

1. INTRODUCTION

1.1. Global epidemiology and burden of disease

Nearly one-third of the global population, i.e. two billion people, is infected with Mycobacterium tuberculosis and at risk of developing the disease. More than eight million people develop active tuberculosis (TB) every year, and about two million die.

More than 90% of global TB cases and deaths occur in the developing world, where 75% of cases are in the most economically productive age group (15-54 years). There, an adult with TB loses on average three to four months of work time. This results in the loss of 20-30% of annual household income and, if the patient dies of TB, an average of 15 years of lost income. In addition to the devastating economic costs, TB imposes indirect negative consequences - children leave school because of their parents' tuberculosis, and women are abandoned by their families as a result of their disease. Co-infection with the human immunodeficiency virus (HIV) significantly increases the risk of developing TB. Countries with a high prevalence of HIV, particularly those in sub-Saharan Africa, have witnessed a profound increase in the number of TB cases, with reported incidence rates increasing two- or threefold in the 1990s. At the same time, multi-drug resistance, which is caused by poorly managed TB treatment, is a growing problem of serious concern in many countries around the world.

Reasons for the global TB burden

The main reasons for the increasing burden of TB globally are:

- Poverty and the widening gap between rich and poor in various populations, e.g. developing countries, disenfranchised urban populations in developed countries;
- Neglect of the disease (inadequate case detection, diagnosis and cure);
- Collapse of the health infrastructure in countries experiencing severe economic crisis or civil unrest;
- The impact of the HIV pandemic.

1.2. Burden of TB in Sudan:

Sudan is shouldering 8-11% of the TB burden in the **Eastern Mediterranean Region, EMR**. In the year 2003, the estimated incidence of new smear-positive cases of 97 per 100,000 populations, that gives a total of 32,614 estimated new smear-positive cases for a 33.6 million population of the whole Sudan. In addition, it has been estimated that the prevalence of all cases in 2003 was to be 364 cases per 100,000 populations. The overall estimated death rate including HIV infected TB cases was 62 per 100,000 population in 2003. The overall case notification among 28.6 million populations covered by the national TB programme (1999-2003) averaged to about 25,144 cases of all forms of TB, with 54% smear-positive cases (47% new smear positive and 7% re-treatment cases). In the year 1999, maximum case notification was reached (26,950), but since then, case notification showed gradually declining plateau. In the year 2003, notification of all forms was 25103 cases (detection rate all forms of 39.9%), with a case detection rate among smear-positive cases of (40%).

In addition, males constitute the greater proportion among new smear-positive cases in the years 2003 & 2004 (60%) giving a male to female ratio of 1.5:1. In the year 2003, age distribution of new smear-positive cases shows that the majority (75.8%) of cases were between 15 and 54 years of age (75.6% for males & 76.2% for females). These data are in compliance with the global trends that the majority of cases are in their productive ages. This may reflect also the economical burden, patients' families are shouldering. Children under 14 years comprise about 8.5% of all new smear-positive cases. It was also observed that, the ratios of males to females were about 1:1 at younger ages and the gap increases in the favorite of males in advanced ages to be 2:1. Further more, these data has exposed some sort of inaccessibility to women, children, and elderly people..

Although states' ARI deviations from average are not substantial, only seven out of 22 states (Khartoum, Gezera, White Nile, Gadarif, Kassala, Red Sea, and North Kordofan) account for 75% of the total case notification in Sudan (18707 out of 25103 cases). Khartoum State (population of 5.4 million) alone shoulders 30% of total case notification in Sudan. Although this might be attributed to population densities and stability of TB control efforts and services compared to other states, but in fact might reflect also an inequality bias in the distribution of health services between different states. The above-mentioned 7 states account for 48% of the total population of the Sudan (33.6 million). The average new smear-positive detection rate for these states was 46% and for all cases was 55%. Khartoum and Red Sea states had achieved 70% detection of new smear-positive in 2003. In contrast, some states like those of western Sudan are very far away from this target. For example, the detection rates of new smear-positive were 23%, 12%,

3%, 2% for N. Darfur, W. Kordofan, S. Darfur, and W. Darfur states respectively. These states account for 22.4% of the total population of Sudan but on the other hand share with only 4% of the total case notification in the country. In conclusion, again the question of accessibility and distribution of TB services is raised despite the demographic coverage that been reached by the end of 2002.

TB hits hard people of low socio-economic classes, marginalized population and IDPs. As shown by unpublished study on delay in the diagnosis in 2004, 80% of all TB cases in the study were with family income of less than \$100 per month and that less than 5% were with incomes of more than \$200 per month. Moreover, 66% of the TB patients were either illiterate or with less than 6 years of schooling (Abdel Rahim M. et al, 2004). Apart from the existing poverty, TB is worsening the situation by affecting the economically active members of these families.

Lastly, 93.9% of the new smear-positive cases had been evaluated for their treatment outcome in the year 1999, with a treatment success rate of 75% of all registered new smear-positive cases. On the same way, the evaluation rate jumped to 97% in the year 2002, while the treatment success rate was 82.9% of all registered new smear-positive cases. It was clear that treatment success rates were affected mainly by the high defaulter rates. The defaulter rates were 7.9% and 7.8% in 1999 and 2002 respectively. Meanwhile, death rates were swinging between 4.7% in 1999 and 3.6% in 2002.

With regards to the situation of MDR-TB in the Sudan, there is no national survey been carried out to determine the magnitude of MDR-TB. Although the prevalence of MDR-TB in new smear-positive TB cases is estimated to be 10.1% (estimates from JID 2002; 185: 1197-1202) this figure is believed to be higher than reality. This assumption is built upon observations from case notification (1993-2004) and treatment outcomes (1995-2003); the average percentage of all re-treatment cases were 6.7% of notified cases and the average failure rate 2.7% in all treated new smear-positive cases respectively. The NTP has established its TB reference laboratory during 2003-2005. The laboratory is capable of performing primary culture and by the end of this year it will be capable of performing DST. The NTP, in collaboration with the Epi-lab, IUATLD, LHL, and WHO, is planning to conduct a national MDR-TB survey by the end of 2006.

2. STRATEGY AND FRAMEWORK FOR EFFECTIVE TUBERCULOSIS CONTROL

2.1. Background

The World Health Organization declared TB a global emergency in 1993 in recognition of its growing importance as a public health problem. Governments in many high-burden countries have neglected TB control in the past. Tuberculosis programmes have failed to achieve high detection and cure rates for infectious (smear-positive) patients. Besides poverty, population growth and migration, and an increase in the number of TB cases attributable to the HIV epidemic in some countries, the persistence of TB has been chiefly due to:

- Failure to ensure accessible diagnosis and treatment services, including directly observed therapy;
- Inadequate treatment regimens and failure to use standardized treatment regimens;
- Lack of supervision and an information management system for the rigorous evaluation of treatment outcomes of TB patients;
- Misguided policies for health sector reform, with cuts in health care budgets and resultant reduction in financial support to peripheral health services.

In response to this situation, a new framework for effective TB control was developed and a global strategy called DOTS was introduced.

2.2. Five components of the DOTS strategy

- 1 Sustained political commitment.
- 2 Access to quality-assured sputum microscopy.
- 3 Standardized short-course chemotherapy for all cases of TB under proper case management conditions, including direct observation of treatment.
- 4 Uninterrupted supply of quality-assured drugs.
- 5 Recording and reporting system enabling outcome assessment of all patients and assessment of overall programme performance.

2.3. The organizational principles of the DOTS strategy are:

- Availability of a decentralized 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 evaluation system of case-finding and cohort analysis of treatment outcomes.

The WHO framework for effective TB control includes the objectives and targets, DOTS strategy, a policy package, key operations for implementation, and indicators to measure progress.

2.4. Objectives and targets of TB control

Goal:

The aim of an NTP is to reduce TB mortality, morbidity and disease transmission, while preventing the development of drug resistance. It also aims to reduce human suffering and the socioeconomic burden of Sudanese families and communities as a consequence of tuberculosis.

The main intervention for TB control is standardized short-course chemotherapy provided under direct observation - at least during the initial phase of treatment - for all identified smear-positive TB cases, the main sources of infection.

Targets:

The global targets for TB control, adopted by the World Health Assembly, are:

- To cure 85% of newly detected cases of sputum smear-positive TB and
- To detect 70% of the estimated incidence of sputum smear-positive TB.

National TB programme achieving at least an 85% cure rate and 70% detection of patients with sputum smear-positive pulmonary TB has the following impact:

- Rapid reduction of TB mortality, prevalence and transmission, and gradual reduction of TB incidence;
- Less acquired drug resistance, thus making future treatment of TB easier and more affordable.

2.5. Key operations for DOTS implementation

The seven key operations for implementation of the DOTS strategy are:

- 1 Establish a national tuberculosis programme with a strong central unit.
- 2 Prepare a programme development plan and a programme manual, and establish the recording and reporting system allowing cohort analysis of treatment outcomes.
- 3 Plan and initiate a training programme.
- 4 Set up a microscopy services network in close contact with PHC services and subject to regular quality control to ensure that detection and cure of smear positive TB cases remain a priority, through effective decentralization of diagnosis.
- 5 Organize treatment services within the PHC system where directly observed short-course Chemotherapy is given priority.
- 6 Secure a regular supply of drugs and diagnostic material.
- 7 Design and implement a plan of supervision of key operations at the intermediate and district level.

Other important operations essential to strengthen and sustain DOTS implementation include information, education, communication and social mobilization, involving private and voluntary health care providers, economic analysis and financial planning, and operational research.

3. CASE DEFINITION & CATEGORIZING OF TB CASES

3.1. BASIC DEFINITIONS

• **Tuberculosis suspect.** Any person who presents with symptoms or signs suggestive of TB, in particular cough of long duration (more than 2 weeks)

• **Case of tuberculosis.** A patient in whom TB has been bacteriologically confirmed or diagnosed by a clinician.

Note. Any person given treatment for tuberculosis should be recorded as a case. Incomplete "trial" tuberculosis treatment should not be given as a method for diagnosis.

• **Definite case of tuberculosis.** A patient with positive culture for the *Mycobacterium tuberculosis* complex. (In countries where culture is not routinely available, a patient with two sputum smears positive for acid-fast bacilli (AFB) is also considered a "definite" case.

3.2. DIAGNOSIS OF PULMONARY TB:



3.3. Why case definition?

The purposes of case definition are:

- Proper patient registration and case notification;
- Prioritized treatment of sputum smear-positive cases, the main sources of infection in the community;
- Allocation of cases to appropriate standardized treatment regimens;
- Evaluation of the proportion of cases according to site, bacteriology and treatment history;
- Cohort analysis of treatment outcomes.

3.4. Why match standardized treatment regimen to diagnostic category?

The reasons for matching standardized treatment regimen to diagnostic category are:

- To avoid under-treatment of previously treated cases and therefore to prevent acquired resistance;
- To maximize cost-effective use of resources and to minimize side-effects for patients by avoiding unnecessary over-treatment.

3.5. What determines case definition?

The four determinants of case definition are:

1. Site of TB disease.
2. Bacteriology (result of sputum smear).
3. Severity of TB disease.
4. History of previous treatment of TB.

1. Site of TB disease:

1.1 Pulmonary tuberculosis (PTB) refers to disease involving the lung parenchyma. Therefore tuberculous intra-thoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extrapulmonary TB. A patient with both pulmonary and extrapulmonary TB should be classified as a case of pulmonary TB.

1.2 Extrapulmonary tuberculosis (EPTB) refers to tuberculosis of organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges. Diagnosis should be based on one culture-positive specimen, or histological or strong clinical evidence consistent with active EPTB, followed by a decision by a clinician to treat with a full course of tuberculosis chemotherapy.

The case definition of an extrapulmonary TB case with several sites affected depends on the site representing the most severe form of disease.

2. Bacteriology (result of sputum smear) in pulmonary TB

Defining the smear result in pulmonary cases is important to:

- identify smear-positive cases, because they are the most infectious cases and usually have higher mortality;
- record, report and evaluate programme performance (smear-positive cases are the cases for which bacteriological monitoring of treatment progress is most practicable).

2.1 Pulmonary tuberculosis, sputum smear-positive (PTB+) (65% of all PTB cases & 50% of all cases)

- a. Two or more initial sputum smear examinations positive for AFB, or
- b. One sputum smear examination positive for AFB plus radiographic abnormalities consistent with active PTB as determined by a clinician, or
- c. One sputum smear positive for AFB plus sputum culture positive for *M. tuberculosis*.

2.2 Pulmonary tuberculosis, sputum smear-negative (PTB-)

Case of PTB that does not meet the above definition for smear-positive TB. This group includes cases without smear result, which should be exceptional in adults but are relatively more frequent in children.

Note. In keeping with good clinical and public health practice, diagnostic criteria for PTB-should include:

- At least three sputum specimens negative for AFB, and
- Radiographic abnormalities consistent with active PTB, and
- No response to a course of broad-spectrum antibiotics, and
- Decision by a clinician to treat with a full course of antituberculosis chemotherapy.

3. Severity of TB disease

Severity of disease is determined by:

- Bacillary load,
- Extent of disease and
- Anatomical site

Involvement of an anatomical site results in classification as severe disease if there is:

- A significant acute threat to life (e.g. pericardial TB),
- A risk of subsequent severe handicap (e.g. spinal TB), or
- Both (e.g. meningeal TB).

Severe forms of EPTB:

Miliary, disseminated TB, meningeal, pericardial, peritoneal, bilateral or extensive pleural effusive, spinal, intestinal, genitourinary

Less severe forms of EPTB:

Lymph node, pleural effusion (unilateral), bone (excluding spine), peripheral joint and skin tuberculosis

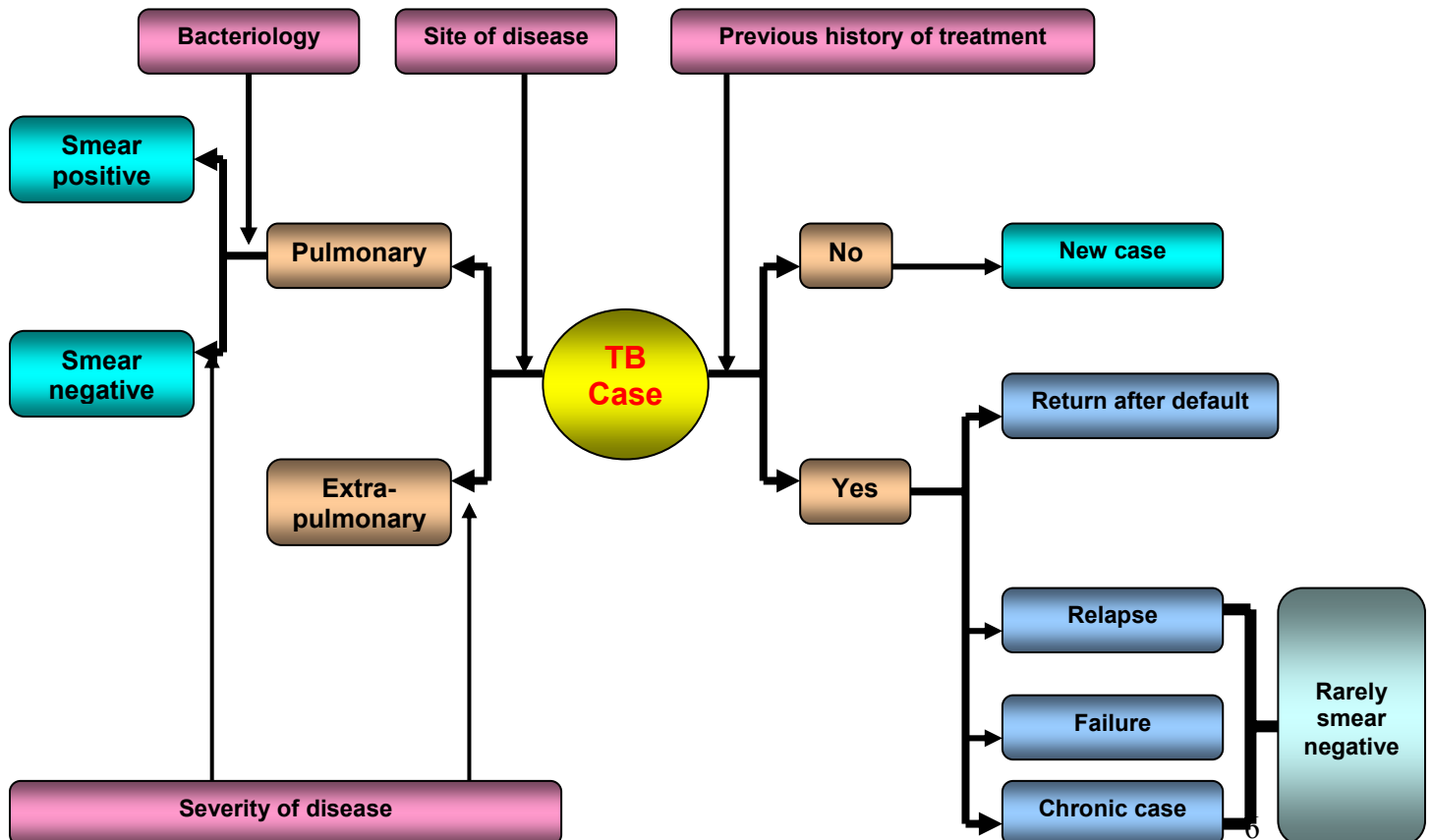
4. History of previous treatment: category of patient for registration on diagnosis

In order to identify those patients at increased risk of acquired drug resistance and to prescribe appropriate treatment, a case should be defined according to whether or not the patient has previously received TB treatment. This distinction is also essential for epidemiological monitoring of the TB epidemic at regional and country level. The following definitions are used:

- 1. New.** A patient who has never had treatment for TB or who has taken antituberculosis drugs for less than 1 month.
- 2. Relapse.** A patient previously treated for TB who has been declared cured or treatment completed, and is diagnosed with bacteriologically positive (smear or culture) tuberculosis.
- 3. Treatment after failure.** A patient who is started on a re-treatment regimen after having failed previous treatment.
- 4. Treatment after default.** A patient who returns to treatment, positive bacteriologically, following interruption of treatment for 2 months or more.
- 5. Transfer in.** A patient who has been transferred from another TB register to continue treatment.
- 6. Other.** All cases that do not fit the above definitions. This group includes **chronic case**, a patient who is sputum-positive at the end of a re-treatment regimen.

Note. Smear-negative pulmonary and extrapulmonary cases may also be relapses, failures, returns after default or chronic cases. This should, however, be a rare event, supported by pathological or bacteriological evidence (culture).

Determinants of case definition



3.6. Categorization of TB patients (treatment categories):

Rationale for prioritizing TB diagnostic categories

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

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

Category	Patient
CAT I	<ul style="list-style-type: none">- New smear-positive patients;- new smear-negative PTB with extensive parenchymal involvement;- concomitant HIV disease or severe forms of extrapulmonary TB
CAT II	Previously treated sputum smear-positive PTB: <ul style="list-style-type: none">- relapse;- treatment after default- treatment failure of CAT I
CAT III	<ul style="list-style-type: none">- New smear-negative PTB (other than in category I) and- less severe forms of extra-pulmonary TB
CAT IV	<ul style="list-style-type: none">- Chronic (still sputum-positive after supervised re-treatment);- Proven or suspected MDR TB cases

4. Standardized treatment regimens

4.1. Aims of treatment

The aims of treatment of TB are:

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

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

4.2. Choice of Standardized regimens:

There are several possible regimens. The regimens recommended in each country's NTP depend on:

- Country's budget,
- Access of patients to PHC services,
- Qualifications of health staff at peripheral level and current best medical practice.

The choice of standardized regimens should be based on:

1. The availability of financial resources,
2. Efficacy, effectiveness and
3. Applicability in the current health system network, and population distribution and mobility.

Standardized regimens have the following advantages over individualized prescription of drugs:

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

4.3. Recommended standardized treatment regimens

4.3.1. New cases

Treatment regimens have an initial (or intensive) phase lasting 2 months and a continuation phase usually lasting 4 or 6 months. During the initial phase, the tubercle bacilli are killed rapidly. Infectious patients quickly become noninfectious (within approximately two weeks). Symptoms abate & most patients with sputum smear-positive TB become smear-negative within two months. During the continuation phase, fewer drugs are necessary but they must be given for a longer time. The sterilizing effect of the drugs eliminates the remaining bacilli and prevents subsequent relapse.

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

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

4.3.2. Treatment of extrapulmonary TB

Although most commonly affecting the lungs, TB can involve virtually any organ of the body. In countries with comprehensive diagnostic and reporting systems, EPTB accounts for 20-25% of

reported cases, being relatively more frequent in children and persons with HIV infection. Of specific forms, lymphatic, pleural, and bone or joint disease are the most common, while pericardial, meningeal, and disseminated (miliary) forms are more likely to result in a fatal outcome.

In general, EPTB is more difficult to diagnose than pulmonary disease, often requiring invasive procedures to obtain diagnostic specimens and more sophisticated laboratory techniques than sputum microscopy. From a public health perspective, EPTB is not of great importance, because patients with this form of disease are not infectious unless they also have pulmonary involvement. Perhaps as a consequence of these two factors, most guidelines for TB treatment intended for use in low-income countries have not addressed in any detail the treatment of EPTB.

Treatment recommendations are further complicated by the paucity of data from controlled clinical trials of extrapulmonary forms of TB. In the pre-rifampicin era, most experts believed that 18-24 months of isoniazid-based treatment (together with *p*-aminosalicylic acid or ethambutol and supplemented by initial streptomycin) was required to achieve satisfactory results. Subsequently, a number of clinical trials demonstrated that rifampicin-based treatment for 6-9 months gave comparable results. Consequently, most experts now agree that virtually all forms of EPTB can be treated with the regimens shown in Table 4.3.

Eight-month regimens (2 HRZ/6 HE) have not been evaluated in EPTB, but would probably be satisfactory for treatment of less severe forms of disease. In meningeal TB, a 6-month regimen with rifampicin throughout was shown to be as effective as the traditional 9-12 month-regimens, with streptomycin used instead of ethambutol in the initial phase¹. Finally, adjunctive steroids may be useful in pericardial and meningeal TB. Surgery plays little role in the treatment of EPTB, being reserved for management of late complications of disease such as hydrocephalus, obstructive uropathy, constrictive pericarditis, and neurological involvement from Pott disease (spinal TB).

Management of CAT J & JJJ:

Category	Patient	Initial phase	Continuation phase
Category I	<ul style="list-style-type: none"> - New smear-positive patients; - new smear-negative PTB with extensive parenchymal involvement; - concomitant HIV disease or severe forms of EPTB 	2 HRZS[®]	6 HE
Category III	<ul style="list-style-type: none"> • New smear-negative PTB (other than in category I) and • Less severe forms of EPTB 	2 HRZS[®]	6 HE

4.3.3. Considerations for the choice of continuation phase regimen in new patients (Category I and III)

National TB programmes may choose one of the continuation phase regimens listed in the table above. Some advantages and disadvantages are noted below. However, national recommendations should be as simple as possible, and avoid multiple alternatives, to facilitate training, drug procurement and supply, and drug administration, and to avoid errors in prescription. The options are:

Comparison between 4HR and 6 HE:

4HR	6HE
- Shorter duration of treatment	- Longer duration of treatment
- Observation throughout treatment: - Increased cost - Time loss	- Self-administered during continuation: - No assurance that the patient is taking all the drugs. - Treatment interruption notified only when patient doesn't return to collect drugs. - Although drug costs for this regimen are essentially equivalent to that of 4HR, the costs of supervision are much less.
- Combined failure + relapse rate of 5%	- Combined failure + relapse rate of 11%
- Failures of this regimen have higher probability of being MDR - Less room for CAT II in case of CAT I failure	- More suitable for mobile populations & patients with limited access to health services
- Interactions with some antiretroviral drugs used for HIV-infected patients	- Appropriate for countries with limited access to PHC & unable to organize a system of DOTS through health facilities, community health workers or volunteers.
- Requires patient oriented measures to ensure adherence to treatment including: - Wider community and/or family participation in treatment observation, - Support and health education for the patients and their families, and - In some settings the use of incentives and enablers.	- Not using (R) in the continuation phase may reduce acquired resistance to this drug.
	- Expected to cure the large majority of adherent patients.
	- Allow reliance on a rifampicin-based re-treatment regimen for failures or relapses
	- Unlike (4HR), this regimen can be used concomitantly with ART among HIV-infected patients.

4.3.4. Re-treatment cases

Previously treated TB patients include those patients treated as new cases for more than one month who are now smear- or culture-positive (failure, relapse, return after default). Re-treatment cases have a higher likelihood of drug resistance, which may have been acquired through inadequate prior chemotherapy. They are also more likely than new patients to harbour and excrete bacilli resistant to at least isoniazid. The re-treatment regimen consists of 5 drugs in the initial phase and 3 drugs in the continuation phase. Three of the drugs - RHE - are given throughout the treatment. This standardized regimen can cure patients excreting bacilli still fully sensitive to the drugs and those excreting bacilli resistant to isoniazid and/or streptomycin. Under proper case management conditions, MDR-TB cases are those most at risk of failure in the re-treatment regimen.

Patient	Initial intensive phase	Continuation phase
Previously treated smear-positive PTB: - Relapse; - Treatment after default	2 HRZES / 1 HRZE ®	5 HRE ®
- Treatment failure of Category I* In settings where: - Representative DRS data show low rates of MDR TB or individualized DST shows drug-susceptible disease Or In settings of: - Poor program performance, - Absence of representative DRS data, - Insufficient resources to implement Category IV treatment	2 HRZES / 1 HRZE ®	5 HRE ®

* Treatment failures may be at increased risk of MDR TB, particularly if rifampicin was used in the continuation phase. Drug susceptibility testing is recommended for these cases if available. Treatment failures with known or suspected MDR TB should be treated with a Category IV regimen

4.3.5. Considerations for the choice of regimen for cases who fail Category I regimen

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

For this reason, countries with a high proportion of MDR-TB among failures of the Category I regimen should consider to treat such failures with a Category IV regimen. However, it needs to be stressed that the introduction of these regimens for failures of the Category I regimen requires either individualized susceptibility testing (DST) or representative drug-resistance surveillance (DRS) data in the patient category concerned. Culture and DST should be quality assured and all programmatic conditions for the introduction of a DOTS-plus component within the regular DOTS-programme should be met. **In principle, Category IV regimens should only be introduced in well performing DOTS programmes and be tailored to the local situation (drug-resistance patterns, history of drug-use in the country, human and financial resources).**

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

5. Essential antituberculosis drugs

There are three main properties of antituberculosis drugs:

1. Bactericidal activity,
2. Sterilizing activity and
3. The ability to prevent resistance.

The essential antituberculosis drugs possess these properties to different extents:

- Isoniazid and rifampicin are the most powerful bactericidal drugs, active against all populations of TB bacilli.
- Rifampicin is the most potent sterilizing drug available.
- Pyrazinamide and streptomycin are also bactericidal against certain populations of TB bacilli.
- Pyrazinamide is only active in an acid environment.
- Streptomycin is bactericidal against rapidly multiplying TB bacilli.
- Ethambutol and thioacetazone are used in association with more powerful drugs to prevent the emergence of resistant bacilli.

5.1. Anti-TB drugs and daily dosage for adults

Drug & Strength	Therapeutic dose mg/Kg	Weight in Kg			
		30 – 39	40 – 54	55 – 70	> 70
Streptomycin (S) – 1 Gram	15 (12 – 18)	½	¾	1 [⊗]	1 [⊗]
Rifina (RH) – (150 + 75)	R: 10 (8 – 12) H: 5 (4 – 6)	2	3	4	5
Pyrazinamide (Z) – 400	25 (20 – 30)	2	3	4	5
Ethambutol (E) – 400	15 (15 – 20)	1.5	2	3	3.5
Isoniazid (H) – 100	5 (4 – 6)	1.5	2.5	3	3.5
Ethina (EH) – (400 + 150)	E: 15 (15 – 20) H: 5 (4 – 6)	1.5	2	3	3

[⊗] If the patient is older than 50 years, reduce the dose of streptomycin from 1g to ¾ g.

6. Monitoring the patient

6.1. Monitoring the treatment response

Patients with sputum smear-positive pulmonary TB should be monitored by sputum smear examination. These are the patients for whom bacteriological monitoring is possible. It is unnecessary, unreliable and wasteful of resources to monitor patients by chest radiography. For patients with sputum smear-negative PTB and EPTB, clinical monitoring is the usual way of assessing the response to treatment. Under programme conditions in countries with a high incidence of TB, routine monitoring by sputum culture is not feasible or recommended. Culture can be used to confirm or reject treatment failure and to determine the drug susceptibility pattern in failure cases.

Month	New smear-positive	Re-treatment	New smear-negative
0	Diagnosis	Diagnosis	Diagnosis
2 or 3	End of 2	End of 3	End of 2
5	Beginning	End	
8	Outcome	Outcome	

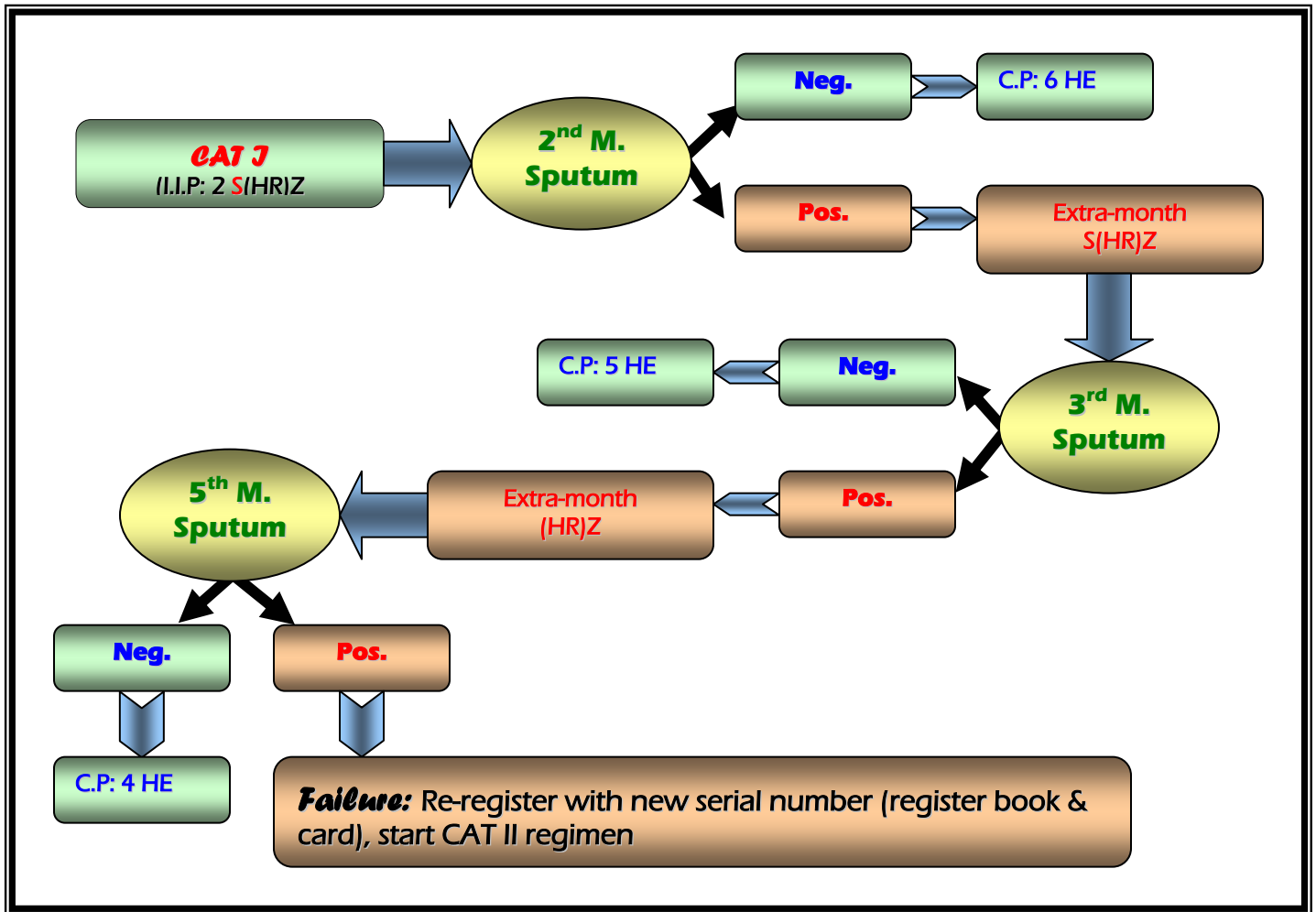
6.2. New sputum smear-positive pulmonary TB patients (Category I)

Response to treatment should be monitored by sputum smear examination. In general, **two sputum specimens should be collected for smear examination at each follow-up sputum check**. Sample collection should be done without interrupting treatment.

Sputum smears should be performed at the **end of the second month**, during the **fifth month** and **i8-month** treatment regimens. Negative sputum smears indicate good treatment progress, which encourages the patient and the health worker responsible for supervising treatment. At the end of the second month of treatment, most patients will have a negative sputum smear and 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:

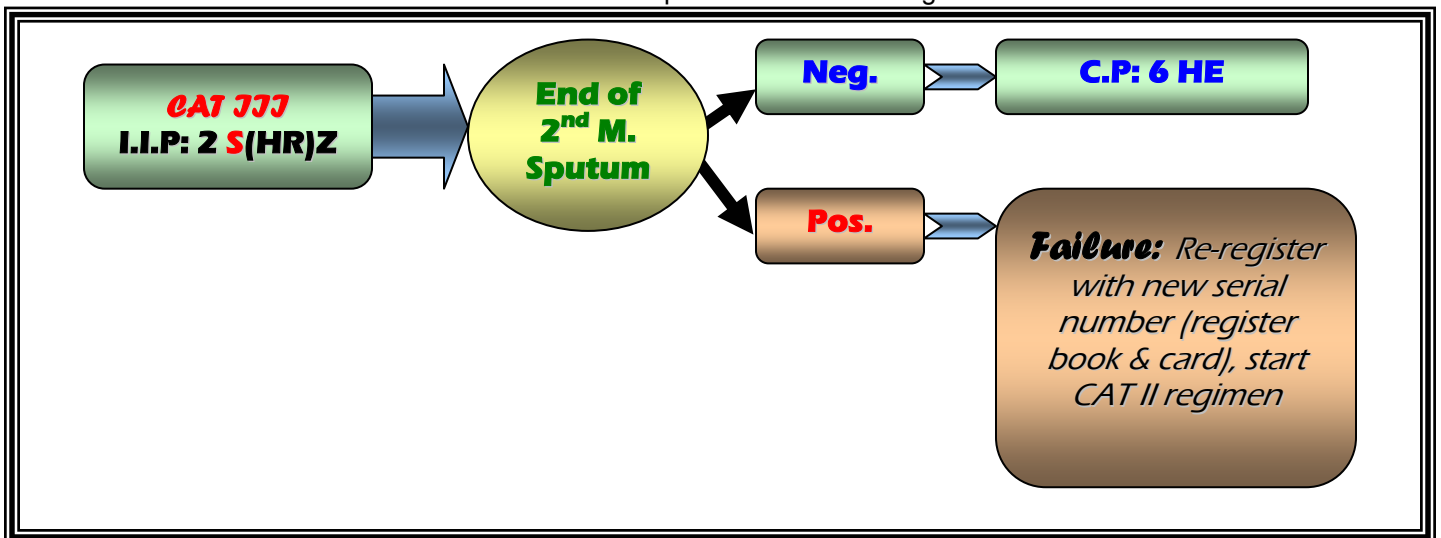
- most frequently, that the initial phase of therapy was poorly supervised and that patient adherence was poor;
- sometimes, that there is a slow rate of progress with sputum smear conversion, e.g. if a patient had extensive cavitation and a heavy initial bacillary load;
- rarely, that the patient may have drug-resistant TB that 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. Smears may be checked at the end of the third month to evaluate smear conversion in the cohort. **If the smear result is still positive at the end of the third month, the initial intensive phase is prolonged again for one month (without streptomycin)**. If the sputum smears are still positive **at the beginning of the fifth month**, this constitutes treatment failure. The patient is reregistered as a treatment failure and starts a full course of re-treatment regimen, either with a Category II or a Category IV regimen with reserve drugs. Countries where culture is routinely available may use it to confirm treatment failure before starting re-treatment. However, this may result in delays of 2 months or more, with increased transmission and deterioration of smear-positive culture-positive cases.



6.3. New sputum smear-negative pulmonary TB patients (Category III)

Sputum smear-negative patients should be monitored clinically; body weight is a useful progress indicator. Sputum smears should be checked at the end of the second month in case of the following possibilities: disease progress due to non-adherence to treatment, or an error at the time of initial diagnosis (i.e. a true smear-positive patient misdiagnosed as smear-negative) plus drug resistance. A patient initially diagnosed as sputum smear-negative and treated as a Category III patient who has positive sputum smears (*two positive samples, to reduce errors*) at the end of the second month should start a full course of Category II treatment. The outcome of the initial treatment should be failure and the patient should be reregistered.



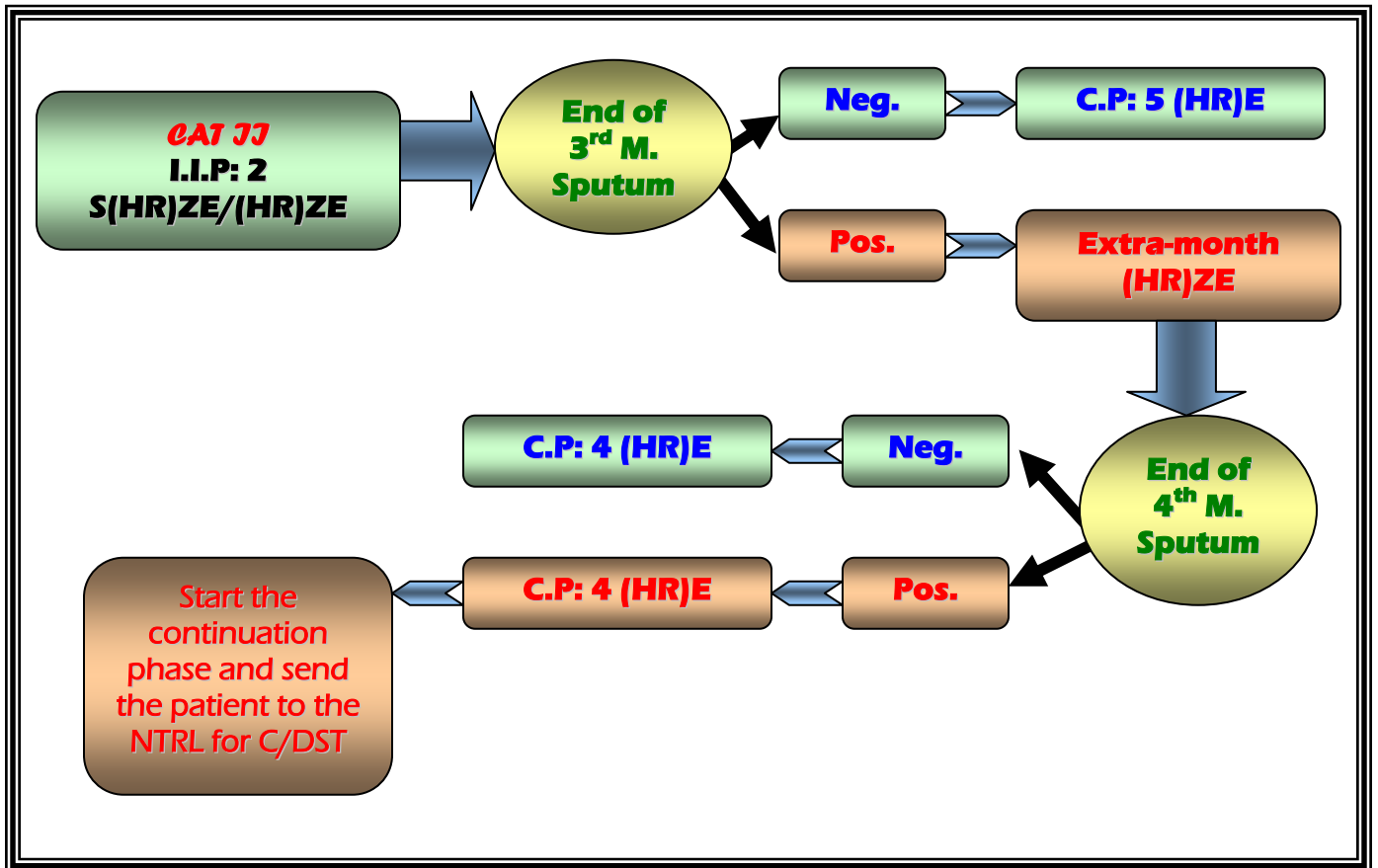
6.4. Extrapulmonary TB

Response to treatment can be monitored only through clinical observation. As in pulmonary smear-negative disease, the weight of the patient is a useful indicator.

6.5. Previously treated P 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 (second month after starting continuation) and at the end of treatment.

If the patient is sputum smear-positive at the end of the third month, the initial phase of treatment with 4 drugs is extended by another month and sputum smears are examined again at the end of the fourth month. If the patient still has positive smears at the end of the fourth month, sputum is sent to the laboratory for culture and sensitivity testing, where possible, and the patient then starts the continuation phase. If the culture and sensitivity results show resistance to 2 of the 3 drugs employed in the continuation phase, the patient should be referred to a specialized centre for consideration of treatment with reserve antituberculosis drugs. Where there are no facilities for culture and sensitivity testing, the patient continues treatment right until the end of the re-treatment regimen. Positive smears at the end of the fifth month indicate failure of the re-treatment regimen and, if a standard regimen for chronic and drug resistant patients is available, the patient should be referred.



6.6. Recording standardized treatment outcomes

At the end of the treatment course for each patient with sputum smear-positive PTB, the District TB Officer records the treatment outcome in the District TB Register. The table below shows the definitions of standardized treatment outcomes.

Cure	Patient who is sputum smear-negative in the last month of treatment and on at least one previous occasion
Treatment completed	Patient who has completed treatment but who does not meet the criteria to be classified as a cure or failure
Treatment failure	Patient who is sputum smear-positive at 5 month or later during treatment or a patient who was initially smear-negative before starting treatment and became smear-positive after completing the initial phase of treatment
Died	Patient who dies for any reason during the course of treatment
Default	Patient whose treatment was interrupted for two consecutive months or more
Transfer out	Patient who has been transferred to another TBMU and for whom the treatment outcome is not known

6.7. Cohort analysis of treatment outcome in smear-positive pulmonary TB patients

A cohort is a group of patients diagnosed and registered for treatment during a specific time period (usually 3 months). Evaluation of treatment outcome in new pulmonary smear-positive patients is used as a major indicator of programme quality. Outcome in other patients (re-treatment, pulmonary smear-negative, extrapulmonary) may also be analysed, in separate cohorts.

Cohort analysis is the key management tool for evaluating the effectiveness of the NTP. It allows the identification of problems, so that the NTP can institute appropriate action to overcome them and improve programme performance. Evaluation of the results of treatment and trends must be done at peripheral, district, regional and national level if corrective action is to be taken. The District TB Officer should perform cohort analysis of treatment outcome every 3 months and at the end of every year. A typical cohort consists of all those new pulmonary sputum smear-positive TB patients registered during a quarter (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 (relapses, return after default, failures) should be analysed as separate cohorts, because they have different characteristics and expected results. Evaluation of outcome at the end of treatment takes place about three months after all patients in the cohort have time to complete their course of treatment. Transmission of this information is done in quarterly reports. District quarterly reports on treatment outcome are forwarded to the region. The Regional TB Officer should verify that district reports are correct, complete and consistent, compile cohort analysis reports on the sputum smear-positive patients in the region, and submit the report to the central unit of the NTP. The NTP compiles cohort analysis reports on the smear-positive TB patients registered nationally, evaluates and provides feedback to the programme staff.

7. Adherence to treatment

Because of the importance of tuberculosis in public health, drugs for TB treatment should be provided free of charge to all patients. Ensuring patient compliance versus defaulter tracing

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

Promoting compliance through a **patient-centered approach**, which includes facilitating access to treatment, choosing with the patient the most convenient time and place for direct observation of treatment and, when possible, providing other social and medical services, is much more effective than spending resources on defaulter tracing. Facilitating access includes providing drugs and sputum smear controls free of charge, reducing the time and cost to the patient of obtaining treatment, and providing good and rapid attention.

Convenience to the patient must be balanced against the assurance of regular drug intake and monitoring, important to give the patient the best chances of cure. Patients who self-administer treatment often take drugs irregularly, and tracing is difficult and often unproductive, especially in low-income countries. In addition, there is a much longer period between interruption of treatment and action by the health system. It is vital for health staff and community workers to offer polite and efficient attention, and to consider the needs of the patient at every contact with them.

7.1. Why directly observed treatment?

Directly observed treatment is required to **ensure treatment adherence**. It helps to reinforce patients' motivation to continue treatment and counters the tendency of some to interrupt treatment – it is impossible to predict who will or will not comply. Directly observed treatment also ensures the accountability of TB services and helps to prevent the emergence of drug resistance. It is recommended in:

- The initial phase of treatment, at least for all smear-positive cases;
- The continuation phase of rifampicin-containing regimens.

A patient who misses one attendance for DOT should be traced and returned to treatment. When DOT for all patients throughout the whole treatment is not always practicable, it is recommended to use the 8-month regimen containing isoniazid plus ethambutol for daily self-administration in the continuation phase, with monthly clinical visits and medication refills.

7.2. Interruption of treatment: what to do?

7.2.1. Preventive measures to minimize treatment interruption

At the time of registration of a TB patient starting treatment, sufficient time should be set aside to meet with the patient (and preferably also with the patient's family members). This initial meeting provides an important opportunity to advise and counsel the patient. During the meeting, it is vital to record the patient's address and other relevant addresses (e.g. partner or spouse, parents, work place, place of study) in order to maximize the probability of locating patients who interrupt treatment. Where resources permit, it is helpful for a health staff member to accompany the patient to their residence following the initial meeting. It is also important to identify potential problems that the patient may face during the initial phase of treatment. Health staff must inform the patient about the duration of treatment, and the need to consult ahead of time in case of permanent or temporary change of address, to facilitate continuation of treatment. In the meeting at the end of the initial phase of treatment, 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 before or during the initial phase of treatment allows verification of the exact address and at the same time provides an opportunity to arrange for screening of household contacts, especially children aged under 5 years.

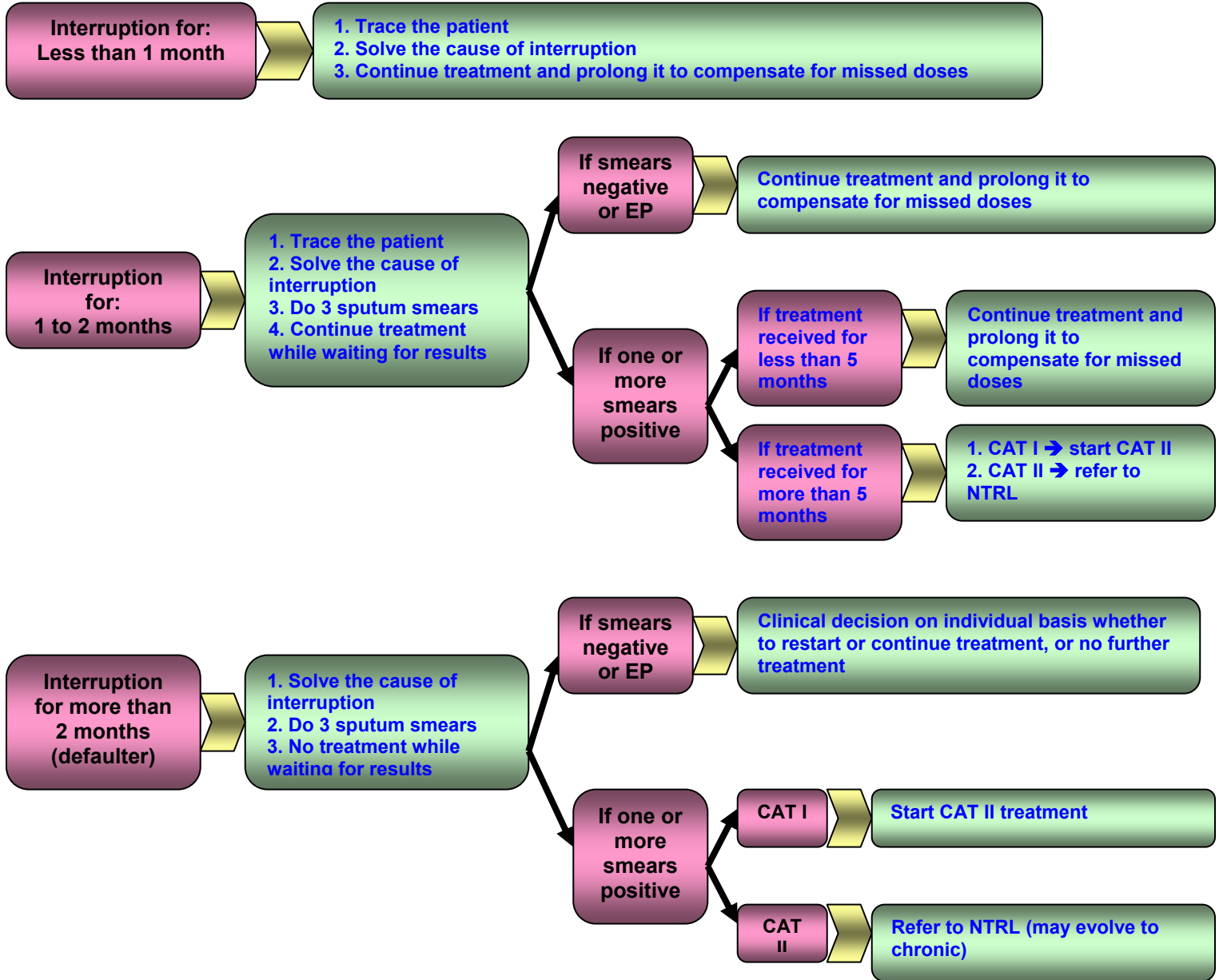
7.2.2. Corrective measures to minimize the duration of treatment interruption

Enquiries should be made about any patient who misses an arranged appointment to receive treatment, using the contact addresses previously obtained and appropriate means of tracing. It is important to find out the cause of the patient's absence in order to take appropriate action and continue treatment. **The patient should be contacted the next day after missing treatment during the initial phase and within a week during the continuation phase.**

7.2.3. What should be done when a patient returns after interrupting treatment?

The management of patients who have interrupted treatment is complex and takes into consideration several variables (immune status, degree of remission of the disease with the previous treatment, drug susceptibility) that may be difficult to assess.

7.3. A simple decision tree:



8. Monitoring & management of adverse effects of anti-TB drugs

8.1. Monitoring of TB patients for significant adverse effects of antituberculosis drugs

Most TB patients complete their treatment without any significant adverse effects of drugs. However, a few patients do experience adverse effects. Health personnel can monitor adverse effects of drugs by teaching patients how to recognize symptoms of common adverse effects and to report if they develop such symptoms, and by asking about symptoms when patients report to collect drugs.

8.2. 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 a numbness, tingling or 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 antituberculosis drugs.

8.3. Adverse effects of antituberculosis drugs

The table below shows a symptom-based approach to the most common adverse effects of the essential antituberculosis drugs. Adverse effects are classified as minor or major. In general, a patient who develops minor adverse effects should continue the TB treatment, 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. Patients with major adverse reactions should be managed in a hospital.

8.4. Symptom-based approach to side-effects of anti-TB drugs

Side-effects	Drug(s) probably responsible	Management
Minor		Continue anti-TB drugs, check drug doses
Anorexia, nausea, abdominal pain	Pyrazinamide, rifampicin	Give drugs with small meals or last thing at night
Joint pains	Pyrazinamide	Aspirin
Burning sensation in the feet	Isoniazid	Pyridoxine 100 mg daily
Orange/red urine	Rifampicin	Reassurance. Patients should be told when starting treatment that this commonly happens and is normal
Major		Stop responsible drug(s)
Itching, skin rash	Thioacetazone (S, H, R, Z)	Stop anti-TB drugs,
Deafness (no wax on auroscopy)	Streptomycin	Stop streptomycin, use ethambutol
Dizziness (vertigo and nystagmus)	Streptomycin	Stop streptomycin, use ethambutol
Jaundice (other causes excluded) hepatitis	Isoniazid, pyrazinamide, rifampicin	Stop anti-TB drugs,
Confusion (suspect drug-induced acute liver failure if jaundice present)	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

8.5. Management of a cutaneous reaction

Management of a cutaneous reaction depends on whether or not the patient is receiving (TH):

8.5.1. Treatment regimen includes thioacetazone

If a patient develops pruritus, with or without a rash, and there is no other obvious cause (e.g. scabies), antituberculosis drugs should be stopped immediately. If there is severe rash, or if there is mucosal involvement or hypotension, the patient will need intravenous fluids, and possibly steroids. Treatment is restarted only when the rash has resolved, replacing thioacetazone with ethambutol. A patient must never receive thioacetazone again after any thioacetazone reaction.

8.5.2. Treatment regimen does not include thioacetazone

If a patient develops itching and there is no other obvious cause (e.g. scabies), the recommended approach is to try symptomatic treatment with antihistamines, reassurance

and avoiding dry skin, continue TB treatment and observe the patient closely. However, if a skin rash develops all antituberculosis drugs must be stopped. Once the reaction has resolved, antituberculosis drugs are reintroduced. The problem is how to reintroduce TB treatment when the particular TB drug responsible for the reaction is not known.

The idea of **drug challenging** is to identify the drug responsible for the reaction. Drug challenge starts with the antituberculosis 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 be less severe than the reaction to a full dose. The dose is gradually increased over three 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, 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. This prolongs the total time of TB treatment, but decreases the risk of relapse.

8.6. Management of drug-induced hepatitis

Most antituberculosis drugs can damage the liver. Isoniazid, pyrazinamide and rifampicin are most commonly responsible, ethambutol rarely. When a patient develops hepatitis during TB treatment, the cause may be the TB treatment or something else. It is important to rule out other possible causes before deciding that the hepatitis is drug-induced. If the diagnosis is drug-induced hepatitis, the antituberculosis drugs should be stopped. The drugs must be withheld until liver function tests have reverted to normal. Sometimes it is not possible to perform liver function tests; in these situations, it is advisable to wait an extra 2 weeks after the jaundice has disappeared before recommencing TB treatment.

Asymptomatic jaundice without evidence of hepatitis is probably due to rifampicin. Once drug-induced hepatitis has resolved, the same drugs are reintroduced one at a time. However, if the hepatitis produced clinical jaundice, it is advisable to **avoid pyrazinamide**. A suggested regimen in such patients is:

- 2 SHE/ 10HE

A severely ill TB patient with drug-induced hepatitis may die without antituberculosis drugs. In this case, the patient should be treated with two of the least hepatotoxic drugs, **streptomycin and ethambutol**. After the hepatitis has resolved, usual TB treatment should be restarted.

9. Tuberculosis in children

9.1. Epidemiology

Children are usually infected with tuberculosis by an adult or an older child with sputum smear-positive PTB, often a family member. Less commonly, they may be infected by contact with smear-negative (often culture-positive) cases. The best way to prevent childhood TB is therefore by proper identification and treatment of infectious patients. **Case notifications of childhood TB usually represent 6-20% of all TB cases registered with the NTP.** Children can present with TB at any age, but the most common age is between 1 and 4 years. The frequency of childhood TB depends on the intensity of the epidemic, the age structure of the population, the available diagnostic tools and whether contact tracing is routinely undertaken.

The ratio of PTB:EPTB in children is usually around 1:3 but varies depending on factors such as age, ability to examine contacts and possibly genetic factors. Children may also be infected with *Mycobacterium bovis* by drinking untreated milk from infected cows. They often present with cervical TB adenitis or intestinal TB but can also develop PTB or disseminated disease.

The risk of infection in children depends on the extent of exposure to infectious droplet nuclei. For example, if a mother has sputum smear-positive PTB, her infant is more likely to become infected because of the very close contact and the higher risk of inhaling a large number of infectious droplets. The majority of infected children do not develop TB disease in childhood. The only evidence of infection may be a positive tuberculin skin test. **The likelihood of developing disease is greatest shortly after infection and declines steadily with time.** Infants and young children aged under 5 years are at particular risk of developing disease. **If an infected child does develop disease, the majority will present with symptoms within one year of infection. For infants particularly, the time-span between infection and disease may be as little as 6-8 weeks.** Various immunosuppressive illnesses may facilitate progression of infection to disease, including:

- HIV infection,
- Measles,
- Whooping cough and
- Protein-calorie malnutrition

9.2. Clinical presentation and diagnosis

The commonest type of TB in children is EPTB, mainly **intrathoracic**. Common forms of EPTB in children include TB lymphadenopathy, TB meningitis, TB effusions (pleural, pericardial and peritoneal) and spinal TB. **The diagnosis of respiratory TB in children is difficult because there is some confusion between primary infection (often without obvious lesions in the lungs) and PTB.**

Pulmonary TB is usually smear-negative. This is because many children present with primary rather than reactivation (cavitary) PTB and because the majority of children with PTB are too young to produce sputum for smear microscopy. Smear-positive PTB is usually diagnosed in school-aged children. The prevalence of PTB is normally low between the ages of 5 and 12 years and then increases slightly again in adolescence, when PTB presents more like adult PTB (i.e. with cavitation).

The presentations of TB in children are:

1. Primary TB disease

- **Often unilateral lymphadenopathy**, hilar or mediastinal, without radiographic abnormalities in the lung (no obvious parenchymal involvement). It is the most frequent (70-80%) and should be classified as EPTB and treated as Category III.
- **Sometimes typical "primary complex"**, combining hilar/mediastinal lymphadenopathy and a small opacity in the lung, 3-10 mm in diameter ("primary lesion"). It is less frequent (20%, usually in children aged under 5 years). This is classified as a case of PTB and should be treated as Category III.
- **Rarely, lobar or segmental opacity** in the lung, combined with unilateral lymphadenopathy on the same side. A PTB case with large parenchymal involvement should be treated as Category I. When bronchial compression has resulted in atelectasis, corticoids in addition to chemotherapy may be helpful. Cavitation of the primary lesion in the lung is exceptional in children, and is classified as PTB, often smear-positive.

2. Acute disseminated post-primary TB (often in children aged under 5 years): miliary with or without meningitis. Classified as severe extrapulmonary, Category I.

3. Post-primary PTB (usually in children aged over 10 years): without cavitation, smear-negative or with cavitation, smear-positive. Category I.

4. Post-primary EPTB: Category I or III.

9.3. Approach to diagnosis

The diagnosis of PTB is difficult in children aged under 6-8 years, particularly in the low-resource setting. Important features include:

1. Contact with a smear-positive PTB case;
2. Respiratory symptoms for more than 2-3 weeks, not responding to broad spectrum antibiotics;
3. Weight loss or failure to thrive;
4. Positive test to the standard dose of tuberculin (2 TU of RT23 or 5 TU of PPD-S): 10 mm or more in unvaccinated children, 15 mm or more in BCG-vaccinated children; however, with severe TB and/or advanced immuno-suppression, the tuberculin test may be negative in infected persons.

There are no specific clinical findings for a diagnosis of PTB. There may be clues to other diagnoses such as asthma, bronchiectasis, whooping cough, inhaled foreign body or cardiac disease.

- Diagnosis of childhood PTB requires chest X-ray (CXR), although CXR findings are often not specific and certainly not diagnostic. Upper and mid-lobe infiltrates are more common, cavitory disease is uncommon. However, radiographic and clinical findings suggestive of TB become more specific when it has been established that the child has been in close contact with a diagnosed case of PTB, especially smear-positive PTB.
- The effort to establish a positive contact history deserves special emphasis. A positive history increases the likelihood that the child does indeed have TB. It may also lead to identification of a previously undiagnosed infectious case. History should therefore include specific enquiry about any symptoms, especially cough, of living or recently deceased household members.
- The readily available usual test for adults and older children with PTB, sputum smear microscopy, is not possible for the majority of young children, who usually swallow their sputum. Other methods of obtaining material, such as gastric lavage, can be problematic to implement as a routine diagnostic procedure, are less sensitive and generally not useful unless facilities are available for *M. tuberculosis* culture. This means that bacteriological confirmation is usually not possible and that the diagnosis of PTB in children is often presumptive.
- Scoring systems have been produced for screening and diagnostic purposes, but their evaluation is difficult in the absence of a “gold standard” diagnosis. They are likely to be even less accurate in regions where childhood malnutrition and HIV infection are common. A “trial of TB treatment” should not be used as a diagnostic maneuver.
- The diagnosis of EPTB in children is usually more straightforward because of characteristic clinical features (e.g. spinal deformity, scrofula or painless ascites) and, infrequently, supportive microscopic findings on specimens such as cerebrospinal fluid, pleural fluid, ascitic fluid and lymph node aspiration or biopsy.
- **Tuberculin skin test:** A positive tuberculin test does not indicate the presence or extent of tuberculosis disease; it only indicates infection. In a child who has not had BCG, a tuberculin test is defined as “positive” when the diameter of skin induration is 10 mm or more. In a child who has had BCG, an induration of 10-14 mm may be due to vaccination or TB infection. A negative tuberculin skin test does not exclude TB infection and some induration, e.g. 5-14 mm, is supportive if the clinical features and contact history are suggestive. The tuberculin test is less likely to be positive in a child with TB if the child also has severe malnutrition, HIV infection or disseminated TB such as miliary disease or TB meningitis.

9.3.1. Impact of HIV on diagnosis of TB in children

HIV makes diagnosis and management of TB in children more difficult for the following reasons:

1. Other HIV-related disease, such as lymphocytic interstitial pneumonitis, may present in a similar way to PTB or miliary TB.
2. Interpretation of tuberculin skin testing and CXR is less reliable.
3. When TB/HIV co-infection is common in adults, a positive contact history is less specific if the contact is the child’s parent. The child is at risk of transmission of either or both diseases.

4. Children with TB and advanced HIV disease may not respond as well to TB treatment. HIV testing can be helpful, especially if the result is negative, as it increases the likelihood of a diagnosis of TB. However, a positive HIV result clearly does not exclude the possibility of TB.

9.4. Management of childhood TB

Thioacetazone can cause severe and often fatal reactions in HIV-infected children and so should not be used in HIV-endemic regions. It has been replaced by ethambutol. There has been understandable caution with the use of ethambutol in children too young to report early visual deterioration, but ethambutol has been safely used in infants and young children at recommended dosages.

Recommended dosages are based on research in adults and yet metabolism of drugs varies with age. The effectiveness of the recommendation of EH for the maintenance or continuation phase has never been studied in children, whereas RH has proven efficacy. Mortality is high and long-term sequelae common with TB meningitis - the best prevention is rapid diagnosis and treatment. In children with TB meningitis, streptomycin should be used instead of ethambutol because ethambutol does not cross the blood-brain barrier. Corticosteroids are sometimes useful in TB meningitis or in lobar/segmental opacity due to a lymphadenopathy.

9.5. Recommended Regimen for treatment of TB in Children:

Category	Patients	Regimen
Category I	1. Smear-positive PTB 2. Smear-negative PTB with extensive parenchymal involvement (acute military, segmental/lobar opacity). 3. Severe EP (disseminated acute TB, abdominal, spinal, and pericardial TB)	2HRZE / 4HR
Category I	TB meningitis	2HRZS / 4HR
Category III	1. Smear-negative PTB 2. Less severe EP (TB adenitis, mediastinal lymphadenopathy)	2HRZ / 4HR

9.6. Management of child contacts of infectious adults

Active tracing of children who are household contacts of smear-positive PTB cases is recommended. Ideally, screening should include at least a thorough history, clinical examination, tuberculin test, CXR and HIV test. Those with a diagnosis of TB are then treated.

- Those who are well and aged less than 5 years should receive prophylaxis (**isoniazid 5 mg/kg daily**). This will significantly reduce the likelihood of their developing TB disease.
- Breastfeeding children of sputum smear-positive mothers are the most important group for preventive therapy. Prophylaxis should be **for at least 6 months** and requires regular (e.g. every 2 months) follow-up.
- Children aged over 5 years who are well do not require prophylaxis, only clinical follow-up.

Children may also be infected by smear-negative PTB cases but, because transmission is less common, routine contact tracing is not recommended in this circumstance.

9.7. Recommended dosage for children

Drug (adult strength)	Weight in Kg		
	5 - 10	11 - 20	21 - 30
HR (75 mg+ 150 mg)	1/2	1	2
Z (400 mg)	1/2	1	2
E (400 mg)	-	-	1
S (1G) in TB meningitis	0.25	0.33	0.5
H (100 mg)	1/2	1	2

10. Treatment regimens in special situations

10.1. Pregnancy

A woman should be asked whether she is pregnant before she starts TB treatment. Most antituberculosis drugs are safe for use in pregnancy. The exception is streptomycin, which is ototoxic to the fetus and should not be used during pregnancy. A pregnant woman should be advised that successful treatment of TB with the recommended standardized regimen is important for successful outcome of pregnancy.

10.2. Breastfeeding

A breastfeeding woman who has TB should receive a full course of TB treatment. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to her baby. All antituberculosis drugs are compatible with breastfeeding; a woman taking them can safely continue to breastfeed. Mother and baby should stay together and the baby continues to be breastfed in the normal way. The baby should be given prophylactic isoniazid for at least 3 months beyond the time the mother is considered to be non-infectious. BCG vaccination of the newborn should be postponed until the end of isoniazid prophylaxis.

10.3. Oral contraception

Rifampicin interacts with oral contraceptive medications with a risk of decreased protective efficacy against pregnancy. A woman receiving oral contraception may choose between two options while receiving treatment with rifampicin: following consultation with a clinician, an oral contraceptive pill containing a higher dose of estrogen (50 µg) may be taken, or another form of contraception may be used.

10.4. Liver disorders

Isoniazid, rifampicin and Pyrazinamide are all associated with hepatitis. Of the three drugs, rifampicin is least likely to cause hepatocellular damage, although it is associated with cholestatic jaundice. Of the three agents, Pyrazinamide is the most hepatotoxic.

Patients with the following conditions can receive the usual short-course chemotherapy regimens provided there is no clinical evidence of chronic liver disease - hepatitis virus carriage, a past history of acute hepatitis, excessive alcohol consumption. However, hepatotoxic reactions to antituberculosis drugs may be more common among these patients and should therefore be anticipated.

10.4.1. Established chronic liver disease

Patients with liver disease should not receive Pyrazinamide. Isoniazid plus rifampicin plus one or two non-hepatotoxic drugs such as streptomycin and ethambutol can be used for a total treatment duration of 8 months. Alternative regimens are 9 RE or SHE in the initial phase followed by HE in the continuation phase, with a total treatment duration of 12 months. Recommended regimens are therefore 2 SHRE/6 HR, 9 RE or 2 SHE/10 HE.

10.4.2. Acute hepatitis (e.g. acute viral hepatitis)

Uncommonly, a patient has TB and concurrently acute hepatitis unrelated to TB or TB treatment. Clinical judgment 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 SE for 3 months is the safest option. If the hepatitis has resolved, the patient can then receive a continuation phase of 6 months isoniazid and rifampicin 6 HR. If the hepatitis has not resolved, SE should be continued for a total of 12 months.

10.5. 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. Patients with severe renal failure 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, streptomycin and ethambutol may be given in reduced doses. Thiocetazone is partially excreted in the urine; however, since the margin between a therapeutic dose and a toxic dose is too narrow, patients in renal failure should not receive this drug. The safest regimen for patients with renal failure is 2 HRZ/4 HR.

11. Annex

(TB 04)

TB LABORATORY FORM REQUEST FOR SPUTUM EXAMINATION

Treatment Unit _____ Date _____

Patient's Name

Age _____ Sex: (M/F) : M F New Received medication

Address (precise)

Reason for examination: Diagnosis follow-up examination

Dr. / Medical Assistant Name: _____

Signature _____

RESULTS (to be completed in laboratory)

Laboratory Serial No.

Date	Specimen appearance	Result (check one)				
		neg	1-9	+	++	+++
	1					
	2					
	3					

Date _____

Examined by (Signature) _____

The completed form (with results) should be sent promptly to the treatment uni

وزارة الصحة الاتحادية المشروع لمكافحة الدرن NTP <u>بطاقة مريض</u>	<u>مرضك قابل للشفاء</u> - هذه البطاقة إذا فقدت اطلب استخراج بطاقة جديدة. - إذا واطبت على علاجك بانتظام واتبعت إرشادات الطبيب فتأكد من الشفاء بأذن الله.
اسم المريض: _____ م	
رقم التسجيل: _____ م	
	مواعيد صرف العلاج

Diagnosis:	ملاحظات	تاريخ الزيارة	الموعد المحدد
New Smear-Positive PTB ()			
Re-treatment Smear-positive:			
- Relapse ()			
- Failure ()			
- Defaulter ()			
Smear - Negative PTB ()			
Extra - Pulmonary TB ()			
Specify: _____			
Treatment Regimen:			
Short Course 2 SRHZ ()			
6 HE ()			
Retreatment 2 SRHZE/1RHZE ()			
5 RHE ()			

المشروع القومي لمكافحة الدرن - السودان

التقرير ربع السنوي عن الحالات المكتشفة للدرن الرئوي الموجب و السالب و خارج الرئة

National Tuberculosis Control Programme – Sudan

Quarterly Report on Case Finding for

Pulmonary Smear- Positive, Smear-Negative & Extra-pulmonary TB

Form (TB 05)

Name of TBMU..... أسم الوحدة التشخيصية العلاجية	Patients registered during: quarter _____ المرضى المسجلين خلال الربع
Name of coordinator: _____ اسم منسق المنطقة	
Date of completion of this form _____ تاريخ ملء الفورم	Signature _____ الامضاء

Pulmonary TB رئوي												EP خارج الرئة		Total المجموع						
Smear-Positive موجب التفاف						Smear-Negative سالب التفاف (3)						(4)		(5)						
New Cases (1) حالات جديدة			Re-treatment (2)									< 14 اقل من 14		> 14 اكثر من 14						
			Relapse انتكاسة		Failure فشل		Defaulter عودة بعد انقطاع		Others أخرى											
ذكر	انثى	مجموع	ذكر	انثى	ذكر	انثى	ذكر	انثى	ذكر	انثى	ذكر	انثى	ذكر	انثى	ذكر	انثى	مجموع			
M	F	Total	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	Total	

New smear-positive cases from column (1) above												الحالات الجديدة الموجبة من العمود (1) اعلاه					
Age groups in years												قطاع العمر بالسنين					
0-14 (1.1)		15-24 (1.2)		25-34 (1.3)		35-44 (1.4)		45-54 (1.5)		55-64 (1.6)		≥ 65 (1.7)		Total (1)			
M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	Total	

Conversion Rate Report					
تقرير معدل التحول					
Year & Quarter السنة و الربع	Total Positive Cases مجموع الايجابى	Examination done* تم فحص التفاف		Not examined لم يفحص التفاف	Conversion Rate معدل التحول
		Converted to Negative تحول الى سالب	Still Positive مازال موجبا		

* smear results at the 2nd or the 3rd month نتائج التفاف عند نهاية الشهر الثانى او الثالث

REPORT ON THE RESULTS OF TREATMENT OF SMEAR- POSITIVE & SMEAR NEGATIVE PULMONARY & EXTRA-PUMONARY TUBERCULOSIS PATIENTS REGISTERED 15-18 MONTHS EARLIER

تقرير نتائج العلاج لمرضى الدرن الرئوي ذو التفاف الإيجابي والسلبي والخارج الرئة المسجلون خلال 18/15 شهر السابقة (TB 06)

Name of district ----- اسم المنطقة				Patients registered during المرضى المسجلين خلال ربع السنة -----quarter of-----			Date of completion of this form: تاريخ ملئ الفورم ----- الإمضاء:				
Tuberculosis coordinator----- اسم منسق المنطقة											
Total No of smear positive patients registered during the above quarter in FORM (TB 05) أجمالي مرضى التفاف الإيجابي المسجلين في الربع (TB 05) أعلاه في الفورم	Total No of smear positive patients evaluated during the above quarter أجمالي مرضى التفاف الإيجابي الذين تم تقييمهم M F Total			Regimen الريجيم	(1) Cured (smear negative) عولج (التفاف سالب)	(2) Treatment completed (no smear results) العلاج انتهى	(3) Died توفي	(4) failure (smear Positive) فشل (تفاف موجب)	(5) Defaulted انقطع	(6) Transferred to another district حول إلي منطقة أخرى	Total number evaluated (sum of Columns 1-6) العدد الذي تم تقييمهم في العمود 1-6
	M	F	TOT								
New smear +ve from (1) in Block (1) الحالات الجديدة الإيجابية المسجلة في العمود (1) في المربع (1)				1. New Cases Smear Positive حالات جديدة إيجابية							
				1.1 DOTS علاج مباشر							
				1.2 Standard علاج تقليدي							
				1.3 Total المجموع							
Smear Negative from (3) in Block (1) الحالات السلبية المسجلة في العمود (3) في المربع (1)				2. Smear Negative (Standard) سلبي (علاج تقليدي)							
Extra Pulmonary from (4) in Block (1) الحالات خارج الرئة المسجلة في العمود (4) في المربع (1)				3 Extra Pulmonary (Standard) خارج الرئة (علاج تقليدي)							
Retreatment Smear +ve from (2) Block (1) الحالات الانتكاسية المسجلة في العمود (2)				4. Re-treatment إعادة العلاج							
				4.1 Relapses انتكاسة							
				4.2 Return after default عودة بعد انقطاع							
				4.3 failure cases حالات فاشلة							
				4.4 Total							