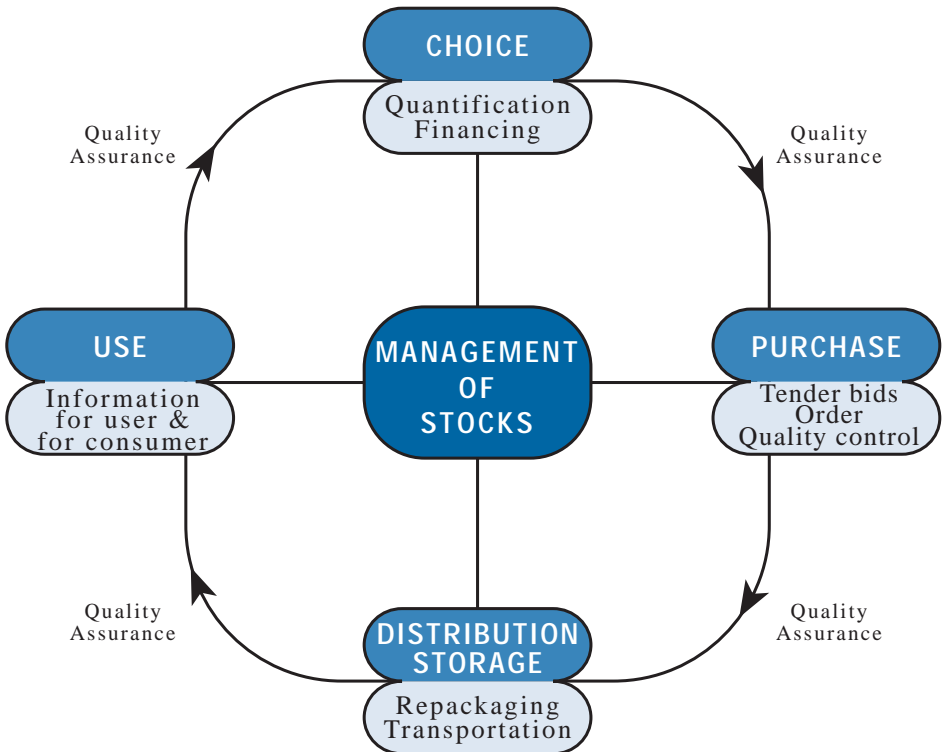
### 8.1 Objectives of chapter

The regular supply of anti-TB drugs and their appropriate use are two prerequisites of success for all NTPs. The essential task of NTP managers is always to ensure a complete curative course of chemotherapy for all detected and registered TB patients. This chapter sets out how NTP managers can ensure the regular supply of anti-TB drugs and their appropriate use.

### 8.2 The drug logistic cycle

To accomplish the task of ensuring the regular supply of anti-TB drugs and their appropriate use, each step of the drug logistic cycle must be followed.

*Figure 2. Drug Logistic Cycle*



### 8.3 Selecting the right drug formulations

The selection of the right formulations of the essential anti-TB drugs constituting the standardised regimens of chemotherapy leads to:

- better therapy
- lower cost
- easier supply.

Several formulations are present on the market and more will be available in the future. NTP programme managers have to select among the formulations available on the market the ones which are the most appropriate for delivery of standardised chemotherapy regimens chosen by the national programme. This selection must take into account the pattern of weight distribution of the TB patients, the training and experience of health care personnel, the extent of health coverage, financial resources, and market conditions. They should then ensure that the national list of essential drugs includes these drugs.

### 8.4 Formulation of the essential anti-TB drugs

Table 10 shows the formulation of the essential anti-TB drugs, based on information in the following publications:

WHO, 1995. Essential Drugs, WHO Model List: revised in December 1995. WHO Drug Information, Vol. 9, No. 4: 223-234.

WHO, 1995. WHO Technical Report Series No. 850, 1995. The use of essential drugs. Sixth report of the WHO Expert Committee.

**Table 10. Formulation of essential anti-TB drugs**

DRUG	DOSE FORM	STRENGTH
<b>Separate drugs</b>		
Isoniazid	Tablet	100 mg, 300 mg
Rifampicin	Capsule or tablet	150 mg, 300 mg
Pyrazinamide	Tablet	400 mg, 500 mg
Ethambutol	Tablet	100 mg, 400 mg
Streptomycin	Powder for injection	1g
<b>Fixed-dose combinations</b>		
• <i>for daily use</i>		
Thioacetazone + isoniazid	Tablet	50 mg + 100 mg 150 mg + 300 mg
Ethambutol + isoniazid	Tablet	400 mg + 150 mg
Rifampicin + isoniazid	Tablet	150 mg + 75 mg 300 mg + 150 mg
Rifampicin + isoniazid + pyrazinamide	Tablet	150 mg + 75 mg + 400 mg
• <i>for intermittent use (thrice weekly)</i>		
Rifampicin + isoniazid	Tablet	150 mg + 150 mg
Rifampicin + isoniazid + pyrazinamide	Tablet	150 mg + 150 mg + 500 mg

### 8.5 Determining the right quantities of each drug

A more complex task than selecting the drugs is deciding on the quantities needed. These quantities should be calculated based on the number of cases in the different treatment categories notified the previous year, the standardised treatment regimens used in the NTP, and the existing stocks. It is essential to plan for reserve stocks for each level, e.g. three months at district level, three months at provincial level, six months at central level. Practical methods to quantify drug needs are fully described in WHO training modules on TB management.

### 8.6 Ensuring the quality of the anti-TB drugs

Good quality assurance and control of pharmaceuticals is of crucial importance in both medical and commercial terms. The quality of drugs (individual and especially combined tablets) to be used in TB control should be assured prior to purchase and through regular quality assessment by periodic random sampling of batches received.

Recently, several fixed-dose drug combinations consisting of two or three drugs have been produced in some countries for local use and for export. A certain number of these combinations have been submitted to human bio-availability studies and found to be associated with low blood levels of rifampicin that are related to treatment failure and acquired drug resistance. On the basis of these results, WHO and the IUATLD recommend the use of only those combinations for which human studies have demonstrated satisfactory bio-availability of rifampicin. In purchasing drugs, countries should specify that clinically employed preparations of fixed drug combinations must be periodically tested for pharmacological evidence of adequate bio-availability by laboratories independent of drug providers.

The quality of drugs depends upon a set of standards being maintained throughout the entire process of manufacture and distribution. This calls for adequate regulation, an inspection system and quality control facilities. Weak regulation and poor enforcement can lead to the presence of counterfeit and substandard drugs on the market.

NTPs should ensure that anti-TB drugs are of good quality by making sure that the drugs:

- are produced following the good manufacturing practices (GMP) recommended by WHO;
- are imported with a WHO certificate (WHO's certification scheme on the quality of pharmaceutical products moving in international commerce);
- when bought by competitive tender, are ordered with the appropriate specifications;
- are stored properly following good storage practice and the FIFO principle (First In/First Out).

### 8.7 Financing and procurement of anti-TB drugs

Better systems of procurement, access to market information and bulk orders can achieve considerable savings. The best way to obtain drugs of good quality at low cost is through competitive tender for bulk drugs in standard packages. Using International Non-proprietary Names (INNs) is essential to standardize drug procurement.

Annexes 4 and 5 present the cost of anti-TB drugs ordered directly through UNICEF, and the cost of WHO recommended regimens (according to the 1996 UNICEF price list).

The prices indicated are valid for the first six months of 1996. (The price list of UNICEF is updated every six months, and indicates FOB prices, excluding insurance, shipping and administrative fees).

The cost of anti-TB drugs has fallen considerably over the last five years. Today, the cost of the necessary drugs for a short-course regimen of six or eight months is no more than the cost of drugs for the previously used long-course, non-rifampicin-containing regimen of 12 months or more. In the developing world it has been demonstrated that one can ensure the ongoing availability of the 30-40 essential drugs needed for primary health care for less than \$1 per capita per year. At the same time, one can ensure the availability of essential anti-TB drugs for about five cents per inhabitant, even in high TB prevalence countries.

Countries or organizations that can estimate their long-term needs can purchase supplies in bulk, and/or with a long-term contract (three years for instance). By joint procurement at intercountry or regional level, countries and/or organizations are also able to buy the drugs at lower prices in the world market through lower price suppliers or procurement agencies.

When calculating and projecting real costs for the programme, it is important to consider factors such as financing, delivery times, insurance, modes of transportation (air/sea/inland) and handling charge. An analysis of these factors should be carefully done in each country: for instance, according to the country, the CIF (cost-insurance-freight) price is obtained by adding 7-30% for shipping cost to the listed FOB (free on board) prices. In addition, import taxes exist in some countries and the cost of distribution inside the country should also be considered to obtain the real cost of TB drugs delivered to the patients, even when they are given free of charge to the patients.

Before making the purchase order, it is essential to ensure the financial resources for purchase (often in hard currencies), and to consider production and delivery delays and other financial resources for distribution and storage inside the country.

### 8.8 Distributing and storing anti-TB drugs

Special consideration should be given to the distribution and storage of anti-TB drugs (as of other essential drugs) at intermediate and peripheral level. Drug stocks should be distributed from national to intermediate level on a regular

quarterly basis, rather than on a yearly basis, to avoid local shortages. The following factors are all of crucial importance: storage conditions (temperature and humidity); management inside the stores (appropriate space for stocks, control of expiry date, implementation of FIFO principle, reserve stocks); the conditions of handling and transportation to the district level; the implementation of a drug accounting system at all levels where the drugs are stored or administered.

### 8.9 Rational use of anti-TB drugs

A drug is not only a chemical substance but also a substance requiring information for use. The provision of adequate information about anti-TB drugs to the prescribers and the public is essential for the rational and safe use of these drugs. Independent, reliable and objective information for prescribers can be provided in a number of ways, that should be applied together:

- by a national drug information bulletin or newsletter;
- by national formularies;
- through training programmes and continuing medical nursing and pharmacy education symposia;
- by guidelines on standardised treatments.

For the patients, many ways can be used to improve drug use and compliance: proper labelling, posters, blister packs, and patient education provided individually and in groups within the existing health services. During supervisory visits to treatment facilities NTP staff can assess locally how anti-TB drugs are administered. Rational use by patients is enhanced by direct observation of drug ingestion. It can also be enhanced by efforts to ensure that drugs are not diverted for private sale.

### 8.10 Role of the national drug regulatory authority

In the context of a national drug policy, a body such as a Drug Regulatory Authority can help the rational supply and use of anti-TB drugs through several mechanisms:

- registration and approval of drugs entering in the national market;
- quality control, including bio-availability studies of essential drugs (and fixed-dose combination of drugs) by a laboratory independent from the producers and the suppliers;
- packaging and labelling of drugs;
- inspection of sites of drug production and of storage;
- quality control during the distribution from central to the most peripheral level;
- monitoring of side-effects (network of “pharmacovigilance”).

## 8.11 Conclusion

The supply and use of anti-TB drugs do not occur in a vacuum. Nearly all countries have a general national drug supply system. When feasible, anti-TB drug supply and training of staff should be integrated into the essential drug programme and into the national system (e.g. procedures for tender bids, storage and distribution, drug quality control). This should lead to increased efficiency and long-term sustainability.

### Suggestions for Further Reading

*WHO, 1988. Guidelines for developing national drug policies. Geneva (New edition in 1998).*

*WHO, 1995. Essential drugs. WHO Model List: revised in December 1995. WHO Drug Information, Vol. 9, No. 4, 223-234.*

*WHO, 1995. WHO Technical Report Series, No.850, 1995. The use of essential drugs. Sixth report of the WHO Expert Committee.*

*Managing tuberculosis at district level. A training course. WHO Global Tuberculosis Programme, Geneva, 1992. WHO/TB/96.211.*

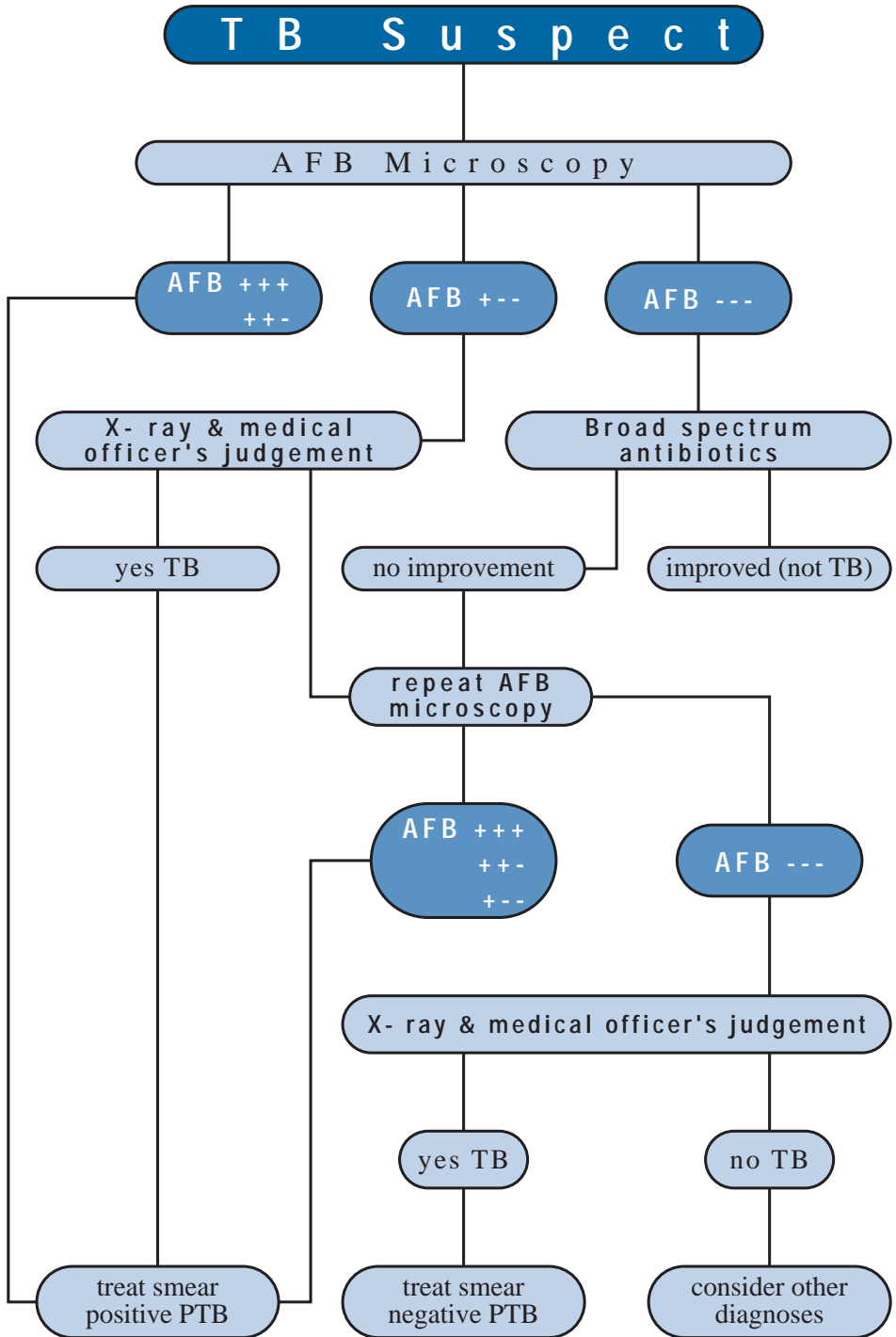
*Managing tuberculosis at national level. A training course. WHO Global Tuberculosis Programme, Geneva, 1996. WHO/TB/96.203.*

*WHO 1992. WHO Expert Committee on specification for pharmaceutical preparations, Thirty-second report, Annex 1: Good manufacturing practices for pharmaceutical products. Annex 3: Proposed guidelines for implementation of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce. WHO Technical Report Series, No. 823, 1992.*

*WHO 1992. Guiding principles for small national drug regulatory authorities, in WHO Expert Committee, Fifth Report. WHO Technical Report Series No. 825, Annex 1, 1992.*



ANNEX 1 STANDARDISED MANAGEMENT PLAN FOR TB SUSPECTS





## ESSENTIAL ANTI-TUBERCULOSIS DRUGS

### ISONIAZID

*Group: antimycobacterial agent*

*Tablet 100 mg, 300 mg*

*Injection 25 mg/ml in 2-ml ampoule*

#### **General information**

Isoniazid, the hydrazide of isonicotinic acid, is highly bactericidal against replicating tubercle bacilli.

It is rapidly absorbed and diffuses readily into all fluids and tissues. The plasma half-life, which is genetically determined, varies from less than one hour in fast acetylators to more than three hours in slow acetylators. It is largely excreted in the urine within 24 hours, mostly as inactive metabolites.

#### **Clinical information**

##### **USES**

A component of all anti-TB chemotherapeutic regimens currently recommended by WHO.

Isoniazid alone is occasionally used to prevent:

- transmission to close contacts at high risk of disease;
- progression of infection to disease in infected, asymptomatic individuals, particularly those who are immunodeficient.

##### **DOSAGE AND ADMINISTRATION**

Isoniazid is normally taken orally but it may be administered intramuscularly to critically ill patients.

##### **TREATMENT (COMBINATION THERAPY)**

Adults and children: 5 mg/kg (4-6 mg/kg) daily, maximum 300 mg  
 10 mg/kg three times weekly  
 15 mg/kg two times weekly

##### **PREVENTIVE THERAPY**

Adults: 300 mg/kg daily for six months at least

Children: 5 mg/kg daily (maximum 300 mg) for six months at least

##### **CONTRAINDICATIONS**

- Known hypersensitivity
- Active hepatic disease

**PRECAUTIONS**

Monitoring of serum concentrations of hepatic transaminases, where possible, is useful in patients with pre-existing chronic liver disease. Patients at risk of peripheral neuropathy as a result of malnutrition, chronic alcohol dependence or diabetes should additionally receive pyridoxine, 10 mg daily. Where the standard of health in the community is low, this should be offered routinely.

Epilepsy should be effectively controlled since isoniazid may provoke attacks.

**USE IN PREGNANCY**

Whenever possible, the six-month regimen based upon isoniazid, rifampicin and pyrazinamide should be used.

**ADVERSE EFFECTS**

Isoniazid is generally well tolerated at recommended doses. Systemic or cutaneous hypersensitivity reactions occasionally occur during the first weeks of treatment.

The risk of peripheral neuropathy is excluded if vulnerable patients receive daily supplements of pyridoxine. Other less common forms of neurological disturbance, including optic neuritis, toxic psychosis and generalized convulsions, can develop in susceptible individuals, particularly in the later stages of treatment and occasionally necessitate the withdrawal of isoniazid.

Hepatitis is an uncommon but potentially serious reaction that can usually be averted by prompt withdrawal of treatment. More often, however, a sharp rise in serum concentrations of hepatic transaminases at the outset of treatment is not of clinical significance, and usually resolves spontaneously during continuation of treatment.

**DRUG INTERACTIONS**

Isoniazid tends to raise plasma concentrations of phenytoin and carbamazepine by inhibiting their metabolism in the liver. The absorption of isoniazid is impaired by aluminium hydroxide.

**OVERDOSAGE**

Nausea, vomiting, dizziness, blurred vision and slurring of speech occur within 30 minutes to three hours of overdosage. Massive poisoning results in coma preceded by respiratory depression and stupor. Severe intractable seizures may occur. Emesis and gastric lavage can be of value if instituted within a few hours of ingestion. Subsequently, haemodialysis may be of value. Administration of high doses of pyridoxine is necessary to prevent peripheral neuritis.

**STORAGE**

Tablets should be kept in well-closed containers, protected from light. Solution of injection should be stored in ampoules protected from light.

## RIFAMPICIN

*Group: antimycobacterial agent*

*Capsule or tablet 150 mg, 300 mg*

### **General information**

A semisynthetic derivative of rifamycin, a complex macrocyclic antibiotic that inhibits ribonucleic acid synthesis in a broad range of microbial pathogens. It has bactericidal action and a potent sterilizing effect against tubercle bacilli in both cellular and extracellular locations.

Rifampicin is lipid-soluble. Following oral administration, it is rapidly absorbed and distributed throughout the cellular tissues and body fluids; if the meninges are inflamed, significant amounts enter the cerebrospinal fluid. A single dose of 600 mg produces a peak serum concentration of about 10 micrograms/ml in two to four hours, which subsequently decays with a half-life of two to three hours. It is extensively recycled in the enterohepatic circulation, and metabolites formed by deacetylation in the liver are eventually excreted in the faeces.

Since resistance readily develops, rifampicin must always be administered in combination with other effective antimycobacterial agents.

### **Clinical information**

#### **USES**

A component of all six and eight month anti-TB chemotherapeutic regimens currently recommended by WHO (see Table 3 page 29).

#### **DOSAGE AND ADMINISTRATION**

Rifampicin should preferably be given at least 30 minutes before meals, since absorption is reduced when it is taken with food.

Adults and children: 10 mg/kg (8-12 mg/kg) daily, maximum 600 mg daily, two or three times weekly

#### **CONTRAINDICATIONS**

- Known hypersensitivity to rifamycins
- Hepatic dysfunction

#### **PRECAUTIONS**

Serious immunological reactions resulting in renal impairment, haemolysis or thrombocytopenia are on record in patients who resume taking rifampicin after a prolonged lapse of treatment. In this rare situation it should be immediately and definitely withdrawn.

Careful monitoring of liver function is required in the elderly and in patients who are alcohol-dependent or have hepatic disease.

Patients should be warned that treatment may produce reddish coloration of urine, tears, saliva and sputum, and that contact lenses may be irreversibly stained.

**USE IN PREGNANCY**

Whenever possible, the six month regimen based upon isoniazid, rifampicin and pyrazinamide should be used.

Vitamin K should be administered to the infant at birth because of the risk of postnatal haemorrhage.

**ADVERSE EFFECTS**

Rifampicin is well tolerated by most patients at currently recommended doses, although gastrointestinal tolerance can be unacceptably severe. Other adverse effects (skin rashes, fever, influenza-like syndrome and thrombocytopenia) are more likely to occur with intermittent administration. Exfoliative dermatitis is more frequent in HIV-positive TB patients. Temporary oliguria, dyspnoea and haemolytic anaemia have also been reported in patients taking the drug three times weekly. These reactions usually subside if the regimen is changed to one with daily dosage.

Moderate rises in serum concentrations of bilirubin and transaminases, which are common at the outset of treatment, are often transient and without clinical significance. However, dose-related hepatitis can occur which is potentially fatal. It is consequently important not to exceed the maximum recommended daily dose of 10 mg/kg (600 mg).

**DRUG INTERACTIONS**

Rifampicin induces hepatic enzymes, and may increase the dosage requirements of drugs metabolized in the liver. These include corticosteroids, steroid contraceptives, oral hypoglycaemic agents, oral anticoagulants, phenytoin, cimetidine, cyclosporin and digitalis glycosides. Since rifampicin reduces the effectiveness of the oral contraceptive pill, women should consequently be advised to choose between one of the following two options for contraception. Following consultation with a physician, she could take an oral contraceptive pill containing a higher dose of oestrogen (50mcg). Alternatively she could use a nonhormonal method of contraception throughout rifampicin treatment and for at least one month subsequently.

Biliary excretion of radiocontrast media and sulfobromophthalein sodium may be reduced and microbiological assays for folic acid and vitamin B12 disturbed.

**OVERDOSAGE**

Gastric lavage may be of value if undertaken within a few hours of ingestion. Very large doses may depress central nervous function. There is no specific antidote and treatment is supportive.

**STORAGE**

Capsules and tablets should be kept in tightly closed containers, protected from light.

## ISONIAZID/RIFAMPICIN

### *General information*

A fixed combination of rifampicin and isoniazid has been developed as an aid to compliance. It is essential that all such products are shown to have adequate bio-availability.

### *Clinical information*

#### USES

Both drugs are components of all six and eight month anti-TB chemotherapeutic regimens currently recommended by WHO.

#### DOSAGE ADMINISTRATION

There are different dosage forms, for daily use and for intermittent use.

Dosage forms recommended:

- for daily use  
tablets of 150 mg isoniazid + 300 mg rifampicin  
75 mg isoniazid + 150 mg rifampicin;
- for intermittent use (three times weekly)  
tablets of 150 mg isoniazid + 150 mg rifampicin.

## PYRAZINAMIDE

*Group: antimycobacterial agent*

*Tablet: 400 mg, 500 mg*

### *General information*

A synthetic analogue of nicotinamide that is only weakly bactericidal against *M.tuberculosis*, but has potent sterilizing activity, particularly in the relatively acidic intracellular environment of macrophages and in areas of acute inflammation. It is highly effective during the first two months of treatment while acute inflammatory changes persist and its use has enabled treatment regimens to be shortened and the risk of relapse to be reduced.

It is readily absorbed from the gastrointestinal tract and is rapidly distributed throughout all tissues and fluids. Peak plasma concentrations are attained in two hours and the plasma half-life is about 10 hours. It is metabolized mainly in the liver and is excreted largely in the urine.

### *Clinical information*

#### USES

A component of all six and eight month anti-TB chemotherapeutic regimens currently recommended by WHO.

**DOSAGE AND ADMINISTRATION**

Adults and children (for the first two or three months)  
25 mg/kg daily (20-30 mg/kg),  
35 mg/kg (30-40 mg/kg) three times weekly,  
50 mg/kg (40-60 mg/kg) two times weekly.

**CONTRAINDICATIONS**

- Known hypersensitivity
- Severe hepatic impairment

**PRECAUTIONS**

Patients with diabetes should be carefully monitored since blood glucose concentrations may become labile. Gout may be exacerbated.

**USE IN PREGNANCY**

Although the safety of pyrazinamide in pregnancy has not been established, the six month regimen based upon isoniazid, rifampicin and pyrazinamide should be used whenever possible.

**ADVERSE EFFECTS**

Pyrazinamide is usually well tolerated. Hypersensitivity reactions are rare, but some patients complain of slight flushing of the skin.

Moderate rises in serum transaminase concentrations are common during the early phases of treatment. Severe hepatotoxicity is rare.

As a result of inhibition of renal tubular secretion, a degree of hyperuricaemia usually occurs, but this is often asymptomatic. Gout requiring treatment with allopurinol occasionally develops. Arthralgia, particularly of the shoulders, commonly occurs and is responsive to simple analgesics. Both hyperuricaemia and arthralgia may be reduced by prescribing regimens with intermittent administration of pyrazinamide.

**OVERDOSAGE**

Little had been recorded on the management of pyrazinamide overdose. Acute liver damage and hyperuricaemia have been reported. Treatment is essentially symptomatic. Emesis and gastric lavage may be of value if undertaken within a few hours of ingestion. There is no specific antidote and treatment is supportive.

**STORAGE**

Tablets should be stored in tightly closed containers, protected from light.

## STREPTOMYCIN

### *General information*

An aminoglycoside antibiotic derived from *Streptomyces griseus* that is used in the treatment of TB and sensitive Gram-negative infections.

Streptomycin is not absorbed from the gastrointestinal tract but, after intramuscular administration, it diffuses readily into the extracellular component of most body tissues and it attains bactericidal concentrations, particularly in tuberculous cavities. Little normally enters the cerebrospinal fluid, although penetration increases when the meninges are inflamed. The plasma half-life, which is normally two to three hours, is considerably extended in the new-born, in the elderly and in patients with severe renal impairment. It is excreted unchanged in the urine.

### *Clinical information*

#### USES

A component of several anti-TB chemotherapeutic regimens currently recommended by WHO.

#### DOSAGE AND ADMINISTRATION

Streptomycin must be administered by deep intramuscular injection. Syringes and needles should be adequately sterilized to exclude any risk of transmitting viral pathogens.

Adults and children:

15 mg/kg (12-18 mg/kg) daily, or two or three times weekly.

Patients over 60 years may not be able to tolerate more than 500-750 mg daily.

#### CONTRAINDICATIONS

- Known hypersensitivity
- Auditory nerve impairment
- Myasthenia gravis.

#### PRECAUTIONS

Hypersensitivity reactions are rare. If they occur (usually during the first weeks of treatment) streptomycin should be withdrawn immediately. Once fever and skin rash have resolved, desensitization may be attempted.

Streptomycin should be avoided, when possible, in children because the injections are painful and irreversible auditory nerve damage may occur. Both the elderly and patients with renal impairment are also vulnerable to dose-related toxic effects resulting from accumulation. Where facilities are available to monitor and function closely it may be possible to give streptomycin in reduced doses to patients with renal impairment. Where possible, serum levels should be monitored

periodically and dosage adjusted appropriately to ensure that plasma concentrations, as measured when the next dose is due, do not rise above 4 mg/ml.

Protective gloves should be worn when streptomycin injections are administered, to avoid sensitization dermatitis.

#### **USE IN PREGNANCY**

Streptomycin should not be used in pregnancy. It crosses the placenta and can cause auditory nerve impairment and nephrotoxicity in the fetus.

#### **ADVERSE EFFECTS**

Injections are painful and sterile abscesses can form at injection sites. Hypersensitivity reactions are common and can be severe.

Impairment of vestibular function is uncommon with currently recommended doses. Dosage should be reduced if headache, vomiting, vertigo and tinnitus occur.

Streptomycin is less nephrotoxic than other aminoglycoside antibiotics. Dosage must be reduced by half immediately if urinary output falls, if albuminuria occurs or if tubular casts are detected in the urine.

Haemolytic anaemia, aplastic anaemia, agranulocytosis, thrombocytopenia and lupoid reactions are rare adverse effects.

#### **DRUG INTERACTIONS**

Other ototoxic or nephrotoxic drugs should not be administered to patients receiving streptomycin. These include other aminoglycoside antibiotics, amphotericin B, cephalosporins, ethacrynic acid, cyclosporin, cisplatin, furosemide and vancomycin.

Streptomycin may potentiate the effect of neuromuscular blocking agents administered during anaesthesia.

#### **OVERDOSAGE**

Haemodialysis can be beneficial. There is no specific antidote and treatment is supportive.

#### **STORAGE**

Solutions retain their potency for 48 hours after reconstitution at room temperature and for up to 14 days when refrigerated. Powder for injection should be stored in tightly closed containers protected from light.

## ETHAMBUTOL

*Group: antimycobacterial agent*

*Tablet 100 mg, 400 mg (hydrochloride)*

### **General information**

A synthetic congener of 1,2-ethanediamine that is active against *M. tuberculosis*, *M. bovis* and some non-specific mycobacteria. It is used in combination with other anti-TB drugs to prevent or delay the emergence of resistant strains.

It is readily absorbed from the gastrointestinal tract. Plasma concentrations peak in two to four hours and decay with a half-life of three to four hours. Ethambutol is excreted in the urine both unchanged and as inactive hepatic metabolites.

About 20% is excreted in the faeces as unchanged drug.

### **Clinical information**

#### **USES**

A component of several anti-TB chemotherapeutic regimens currently recommended by WHO.

#### **DOSAGE AND ADMINISTRATION**

Adults: 15 mg/kg (15-20 mg/kg) daily  
30 mg/kg (25-35 mg/kg) three times weekly, or  
45 mg/kg (40-50 mg/kg) two times weekly.

Children: maximum 15 mg/kg daily

Dosage must always be carefully calculated on a weight basis to avoid toxicity, and should be reduced in patients with impaired renal function.

#### **CONTRAINDICATIONS**

- Known hypersensitivity
- Pre-existing optic neuritis from any cause
- Inability (for example due to young age) to report symptomatic visual disturbances
- Creatinine clearance of less than 50 ml/minute.

#### **PRECAUTIONS**

Patients should be advised to discontinue treatment immediately and to report to a doctor should their sight or perception of colour deteriorate. Patients who are too young or who are otherwise unable to comprehend this warning should not receive ethambutol.

If there is suspicion of renal impairment, renal function should be assessed before treatment.

**USE IN PREGNANCY**

The six month regimen based upon isoniazid, rifampicin and pyrazinamide should be used. If a fourth drug is needed during the initial phase, ethambutol should be preferred to streptomycin.

**ADVERSE EFFECTS**

Dose-dependent optic neuritis can readily result in impairment of visual acuity and colour vision. Early changes are usually reversible, but blindness can occur if treatment is not discontinued promptly.

Signs of peripheral neuritis occasionally develop in the legs.

**OVERDOSAGE**

Emesis and gastric lavage may be of value if undertaken within a few hours of ingestion. Subsequently, dialysis may be of value. There is no specific antidote and treatment is supportive.

**STORAGE**

Tablets should be stored in well-closed containers.

**THIOACETAZONE/ISONIAZID*****General information***

A fixed combination of thioacetazone and isoniazid that is almost as cheap as isoniazid alone and is intended to promote compliance and to prevent emergence of isoniazid-resistant bacilli. Thioacetazone, a thiosemicarbazone that is bacteriostatic against *M. tuberculosis*, is used in anti-TB chemotherapy to inhibit the emergence of resistance to isoniazid, particularly in the continuation phase of the long-term regimens. It is well absorbed from the gastrointestinal tract. Peak concentrations in plasma are attained after four to six hours and the plasma half-life is about 12 hours. About one-third of the oral dose is excreted in the urine unchanged. (For general information on isoniazid see above).

***Clinical information*****USES**

A component of some of the longer anti-TB chemotherapeutic regimens currently in use in some countries.

**DOSAGE AND ADMINISTRATION**

Adults: 150 mg thioacetazone + 300 mg isoniazid daily.

Children: 50 mg thioacetazone + 100 mg isoniazid daily.

**CONTRAINDICATIONS**

Known hypersensitivity to either component

**PRECAUTIONS**

Treatment should be withdrawn immediately if a rash or other signs suggestive of hypersensitivity occur.

**ADVERSE EFFECTS**

Effects attributable to isoniazid are listed above. The thioacetazone component frequently causes nausea, vomiting, diarrhoea and skin rashes. Rare cases of fatal exfoliative dermatitis and acute hepatic failure have been reported. Cases of agranulocytosis, thrombocytopenia and aplastic anaemia are also on record. These adverse effects are more frequent in HIV-positive TB patients.

Dose-related ototoxicity is rare, but particularly careful monitoring is required when thioacetazone is used in combination with streptomycin.

**OVERDOSAGE**

Emesis and gastric lavage may be of value if undertaken within a few hours of ingestion. There is no specific antidote and treatment is supportive.

**STORAGE**

Tablets should be kept in well-closed containers.

**ETHAMBUTOL/ISONIAZID**

*Group: antimycobacterial agent*

*Tablet 400 mg ethambutol + 150 mg isoniazid*

***General information***

A fixed dose combination of two drugs previously described, intended to promote compliance.

**USE**

- only for continuation phase;
- always daily (not three times weekly) for this fixed dose combination;
- can substitute thioacetazone + isoniazid combination in patients with side effects due to thioacetazone.

**RIFAMPICIN/ISONIAZID/PYRAZINAMIDE**

*Group: antimycobacterial agent*

***General information***

Two fixed dose combinations of three drugs previously described, intended to promote compliance.

Daily: tablet 150 mg rifampicin + 75 mg isoniazid  
+ 400 mg pyrazinamide

Three times weekly: tablet 150 mg rifampicin + 150 mg isoniazid  
+ 500 mg pyrazinamide

## FIXED-DOSE COMBINATIONS OF ANTI-TUBERCULOSIS DRUGS

Fixed-dose combination (FDC) tablets incorporate two or more drugs within the same tablet. The use of 2-drug combinations (e.g. rifampicin and isoniazid) is widespread and there is increasing use of rifampicin, isoniazid and pyrazinamide combinations.

### *Advantages of FDCs*

- When programmes use FDCs, providers and patients use single anti-TB drugs less. This reduces the risk of emergence of drug-resistant organisms. In a programme using drugs supplied only in FDCs, in the event of interruption of treatment and relapse, organisms will remain sensitive to rifampicin and isoniazid.
- Physicians are more likely to prescribe an effective regimen.
- The opportunity for inadvertent medication errors is decreased.
- Many of the logistic problems which cause shortages of individual drugs are eliminated. (Shortages of individual drugs may result in patients either receiving monotherapy, or changing regimen, both of which may increase the risks of resistance).
- The procurement, management and handling of drugs is simplified. In many national and district programmes there are major problems with inadequate and uncoordinated drug supplies, and the ordering, shipping and storage of the individual drugs adds enormously to the costs. If combination drugs are used, there will only be one or two components to be ordered, delivered and stored, with resulting savings in costs and increased efficiency.
- The regimen is simpler for the patient, involves consumption of fewer tablets, and promotes patient adherence to treatment.
- The provision of rifampicin only in FDCs may decrease the black market use of rifampicin as a treatment for infections other than TB.

### *Disadvantages of FDCs*

- The bio-availability of drugs, especially rifampicin, can decrease when combined in FDCs. The decrease in bio-availability is a particular problem with FDCs of rifampicin and two other drugs. Many FDCs currently available may result in subtherapeutic blood levels of rifampicin. Bio-availability may vary between batches of drugs, and following minor changes in the manufacturing process. Therefore programmes must monitor regularly the bio-availability of drugs, especially isoniazid and rifampicin, in FDCs. WHO and the IUATLD recommend the use of only those FDCs for which human studies have demonstrated satisfactory bio-availability of rifampicin.
- Currently chemotherapy using FDCs is more costly. From a programme point of view, however, there will be long-term savings as fewer patients develop drug resistant disease and receive the more expensive retreatment regimen. Prices may fall as the use of FDCs becomes more widespread.

- Occasionally it is necessary to adjust the dosages for an individual patient, or to adjust the regimen when serious side effects are experienced. Programmes using FDCs still require limited amounts of single drugs for flexible prescribing by senior medical officers.

### *Selection of FDCs*

- The optimal formulation of FDCs chosen for a programme will depend upon the average weight of patients, and regimens used (whether daily or intermittent).
- It is usually advisable to choose only one FDC for a programme, to avoid stock management problems and confusion between different formulations.
- If a programme uses FDCs of different formulations, then the colour and shape of the tablets for each formulation should be different to avoid confusion.
- Several FDCs are currently available. It is likely that manufacturers will produce more FDCs, including FDCs of four drugs.

### *Daily and intermittent use of FDCs*

Most TB patients fall within a certain weight band, e.g. 45-55 kg.

The recommended number of tablets of FDCs for patients falling within a certain weight band depends on the weight band defined in each country and the particular FDC formulations provided by the NTP. Tables 11 and 12 show, for daily and intermittent use respectively, examples of the use of FDCs for patients falling within the 45-55 kg weight band.

### **Suggestions for Further Reading**

*Moulding T, Asim K. Fixed dose combinations of antituberculous medications to prevent drug resistance. Ann Intern Med 1995; 122: 951-954.*

*Acocella G. Studies of bioavailability in man. Int Bulletin Tuberc Lung Disease 1989; 64: 40-42.*

*The promise and the reality of fixed-dose combinations with rifampicin. A joint statement of the International Union Against Tuberculosis and Lung Disease and the Tuberculosis Programme of the World Health Organisation. Tuberc Lung Dis 1994; 75: 180-181.*

*Table 11. Examples of daily use of FDCs appropriate for a 45-55 kg weight band***Treatment Regimens**

TREATMENT CATEGORY	INITIAL PHASE	CONTINUATION PHASE
Category I	2 ERHZ or 2 SRHZ	4 RH or 6 EH (or 6 TH)
Category II	2 SERHZ/1 ERHZ	5 ERH
Category III	2 RHZ	4 RH or 6 EH (or 6TH)

**Initial Phase**

Drugs	Rifampicin + Isoniazid + Pyrazinamide 150mg      75mg      400mg	Ethambutol 400 mg	Streptomycin 1g (vial)
Daily dose (mg)	450      + 225      + 1200	1000	750
Quantity	3 tablets	2 1/2 tablets	3/4 vial

**Continuation Phase**

Drugs	Rifampicin + Isoniazid 150mg      75mg	Ethambutol 400mg	Ethambutol + Isoniazid 400mg      150mg	Thioacetazone + Isoniazid 150mg      300mg
Daily dose (mg)	450      +225	800	800      + 300	150      + 300
Quantity	3 tablets	2 tablets	2 tablets	1 tablet

**Table 12. Examples of intermittent thrice weekly use of FDCs appropriate for a 45-55 kg weight band.**

### Treatment Regimens

TREATMENT CATEGORY	INITIAL PHASE	CONTINUATION PHASE
Category I	2 E <sub>3</sub> R <sub>3</sub> H <sub>3</sub> Z <sub>3</sub> or 2 S <sub>3</sub> R <sub>3</sub> H <sub>3</sub> Z <sub>3</sub>	4 R <sub>3</sub> H <sub>3</sub>
Category II	2 SERHZ/ 1 E <sub>3</sub> R <sub>3</sub> H <sub>3</sub> Z <sub>3</sub>	5 E <sub>3</sub> R <sub>3</sub> H <sub>3</sub>
Category III	2 R <sub>3</sub> H <sub>3</sub> Z <sub>3</sub>	4 R <sub>3</sub> H <sub>3</sub>

### Initial Phase

Drugs	Rifampicin + Isoniazid + Pyrazinamide 150mg      150mg      500mg	Ethambutol 400 mg	Streptomycin 1g (vial)
Dose (mg)	450      + 450      + 1500	1600	1g (or 750mg)
Quantity	3 tablets	4 tablets	1 vial

### Continuation Phase

Drugs	Rifampicin + Isoniazid 150mg      150mg	Ethambutol 400mg
Dose (mg)	450      + 450	1600
Quantity	3 tablets	4 tablets

## ANNEX 4 PRICE LIST OF ESSENTIAL ANTI-TUBERCULOSIS DRUGS

DRUG	DOSAGE FORM/STRENGTH	QUANTITY	UNICEF PRICE <sup>(a)</sup> (US DOLLARS)	LOWEST PRICE OBTAINABLE <sup>(b)</sup> (US DOLLARS)
Isoniazid	Tablet	1 000	2.89	2.30
		1 000	8.45	5.80
Rifampicin	Capsule or tablet	1 000	39.0	33.0 (1995)
		1 000	56.2	57.4 (1995)
Pyrazinamide	Tablet	1 000	35.07	31.5
Ethambutol	Tablet	1 000	25.06	18.3
Streptomycin	Powder for injection	100	22.7	7.3
water	1 g base in vial	100	3.14	2.67
disposable syringe and needle	5 ml in vial	100	-	2.8
Thioctazone + isoniazid	Tablet	1 000	4.52	3.62
	50 mg + 100 mg	1 000	10.33	7.35
	150 mg + 300 mg			
Ethambutol + isoniazid	Tablet	1 000	-	22
	400 mg + 150 mg			
Rifampicin + isoniazid	Tablet	1 000	-	24
	150 mg + 100 mg	1 000	-	55
	300 mg + 150 mg			
Rifampicin + isoniazid + pyrazinamide <sup>(c)</sup>	Tablet	1 000	-	40
	120 mg + 50 mg + 300 mg			

<sup>(a)</sup> The free on board (FOB) price of purchases ordered through UNICEF is calculated by adding 6% to the price indicated in: UNICEF, Essential drugs price list, January - June 1996 [address: Supply division, UNICEF PLADS, Freeport, DK 2100 Copenhagen, DENMARK. Telefax 45/3526.94.21].

<sup>(b)</sup> Usually FOB price (including handling charges, excluding insurance and freight): special tariff 1996 (except as otherwise indicated) applied to international aid organizations for national programmes. See other prices in: International drug price indicator guide, Management Sciences for Health, 1995. [address: MSH, Drug management programme, 1655 North Fort Myer Drive, Suite 920, Arlington, VA 22209-3108, USA. Telefax (703) 524-7898].

<sup>(c)</sup> Available in this formulation from private, including non-profit, suppliers.



## ANNEX 5 COST OF RECOMMENDED TREATMENT REGIMENS

INITIAL PHASE <sup>(a) (b)</sup>	COST <sup>(c)</sup> (US DOLLARS)	CONTINUATION PHASE <sup>(a) (b)</sup>	COST <sup>(c)</sup> (US DOLLARS)
2 ERHZ	19.3	4 RH	15.4
2 SRHZ	32.6 <sup>(d)</sup>	4 R <sub>3</sub> H <sub>3</sub>	6.6
2 E <sub>3</sub> R <sub>3</sub> H <sub>3</sub> Z <sub>3</sub>	9.5	6 TH	2.0
2 S <sub>3</sub> R <sub>3</sub> H <sub>3</sub> Z <sub>3</sub>	14.2 <sup>(d)</sup>	6 EH	11.2
2 RHZ	14.5		
2 R <sub>3</sub> H <sub>3</sub> Z <sub>3</sub>	7.0		
2 SERHZ/1 ERHZ	46.4 <sup>(d)</sup>	5 ERH	27.2
2 SERHZ/1E <sub>3</sub> R <sub>3</sub> H <sub>3</sub> Z <sub>3</sub>	42.3 <sup>(d)</sup>	5 E <sub>3</sub> R <sub>3</sub> H <sub>3</sub>	14.6

<sup>(a)</sup> The drugs utilized in these regimens are conventionally represented by the following letters:

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

<sup>(b)</sup> The number preceding the first letter indicates the duration in months of the phase of treatment (initial and continuation); the number which follows the letter represents the number of weekly doses if the regimen is intermittent.

<sup>(c)</sup> Refers to the approximate drug cost of treatment for adults of more than 50 kg weight, calculated on the basis of UNICEF price list 1996, including a handling charge of 6%.

<sup>(d)</sup> Includes the cost of water and disposable syringes for injections

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