TB Treatment Guidelines
For Somalia

December 2012
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<th>Full Form</th>
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<tr>
<td>AIDS</td>
<td>Acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>CIF</td>
<td>Cost-insurance-freight</td>
</tr>
<tr>
<td>CXR</td>
<td>Chest X-ray</td>
</tr>
<tr>
<td>DOT</td>
<td>Directly observed treatment</td>
</tr>
<tr>
<td>DOTS</td>
<td>WHO and IUATLD recommended strategy for TB control</td>
</tr>
<tr>
<td>DR-TB</td>
<td>Drug Resistant TB</td>
</tr>
<tr>
<td>E</td>
<td>Ethambutol</td>
</tr>
<tr>
<td>EDL</td>
<td>Essential Drugs List</td>
</tr>
<tr>
<td>FDC</td>
<td>Fixed dose combination</td>
</tr>
<tr>
<td>FIFO</td>
<td>First in, first out</td>
</tr>
<tr>
<td>FM</td>
<td>Fluorescence Microscopes</td>
</tr>
<tr>
<td>FOB</td>
<td>Free on board</td>
</tr>
<tr>
<td>GOP</td>
<td>Good manufacturing practices</td>
</tr>
<tr>
<td>GX</td>
<td>Gene Xpert</td>
</tr>
<tr>
<td>H</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>HAART</td>
<td>Highly active antiretroviral therapy</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>INNs</td>
<td>International Non-proprietary Names</td>
</tr>
<tr>
<td>IUATLD</td>
<td>International Union Against Tuberculosis and Lung Disease</td>
</tr>
<tr>
<td>MDR-TB</td>
<td>Multidrug-resistant TB, resistance to at least rifampicin and isoniazid</td>
</tr>
<tr>
<td>MODS</td>
<td>Microscopic Observed Direct Susceptibility</td>
</tr>
<tr>
<td>NGO</td>
<td>Non-governmental organization</td>
</tr>
<tr>
<td>NTP</td>
<td>National tuberculosis Program</td>
</tr>
<tr>
<td>PHC</td>
<td>Primary health care</td>
</tr>
<tr>
<td>PLWH</td>
<td>People living with HIV/AIDS</td>
</tr>
<tr>
<td>R</td>
<td>Rifampicin</td>
</tr>
<tr>
<td>S</td>
<td>Streptomycin</td>
</tr>
<tr>
<td>SCC</td>
<td>Short-course chemotherapy</td>
</tr>
<tr>
<td>SLD</td>
<td>Second Line Drugs</td>
</tr>
<tr>
<td>STB</td>
<td>WHO Tuberculosis Program (Stop-TB)</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TB/HIV</td>
<td>HIV-related TB</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>Z</td>
<td>Pyrazinamide</td>
</tr>
<tr>
<td>ZN</td>
<td>Ziehl-Neelsen</td>
</tr>
</tbody>
</table>
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The guidelines are expected to be revised and updated in the future according to the indications from the personnel on the field and from all partners involved in Tuberculosis control in Somalia.
INTRODUCTION

1. TB CONTROL IN SOMALIA

1.1 Situational Analysis

Somalia has a high incidence rate of TB, the estimated incidence of TB cases is estimated at 286/100,000 while the prevalence is estimated to be 523/100,000 population. Tuberculosis MDR survey conducted in Somalia in 2010/2011 indicated that MDR incidence in the country among new sputum smear positive case is 5% while among the previously treated cases is 41%, (WHO Somalia/NTP). TB is therefore an important public health problem.

The TB Program started implementing DOTS in 1995, and achieved the targets of DOTS ALL OVER, based on the presence of at least one TB center in each of 18 regions. However, vast regions with the nomadic lifestyle of Somalis may contribute to the inaccessibility of these centers, therefore expansion of the TB centers to have more than one center in the big regions/towns are expected to contribute to improving the case detection rate. The number of TB centers has increased from 18 TB centers in 1995 to 65 TB centers in 2011.

![Graph 1. Number of TB centers as from 1995 to 2011](image)

*Figure 1* TB Progressive growth of TB Centers since 1995
According to the new WHO Data of 2012 report, Somalia detected 11,653 TB cases in 2011. Among these patients sputum smear positive cases accounted for 5884 cases. The number of cases detected has been increasing over the years. In 1995, TB cases detected in Somalia were only 2,504 cases. This number has progressively increased up to 11,653 in 2011.

Figure 1 Trend of TB cases detected from 1995 to 2011

Treatment success rate in 2010 was 89% while cure rate was 87%. In order to accomplish universal access for all TB cases in Somalia and to maintain the achieved target of the treatment success rate (currently over 89%) the NTP is trying to involve all possible Partners including other health care providers (DOTS comprehensiveness). Since 1995
2. Goals

To decrease the burden of tuberculosis in Somalia, with emphasis on accessibility, affordability, quality, equity, sustainability, and patient satisfaction, in line with the MDGs and the Stop TB targets.

Impact targets:
To halve the prevalence and mortality from TB in 2014 compared to the baseline of 1990

Objectives

1- To detect at least 70% of estimated new sputum smear positive TB patients by 2014
2- To detect at least 65% of estimated all forms of TB by 2014
3- To treat successfully at least 85% of new sputum smear positive pulmonary patients by 2014
4- To detect and treat 60% of the estimated annual incident sputum smear positive MDR cases by 2014
5- To establish HIV surveillance for all forms of TB cases by 2013
6- To provide HIV care for at least 80% of TB/HIV co-infected individuals by 2014
7- To strengthen and maintain the supervisory capacity of the three NTP offices in supervision, monitoring and evaluation of the program by 2013
2 CASE DEFINITIONS

2.1 Objectives of chapter

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

2.2 Purposes for case definitions

The box shows the purposes of making case definitions.

— Proper patient registration and case notification;
— Selecting appropriate standard treatment regimens (see Chapter 3);
— Standardizing the process of data collection for TB control;
— Evaluating the proportion of cases according to site, bacteriology and treatment history;
— Cohort analysis of treatment outcomes;
— Accurate monitoring of trends and evaluation of the effectiveness of TB Programs within and across districts, countries and global regions.

2.3 Reasons for matching treatment to standardized category

The box shows the reasons for matching treatment to standardized category.

• To avoid under-treatment of previously treated cases and therefore to prevent acquired resistance
• To increase cost-effective use of resources and to minimize side-effects for patients by avoiding unnecessary over-treatment
2.4 Determinants of case definitions

The box shows the four determinants of case definition.

<table>
<thead>
<tr>
<th>Determinant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Site of TB disease</td>
</tr>
<tr>
<td>2) Bacteriology</td>
</tr>
<tr>
<td>3) Severity of TB disease</td>
</tr>
<tr>
<td>4) History of previous treatment of TB</td>
</tr>
</tbody>
</table>

2.5 Case definitions

The TB case definitions below are based on the level of certainty of the diagnosis and on whether or not laboratory confirmation is available.

- **Presumptive TB case.** Any person who presents with symptoms or signs suggestive of TB

  *Recommended 1. The following symptoms and signs are suggestive of TB:*
  
  a) **Productive cough for more than 2 weeks, which may be accompanied by other respiratory symptoms such as shortness of breath, chest pains, haemoptysis and/or**
  
  b) **Constitutional symptoms such as loss of appetite, weight loss, fever, night sweats, and fatigue**

- **A clinically-diagnosed TB case.** This is a TB case who is started on a full treatment for active TB but who does not fulfill the criteria to be considered bacteriologically confirmed. This includes cases diagnosed on the basis of X-ray abnormalities, suggestive histology and extrapulmonary cases without a laboratory confirmation.

  *Recommendation 2. Any clinically diagnosed cases subsequently found to be bacteriologically-positive before or after starting treatment, should therefore be re-classified as bacteriologically-confirmed.*

- **A bacteriologically confirmed TB case.** This is a TB cases who is tested positive upon sputum-smear microscopy, culture or WHO-approved rapid diagnostics such as Xpert MTB/RIF (WRD).

  *Recommendation 3. All TB cases that are bacteriologically confirmed should be notified regardless of whether TB treatment was started or not.*
TB Cases are also classified according to the:
   1. Anatomical site of disease;
   2. Bacteriological results (including drug resistance);
   3. History of previous treatment;
   4. HIV status of the patient.

Each of these key features of TB cases is discussed below.

### 2.6 Anatomical site of TB disease

In general, recommended treatment regimens are similar, irrespective of site. However, defining the site is important for recording and reporting purposes and to identify the more infectious patients particularly those pulmonary involvement that are further subdivided by smear status.

**Pulmonary tuberculosis** (PTB) refers to a case of TB (defined above) involving the lung parenchyma. Miliary tuberculosis is classified as pulmonary TB because there are lesions in the lungs. Tuberculosis intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculosis 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.

**Recommendation 3.** All persons with otherwise unexplained productive cough lasting 2–3 weeks or more should be evaluated for TB.

**Extra pulmonary tuberculosis** (EPTB) refers to a case of pulmonary TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges. Diagnosis should be based on at least one specimen with confirmed *M. tuberculosis* 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 EPTB case with several sites affected depends on the site representing the most severe form of disease. For patients suspected of having EPTB, specimens should be obtained from the suspected sites of involvement. Where available, culture and histopathological examination should also be carried out. Additionally, a chest X-ray and examination of sputum may be useful, especially in persons with HIV infection.

**Recommendation 4.** Unless a case of EPTB is confirmed by culture as caused by *M. tuberculosis*, it cannot meet the “definition of bacteriologically confirmed TB case as defined in section 2.5 above.”
2.7 Bacteriological results

Bacteriology refers to the smear status of pulmonary cases and the identification of *M. tuberculosis* for any case by culture or newer methods such as Gene Xpert Culture

**Recommendation 5.** All patients presumed of having pulmonary TB should submit at least two sputum specimens for microscopic examination in a quality-assured laboratory. When possible, at least one early-morning specimen should be obtained, as sputum collected at this time has the highest yield.

**Recommendation 6.** All persons with chest radiographic findings suggestive of TB should submit sputum specimens for microbiological examination

Note: Smear-positive cases are the most infectious and most likely to transmit their disease in their surroundings; they are the focus for infection control measure and contact investigation. Bacteriological monitoring of treatment progress is most feasible and practicable in these patients. However, it is also important to identify smear-negative cases, especially in persons living with HIV for whom mortality is higher than in smear-positive pulmonary TB cases.

**Recommendation 7.** A case of pulmonary TB is considered to be smear-positive if one or more sputum smear specimens at the start of treatment are positive for AFB provided that there is a functional EQA system with blind rechecking.

**Recommendation 8.** Presence of at least one acid fast bacillus (AFB+) in at least one sputum sample defines a new sputum smear-positive pulmonary TB case provided that Somalia continuous to have well functioning EQA system

**Recommendation 9.** Pulmonary TB cases without smear results are no longer classified as smear-negative instead; they are recorded as “smear not done” on all TB register.

2.8 History of previous treatment: patient registration group

A TB patient meeting the case definition can also be classified at the time of registration according to whether or not he or she has previously received TB treatment and, if possible by the outcome of the previous treatment if known. This is important in order to identify previously treated patients because they are at increased risk of drug resistance, including MDR-TB.

**Recommendation 10.** For all previously treated TB patients, specimens should be obtained for culture and DST at start of treatment where possible.

**New patients:** These are patients who have never had treatment for TB, or have taken anti-TB drugs for less than 1 month. New patients may have positive or negative bacteriology and
may have disease at any anatomical site.

**Previously treated patients:** These are patients, who have received 1 month or more of anti-TB drugs in the past, may have positive or negative bacteriology and may have disease at any anatomical site. They are further classified by the outcome of their most recent course of treatment as shown in Table 1 below.

**Recommendation 11. All Patients whose sputum is smear-positive at the end of a second treatment, during second treatment or any subsequent course of treatment are no longer defined as “chronic”. These patients shall be classified by the outcome of their most recent retreatment course as relapsed, loss to follow-up or failed.**

Table 1. Registration group by outcome of most recent TB treatment

<table>
<thead>
<tr>
<th>Registration group</th>
<th>Bacteriology</th>
<th>Outcome of most recent prior treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>New</td>
<td>+ or -</td>
<td></td>
</tr>
<tr>
<td>Previously treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>+</td>
<td>Cured</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment completed</td>
</tr>
<tr>
<td>Failure</td>
<td>+</td>
<td>Treatment failed</td>
</tr>
<tr>
<td>Loss to treatment</td>
<td>+</td>
<td>Defaulted (lost to treatment)</td>
</tr>
<tr>
<td>Transfer in: A patient who has been transferred from another TB register to continue treatment</td>
<td>+ or-</td>
<td>Still on treatment</td>
</tr>
<tr>
<td>Other</td>
<td>+ or -</td>
<td>All cases that do not fit above definitions, such as patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• For whom it is not known whether they have been previously treated:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Who were previously treated but with unknown outcome of that previous treatment: and/or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Who have returned to treatment with smear negative PTB or bacteriologically negative EPTB</td>
</tr>
</tbody>
</table>

**2.9 HIV status**

Determining and recording the patient’s HIV status is critical for treatment decisions as well as for monitoring trends and assessing Program performance. Somalia TB Treatment Card
and TB Register has included profiles on HIV testing, starting co-trimoxazole, and starting ART.

3. Tuberculosis Laboratory Services

3.1. Aims of the bacteriological service

The aims of the bacteriological service are, first, the diagnosis of new, retreatment cases and, second, the monitoring of their treatment.

The tuberculosis laboratory service consists of a network of multipurpose laboratories at district and regional levels throughout the country which carry out, as part of their work, microscopic examination of sputum smears stained by the Ziehl-Neelsen method, Fluorescent microscopy and Gene Xpert.

A practical description of all procedures related to sputum examination by direct microscopy is given in a “Technical Guide for Sputum Examination for Tuberculosis by Direct Microscopy”.

The Reference Laboratory of Tuberculosis (when established) should supervise the network of microscopy centers, provide culture and sensitivity testing services and, in addition, perform direct smear examination for quality control.

3.2. Extension of the periphery

Efficient peripheral laboratories play a crucial role in the success of case finding Programs based on the detection of smear-positive cases. A good reliable laboratory service is a prerequisite to initiation of a tuberculosis Program.

3.3. Culture

Direct smear examination has the highest priority. Culture of sputum from symptomatic suspects with chest x-ray abnormalities compatible with tuberculosis, but smear-negative, may result in more frequent and earlier diagnosis. As soon as sputum cultures become feasible it will be necessary to carry out culture of tubercle bacilli for routine diagnosis for TB cases

**Recommendation 1:** The national TB Program recommends that the following category of patients presenting to health facilities should be screened for TB:

- All patients having cough for 2 weeks
• **TB contacts particularly children living with sputum smear positive patients/guardians**
• **Persons living with HIV/AIDS**
• **Suspects of MDR –TB case**

**Recommendation 2:** All patients with sputum results positive at follow up at 3 months, as well as retreatment cases should have culture and DST done for them.

3.4. Quality Control

Quality control of tuberculosis bacteriology, including direct smears, cultures and sensitivity tests, is very important. This will be conducted in under the guidance of the Central Reference Laboratory as soon as it is completed.

3.5. Supervision

The tuberculosis laboratory coordinators at various levels (central, regional and district) are responsible for supervision of the laboratory services at their administrative levels, and consequently, should have some knowledge of the techniques of bacteriological examination.

4. STANDARDISED TREATMENT REGIMENS

4.1 Objectives of chapter

This chapter describes the recommended standardized 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;
- to prevent the development and transmission of acquired drug resistance tuberculosis.
It is vital to achieve these aims while preventing the selection of resistant bacilli in infectious patients.

4.3 The essential TB drugs

There are three main properties of TB drugs: bactericidal activity, sterilizing activity and the ability to prevent resistance. The TB 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 is used in association with more powerful drugs to prevent the emergence of resistant bacilli.

All anti-TB drugs should be quality-assured, and management of anti-TB drugs should be incorporated into the management of other essential medicines by the MOH.

Table 2: Recommended doses of the first line antituberculosis drugs for adults

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended dose</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily</td>
<td>3 times a week</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose and range (mg/kg body weight)</td>
<td>Maximum</td>
<td>Dose and range (mg/kg body weight)</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>5 (4-6)</td>
<td>300</td>
<td>10 (8-12)</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>10 (8-12)</td>
<td>600</td>
<td>10 (8-12)</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>25 (20-30)</td>
<td>35 (30-40)</td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15 (15-20)</td>
<td>30 (25-35)</td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>15 (12-18)</td>
<td>15 (12-18)</td>
<td>1000</td>
</tr>
</tbody>
</table>

Fixed-dose combination tablets (FDC)

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

There are also disadvantages of FDC. First, if prescription errors do occur, this may result in excess dosage (risk of toxicity) or sub-inhibitory concentrations of all drugs (favoring development of drug resistance). Health care workers might be tempted to evade directly observed therapy erroneously believing that adherence is automatically guaranteed. Poor Rifampicin bioavailability has been found for some FDC, particularly in combinations of 3 and 4 drugs. Thus, quality assurance is essential. Finally, using FDC does not obviate the need for separate drugs for a small number of cases that develop drug toxicity.

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

Table 3: WHO recommended formulations of essential tuberculosis drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose form</th>
<th>Strength for daily use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid + rifampicin</td>
<td>Tablet</td>
<td>75mg +150mg</td>
</tr>
<tr>
<td></td>
<td>Tablet or pack of granules *</td>
<td>150mg +300mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60mg + 30mg</td>
</tr>
<tr>
<td>Isoniazid + ethambutol</td>
<td>Tablet</td>
<td>150mg + 400mg</td>
</tr>
<tr>
<td>Isoniazid + rifampicin + pyrazinamide</td>
<td>Tablet</td>
<td>75mg + 150mg + 400mg</td>
</tr>
<tr>
<td></td>
<td>Tablet or pack of granules *</td>
<td>30mg + 60mg + 150mg</td>
</tr>
<tr>
<td>Isoniazid + rifampicin + pyrazinamide + ethambutol</td>
<td>Tablet</td>
<td>75mg + 150mg + 400mg + 275mg</td>
</tr>
</tbody>
</table>

* For paediatric use

From WHO Model list (revised December 1999)
Standard regimens

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

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

To facilitate procurement, distribution and administration of treatment to patients, the daily dose are standardized for 3 or 4 body weight bands - for instance, 30-39, 40-54, 55-70 and over 70 kg - or a single dosage for most patients with additional rifampicin for patients over 60 kg and individual calculation for children.

4.4 Recommended standard treatment regimens.

New cases

New patients are defined as those who have no history of prior TB treatment or who received less than 1 month of anti-TB drugs regardless of whether their smear or culture results are positive or not. In a situation where there is a high prevalence of isoniazid resistance in new patients and when patients have developed active TB after known contact with a patient documented to have drug-resistant TB; these patients are likely to have a similar drug resistance pattern to the source case. In this case DST should be carried out at the start of treatment. While DST results of the patient are awaited, a regimen based on the DST of the presumed source case should be started.
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, normally consisting of isoniazid, rifampicin, pyrazinamide and ethambutol, there is rapid killing of tubercle bacilli. Infectious patients become rapidly non-infectious (within approximately 2 weeks). Symptoms abate.

The vast majority of patients with sputum smear-positive TB cases 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 a large bacillary load (smear-positive pulmonary TB and many HIV-infected patients with smear-negative pulmonary TB), there is an increased risk of selecting resistant bacilli, because of a large population of bacilli that 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 of selecting resistant bacilli. These regimens are highly efficient in patients with susceptible bacilli and almost as effective in patients with initially isoniazid-resistant organisms.

In HIV-negative patients with smear-negative pulmonary or extra-pulmonary TB that is fully drug-susceptible there is little risk of selecting resistant bacilli since these patients generally harbor fewer bacilli in their lesions. However, because 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 and extra-pulmonary TB.

**Recommendation 1:** New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR

This recommendation also applies to extrapulmonary TB except TB of the central nervous system, bone or joint for which some expert groups suggest longer therapy. It is recommended that central nervous system TB should be treated for 9-12 months while treatment for bone TB should take 9 months. This is because of high risk of disability and mortality in central nervous system TB and difficulties in access treatment response in bone TB. In order ensure completion of full treatment, these regimens should be provided under strict supervision and support for all patients.

**Recommendation 2:** New patients with pulmonary TB should receive a daily intensive phase followed by daily continuation phase 2HRZE/4(HR) and that each dose is directly observed
This regimen should apply for both HIV infected TB cases because three times weekly dosing is not recommended for persons living with HIV or patients living in high HIV prevalence area.

**Recommendation 3:** The 2HRZE/6HE treatment regimen is not longer recommended in Somalia.

Table 4: Standard regimens for new TB patients

<table>
<thead>
<tr>
<th>Intensive phase</th>
<th>Continuation phase</th>
<th>Dosing frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 months of HRZE</td>
<td>4 months of HR</td>
<td>Daily</td>
</tr>
</tbody>
</table>

\( \text{H-} \text{Isoniazid} \)
\( \text{R-} \text{Rifampicin} \)
\( \text{Z-} \text{Pyrazinamide} \)
\( \text{E-} \text{Ethambutol} \)

**Retreatment cases**

Previously treated patients include all TB patients who were treated as new cases for more than one month and are now smear or culture positive (failure, relapse, return after default). They have a higher likelihood to have drug resistance which may have been acquired through inadequate prior chemotherapy. They are more likely than new patients to harbour and excrete bacilli resistant to at least isoniazid. In the recently concluded Drug Resistance Survey conducted in Somalia, Multidrug resistance (MDR) among previously treated cases was found to be 41% compared to 5% among new cases. Previous TB treatment is therefore a strong determinant of drug resistance. Of all the forms of drug resistance, it is most critical to detect multidrug resistance (MDR) because it makes regimens with first-line drugs much less effective and resistance can be further amplified. Prompt identification of MDR and initiation of MDR treatment with second-line drugs gives a better chance of cure and prevents the development and spread of further resistance. Currently Somalia has no culture and DST laboratory but has installed 4 Gene Xpert machines that can detect Rifampicin resistant. Rifampicin resistance is a proxy to MDR diagnosis and all patients known to have rifampicin resistance should be treated as MDR cases.

**Recommendation 1:** Specimens for Gene Xpert examination should be obtained from all previously treated TB patients at or before the start of treatment. This should be performed for rifampicin resistance.

In a situation where it is not possible to do Gene Xpert examination to guide the management of the individual patients, empiric treatment should be started as follows:

**Recommendation 2:** TB patients whose treatment has failed or other patient groups with high likelihood of multidrug-resistant TB (MDR) should be started on an empirical
MDR regimen \{8(Am-Lfx-Cs-Eth-(PAS)+Z)/16(Lfx-Cs-Eth-(PAS)+Z)\} when MDR treatment is started in Somalia this year.

Other cases that are highly suspect for MDR are those relapsing or returning after lost to follow-up after their second or subsequent course of TB treatment

**Recommendation 3:** TB patients returning after loss to follow-up or relapsing from their first treatment course should receive the retreatment regimen containing first-line drugs 2HRZES/1HRZE/5HRE.

**Recommendation 4:** Previously treated TB patients should receive a daily intensive phase followed by daily continuation phase 2HRZES/1HRZE/5HRE and that each dose is directly observed.

This regimen should apply for both HIV infected TB cases because three times weekly dosing is not recommended for persons living with HIV or patients living in high HIV prevalence area.

Table 5: Standard regimens for new TB patients

<table>
<thead>
<tr>
<th>Intensive phase</th>
<th>Continuation phase</th>
<th>Dosing frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 months of HRZES/one month of HRZE</td>
<td>5 months of HRE</td>
<td>Daily</td>
</tr>
</tbody>
</table>

H-Isoniazid
R-Rifampicin
Z-Pyrazinamide
E-Ethambutol
S-Streptomycin

**4.5 Rationale for prioritization of patient treatment categories.**

From the public health perspective the highest TB control Program 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 prioritize TB treatment categories according to the impact and 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 TB drug has an abbreviation. A regimen consists of 2 phases. The number before a phase is the duration of that phase in months. Letters between parentheses indicate fixed dose combinations of those drugs.

Example:

2 (RHZE) /4(RH) (Standard)
The initial phase is 2 RHZE. The duration of the phase is 2 months. Drug treatment is daily, with isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) in fixed dose combination.
The continuation phase is 4 (RH). The duration is 4 months, drug treatment is daily with isoniazid and rifampicin, in fixed dose combination.

4.10 Treatment of extra-pulmonary TB and Treatment regimens in special situations

Although most commonly affecting the lungs, tuberculosis can involve virtually any organ of the body, being relatively more frequent in children and persons with HIV infection. Of specific forms, lymphatic, pleural, and bone/joint disease are the most common, while pericardial, meningeal, forms are more likely to result in a fatal outcome.

In general, extra-pulmonary tuberculosis 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, extra-pulmonary tuberculosis is not of great importance, because patients with this form of disease are not infectious unless they also have pulmonary involvement. However Extrapulmonary TB is considered to be WHO clinical stage 4 HIV disease. People living with HIV are more likely to present with extrapulmonary or sputum smear-negative TB, especially as immunosuppression advances. This can result in misdiagnosis or delays in diagnosis and, in turn, higher morbidity and mortality. HIV testing is therefore especially important in persons with or suspected of having EPTB because of the increased frequency of extrapulmonary involvement in persons with immunosuppression. Treatment regimen of Extrapulmonary tuberculosis is similar to pulmonary tuberculosis except that TB meningitis should be treated for 9–12 months given the serious risk of disability and mortality and TB of the bones or for 9 months because of the difficulties of assessing treatment response.
**Recommendation 1:** All Extrapulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR

**Recommendation 2:** All Extrapulmonary TB patients should receive a daily intensive phase followed by daily continuation phase 2HRZE/4HR and that each dose is directly observed

In case of meningitis and pericarditis, adjuvant corticosteroid treatment is recommended if drug resistance is ruled out. In addition, ethambutol should be replaced by streptomycin in TB meningitis because streptomycin penetrates the meningitis better than ethambutol

**Drug interactions**

Many TB patients tend to have concomitant disease and it is always advisable to ask TB cases about drugs that they are taking before starting TB treatment. The commonest antituberculosis drug that interacts with other drugs is Rifampicin. Rifampicin induceth pathways that metabolize other drugs, thereby reducing the concentration and effect of those drugs. To maintain a therapeutic effect, dosages of the other drug(s) may need to be increased. When rifampicin is discontinued, its metabolism-inducing effect resolves within about 2 weeks, and dosages of the other drug(s) will need to be reduced. The drugs whose concentrations and effects are substantially reduced by rifampicin include:

- Anti-infectives including certain antiretroviral drugs discussed in section 5.6.1, mefloquine, azole antifungal agents, clarithromycin, erythromycin, doxycycline, atovaquone, chloramphenicol
- Hormone therapy, including ethinylestradiol, norethindrone, tamoxifen, levothyroxine;
- Methadone;
- Warfarin;
- Cyclosporin;
- Corticosteroids;
- Anticonvulsants (including phenytoin);
- Cardiovascular agents including digoxin (among patients with renal insufficiency), digitoxin, verapamil, nifedipine, diltiazem, propranolol, metoprolor, enalapril, losartan, quinidine, mexiletine, tocainide, propafenone;
- Theophylline;
- Sulfonylurea hypoglycaemics;
4.7 Treatment regimens in special situations

Treatment for pregnant women

It is important to ask a woman before starting TB treatment if she is pregnant. Most TB drugs are safe for use in pregnant women. The exception is streptomycin which is ototoxic to the foetus and should not be used in pregnancy. It is should be explained to a pregnant woman that successful treatment of TB with the recommended standardised regimen is important for a successful outcome of pregnancy.

**Recommendation 1: 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 the baby. Mother and baby should stay together and the baby should continue to breastfeed.

**Recommendation 2: When active TB in the baby is ruled out, the baby should be given 6 months of isoniazid preventive therapy, followed by BCG vaccination**

**Recommendation 3: Pyridoxine supplementation is recommended for all pregnant or breastfeeding women taking isoniazid**

Treatment for women taking the oral contraceptive pill

Rifampicin interacts with the contraceptive medications with a risk of decreased protective efficacy against pregnancy. A woman who is receiving contraception 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**

Although antituberculosis are hepatotoxic, patients with the following conditions can receive the usual TB regimens provided that there is no clinical evidence of chronic liver disease:

- Hepatitis virus carriage,
- A past history of acute hepatitis,
- Current excessive alcohol consumption.

However, hepatotoxic reactions to anti-TB drugs may be more common among these patients and should therefore careful monitoring of these patients is crucial.
For ant TB patients having unstable or advanced liver disease, liver function tests should be done at the start of treatment, if possible. If the serum alanine aminotransferase level is found to be more than 3 times normal before the initiation of treatment, the following regimens are recommended:

**Recommendation 1: In more unstable or severe the liver disease is, TB regimens with fewer hepatotoxic drugs should be used and the options are:**

1) **Two hepatotoxic drugs (rather than the three in the standard regimen):**
   a) 9 months of isoniazid and rifampicin, plus ethambutol (until or unless isoniazid susceptibility is documented);
   b) 2 months of isoniazid, rifampicin, streptomycin and ethambutol, followed by 6 months of isoniazid and rifampicin;
   c) 6–9 months of rifampicin, pyrazinamide and ethambutol.

2) **One hepatotoxic drug:**
   a) 2 months of isoniazid, ethambutol and streptomycin, followed by 10 months of isoniazid and ethambutol.

3) **No hepatotoxic drugs:**
   a) 18–24 months of streptomycin, ethambutol and a fluoroquinolone.

In advance or more unstable liver diseases, it is recommended that Expert consultation should be required.

**Treatment of patients with renal failure**

Isoniazid, rifampicin and pyrazinamide are either eliminated almost entirely by biliary excretion or metabolized into non-toxic compounds. Isoniazid and rifampicin are eliminated by biliary excretion, so no change in dosing is necessary. There is significant renal excretion of ethambutol and metabolites of pyrazinamide, and doses should therefore be adjusted. Three times per week administration of these two drugs at the following doses is recommended: pyrazinamide (25 mg/kg), and ethambutol (15 mg/kg).

**Recommendation 1: TB patients with renal failure should be treated with 2HRZE/4RH**

Patients with severe renal insufficiency or failure who are receiving isoniazid should also be given pyridoxine in order to prevent peripheral neuropathy. Because of an increased risk of
nephrotoxicity and ototoxicity, streptomycin should be avoided in patients with renal failure. If streptomycin must be used, the dosage is 15 mg/kg, two or three times per week, to a maximum of 1 gram per dose, and serum levels of the drug should be monitored.

5. MANAGEMENT OF MULTIDRUG-RESISTANT CASES

5.1 Objectives of chapter

This chapter describes briefly the management of MDR in Somalia. The details of the guidelines for MDR management are contained in separate guidelines for MDR management in Somalia. However included here are few recommendations but for detailed guidelines the reader is referred to the “National Guidelines for Management of Drug Resistant TB” in Somalia. According to the national Drug resistance Survey conducted in Somalia in 2010-2011, incidence of MDR among new sputum smear cases was 5.2% while among previously treated cases it was 41%. This means Somalia has the highest MDR incidence in the region and therefore MDR management is essential in Somalia.

5.2 Definitions of Drug Resistant TB

Diagnostic Definitions of Drug Resistant TB (DR-TB):

There are four different categories of drug resistance (DR) to Mycobacterium tuberculosis (MTB). These are:

I. Mono-resistance: resistance to one anti-tuberculosis drug.
II. Poly-resistance: resistance to more than one first line anti-tuberculosis drug other than both Isoniazid and Rifampicin.
III. Multidrug-resistance: resistance to both Isoniazid and Rifampicin with or without resistance to any other drug.
IV. Extensive drug-resistance: resistance to any Fluoroquinolone, and at least one of three injectable second-line drugs (Capreomycin, Kanamycin, or Amikacin) in addition to multidrug-resistance.
V. Rifampicin resistance (RR-TB): resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. This includes any resistance to rifampicin, in the form of
monoresistance, multidrug resistance, polydrug resistance or extensive drug resistance.

These categories are not all mutually exclusive. When enumerating RR-TB, for instance, MDR-TB and XDR-TB are also included. While it has been the practice until now to limit the definitions of mono-resistance and polydrug resistance to first-line drugs only, future drug regimens may make it important to classify patients by their strain resistance patterns to fluoroquinolones, second-line injectable agents as well as any other anti-TB drug for which reliable DST becomes available. DR-TB is typically confirmed through laboratory tests showing that infecting isolates of MTB can grow in vitro in the presence of one or more anti-tuberculosis drugs (culture and drug susceptibility testing).

5.3 Bacteriology and Sputum Conversion

Bacteriological examinations used in patients with DR-TB include sputum smear microscopy, culture and drug susceptibility testing (DST). These tests should be performed and results reported according to international standards of WHO guidelines. These examinations should be done at the start of treatment to confirm TB disease by bacteriology and to group patients according to infectiousness.

Sputum conversion in patients with DR-TB is defined as two sets of consecutive negative smears (each set includes 3 consecutive samples collected on 3 separate days) and cultures from samples collected at least 30 days apart. Both bacteriological techniques (smear and culture) should be used to monitor patients throughout therapy. The date of the first set of negative cultures and smears is used as the date of conversion (this date is also used to determine the length of the initial phase of treatment).

Recommendation 1: Rapid drug susceptibility testing (DST) of isoniazid and rifampicin or of rifampicin alone is recommended over conventional testing or no testing at the time of diagnosis of TB, subject to available of Culture and sensitivity laboratory or Gene Xpert machine.

5.4 DR-TB Patient Registration Group based on history of previous anti-tuberculosis treatment
DR-TB patients should be assigned a registration group based on their treatment history which is useful in assessing the risk for MDR-TB. The **treatment history should be assessed at the time of collecting the sputum sample which is ultimately used to confirm MDR-TB using culture and DST.**

**Classification according to history of previous treatment** with antituberculosis drugs (mainly to assign the appropriate treatment regimen)

- **New:** A patient who has received antituberculosis drugs less than one month or never received anti-tuberculosis treatment. Patients are placed in this group if their sputum was collected for Drug Sensitivity Testing (DST) at the start of a Category I regimen and were then switched to a DR-TB regimen because MDR-TB was later confirmed. They should be considered “new” if DST was performed within one month of the start of treatment (even if they have received more than one month of Category I treatment by the time the results of DST are returned and are consequentially registered as DR-TB).

- **Previously treated with first line drugs only:** A patient who has been treated for one month or more for TB with only first-line drugs.

- **Previously treated with second line drugs:** A patient who has been treated for one month or more for TB with one or more second-line drugs, with or without first-line drugs.

- **Relapse:** A patient whose most recent treatment outcome was “cured” or “treatment completed” and is later diagnosed with bacteriologically positive TB by sputum smear microscopy or culture.

- **Treatment after loss to follow-up:** A patient who returns for treatment, bacteriologically positive by sputum smear microscopy or culture, following interruption of treatment for two or more consecutive months.

- **Treatment after Failure of Category I:** A patient who has received Category I treatment for TB yet treatment has failed. Failure is defined as sputum smear positive at five months or later since treatment inception.

- **Treatment after Failure of Category II:** A patient who has received Category II treatment for TB yet treatment has failed. Failure is defined as sputum smear positive at five months or later since treatment inception.

- **Transfer In:** A patient who has transferred in from another register for treatment of DR-TB to continue DR-TB treatment.
• **Other:** There are several types of patients who may not fit into any of the above categories. These include sputum smear positive patients with unknown previous treatment outcome, sputum smear positive patients who received treatment other than Category I or II, previously treated patients with extra-pulmonary TB, and patients who have received several unsuccessful treatments and were considered incurable by health staff and have lived with active TB disease with little or no adequate treatment for a period of time until DR-TB treatment became available.

### 5.5 Definitions of Treatment Outcomes of DR-TB Patients

The following are mutually exclusive DR-TB outcome definitions that rely on the use of laboratory smear and culture as a monitoring tool.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured</td>
<td>Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.</td>
</tr>
<tr>
<td>Treatment completed</td>
<td>Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.</td>
</tr>
</tbody>
</table>
| Treatment failed | Treatment terminated or need for permanent regimen change of ≥2 anti-TB drugs because of  
- lack of conversion in the continuation phase, *or*  
- bacteriological reversion* in the continuation phase after conversion* to negative, *or*  
- evidence of additional acquired resistance, *or*  
- adverse drug reactions (ADRs) |
| Died             | A patient who dies for any reason during the course of treatment.                                                                        |
| Lost to follow-up | A patient whose treatment was interrupted for 2 consecutive months or more. (This category was previously known as defaulted.)          |
| Not evaluated    | A patient for whom no treatment outcome is assigned. (This includes cases “transferred out” to another treatment unit and whose treatment outcome is unknown) |
| Treatment success | The sum of cured and treatment completed                                                                                       |
*Conversion (to negative):* culture is considered to have converted to negative when two consecutive cultures taken at least 30 days apart are found to be negative. In such case, the date of the first negative culture is used as the date of conversion.

*Reversion (to positive):* culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures taken at least 30 days apart are found to be positive. For the purpose of defining Treatment failed, reversion is only considered when it occurs in the continuation phase.

5.6 Case Finding Strategies and Laboratory Aspects

It is very important to identify DR-TB cases as early as possible and initiate treatment to prevent the patient from spreading the disease to other members of the community.

*Recommendation 2: The follow type of TB cases should be screened for MDR in Somalia.*

- Failure of re-treatment regimens and chronic TB cases
- Exposure to a known MDR-TB case
- Failure of Category I
- Failure of anti-tuberculosis treatment in the private sector
- Relapse and return after default without recent treatment failure
- HIV positive TB cases

5.7 Treatment Strategies for DR-TB

General Principles

For case finding and selection please refer to chapter III of this guideline. Any patient who is diagnosed with DR-TB should fall under the diagnostic DR-TB and will require specialized treatment termed DR-TB Regimen. The patient should be referred to the closest available and convenient treatment site.

5.8 Classes of Anti-Tuberculosis drugs:

Anti-Tuberculosis drugs are divided into five groups:
**Group 1:** First-line oral anti-tuberculosis drugs which include Isoniazid (H), Rifampicin (R), Ethambutol (E), and Pyrazinamide (Z)

**Group 2:** Injectable anti-tuberculosis drugs which include Streptomycin (S), Kanamycin (Km), Amikacin (Amk), Capreomycin (Cm), and Viomycin (Vi)

**Group 3:** Fluoroquinolones (FQ) which include, Levofloxacin (Lfx), Moxifloxacin (Mfx) or higher generation FQ.

**Group 4:** Oral bacteriostatic second-line anti-tuberculous drugs such as Ethionamide (Eto), Prothionamide (Pto), Cycloserine (Cs), Terizidone (Trd), and P-aminosalicylic acid (PAS)

**Group 5:** Anti-tuberculosis drugs with unclear efficacy (not recommended by WHO for routine use in MDR-TB patients). These may include Clofazimine (Cfz), Amoxicillin/Clavulanate (Amx/Clv), Clarithromycin (Clr), Linezolid (Lzd), Thioacetazone(Thz), Imipenem/Cilastin(Imp/Cln), and High Dose Isoniazid.

### 5.9 Standardized vs Individualized treatment regimen

Access to DST is required in all programs. However, while waiting for the culture and DST results, the two groups that are most likely to be considered for direct enrolment in a DR-TB standardized regimen are:

- **Category II failures (chronic TB cases).** Patients in whom Category II treatment has failed in sound NTPs often have DR-TB. If the quality of DOT is poor or unknown (i.e. if regular ingestion of the medicines during Category II treatment is uncertain), patients may fail Category II treatment for reasons other than DR-TB.

- **Close contacts of DR-TB cases who develop active TB disease.** Close contacts of DR-TB patients who develop active TB disease can be enrolled for treatment with DR-TB regimens.

However, the rate of DR-TB in these groups can vary.

*Recommendation 3: MDR among these patients should be confirmed among these patents by using culture and sensitivity or Gene Xpert.*
5.10 Designing a Treatment Regimen

General Principles

The following are the basic principles involved in any SLD treatment regimen design:

- Regimens should be based on the history of drugs taken by the patient.
- Drugs commonly used in the country and prevalence of resistance to first line and second-line drugs should be taken into consideration when designing a regimen.
- Regimens should consist of at least four drugs with either certain or almost certain effectiveness. If the evidence about the effectiveness of a certain drug is unclear, the drug can be part of the regimen but it should not be solely depended upon for success. Often, more than four drugs may be started if the susceptibility pattern is unknown, effectiveness is questionable for one or more drugs or if extensive, bilateral pulmonary disease is present.
- When possible, Pyrazinamide, Ethambutol and Fluoroquinolones should be given once per day as high peaks attained in one/day dosing may be more efficacious. Once/day dosing is permitted for other second-line drugs depending on patient tolerance; however Ethionamide/Protonamide, Cycloserine and PAS are given in split doses during the day to reduce adverse effects.
- The drug dosage should be determined by body weight.
- Treatment of adverse drug effects should be immediate and adequate in order to minimize the risk of treatment interruptions and prevent increased morbidity and mortality due to serious adverse effects.
- An injectable agent should be used for a minimum of eight months and at least six months past culture conversion.
- The minimum length of treatment is 18 months after culture conversion.
- Each dose is given as DOT throughout the treatment. A treatment card is marked for each observed dose.

Recommendation 4: The following recommendations in the treatment of patients with MDR-TB,

- Fluoroquinolone should be used.
- Later-generation fluoroquinolone rather than an earlier-generation fluoroquinolone should be used.
- Ethionamide (or prothionamide) should be used.
- **Four second-line anti-tuberculosis drugs likely to be effective (including a parenteral agent), as well as pyrazinamide, should be included in the intensive phase.**
- **Regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and either cycloserine or PAS (p-aminosalicylic acid) if cycloserine cannot be used.**

**Standardized** regimens will be used for treatment which might be adjusted according to resistance patterns when DST results are available.

The following standardized regimens will be used in Somalia:

- **MDR-TB confirmed by laboratory (specimen was tested within 30 days from enrolment). Patient did not use SLD before:**
  8Am-Lfx-Eto-Cs-Z and B6/ 16 Lfx-Eto-Cs-Z and B6

- **MDR-TB confirmed by laboratory (specimen was tested within 30 days from enrolment). Patient received Amikacin previously:**
  Cm-Lfx-Eto-Cs-Z and B6/ 16 Lfx-Eto-Cs-Z and B6

- **MDR-TB confirmed by laboratory (specimen was tested within 30 days from enrolment). Patient received Fluoroquinolones previously:**
  8 Am-Lfx-Eto-Cs-PAS- Z + B6/ 16 Lfx-Eto-Cs-PAS- Z + B6

**Duration of Treatment**

The following recommendations are made for the duration of treatment of MDR cases.

**Recommendation 4:** The duration for intensive phase of treatment of MDR should at least be 8 months.

**Recommendation 5:** A total treatment duration of at least 20 months is recommended in patients without any previous MDR-TB treatment

These recommendations are made because a high value is placed on outcomes such as preventing death and transmission of MDR-TB as a result of failed treatment as well as avoiding harms and minimizing use of resources.
5.11 Use of antiretroviral drugs in patients on second-line anti-tuberculosis regimens

HIV infection is a common complication in TB patients and it leads to high mortality. Likewise TB is easily transmitted to People Living with HIV. In order to reduce mortality and transmission of TB in this group of patients, early treatment with antiretroviral drugs is crucial.

Recommendation 6: Antiretroviral therapy is recommended for all patients with HIV and drug-resistant TB requiring second-line anti-tuberculosis drugs, irrespective of CD4 cell-count, as early as possible (within the first 8 weeks) following initiation of anti-tuberculosis treatment.

5.11 Models of care for managing MDR-TB patients

Considering the mounting evidence that ambulatory care provides more advantages than hospital based care and appreciating the fact that Some MDR cases in Somalia may need hospital care because of either the distances they have to travel, severity of the disease, drug complications or inability to afford daily expenses for ambulatory MDR management, program has adopted mixed models for MDR management namely hospital based treatment for at least the first 2 months of initial phase of treatment and complete ambulatory management.

Recommendation 7: Patients with MDR-TB should be treated using mainly ambulatory care but in cases cited above, models of care based principally on hospitalization can be done provided it is only for the first 2 months of the initial phase of treatment.

5.12 Monitoring the response to MDR-TB treatment

Monitoring of MDR patients under treatment is important because delayed detection of failure is expected to increase transmission and increase the probability of acquisition of resistance.

Recommendation 8: The use of sputum smear microscopy and culture rather than sputum smear microscopy alone is recommended for the monitoring of patients with MDR-TB during treatment.
Performing monthly sputum smear microscopy and culture was the best strategy in identifying failures earlier. Sputum smear microscopy alone resulted in delayed detection of failure. When sputum smear microscopy is done at monthly rather than two monthly intervals it increases the detection of failure slightly.
6. ADHERENCE TO TREATMENT

6.1 Objectives of chapter

The public health priority of TB Program is curing smear-positive cases, while preventing the emergence of drug resistance. Ensuring adherence to treatment is necessary to achieve this priority. This chapter gives recommendations on how to ensure treatment compliance.

Due to the importance of tuberculosis in public health, all TB care services should be provided free of charge to all patients

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, their family members, those who care for them, and those responsible for TB Program.

Promoting compliance through a patient-centered approach that 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 smears controls free of charge, reducing the time and cost to the patient to obtain treatment, and providing good and rapid attention.

Convenience to the patient must be balanced with the assurance of regular drug intake and monitoring, important to give the patient the best chances of cure. When patients receive self-administered treatment, patients often take drugs irregularly, and tracing is difficult and often unproductive. 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 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 an important element in the WHO recommended policy package for TB control. Directly observed treatment means that an observer watches the patient swallowing the tablets, in a way that is sensitive and supportive to the patient needs. This ensures that a TB patient takes the right drugs, in the right doses, at the right intervals. Many countries have used directly observed treatment in inpatient settings in hospitals or in sanatoria. Directly observed treatment is also applicable in out-patient settings. In practice, it means providing a treatment observer acceptable to the patients, to enable them to complete treatment. The observer may be a health worker or a trained and supervised community member. There may be an incentive of some sort for community members to be observers of TB treatment. The NTP trains and monitors the community treatment observers. There must be a clearly defined line of accountability from NTP staff to general health services staff and the treatment observer. It is important to ensure confidentiality and that directly observed treatment is acceptable to the patient. The TB drugs should remain with the treatment observer and only given to the patient at the time of intake.

6.3.2 Why directly observed treatment?

Directly observed treatment is required to ensure treatment adherence. It helps reinforce patient’s motivation to continue treatment and counter 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 prevent emergence of drug resistance. It is recommended in:

Recommendation 1: All patients in Somalia should be treated under directly observed therapy.

If a TB patient misses one attendance for directly observed treatment, it is necessary to trace and bring back that patient to treatment.

6.3.3 How to apply directly observed treatment to fit patients’ needs?

A TB patient who has to travel far for treatment is less likely to adhere to treatment. One of the aims of a TB Program is to organize TB services so that the patient has TB treatment as close to
home (or the workplace) as possible. A TB Program brings TB services close to TB patients by integrating them with general health services. Many TB patients live close to a health facility (e.g. health center, health post, hospital). For these patients, the treatment observer will be one of the staff in the health facility, and this should be the chosen alternative if it fits the patient’s convenience. Some TB patients live far away from a health facility. For them the observer will be a community health worker or a trained local community member. In general members of the patient’s family should not serve as treatment observers. Collaboration with other Programs allows the identification of staff from these Programs who may observe TB treatment. Some areas have HIV/AIDS community care schemes. The HIV/AIDS home care providers with suitable training and monitoring can observe TB treatment.

6.3.4 How to facilitate directly observed treatment?

- The aim is to maximize ambulatory treatment as close to the patient's home (or workplace) as possible. Where possible, general health service staff should directly observe treatment. When this is not possible, community members can directly observe treatment. Cured patients may be successful DOT providers.
- Use fixed drug combinations and blister packs to help reduce medication error.
- Incentives for volunteers and patients may be considered, bearing in mind the advantages and disadvantages of incentive schemes.

6.3.5 Community support of TB patients, including directly observed treatment

NTPs, health services and communities should seriously consider how they can promote community contribution to TB care in their settings. This is especially so for settings where the TB case load is overwhelming available resources. Community based DOT may be used to expand access to treatment for some underserved patient groups and further improve treatment outcomes. Community contributions to TB care should be seen as complementing and extending NTP capacity, not replacing NTP activity.
Recommendation 2:

- Effective community contributions to TB care, especially community based DOT, require a strong reporting system, access to laboratory facilities and a secure drug supply, through the NTP.
- Existing community groups and organizations should first be approached to determine how they might be able to make a contribution to community TB care, rather than setting up new systems, groups and organizations.
- While community care and DOT is cheaper and more cost-effective than hospital based care, resources are needed for training and supervising community treatment observers. Community volunteers need regular support, motivation, instruction and supervision by NTP staff to ensure quality outcomes are maintained.
- Selection of community volunteers should be a cooperative activity including NTP staff, TB patients, community representatives and community group leaders.
- Training requirements may vary depending on the setting, ranging from “on the job instruction” by NTP staff to more formal short courses of instruction supported by regular updates.
- Regular audit and reporting of results is important to define and clarify the community contribution to TB care in each program.

6.3.6 How to apply directly observed treatment in different settings?

Implementation of directly observed treatment depends on the setting, facilities, resources and environment. There must therefore be flexibility in applying directly observed treatment, with adaptation in different districts and countries. Major factors which influence treatment interruption are access to treatment (distance, cost of transport, time and wages lost, quality and speed of drug delivery), knowledge level about TB and the need to complete treatment, and flexibility for transfer to another facility.

For any chosen method of supervision and administration of treatment, a Program must show high sputum smear conversion and cure rates, under routine conditions in both rural and urban areas. 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 implementing directly observed treatment can be a model for other districts or regions.

6.4 Interruption of treatment: what to do?

Directly observed 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 directly observed treatment, and also during the continuation phase of treatment, there may be treatment interruptions.

6.4.1 Preventive measures to minimize 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 family members). This is an important opportunity to advice and counsel the patient. During this meeting it is vital to record the patient’s address and other addresses (e.g. spouse, parents, work place, place of study, Damiiin) 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 his/her residence following the initial meeting. Also, it is important to identify potential problems which 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 with the patient 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 patient’s exact address and at the same time provides an opportunity to arrange for screening of household contacts, especially children under the age of 5 years.

In addition, all visits of the patient to the clinician should reinforce the need for regular and complete intake of treatment and elicit any problem which may cause interruption.
6.4.2 Corrective measures to minimize the duration of treatment interruption

When a patient doesn’t keep an arranged appointment to receive treatment, it is necessary to inquire after the patient, using the contact addresses previously obtained and appropriate means of tracing the patient. 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.

6.4.3 What to do when a patient returns after interrupting treatment?

The management of patients who have interrupted treatment is complex and takes into consideration multiple variables (immune status, degree of remission of the disease with the previous treatment, drug susceptibility), which may be difficult to measure. A simple decision tree is suggested in table 6.1. More detailed trees can be utilized but require further training.
<table>
<thead>
<tr>
<th>Interruption for less than one month</th>
<th>Action 1</th>
<th>Action 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Trace patient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Solve the cause of interruption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Do 3 sputum smears.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• While waiting, continue treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If smears negative or EP</td>
<td>Continue treatment and prolong it to compensate for missed doses</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interruption for one to two months</th>
<th>Action 1</th>
<th>Action 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Do 3 sputum smears</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Solve the cause of interruption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• If one or more smears positive</td>
<td>Treatment received:</td>
<td>Continue treatment and prolong it to compensate for missed doses</td>
</tr>
<tr>
<td></td>
<td>&lt; 5 months</td>
<td>&gt; 5 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cat I: Start cat II Cat II: Refer for C&amp;S (may evolve to chronic)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interruption for two months or more (defaulter)</th>
<th>Action 1</th>
<th>Action 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Do 3 sputum smears</td>
<td>Negative smears or EP</td>
<td>Clinical decision on individual basis whether to re-start or continue treatment, or no further treatment.</td>
</tr>
<tr>
<td>• Solve the cause of interruption, if possible</td>
<td>One or more smears positive.</td>
<td>Cat I Start cat II</td>
</tr>
<tr>
<td>• No treatment while waiting for results</td>
<td>Cat II Refer for C&amp;S (may evolve to chronic)</td>
<td></td>
</tr>
</tbody>
</table>
7. MONITORING THE PATIENT

7.1 Objectives of chapter

- Monitor and record the response to treatment, and decide on actions to take in response to monitoring results;
- Use cohort analysis to evaluate treatment outcomes;
- Manage treatment interruption;
- Detect and manage drug-induced toxicity

MONITORING THE TREATMENT RESPONSE

All patients should be monitored to assess their response to therapy. Monitoring of patients regularly also facilitates treatment completion and allows the identification and management of adverse drug reactions. All patients, their treatment supporters and health workers should be instructed to report the persistence or reappearance of symptoms of TB (including weight loss), symptoms of adverse drug reactions, or treatment interruptions. Patient weight should be monitored each month, and dosages should be adjusted if weight changes. A written record of all medications given, bacteriological response and adverse reactions should be maintained for every patient on the TB Treatment Card

7.2 Monitoring the treatment response

Patients with sputum smear-positive pulmonary TB should be monitored by sputum smear examination. These are the TB patients for whom bacteriological monitoring is possible. It is unnecessary, unreliable 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.

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

The treatment response should be monitored by sputum smear examination. In general, one sputum specimens should be collected for smear examination at each follow-up sputum check. Sample collection should be done without interrupting treatment.

Recommendation 1: For smear-positive pulmonary TB patients treated with first-line drugs, sputum smear microscopy should be performed at completion of the intensive phase of treatment
If the Sputum smear is positive at fifth month culture and sensitivity should be done. Similarly culture and sensitivity should be done if the sputum smear is positive at sixth month.

If a patient is found to have a multidrug-resistant strain of TB at any time during therapy, treatment is declared a failure and the patient is re-registered and should be referred to an MDR-TB treatment program.

If smear positive at month 2, do sputum again at month 3 and if smear is positive do culture and DST.

<table>
<thead>
<tr>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
</tr>
<tr>
<td>Time of SM Testing</td>
</tr>
</tbody>
</table>

Negative sputum smears indicate good treatment progress, which encourages the patient and the health worker responsible for supervising the treatment. Omit doing sputum smear examinations at month 5 and month 6 if patient was smear-negative at the start of treatment and at 2 months.

Smear- or culture-positivity at the fifth month or later (or detection of MDR-TB at any point) is defined as treatment failure and necessitates re-registration and change of treatment to MDR treatment. Additional sputum monitoring is needed for new patients whose sputum smear is positive at the end of the intensive phase and so the following recommendations are made:

**Recommendation 2:** In new patients, if the specimen obtained at the end of the intensive phase (month 2) is smear-positive, sputum smear microscopy should be obtained at the end of the third month.

**Recommendation 3:** In new patients, if the specimen obtained at the end of month 3 is smear positive, sputum culture and drug susceptibility testing (DST) should be performed.
The main aim of doing cultures at this stage is to detect drug resistance without waiting until the fifth month to change to appropriate therapy. Note that treatment is declared a failure if a patient is found to harbour MDR-TB at any point in time during treatment.

**Recommendation 4: In a patient treated with the regimen of 2HRZE/4HR throughout the period of treatment, if a positive sputum smear is found at end of the intensive phase (end of month 2), the extension of the intensive phase is not recommended.**

Positive sputum smear at the end of this phase should trigger a careful review of the quality of the patient support and supervision, with prompt intervention if needed.

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

For patients who were previously treated for TB, sputum smear examination should be performed at the end of the intensive phase of treatment (the 3rd month), at the end of the fifth month and at the end of treatment (the eighth month).

<table>
<thead>
<tr>
<th>Monitoring of previously treated TB patients</th>
<th>Month</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM Testing</td>
<td></td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If SM+ do culture, DST</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If SM+ do culture, DST</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If SM+ do culture, DST</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>*</td>
</tr>
</tbody>
</table>

Smear- or culture-positivity at the fifth month or later (or detection of MDR-TB at any point) is defined as treatment failure and necessitates reregistration and change of treatment to MDR treatment.

All the recommendations apply both to new patients treated with regimens containing 6 months of rifampicin (2HRZE/4HR) and to previously treated patients receiving the 8-month retreatment regimen with first-line drugs (2HRZES/1HRZE/5HRE). Sputum should be collected when the patient is given the last dose of the intensive-phase treatment. The end of the intensive phase is at 2 months in new patients and 3 months in previously treated patients receiving the 8-month regimen of first-line drugs. This recommendation also applies to smear-negative patients.

Sputum specimens should be collected for smear examination at each follow-up sputum check. They should be collected without interrupting treatment and transported to the laboratory as soon as possible thereafter; if a delay is unavoidable, specimens should be refrigerated or kept in as cool a place as possible.

Smear status at the end of the intensive phase is a poor predictor of which new patients will relapse. However, detection of a positive sputum smear remains important as a trigger for the
patient assessment. The proportion of smear-positive patients with sputum smear conversion at the end of the intensive phase is also an indicator of TB program performance.

A positive sputum smear at the end of the intensive phase may indicate any of the following:

- The initial phase of therapy was poorly supervised and patient adherence was poor;
- Poor quality of anti-TB drugs;
- Doses of anti-TB drugs are below the recommended range;
- Resolution is slow because the patient had extensive cavitation and a heavy initial bacillary load;
- There are co-morbid conditions that interfere either with adherence or with response;
- The patient may have drug-resistant *M. tuberculosis* that is not responding to first-line treatment;
- Non-viable bacteria remain visible by microscopy (3).

In such situations, the quality of the patient’s support and supervision should carefully be reviewed and intervention is done promptly if necessary. Patient treatment records should be reviewed with the responsible health care worker, and reasons for any interruptions should be explored and addressed. It is unnecessary, unreliable and wasteful of resources to monitor the patient by chest radiography.

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

Category III is now treated as Category I.

Sputum smear negative patients should be followed clinically; body weight is a useful progress indicator. It is recommended to check sputum smears at the end of the second month because the disease may progress due to non-adherence to treatment, or an error at the time of initial diagnosis could have occurred.

### 7.6 Extra-pulmonary tuberculosis

The response of extra-pulmonary tuberculosis to treatment can only be monitored through clinical observation. As in pulmonary smear negative disease, the weight of the patient is a useful indicator.
7.7 Recording standardized 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 7.1 shows the standardized definitions of treatment outcomes.

Table 7.1 Recording treatment outcome in smear-positive TB patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured</td>
<td>A pulmonary TB patient whose sputum is bacteriologically-confirmed at the beginning of treatment and who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.</td>
</tr>
<tr>
<td>Treatment completed</td>
<td>A TB patient who completed treatment without evidence of failure BUT there is no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion are negative, either because they were not done or because results were not available.</td>
</tr>
<tr>
<td>Treatment failed</td>
<td>A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.</td>
</tr>
<tr>
<td>Died</td>
<td>A TB patient who dies for any reason before starting or during the course of treatment.</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.</td>
</tr>
<tr>
<td>Not evaluated</td>
<td>A TB patient for whom no treatment outcome is assigned. (This includes cases “transferred out” to another treatment unit and whose treatment outcome is unknown).</td>
</tr>
<tr>
<td>Treatment success</td>
<td>The sum of cured and treatment completed.</td>
</tr>
</tbody>
</table>

7.8 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 one quarter of a year). Evaluation of treatment outcome in new pulmonary smear
positive patients is used as a major indicator of Program quality. Outcome in other patients (re-treatment, pulmonary smear negative, extra-pulmonary) may also be analysed, in separate cohorts.

Cohort analysis is the key management tool used to evaluate the effectiveness of the NTP. It enables the identification of problems, so that the NTP can institute appropriate action to overcome them and improve Program performance. Evaluation of the results of treatment and trends must be done at peripheral, district, regional and national level to take corrective action if needed.

The District TB Officer should perform cohort analysis of treatment outcome every quarter-year and at the end of every year. A typical cohort consists of all those new pulmonary sputum smear-positive/negative and extra-pulmonary 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). Previously treated patients (relapses, return after default, failure) should be analysed as same 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 Central Unit of the National TB Control Program (NTP). The NTP compiles cohort analysis reports on all TB patients registered nationally in that cohort, evaluates and provides feedback to the Program staff.

Cohort analysis of treatment outcome in Drug Resistant-TB patients

The Drug Resistant (DR-TB) patients cohort analysis will be considered under a separate guideline (See Somali DR-TB Guidelines)
MONITORING AND MANAGING DRUG TOXICITY

7.9 Monitoring of TB patients for significant adverse effects of TB drugs

Most TB patients complete their treatment without any significant adverse effects of drugs. However, a few patients do develop adverse effects. It is important that patients be clinically monitored during treatment, so that adverse effects can be detected promptly and managed properly. Routine laboratory monitoring is not necessary.

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 asking about symptoms when patients report to collect drugs.

7.10 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 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 TB drugs.

7.11 Adverse effects of TB drugs

Table 7.2 shows a symptom-based approach to the most common adverse effects of the essential 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. Further management depends on the nature of the adverse reaction. Patients with major adverse reactions should be managed in a hospital.
<table>
<thead>
<tr>
<th>Side effects</th>
<th>Drug(s) probably responsible</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minor</strong></td>
<td></td>
<td>Continue TB drugs, check drug doses</td>
</tr>
<tr>
<td>Anorexia, nausea, abdominal pain</td>
<td>Pyrazinamide, rifampicin</td>
<td>Give drugs with small meals or last thing at night</td>
</tr>
<tr>
<td>Joint pains</td>
<td>Pyrazinamide</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Burning sensation in the feet</td>
<td>Isoniazid</td>
<td>Pyridoxine 100 mg daily</td>
</tr>
<tr>
<td>Orange/red urine</td>
<td>Rifampicin</td>
<td>Reassurance. Patients should be told when staring treatment that this commonly happens and is normal</td>
</tr>
<tr>
<td><strong>Major</strong></td>
<td></td>
<td>Stop responsible drug(s)</td>
</tr>
<tr>
<td>Itching, skin rash</td>
<td>(S, H, R, Z)</td>
<td>Stop TB drugs, see below</td>
</tr>
<tr>
<td>Deafness (no wax on auroscopy)</td>
<td>Streptomycin</td>
<td>Stop streptomycin, use ethambutol</td>
</tr>
<tr>
<td>Dizziness (vertigo and nystagmus)</td>
<td>Streptomycin</td>
<td>Stop streptomycin, use ethambutol</td>
</tr>
<tr>
<td>Jaundice (other causes excluded), hepatitis</td>
<td>Isoniazid, pyrazinamide, rifampicin</td>
<td>Stop TB drugs, see below</td>
</tr>
<tr>
<td>Confusion (suspect drug-induced acute liver failure if jaundice present)</td>
<td>Most TB drugs</td>
<td>Stop TB drugs. Urgent liver function tests and prothrombin time test</td>
</tr>
<tr>
<td>Visual impairment (other causes excluded)</td>
<td>Ethambutol</td>
<td>Stop ethambutol</td>
</tr>
<tr>
<td>Shock, purpura, acute renal failure</td>
<td>Rifampicin</td>
<td>Stop rifampicin</td>
</tr>
</tbody>
</table>
7.12 Management of a cutaneous 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, reassurance and avoiding dry skin, continue TB treatment and observe the patient closely. However, if a skin rash develops then all TB drugs must be stopped. Once the reaction has resolved, TB drugs are re-introduced. The problem is how to re-introduce 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 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, 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.

7.13 Management of drug-induced hepatitis

Isoniazid, pyrazinamide and rifampicin can all cause liver damage (drug-induced hepatitis). Rifampicin alone can cause asymptomatic jaundice without evidence of hepatitis. It is important to try to rule out other possible causes before deciding that the hepatitis is induced by the TB regimen. The management of hepatitis induced by TB treatment depends on:

- Whether the patient is in the intensive or continuation phase of TB treatment;
- The severity of the liver disease;
- The severity of the TB;
- The capacity of the health unit to manage the side-effects of TB treatment.

Once is it known that the liver disease is caused by the anti-TB drugs, all drugs should be stopped. However, in severely ill TB patient whose TB treatment is considered unsafe to be stopped, this patient can be treated with a non-hepatotoxic TB regimen consisting of streptomycin, ethambutol and a fluoroquinolone.
However, in case where the TB treatment has been stopped, it is necessary to wait for liver function tests to revert to normal and clinical symptoms (nausea, abdominal pain) to resolve before reintroducing the anti-TB drugs. If it is not possible to perform liver function tests, it is advisable to wait an extra 2 weeks after resolution of jaundice and upper abdominal tenderness before restarting TB treatment. In a cases where the signs and symptoms do not resolve and the liver disease is severe, the non-hepatotoxic TB regimen consisting of streptomycin, ethambutol and a fluoroquinolone should be started (or continued) for a total of 18–24 months.

Once drug-induced hepatitis has resolved, the drugs are reintroduced one at a time. If symptoms recur or liver function tests become abnormal as the drugs are reintroduced, the last drug added should be stopped. In this situation, it is advisable to start with rifampicin because it is less likely than isoniazid or pyrazinamide to cause hepatotoxicity and is the most effective agent. This should be followed by reintroducing isoniazid after 3–7 days.

In all patients who have had jaundice but tolerated the reintroduction of rifampicin and isoniazid, pyrazinamide should be avoided.

Other alternative regimens for treating hepatitis depend on which drug is implicated as the cause of the hepatitis.

- If rifampicin is implicated, a suggested regimen without rifampicin is 2 months of isoniazid, ethambutol and streptomycin followed by 10 months of isoniazid and ethambutol.
- If isoniazid cannot be used, 6–9 months of rifampicin, pyrazinamide and ethambutol can be considered.
- If neither isoniazid nor rifampicin can be used, the non-hepatotoxic regimen consisting of streptomycin, ethambutol and a fluoroquinolone should be continued for a total of 18–24 months.

Management of hepatitis by reintroducing one drug at a time demands that stock limited quantities of single anti-TB drugs for use must be available. However, in cases where they are not available the following approaches are recommended depending on whether the hepatitis with jaundice occurred during the intensive or the continuation phase.

- **When hepatitis with jaundice occurs during the intensive phase** of TB treatment with isoniazid, rifampicin, pyrazinamide and ethambutol: once hepatitis has resolved, restart the same drugs EXCEPT replace pyrazinamide with streptomycin to complete the 2-month course of initial therapy, followed by rifampicin and isoniazid for the 6-month continuation phase.

- **When hepatitis with jaundice occurs during the continuation phase**: once hepatitis has resolved, restart isoniazid and rifampicin to complete the 4-month continuation phase of therapy.
8. TUBERCULOSIS IN CHILDREN

Management of tuberculosis in children is a separate guideline altogether. However, brief description of TB in children will en outlined here particularly the epidemiology, clinical presentation, diagnosis and management of TB. In fact TB treatment in children does not differ from treatment of TB in adults.

8.1 Objectives of chapter

This chapter describes the epidemiology, clinical presentation and management of childhood TB.

8.2 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. Children (0-14 years) account for up to one-third of all TB cases. Most cases are pulmonary TB (PTB) cases. Extrapulmonary TB (EPTB) is also common and presentation varies with age.

Children can present with TB at any age but the commonest age is between 1 and 4 years of age. Most TB cases occur in children less than 5 years of age. The younger the child, the more likely a close contact with TB disease can be identified. TB disease can be more severe and of rapid onset in infants and young children. Children with TB disease usually have poor weight gain, may lose weight or be malnourished. The presentation and approach to diagnosis of pulmonary TB in older children (>10 years) and adolescents is similar to that for adults. Any child with suspected or confirmed TB should be tested for HIV TB/HIV co-infection is common in children in sub-Saharan Africa. HIV-infected children are at greater risk for TB infection and for TB disease. Therefore, 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. Diagnosis and management can be more challenging in HIV-infected. BCG is not fully protective against TB disease in children.

Recommendation 1: The diagnosis of TB can be made with confidence in the majority of children using careful clinical assessment

Clinical Diagnosis: PTB

The most common clinical presentation of pulmonary TB is persistent respiratory symptoms and poor weight gain. However, in at-risk groups such as infants or HIV infected,
pulmonary TB in children can also present as acute pneumonia. Diagnosis of TB in HIV-infected children should similarly be approached like that one in non-HIV infected children. In diagnosis of TB in children the following symptoms are important:

- Cough especially if persistent and not improving
- Weight loss or failure to gain weight
- Fever and/or night sweats
- Fatigue, reduced playfulness, less active

Particularly when the symptoms persist for 2 to 3 weeks without improvement following other appropriate therapies such as broad-spectrum antibiotics for cough; antimalarial treatment for fever; or nutritional rehabilitation for malnutrition.

- History of contact. A child can be exposed to TB in the following situations:
  a. Close contact: such as with a source case of TB living in the same household
  b. Contact may be with a source case of TB from outside the household such as with a neighbor or relative with whom the child has had frequent contact
  c. A source case with sputum smear-positive PTB is more likely to infect contacts than cases with sputum smear-negative PTB
  d. If no source case is identified, always ask about anyone in household with chronic cough and if there is someone, request assessment of that person for possible TB
  e. In older children the contact with a TB source case may be outside the household e.g. school

Children usually develop TB within 2 years after exposure. Indeed 90% of the children develop TB within the first year

**Clinical examination**

When examining the child, the following signs must be carefully looked for:

- Weigh child accurately and compare to previous weights: Look for weight loss or poor weight gain. Check for evidence of growth faltering
- Fever and increased respiratory rate
- Signs of respiratory distress. Auscultation and percussion may usually be normal but it may reveal signs of lung disease such as crackles, bronchial breathing or pleural effusion such as dullness and reduced breath sounds
- Clinical features that might suggest other causes of chronic lung disease such as generalized lymphadenopathy, oral thrush, parotid enlargement suggest HIV infection, finger clubbing such as in bronchiectasis and recurrent cough and/or wheeze which can suggest asthma attack.
Atypical presentation of TB can also occur in children. This includes:

- Acute severe pneumonia which is characterized by fast breathing and chest in-drawing. This usually occurs in infants and HIV-infected children.
- TB should be suspected if a child has poor response to antibiotic therapy.
- In HIV infected suspect any other HIV-related lung disease.

**Recommendation 2:** wheeze due to asthma is usually recurrent and variable rather than persistent, responsive to inhaled bronchodilator and is not associated with other typical features of TB such as poor weight gain and persistent fever.

**Suggested Algorithm for TB diagnosis non-HIV infected children**

<table>
<thead>
<tr>
<th>TB suspected on basis of typical and persistent symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum smear</td>
</tr>
<tr>
<td><strong>Negative or not done</strong></td>
</tr>
<tr>
<td><strong>Sputum smear positive</strong></td>
</tr>
<tr>
<td><strong>Clinical Diagnosis</strong></td>
</tr>
<tr>
<td>- Positive contact history</td>
</tr>
<tr>
<td>- Physical signs suggestive of PTB</td>
</tr>
<tr>
<td>- CXR suggestive of PTB</td>
</tr>
<tr>
<td><strong>TREAT FOR TB</strong></td>
</tr>
<tr>
<td><strong>If only one or none of the features are present</strong></td>
</tr>
<tr>
<td><strong>If child sick, admit to hospital for further investigation</strong></td>
</tr>
<tr>
<td><strong>If child well, review after 2-4 weeks</strong></td>
</tr>
<tr>
<td><strong>Make a diagnosis of TB if two or more of these features are present</strong></td>
</tr>
</tbody>
</table>

**Recommendation 3:** If child does not fit definite criteria to start anti-TB treatment, decision for further review as outpatient or for inpatient management or for referral for further opinion or investigation will depend upon clinical state of the child and available levels of care.
Suggested Algorithm for TB diagnosis HIV infected children

Investigation of a child suspected of TB

1. **HIV test**
   - Any child with suspected TB should have an HIV test. A positive HIV test will enable the child to have other HIV-related care for the child and possibly other family members

2. **Sputum**
   - Two sputum smears for acid fast bacilli (AFB) microscopy should be done. Usually children older than 10 years sometimes even young as 5 years old can produce sputum

3. **Chest X-Ray**
   - CXR remains an important tool for diagnosis of PTB in children who are sputum smear negative or who cannot produce sputum. Chest X-ray may show the following: enlarged hilar lymph nodes and opacification in the lung tissue, miliary mottling in lung tissue, cavitation (tends to occur in older children), pleural or pericardial effusion that tend to occur in older children
• The finding of marked abnormality on CXR in a child with no signs of respiratory distress is supportive of TB

4. Tuberculin skin test
• TST is useful to support a diagnosis of TB in children with suggestive clinical features who are sputum smear negative or who cannot produce sputum. TST is positive if induration is $\geq 10$ mm irrespective of BCG immunization or $\geq 5$ mm in HIV-infected or severely malnourished child
• A positive TST is particularly useful to indicate TB infection when there is no known TB exposure on clinical assessment i.e. no positive contact history
• A positive TST does not distinguish between TB infection and active disease
• A negative TST does not exclude TB disease

5. Gastric aspirate or induced sputum
• This is usually done in children who cannot provide sputum by coughing
• It is particularly useful in child suspected of MDR TB

TB treatment in children

TB in children should be treated with the same CAT 1 Regimen as in adults. This regimen also applies to TB in children infected with HIV.
Recommendation 1: All children newly infected with TB regardless of the type TB (all forms of PTB and EPTB except for TB meningitis and TB of the bones should be treated with 2HRZE/4HR

Recommendation 2: All children newly infected with TB should receive a daily intensive phase followed by daily continuation phase 2HRZE/4HR and that each dose is directly observed

Recommendation 3. All children having TB meningitis or bone TB should be treated with 2HRZE/10HR

Recommendation 4: All children newly infected TB meningitis or bone TB should receive a daily intensive phase followed by daily continuation phase 2HRZE/10HR and that each dose is directly observed
Table 7.3: Recommended antituberculosis drug doses for children

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dose in kg/body weight</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>Maximum</td>
</tr>
<tr>
<td>Isoniazid (H)</td>
<td>10-15</td>
<td>300</td>
</tr>
<tr>
<td>Rifampicin (R)</td>
<td>10-20</td>
<td>600</td>
</tr>
<tr>
<td>Pyrazinamide (Z)</td>
<td>30-40</td>
<td>2000</td>
</tr>
<tr>
<td>Ethambutol (E)</td>
<td>15-25</td>
<td>1200</td>
</tr>
</tbody>
</table>

Child contact screening and management

Isoniazid preventive therapy (IPT) greatly reduces the risk of an infant or young child with TB infection from developing disease. Therefore:

- All children who are close contacts with cases with smear-positive TB should be screened for TB
- If the TB source case is the child’s parent and is HIV-infected, test all the children for HIV
- Screening can be done at the primary health care level. Symptoms alone are used to screen child contacts for possible TB disease

Recommendation 1: Any child contact with symptoms should be carefully assessed for TB disease

Recommendation 2: IPT is indicated for all young children (< 5 years) and HIV-infected children of any age that are household contacts of a case with sputum smear-positive TB AND do not have any evidence of TB disease

Recommendation 3: IPT must be given for a full 6 months to be effective. Dosage (10-15 mg/kg) is same as for treatment.
9. Recording, Reporting and Evaluation of Case-Finding and Treatment Results

The accurate keeping of records on all individual patients, and periodic reporting – with statistics on patients, and activities, together with explanatory remarks – is essential for planning of procurement of drugs, laboratory reagents, sputum containers, hospital beds for tuberculosis, of manpower, as well as for evaluation of control measures applied in the tuberculosis Program. The number of documents used in the Program is limited as much as possible. There are eight basic forms, registers and reports. These include:

- Request for examination of biological specimen
- Basic Management Unit (BMU) TB Register
- Second-line TB treatment Register
- Laboratory Register for smear microscopy and X-pert MTB/Rif
- Laboratory Register for culture, X-pert MTB/Rif and drug susceptibility testing (DST)
- Quarterly Report on TB case Registration in the Basic Management Unit
- Quarterly Report on TB Treatment Outcomes in the Basic Management Unit
- Combined annual Outcomes report for Basic TB and for RR-/MDR-TB

Separate documents for patient management such as TB treatment card, drug stocks, laboratory reagents, X-rays and other consumables are developed but not essential to include in this list.

9.1. Recording

The following records are to be used in the TB Program

Request for examination of biological specimen for TB (B.3.1)

This is the standard form which accompanies a biological sample being referred to a laboratory for smear microscopy, culture, Xpert MTB/RIF or DST. The form contains the basic information that includes the date of specimen collection, type of specimen, laboratory serial number, and visual appearance of the specimen, results of sputum microscopy, Gen X-pert, culture and drug sensitivity results.

Basic Management Unit (BMU) TB Register (B.3.2)

The BMU TB Register is primarily used to record data needed to monitor BMU performance based on indicators and reports about TB patients and is also a tool for following up the adequacy of testing and treatment decisions. The registers basically contains the particulars of
the patient, history of previous treatment, site of the disease, treatment category, TB/HIV activities, results of investigations and treatment outcome of the patient.

**Second-line TB Treatment Register (B.3.3)**

This register is primarily intended to keep a record of those data that are important for generating indicators and reports among patients placed on second-line regimens for RR-TB or MDR-TB. It is also used to follow the adequacy of testing and treatment decisions. The register contains details on the particulars of the patient, disease site, registration group of the patient, type of second-line drugs received, results of the investigations including DST, TB/HIV activities and follow up results during treatment.

**Laboratory Register for smear microscopy and X-pert MTB/RIF (B.3.4)**

This register is used for both sputum-smear microscopy and Xpert MTB/RIF examinations. The Register contains particulars of the patient, examination type which could be diagnosis or follow-up and results of the examinations

**Laboratory Register for culture, Xpert MTB/RIF and drug-susceptibility testing (DST) (B.3.5)**

This is intended to be used in the reference laboratory in Hargeisa. The registers contains essentially the particulars of the patient, TB/HIV status, patient’s previous history of treatment, details of the specimen and results of the tests including DST

**Quarterly Report on TB Case Registration in Basic Management Unit (B.3.6)**

This register depicts the standard aggregated report of cases as recorded in the BMU TB Register and of laboratory activity as recorded in the Laboratory Register. It is used for to monitor the program and report on the indicators to both WHO and Principal Recipient of the Global Fund. The report stratifies the case categories into bacteriologically-confirmed or clinically diagnosed and site of the disease. For all incident cases such as the new and relapse cases, these are differentiated by age-group and sex is requested. The form also captures the yield of bacteriological tests and the yield of HIV testing among TB cases tested.
Quarterly Report on TB Treatment Outcomes in Basic Management Unit (B.3.7)

This is the standard quarterly report used to monitor treatment outcomes for all TB cases. It excludes all TB cases not started on second-line treatment. This is because treatment outcomes for RR-TB, MDR-TB and XDR-TB cases that are put on second-line treatment are usually compiled annually rather than quarterly. It contains treatment outcomes for patients recorded in the BMU TB Register in the quarter that ended 12 months previously. TB/HIV activities are also included in the report. However, patients transferred in from another register and patients found to have RR-TB or MDR during treatment and were moved to second-line drugs are excluded.

Combined annual outcomes report for basic TB and for RR-/MDR-TB (B.3.8)

This form captures on one sheet the outcomes for patients on first-line and second-line TB treatment. It contains two blocks. Block one is the same as standard DOTS treatment cohort annual report for the year minus 2. Minus 2 means the outcomes of the patients collated in the current calendar year is a cohort of patients registered 2 years previously. Block two is intended for the second-line treatment outcome (year minus 3) and is treatment cohort annual report for the year minus 3. Minus 3 means the outcomes collated for patients on second-line drugs in the current calendar year is the cohort registered on second-line 3 years previously. Patients in Block one excludes patients who were transferred in from another BMU and patients who were found to have RR-TB or MDR and were started on full MDR treatment regimen and were moved to the second-line treatment register.

9.2. Reporting

All TB facility coordinators must submit reports on case-finding and results of treatment to the focal point for tuberculosis control (NTP). The forms to be used are:

1. Quarterly Report on TB Case Registration in Basic Management Unit (B.3.6)
2. Quarterly Report on TB Treatment Outcomes in Basic Management Unit (B.3.7)
3. Combined annual outcomes report for basic TB and for RR-/MDR-TB (B.3.8)
These three forms are to be completed in duplicate by each TB facility coordinator, and one will be sent to the focal point for tuberculosis control (NTP) and the other retained for his records.

The quarterly reports are made in a manner to permit cohort analysis. (A cohort refers to a group of individuals with a common characteristic; in this case the cohort includes all patients registered in a district during a quarter).

**Evaluation of case-finding and treatment results, and program management**

A built-in evaluation system is an integral component of any tuberculosis Program. It is mandatory to regularly collect information detection of all TB cases
Quarterly reports No. 1, No. 2 and No. 3 will be analyzed at the focal point for tuberculosis control.

The dates for analyzing the results of the treatment of patients who started treatment during e.g. 2013 will be as follows:

<table>
<thead>
<tr>
<th>Start of treatment</th>
<th>Date of Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Jan – 31 March 2013</td>
<td>1 Jan 2014</td>
</tr>
<tr>
<td>1 Apr –30 June 2013</td>
<td>1 April 2014</td>
</tr>
<tr>
<td>1 July – 30 Sept 2013</td>
<td>1 July 2014</td>
</tr>
</tbody>
</table>
10. HIV INFECTION AND TUBERCULOSIS

10.1 Objectives of chapter

This chapter briefly describes:
- HIV-related TB as part of the overall TB epidemic
- HIV-related TB as part of the overall HIV/AIDS epidemic
- Patterns of HIV-related TB and the effect of HIV on diagnosis
- The implications of HIV for treatment of TB in HIV-infected patients
- The implications of HIV for TB control Programs
- HIV voluntary counseling and testing
- TB treatment and antiretroviral therapy
- The collaboration between TB and HIV/AIDS Programs.

10.2 HIV-related TB as part of the overall TB epidemic

Untreated HIV infection leads to progressive immunodeficiency and increased susceptibility to infections, including TB. HIV fuels the TB epidemic through promotion of progression of recent and latent *M. tuberculosis* infection to active TB disease. HIV also increases the rate of recurrent TB. Increasing TB cases in persons living with HIV/AIDS (PLWH) pose an increased risk of TB transmission to the general community. Although only a small fraction of the two billion persons infected with TB also have HIV (TB/HIV co-infection), this small group has a high risk of developing TB disease. TB disease occurs in probably half of people co-infected with TB and HIV.

10.3 Patterns of HIV-related TB and effect of HIV on diagnosis

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.

**Adult Pulmonary TB**

Even in HIV-infected patients, pulmonary TB is still the commonest form of TB. The presentation depends on the degree of immuno-suppression. 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 10.1  How pulmonary TB differs in early and late HIV infection

<table>
<thead>
<tr>
<th>Features of pulmonary TB</th>
<th>Stage of HIV infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early</td>
</tr>
<tr>
<td>Clinical picture</td>
<td>Often resembles post-primary pulmonary TB</td>
</tr>
<tr>
<td>Sputum smear result</td>
<td>Often positive</td>
</tr>
<tr>
<td>Chest X-ray appearance</td>
<td>Often cavities (may be normal)</td>
</tr>
</tbody>
</table>

Reported case rates of smear-negative pulmonary TB have increased 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 and to ensure good quality control of sputum smear-microscopy in order to diagnose smear-negative pulmonary TB as accurately as possible. (e.g. with Fluorescent Microscopy and Gene Xpert)

Adult extra-pulmonary TB
The commonest forms are pleural effusion, lymphadenopathy, pericardial and meningeal disease.

Childhood TB
The most frequent presentation is extra-pulmonary TB (most commonly intrathoracic). Pulmonary TB is usually smear-negative. 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. The current diagnostic approach to childhood TB is even more limited in HIV-infected patients. In the
absence of improved diagnostic methods, the diagnosis of childhood TB still largely rests on careful clinical assessment and growth monitoring, chest X-ray, and a positive family history of TB.

10.4 Implications of HIV for treatment of TB in HIV-infected patients

10.4.1 TB treatment in HIV-infected TB patients

The same criteria determine treatment categories for TB patients irrespective of HIV status. Thus, HIV-infected new TB patients receive category I treatment if they have smear-positive pulmonary TB, smear-negative pulmonary TB with extensive parenchymal involvement, or severe forms of extra-pulmonary TB.

Generally, TB treatment is the same for HIV-infected as for non-HIV-infected TB patients, with the exception of the use of thioacetazone. Streptomycin remains a useful drug in those countries with the capability to ensure the use of disposable or sterile needles and syringes.

10.4.2 Adverse drug reactions

HIV infection is associated with an increased risk of adverse drug reactions to many TB drugs. 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, and used in general instead of thioacetazone in regions/countries where the level of HIV infection is known to be high.

10.4.3 Response of HIV-infected TB patients to TB treatment

Clinical course during TB treatment

Common HIV-related infections (e.g. pneumonia and diarrhea and their complications, fungal infections) cause considerable morbidity during treatment of HIV-infected tuberculosis patients, and contribute to the increased case fatality rate. Patients should be monitored during TB treatment to identify and treat these infections.

Case fatality

HIV-infected smear-positive TB patients have an increased case fatality. In HIV-infected smear-negative TB patients the case fatality is even higher, probably reflecting their greater
degree of immuno-suppression. Excess deaths in HIV-infected TB patients during and after treatment are partly due to TB itself and partly due to other HIV-related problems.

**Cotrimoxazole prophylaxis**

Prophylaxis against intercurrent infections may decrease morbidity and mortality in HIV-infected tuberculosis patients. UNAIDS and WHO have provisionally recommended the use of cotrimoxazole prophylaxis in HIV-infected individuals in Africa as part of a minimum package of care. The recommended dose of cotrimoxazole (sulphamethoxazole/trimethoprim 5/1) for adults is 960 mg once daily and for children SMX 750 mg/ m² TMP 150 mg/m² once daily.

**Recommendation 1: In all HIV-positive TB patients, co-trimoxazole preventive therapy should be initiated as soon as possible and given throughout TB treatment.**

Co-trimoxazole preventive therapy substantially reduces mortality in HIV-positive TB patients. The exact mode of activity is not clear but co-trimoxazole is known to prevent *Pneumocystis jirovecii* and malaria and is likely to have an impact on a range of bacterial infections in HIV-positive TB patients.

**Response in survivors**

Several studies have assessed the clinical, radiological, and microbiological response to 6 month, rifampicin-based treatment in HIV-positive and HIV-negative TB patients. Excluding patients who died, response rates were similar in HIV-positive and HIV-negative TB patients. There is little information about the efficacy of the 8-month regimen in TB/HIV. However, regimens that do not contain rifampicin in the continuation phase have been associated with a greater risk of failure/relapse compared with 6-month regimens with rifampicin.

**Recurrence of TB after completing TB treatment**

Among TB patients who complete SCC, the recurrence rate is higher in HIV-positive than in HIV-negative TB patients. Post-treatment prophylaxis (for example with isoniazid) can decrease the risk of tuberculosis recurrence in HIV-infected individuals, although does not appear to prolong survival. Further studies are needed to confirm the benefit, establish the optimum regimen (drugs and duration) and assess operational feasibility, before widely recommending treatment aimed at decreasing risk of tuberculosis recurrence.
10.5 Implications of HIV for TB control Programs

10.5.1 Difficulties with targets for cure rates and case detection
Many high HIV prevalence countries cannot meet the global cure rate target of 85%, because of high death rates and high rates of adverse drug reactions giving rise to increased default rates. NTPs need to interpret the cure rate as an indicator of NTP performance taking into consideration the increased death rates associated with high HIV prevalence.

10.5.2 Need for more resources for TB control
Increased TB case numbers as a result of the HIV epidemic have meant a need for increased investment to improve general health service capacity to deliver TB control interventions (human resources, infrastructure and commodities, e.g. laboratory resources, drugs, sputum containers and stationery).

10.5.3 Need for decentralization because of overcrowded TB wards
Large number of patients have led to overcrowding of TB wards, rendering good nursing care difficult and increasing the risk of nosocomial infection. One response of NTPs is to decentralise treatment to peripheral health centres and the community. This is a patient-friendly approach which requires strong managerial capacity to ensure the logistics of directly observed treatment, drug security (especially of rifampicin), supervision, monitoring and recording in the community.

10.5.4 Infection control measures to decrease nosocomial TB transmission
Health care staff in out-patient and in-patient facilities, whose HIV prevalence is similar to that of the general population are at risk of nosocomially acquired TB. HIV-infected patients in the same health facilities as TB patients are at increased risk of TB. Measures are therefore necessary to protect health care staff and patients from nosocomial TB transmission.

10.6 HIV counseling and testing of individual TB patients
HIV prevalence among TB cases in Somalia is estimated to be about 4%. This constitute a significant number of TB cases in Somalia. Therefore, there is great need to initiate HIV counseling and testing for all TB cases in Somalia. TB is often the first clinical indication that
a person has underlying HIV infection, and TB services can be an extremely important entry point to HIV prevention, care and treatment. Knowing the HIV status of TB patients makes a difference to their TB treatment. Detecting HIV infection in a TB patient is also critical for the TB patient’s household members: HIV-positive TB patients may have household members who are also living with HIV. Testing and counselling should be recommended for children and other immediate family members of all people living with HIV. Household contacts of an infectious TB case are a high priority for TB screening and treatment, especially if they are living with HIV and those who are found to have active TB disease need prompt treatment. Among household contacts, people living with HIV (and children, regardless of their HIV status) who do not have active TB are candidates for isoniazid treatment to prevent the development of active TB.

**Recommendation 1:** Irrespective of epidemic setting, HIV testing should be done for patients of all ages who present with signs or symptoms that suggest tuberculosis (7), whether TB is suspected or already confirmed.

**Recommendation 2:** “Provider-initiated” testing, which means that the health care provider recommends HIV testing and counselling as a standard component of care should be done and this can be done at the same time the sputum samples or chest radiographs are obtained

**Recommendation 3:** Informed consent, counselling and confidentiality are essential. “opt-out” approaches is preferred, meaning that individuals must specifically decline the HIV test after receiving pretest information if they do not want the test to be performed.

The provision of HIV testing by the same health worker who provides the TB treatment (or the provision of HIV testing in the same facility) has been shown to facilitate HIV testing for TB patients. If this is not possible, NTPs should take responsibility for ensuring that any referred individual actually goes for a test.

10.7 TB treatment in people living with HIV

Death rates among treated TB patients are higher in HIV-positive than in HIV-negative patients. Case-fatality is higher in people living with HIV with smear-negative pulmonary and extrapulmonary TB, as these patients are generally more immunosuppressed than those with smear-positive TB. The case-fatality rate is reduced in patients who receive concurrent ART.

The first priority for HIV-positive TB patients is to initiate TB treatment, followed by co-trimoxazole and ART. New TB patients living with HIV should be treated with the regimens similar to TB patients not infected with HIV. Therefore the following recommendations are made:
**Recommendation 1:** TB patients with known positive HIV status and all TB patients living in HIV-prevalent settings should receive daily 2HRZE TB treatment at least during the intensive phase.

**Recommendation 2:** For the continuation phase, the optimal dosing frequency is also daily 4HR for these patients

**Recommendation 3:** All TB patients who are living with HIV should receive at least the same duration of TB treatment as HIV-negative TB patients.

### 10.7 TB treatment and antiretroviral therapy

Highly active antiretroviral therapy (HAART) is not a cure for HIV infection but is associated with dramatic reductions in morbidity and mortality in HIV-infected people. Although HAART is now the standard of care worldwide, International pressure is increasing to ensure that more people in high HIV prevalence countries have access to these drugs. There are several requirements for successful treatment of HIV infection with HAART. These include considerable efforts to maintain adherence to life-long treatment and to monitor response to treatment, drug toxicities and drug interactions.

Currently available antiretroviral drugs belong to two major classes:

i) Reverse transcriptase inhibitors (RTIs), which may be nucleoside (NRTIs) or non-nucleoside (NNRTIs)

ii) Protease inhibitors (PIs).

Examples of some of these drugs are given below:

NRTIs - zidovudine (AZT, ZDV), didanosine (ddI), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC), abacavir (ABC).

NNRTIs - nevirapine (NVP), efavirenz (EFV), delavirdine (DLV)

PIs - saquinavir (SQV), ritonavir (RTV), indinavir (IDV), nelfinavir (NFV), amprenavir (APV), lopinavir/ritonavir.

These drugs act by blocking the action of enzymes which are important for replication and functioning of HIV. The drugs must be used in combination, usually three drugs together. Monotherapy (using one drug) is not recommended because of the inevitable development of drug resistance. However, for the specific indication of prevention of mother to child transmission of HIV infection, short course monotherapy is recommended. Dual nucleoside therapy is also not recommended because it has no beneficial impact at a population level in terms of reducing HIV-related mortality.
ART drugs recommended for treatment of TB in Somalia are either Zidovudine (AZT) or tenofovir disoproxil fumarate (TDF), combined with either lamivudine (3TC) or emtricitabine (FTC) and efavirenz (EFV) or nevirapine (NVP). In case of TB patients Efavirenz is recommended

**Recommendation 1: First line regimen for HIV infected TB patients should be those that contain efavirenz.**

However, because of teratogenicity of efavirenz, the following options can be considered: AZT +3TC + NVP or TDF +3TC or FTC + NVP or AZT+3TC+ABC or AZT+3TC+TDF

**Recommendation 2: ART for all HIV infected TB patients should e started as early as possible most probably in the first 8 weeks of initiating antituberculosis treatment.**

This is because most fatalities in TB occur in the first 2 months of the disease. However, this may lead to drug-drug interaction and development of TB-associated immune reconstitution inflammatory syndrome (IRIS).

**Drug interactions**

Rifampicin stimulates the activity of the cytochrome P450 liver enzyme system which metabolises PIs and NNRTIs. This can lead to a reduction in the blood levels of PIs and NNRTIs. PIs and NNRTIs can also enhance or inhibit this same enzyme system, and lead to altered blood levels of rifampicin. The potential drug interactions may result in ineffectiveness of antiretroviral drugs, ineffective treatment of TB, and an increased risk of drug toxicity.

Occasionally, patients with HIV-related tuberculosis may experience a temporary exacerbation of symptoms, signs or radiographic manifestations of TB after beginning tuberculosis treatment. This paradoxical reaction occurs in HIV-infected patients with active tuberculosis and is thought to be a result of immune restitution due to the simultaneous administration of antiretroviral and tuberculosis medications. Symptoms and signs may include high fevers, lymphadenopathy, expanding central nervous system lesions and worsening of chest radiographic findings. The diagnosis of a paradoxical reaction should be made only after a thorough evaluation has excluded other etiologies, particularly tuberculosis treatment failure. For severe paradoxical reactions prednisone (1-2 mg/kg for 1-2 week, then gradually decreasing doses) may be used, although there are no data to support this approach.

Isoniazid can produce peripheral neuropathy. The NRTIs (didanosine, zalcitabine and stavudine) may also produce peripheral neuropathy and there is a potential added toxicity if isoniazid is added. Isoniazid also has a theoretical interaction with abacavir.
10.8 Collaboration between TB and HIV/AIDS Programs

10.8.1 Areas of mutual concern of TB and HIV/AIDS Programs

Since HIV fuels the TB epidemic, HIV Programs and TB Programs share mutual concerns: prevention of HIV should be a priority for TB control and vice versa.

10.8.2 TB control in high HIV prevalence populations

Up to now, the efforts to control TB among HIV-infected people have mainly focused on implementing the DOTS strategy for TB control, i.e. identifying and curing infectious TB cases. This targets the final step in the sequence of events by which HIV fuels TB, namely the transmission of *Mycobacterium tuberculosis* infection by infectious TB cases. The expanded scope of a new approach to TB control in high HIV prevalence populations comprises interventions against TB (intensified case-finding and cure and TB preventive therapy) and interventions against HIV (and therefore indirectly against TB), e.g. condoms, STI treatment or prophylaxis and HAART. Whereas previously TB Programs and HIV/AIDS Programs have largely pursued separate courses, they need to collaborate in areas of mutual concern in their support to general health service providers.

10.8.3 Co-ordinated care of HIV-infected TB patients

NTP staff and general health service staff need to be aware that many HIV-positive TB patients develop other HIV-related illnesses during TB treatment. Delivering interventions to reduce the frequency of opportunistic infections (e.g. cotrimoxazole prophylaxis, antiretroviral therapy) requires effective collaboration with HIV/AIDS Programs. Continuity of care for HIV-infected TB patients requires coordination of care in different settings and at different levels. 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 Program needs to co-ordinate closely with other services providing support and care for HIV-positive individuals. The clinician who treats the HIV-infected TB patient is in a key position to refer the patient to appropriate services for counseling, support, and care of the patient and the family.
11. HEALTH EDUCATION (HE)

Major efforts should be made to make people aware of the natural history of tuberculosis, and the methods for its prevention and cure. People should understand that TB, if not treated properly, results in infection of other people and may cause disability and death to the individual. It must be stressed to them that the disease is nearly 100% curable, so that there is no reason for panic. Tuberculosis must not be associated with a stigma as it was in the past. Community participation may contribute to the prevention of tuberculosis by BCG vaccination, to case-finding by encouraging people to seek medical advice if they develop symptoms of tuberculosis, and to treatment by encouraging the patient’s compliance to treatment.

The general public should be taught the importance of early attendance at a health facility if they have a history of chest symptoms, especially cough, persisting for 2 weeks or more.

Health Education has 2 level of services

- Facility level
- Community level

**Facility level:** In each TB facility there should be continuous formal and informal health education. Lessons should be given to patients, their families and relatives on TB, completion of treatment and related issues.

**At the facility level the messages should include:**

- Spitting at proper places e.g. spit in a defined container that will then be boiled before emptying the content,
- Practice cough hygiene e.g.put mask or a thick layer of cloth while coughing, sneezing and talking
- Avoid sleeping in overcrowded spaces
- Keep away from the children till sputum becomes negative
- Eat nutritious food
- Complete the whole course of treatment as prescribed
- Do not default
- Encourage other family members and/or friends likely to be in contact with the patient for check-up
- Maintain good ventilation at home and workplace
- Avoid any type of smoking
- Avoid drugs and Qat abuse
- Explain that sharing utensils does not transmit infection
- Report any medical happenings like reactions, complications etc immediately to the health workers

**Community Level:**

The community level will target the social sectors e.g education, faith based organization, media and others. This approach will be primarily to resolve the doubts, misconceptions and myths for TB and its treatment. It will also encourage and motivate the community to seek advice at the earliest.

**At the Community levels the main messages should be:**

- TB is curable and preventable disease
- Report anyone having cough of more than 2 weeks to the nearest health facility immediately
- All TB care services are free of charge and available at the public TB facilities
- TB should not be stigmatized
- TB should be diagnosed and treated promptly
- TB if not treated appropriately can be fatal and/or lead to disability.
- If not treated properly with designated drugs and for the given duration , TB can lead to development of resistant type of TB, for which there are limited options.

Health staff should encourage the community to produce posters, songs, poems, dramas about TB, its prevention and cure.
(For more details refer to National ACSM Guideline)
12. TRAINING AND SUPERVISION

Training
Training is a key component of every TB control program. It should be performed regularly on need basis and at all levels (TB coordinators, health workers, lab technicians, PHC Health Workers/ CHWs public and private practitioners etc.).
The trainings are conducted in the following pattern

- Regular Training
- On job training

The regular training are for training the staff who are working in the TB program and is organized based on the given guideline and in a training by training modules. The regular training is imparted in two ways

1. Pre-service training
2. Refresher training

The pre-service training are given to new appointees to be working at new TB facilities. This is an introductory course which covers the basic TB management at the TB facility. The pre-service training is also provided to the newly appointed laboratory technicians on the diagnostics and the lab procedures for TB program. The pre-service is imparted in two weeks both for TB health workers and the TB laboratory technicians.

Refresher trainings are given to the TB staff, both the TB management staff at the facility level and the TB laboratory staff, already on the job. The refresher trainings are imparted on a quarterly basis.

The trainings are to be organized primarily by the MOH (NTP), in collaboration with the WHO and other relevant partners/stakeholders.

On-job training.
The NTP and other stakeholders are also responsible to provide the on-job training to the TB staff including the laboratory technicians on a regular basis. The purpose of the on-job training is to clarify any concerns and issues related to the TB management and the laboratory procedures while doing their job on a regular basis. This is imparted during the regular supervisory visit or, as and when required or contacted by the concerned staff member. The on job training is a very important component of quality improvement in the TB control and
address specific concerns of a given staff member. The NTP supervisory staff has to be prepare
themselves with the updated guidelines the procedure and polices to guide the staff on the
ground. If need be, the NTP supervisory staff can, based on the on-job training recommend a
full refresher training to be given staff member.

Supervision
Supervision is a systematic process for increasing the efficiency of health workers by
developing their knowledge, perfecting their skills, improving their attitudes towards their
work and increasing their motivation. It is carried out in direct contact with the health workers.
Supervision should be performed at all levels of the health infrastructure. All health workers
need help to solve problems and overcome difficulties. They also need feedback on their
performance and encouragement in their work. Supervision should be intensified after training,
to ensure that health workers have fully acquired the skills taught and to provide any guidance
needed.

A good supervisor should be ready to listen with an open mind to any problem and to seek
solutions that will take into account the suggestions of the health workers in question.
Supervision mission must be carefully planned; the supervisor should review the reports of
previous missions. The health facilities to be supervised should be notified in advance of the
date and purposes of the visit. Unscheduled visits can be felt by health workers as associated
with inspection and punitive measures.
Supervision should be continuously carried out by the focal point for TB control of every
health facility providing TB control services. Each health facility should be visited every
month for the newly established TB centers. For the existing functional centers the supervisory
visits will be carried out on quarterly basis. Some health facilities may need more frequent
supervision visits than others if their TB control performance is poor.

Annual supervisory plan should be prepared by the NTP along with all the relevant
stakeholders.

This plan:-

- Will guide who is do what.
- Show the planned supervisory visits and the un-planned supervisory visits to be undertaken.
- Should also detail the names of the centers and the stakeholder responsible for undertaking
  the supervisory visit.
Should clearly mention the time frame by which the report should be submitted to the NTP manager, the timeframe over which feedback needs to be provided to the centers visited and the action points to be undertaken.

The report should be submitted in a prescribed format that is issued by the NTP manager for all to follow. The NTP manager should also prescribe the length of the report and the number of recommendations.

Before starting any supervisory visit the NTP manager will take a stock of the centers present performance based on the data available and have a desk review of the centre/s prepared. Along with the last supervisory visit report and the desk review certain specific areas of concern are already identified which can form the base of the supervision. Also before the supervision takes place the NTP manager is to ensure that the prescribed checklist is available and has been updated if needed.

**During supervision visits:**

- Observe the infrastructure, cleanliness, IEC materiel display, display of data
- All TB center documents, including the cards, registers (including drug and laboratory), forms, etc. should be reviewed
- Health workers should be observed doing their work
- The supervisor should talk with health workers in order to check their knowledge regarding TB and TB control and their work condition
- Stocks of supplies and the conditions of their stockade should be checked
- Check the positioning of the drugs in terms of storage, and first expire first out system
- Check the status of the Laboratory reagents and equipments
- Check specifically the infection control in the clinics and the laboratory including waste disposal methods.
- The supervisor should talk with TB patients in order to check their knowledge about the disease and their treatment
- Community approaches or functions by the TB clinic, including ACSM activities, and contact tracing.
- Other collaborations such as PPM, PAL
- Check wherever applicable the food quality and its storage conditions including complaints from the patients consuming the food.
ANNEX 1  ESSENTIAL TUBERCULOSIS DRUGS

ISONIAZID

*Group*: antimycobacterial agent

*Tablet* 100 mg, 300 mg

**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 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 primary complex in recently infected, asymptomatic individuals
- development of active TB in immunodeficient individuals.

**Dosage and administration**

Isoniazid is normally taken orally.

**Treatment (combination therapy)**

Adults and children: 5 mg/kg (4-6 mg/kg) daily, maximum 300 mg
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.

Isoniazid interacts with anti-convulsants used for epilepsy. It may be necessary to reduce the dosage of these drugs during treatment with isoniazid.

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, activated charcoal, antiepileptics and IV sodium bicarbonate 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 seizures.

**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*

(Check parenteral, in meningitis, ROB)

**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 TB chemotherapeutic regimens currently recommended by WHO (see Table 3 page 22).

**Dosage and administration**

Rifampicin should preferably be given at least 30 minutes before meals, since absorption is reduced when it is taken with food. This however may not be clinically significant and food can reduce intolerance to drugs.

Adults and children: 10 mg/kg (8-12 mg/kg) daily, maximum 600 mg once daily.

**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 at birth to the infant of mother taking rifampicin because of the risk of postnatal haemorrhage.

Adverse effects

Rifampicin is well tolerated by most patients at currently recommended doses, although gastrointestinal intolerance can be unacceptably severe. Other adverse effects (fever, influenza-like syndrome and thrombocytopenia) are more likely to occur with intermittent administration, and skin rashes just as likely. 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. Current antiretroviral drugs (non-nucleoside reverse transcriptase inhibitors and protease inhibitors) interact with rifampicin. This may result in ineffectiveness of antiretroviral drugs, ineffective treatment of TB or an increased risk of drug toxicity.

Biliary excretion of radiocontrast media and sulfobromophthalein sodium may be reduced and microbiological assays for folic acid and vitamin B$_{12}$ 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

Fixed combination of rifampicin and isoniazid intended to promote 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 TB chemotherapeutic regimens currently recommended by WHO.

Dosage administration

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

For daily use tablets of 150 mg isoniazid + 300 mg rifampicin
75 mg isoniazid + 150 mg rifampicin;
tablet or pack of granules for paediatric use: 30 mg isoniazid + 60 mg rifampicin.

PYRAZINAMIDE

Group: antimycobacterial agent
Tablet: 400 mg

General information

A synthetic analogue of nicotinamide that is only weak 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 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).

**Contraindications**

- Known hypersensitivity
- Severe hepatic impairment

**Precautions**

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

**Use in pregnancy**

The six month regimen based upon isoniazid, rifampicin and pyrazinamide should be used whenever possible.

**Adverse effects**

Pyrazinamide may cause gastro-intestinal intolerance. 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, may occur and is responsive to simple analgesics (specially aspirin). Both hyperuricaemia and arthralgia may be reduced by prescribing regimens with intermittent administration of pyrazinamide.

**Overdosage**

Little has 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 newborn, in the elderly and in patients with severe renal impairment. It is excreted unchanged in the urine.

**Clinical information**

**Uses**

A component of several TB chemotherapeutic regimens currently recommended by WHO.
Dosage and administration

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

Adults and children:
15 mg/kg (12-18 mg/kg) daily.
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, cefalosporins, 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 \textit{M. tuberculosis, M. bovis} and some non-specific mycobacteria. It is used in combination with other TB drugs to prevent or delay the emergence of resistant strains.

It is readily absorbed from the gastrointestinal tract. Plasma concentrations peak in 2-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

An optional component of several TB chemotherapeutic regimens currently recommended by WHO.

Dosage and administration

Adults: 15 mg/kg (15-20 mg/kg) daily
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
• 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. Whenever possible, renal function should be assessed before treatment.

Use in pregnancy

The six month regimen based upon isoniazid, rifampicin and pyrazinamide should be used. Ethambutol should be used if a fourth drug is needed during the initial phase

Adverse effects

Dose-dependent optic neuritis can result in impairment of visual acuity and colour vision. Early changes are usually reversible, but blindness can occur if treatment is not discontinued promptly. Ocular toxicity is rare when used for 2-3 months at recommended doses.

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.
ANNEX 2  SECOND LINE ANTI-TB DRUGS (SLD)

AMINOGLYCOSIDES
- Kanamycin and amikacin
- Capreomycin (polypeptide)

THIOAMIDES
- Ethionamide
- Prothionamide

FLUOROQUINOLONONES
- Ofloxacin
- Ciprofloxacin
- Levofloxacin

CYCLOSERINE (AND TERIZIDONE)

PARA-AMINOSALICYCLIC ACID (PAS)

KANAMYCIN AND AMIKACIN

These are bactericidal agents of the aminoglycoside class, obtained from a streptomyces. Their bactericidal effect in vitro and in vivo against Mycobacterium tuberculosis is very similar and their adverse reactions are those of other aminoglycosides.

Their bactericidal effect might be valuable in patients with bacilli resistant to streptomycin. Cross-resistance between kanamycin and amikacin is usual.

Preparation and dose

The drugs are presented as sterile white powder for intramuscular injection in sealed vials containing the equivalent of 250 mg, 500 mg or 1 g of drug. The drug should be dissolved in 2 ml of 0.9% sodium chloride injection or water for injection.
The optimal dose is 15 mg/kg bodyweight, usually 750 mg to 1 g given daily or five days per week, by deep intramuscular injection. Rotation of injection sites avoids local discomfort. The duration of daily therapy is usually 3 to 4 months. When necessary, it is possible to give the drug at the same dose 2 or 3 times weekly during the continuation phase, under close monitoring for adverse reactions.

**Adverse reactions**

These are similar to the side-effects associated with streptomycin and capreomycin. Ototoxicity, deafness or vertigo may occur. Reversible nephrotoxicity may occur.

**Precautions**

In patients with impaired renal function, the daily dose should be reduced and/or the intervals between doses increased, to avoid accumulation of the drug. In these patients, renal function should be monitored regularly during use. This drug should not be used in pregnant women except as a last resort.

**CAPREOMYCIN**

This is a bactericidal agent from the polypeptide class, obtained from *Streptomyces capreolus*.

Its bactericidal effect might be valuable in patients with bacilli resistant to streptomycin, kanamycin and amikacin: there is no cross-resistance with the other aminoglycosides.

**Preparation and dose**

Capreomycin sulphate is supplied as a sterile white powder for intramuscular injection in sealed vials each containing 1000 units approximately equivalent to 1g capreomycin base. This should be dissolved in 2 ml of 0.9 per cent sodium chloride injection in water. Two or three minutes should be allowed for complete solution. The usual dose is 1g in a single dose daily, not exceeding 20 mg/kg for 40-120 days after which the dose must be reduced to 2/3 times weekly, as the risk of important side-effects rises sharply at that time.
**Adverse reactions**

These are similar to the side-effects with streptomycin, mainly tinnitus and vertigo with a lesser risk of deafness. Kidney damage may occur with elevation of serum and urine creatinine. Hypokalaemia, hypocalcaemia and hypomagnesaemia have also been reported. General cutaneous reactions and hepatitis may occur rarely. There may be pain and swelling at injection sites if it is not given by deep intramuscular injection.

**Precautions**

Capreomycin should be avoided if possible in patients with impaired hearing or renal function. Serum urea and electrolytes should be monitored during treatment. It is contra-indicated in pregnancy and best avoided in children.

**ETHIONAMIDE (OR PROTHIONAMIDE)**

These are bactericidal agents from the class of thioamides. Their chemical structure resembles thioacetazone with which there is frequent and partial cross-resistance. (Bacilli resistant to thioacetazone are often sensitive to thioamides, but the reverse is seldom the case).

Before the rifampicin era, ethionamide (or prothioanamide, the drug is similar in its antibacterial effects and adverse reactions) was a basic component of retreatment regimen for tuberculosis patients with bacilli resistant to isoniazid and streptomycin.

**Presentation and dose**

Ethionamide and prothionamide are normally administered in the form of tablets containing 125 mg or 250 mg of drug. The maximum optimum daily dose is 15-20 mg/kg or 1 g. The usual dose is 500 mg to 1 g daily, depending upon body weight and tolerance. Few persons can take more than 750 mg daily. (750 mg for patients weighing 50 kg or more, 500 mg for patient weighing less than 50 kg)

Patients may find the drug was more acceptable if it is administered with orange juice or milk or after milk, or at bed-time to avoid nausea. Among patients on directly observed treatment, a daily dose of 750 mg can be given as 250 mg under strict observation and 500 mg self-administered 10-12 hours later.
**Adverse reactions**

Prothionamide is generally considered to be less unpleasant and better tolerated than ethionamide. But adverse reaction are essentially similar. The main troubles are epigastric discomfort, anorexia, nausea, metallic taste and sulphurous belching. Vomiting and excessive salivation can occur. Tolerance varies in different populations: the drug is usually well tolerated in Asia and in Africa.

Psychotic reactions including hallucinations and depression may occur. Hypoglycaemia is a rare but dangerous occurrence, obviously particularly important in diabetic patients.

Hepatitis may occur in about 10% of cases, but is rarely serious. When major liver damage occurs, jaundice and highly symptomatic disease is created, with prolonged elevation of transaminases (6-8 weeks) and drug administration should be interrupted.

Prolonged administration in large doses may produce hypothyroidism and goitre as the drug has an antithyroid effect. These will reverse when the drug is withdrawn. Other rare side-effects have included gynaecomastia, menstrual disturbance, impotence, acne, headache and peripheral neuropathy.

**Precautions**

This drug should not be administered in pregnancy as it has been shown to be teratogenic to animals. It should be very carefully monitored if given to patients with diabetes, liver disease, alcoholism or mental instability.

**OFLOXACIN AND CIPROFLOXACIN**

These are weak bactericidal agents of the fluoroquinolones class. Both ofloxacin and ciprofloxacin have a bactericidal effect *in vitro* against *Mycobacterium tuberculosis*. Although neither drug has been studied extensively in controlled clinical trials, MIC/PK suggests that ofloxacin may be preferable when one of these is used, along with other effective drugs.

There is no cross-resistance with other antituberculosis agents, but complete cross-resistance between ofloxacin and ciprofloxacin (and between the other fluoroquinolones like levofloxacin) although drug resistance may be incomplete if it is low-dose resistance.
**Presentation and dose**

Fluoroquinolones are supplied in the form of tablets containing:

- 200 or 400 mg of ofloxacin
- 250 or 500 mg of ciprofloxacin

The usual daily dose is 600-800 mg (3-4 tablets) of ofloxacin or 1000-1500 mg (4-6 tablets) of ciprofloxacin during initial phase. If the dose of 800 mg is poorly tolerated, the daily dose can be reduced (400 mg ofloxacin) during the continuation phase. Either can be given in single daily dose (especially applicable in directly observed treatment) or the daily dose can be divided into 12-hour intervals.

**Adverse reactions**

Adverse reactions are uncommon but consist of gastrointestinal disturbance (anorexia, nausea, vomiting) or central nervous system symptoms (such as dizziness, headache, mood changes and rarely convulsions).

**Precautions**

These drugs should not be used in pregnant women or growing children because they may impair growth and produce injury to growing cartilage.

Because of drug interaction, the following drugs should be avoided: antacids, iron, zinc, sucralfate.

**CYCLOSERINE (OR TERIZIDONE)**

Cycloserine is bacteriostatic at the usual dosage. Terizidone is a combination of two molecules of cycloserine. This antibiotic does not share cross-resistance with other drugs. It was valuable in preventing resistance to ethionamide in the retreatment regimens (ethionamide, cycloserine, pyrazinamide or kanamycin) used before rifampicin era. Nowadays, its value remains to prevent resistance to other second line drugs (SLD).
**Preparation and dose**

The drug is given orally in tablets or capsules containing:

- 250 mg of cycloserine
- 300 mg of terizidone.

The maximum daily dose is 15-20 mg/kg; the usual dose is 500-750 mg of cycloserine, 600 mg of terizidone. Few patients tolerate more than 750 mg daily, and in the continuation phase more than 500 mg daily. The daily dose can be given in two intakes:

- cycloserine: 250 mg, in the morning, and 500 mg 12 hours later.
- terizidone: 300 mg twice a day at 12-hour intervals.

**Adverse reactions**

These include dizziness, slurred speech, convulsions, headache, tremor, insomnia, confusion, depression and altered behaviour. The most dangerous risk is that of suicide so mood should be carefully watched. Very rarely there may be a generalised hypersensitivity reaction or hepatitis.

**Precautions**

In view of the above adverse reactions, monitoring for central nervous system reactions is essential when cycloserine is prescribed. To prevent minor adverse reactions like insomnia, administration of small doses of a tranquilliser is sometimes recommended. Pyridoxine may decrease central nervous system effects. The nurses in charge of treatment of inpatients and the families of outpatients should be warned to report any undue depression or personality change immediately.

Cycloserine (and terizidone) should be avoided in patients with a history of epilepsy, mental illness or alcoholism. It should be used very cautiously in patients with renal failure.
PARA-AMINOSALICYLIC ACID (PAS)

This is a bacteriostatic agent: its principal value was as an effective companion drug to isoniazid, preventing the emergence of isoniazid-resistant organisms. PAS was commonly used 30 years ago, but rarely nowadays.

**Preparation and dose**

PAS is bulky and unpleasant to take because of gastrointestinal discomfort. Two presentations are available on the market:

- **Tablets**, sugar-coated, containing sodium salt: sodium para-aminosalicylate, each tablet containing 0.5 g of PAS

- **Granules** of PAS with an acid-resistant outer coating rapidly dissolved in neutral media. Granules are supplied in packets containing 4 g per packet.

The daily dosage of the usual tablet preparation is 150 mg/kg or 10-12 g daily in two divided doses. The recommended schedule is 5 to 6 g (10 to 12 tablets) every 12 hours. The daily dosage of the granular preparation is the same. There is some evidence that a lower dose of 4 g every 12 hours (8 g/day) of the granular preparation is associated with good blood levels and improved tolerance.

**Adverse reactions**

The main adverse reactions are gastrointestinal disturbance and general skin or other hypersensitivity including hepatic dysfunction. Hypokalaemia may also occur.

Anorexia, nausea, vomiting and abdominal discomfort are more common than diarrhoea. They may be lessened by administering the drug after food or with milk. One should not enquire of the patient how well he/she is tolerating the drug. The patient who expects to experience nausea and vomiting is much more likely to do so. Wait until the patient complains. It may be necessary to lower the dose slightly and then increase over a few days.

Prolonged administration in large doses may produce hypothyroidism and goitre as PAS has an antithyroid effect. These will reverse when the drug is withdrawn.
Precautions

PAS is best avoided in renal failure as it may make acidosis worse. The sodium salt should not be given when a restricted sodium intake is indicated. The old preparation (tablets) impaired the absorption of rifampicin, on account of an excipient (bentonite). The new preparation (granules) will not interfere with rifampicin absorption. A urine test for the drug is available (ferric chloride test).¹

For more detailed information, refer to National Drug Resistant-TB Guidelines for Somalia

ANNEX 3  EXAMPLES OF NUMBER OF TABLETS OF TB DRUGS FOR TREATMENT ACCORDING TO WEIGHT BANDS

Table 1 Sample regimens (Category I) with separate drugs in adults

<table>
<thead>
<tr>
<th>Weight in kg</th>
<th>30 – 39</th>
<th>40 – 54</th>
<th>55 – 70</th>
<th>&gt;70</th>
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</thead>
<tbody>
<tr>
<td><strong>Initial phase (daily)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H 100 mg</td>
<td>1.5</td>
<td>2.5</td>
<td>3</td>
<td>3.5</td>
</tr>
<tr>
<td>R 150 mg</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Z 400 mg</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>E 400 mg</td>
<td>1.5</td>
<td>2</td>
<td>3</td>
<td>3.5</td>
</tr>
<tr>
<td><strong>Continuation phase</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>- daily</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Either H 100 mg</td>
<td>1.5</td>
<td>2.5</td>
<td>3</td>
<td>3.5</td>
</tr>
<tr>
<td>R 150 mg</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>or H 100 mg</td>
<td>1.5</td>
<td>2.5</td>
<td>3</td>
<td>3.5</td>
</tr>
<tr>
<td>E 400 mg</td>
<td>1.5</td>
<td>2</td>
<td>3</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Table 2: Sample regimens with FCD of tuberculosis drugs in adults

<table>
<thead>
<tr>
<th>Weight in kg</th>
<th>30 – 39</th>
<th>40 - 54</th>
<th>55 – 70</th>
<th>&gt;70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial phase (daily)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRZE (75mg+150mg+400mg+275mg)</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>or: HRZ (75mg+150mg+400mg)</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Cat. II: add S (vial 1g) for 2 months</td>
<td>0.5</td>
<td>0.75</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Continuation phase - daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Either HR (75mg+150mg)</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Cat II: add E (400mg)</td>
<td>1.5</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>or: HE (150mg+400mg)</td>
<td>1.5</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>


Table 3: Sample regimens (Category I) with separate drugs in children

<table>
<thead>
<tr>
<th>Weight in kg</th>
<th>5 – 10</th>
<th>11 – 20</th>
<th>21 – 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial phase-Daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H 100 mg</td>
<td>½</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>R 150 mg</td>
<td>½</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Z 400 mg</td>
<td>½</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>E 400 mg</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>S 1 g (in TB meningitis)</td>
<td>0.25</td>
<td>0.33</td>
<td>0.5</td>
</tr>
<tr>
<td>Continuation phase-Daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H 100 mg</td>
<td>½</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>R 150 mg</td>
<td>½</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 4  Sample regimens with FCD of tuberculosis drugs in children (paediatric formulations)

<table>
<thead>
<tr>
<th>Weight in kg</th>
<th>Up to 7</th>
<th>8-9</th>
<th>10-14</th>
<th>15-19</th>
<th>20-24</th>
<th>25-29</th>
</tr>
</thead>
</table>

**Initial phase**- daily

<table>
<thead>
<tr>
<th>Drug</th>
<th>Up to 7</th>
<th>1 ½</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRZ (30mg+60mg+150mg)</td>
<td>1</td>
<td></td>
<td>1 ½</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>E 400mg</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>S 1 g</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>0.33</td>
<td>0.50</td>
<td>0.50</td>
</tr>
</tbody>
</table>

**Continuation phase**- daily

<table>
<thead>
<tr>
<th>Drug</th>
<th>Up to 7</th>
<th>1 ½</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (60mg + 30mg)</td>
<td>1</td>
<td>1 ½</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Annex 6 Quality Control

QUALITY CONTROL

Quality control of sputum microscopy is an indispensable part of effective TB control. The aim of quality control is to ensure that the results obtained by the laboratory are accurate, reliable, thus improving trust in laboratory results.

Quality control involves the monitoring of all aspects of sputum microscopy including:

- quality of specimens
- performance of microscopy procedures
- reagents
- equipment
- reviewing of microscopy results

Quality control should be performed on a regular basis and should be applied to:

- laboratory arrangement
- equipment
- reagents and methods
- sputum collection
- smear preparation
- smear staining
- microscopic examination of stained smears
- recording and reporting of results

The keys to successful quality control are:

- Adequately trained, interested and committed staff.
- strict following of practical procedures
- a willingness to admit and rectify mistakes
Effective communication.

Quality control measures that must be in place in all Tuberculosis laboratories include:

1. **LABORATORY ARRANGEMENT AND ADMINISTRATION**

   Work areas, equipment and supplies should be arranged in such a way as to allow for efficient workflow.
   The laboratory should be kept clean at all times.
   Laboratory benches and wall-shelves should be swabbed with an appropriate disinfectant twice daily, in the morning before work starts and in the evening after work is completed.
   Laboratory procedures used routinely should be published in the manual for laboratory technicians.
   Records should be kept well for future reference.

2. **LABORATORY EQUIPMENT**

   Good quality equipment should be used.
   Laboratory equipment should be covered when not in use, to protect the equipment from dust.
   The microscope objectives, condenser and ocular lenses should be kept clean at all times by regularly cleaning them with lens paper

   For more details, refer to Laboratory SOPs

3. **SPECIMENS AND REQUEST FORMS**

   Requests for sputum microscopy should be written by authorized persons. Request forms should be adequately completed, containing all the relevant information about the patient.
   Specimens should be kept separate from the request forms to prevent contamination of request forms. Specimens should be properly labeled. Specimens that cannot be identified should be rejected.
   Leaking and broken specimen containers should be discarded by autoclaving or burning.
4. PREPARATION, STAINING AND EXAMINATION OF SPUTUM SAMPLES

Preparation, staining and microscopic examination of smears should be done according to the laid down procedures contained in the Manual for Laboratory Technicians.

5. RECORDING AND REPORTING OF RESULTS

Laboratory results should be recorded in the TB Laboratory Register according to procedures laid down in the laboratory manual. Laboratory results should be sent out to the treatment unit, within 24 hours of the receipt of the sputum specimen.

6. QUALITY CONTROL OF REAGENTS

Locally or commercially prepared reagents must be tested before they are used for staining sputum smears of patients. Prepare sputum smears from a patient with confirmed AFB and stain with Ziehl-Neelsen/FM staining technique. Sputum smears for quality control purposes can be prepared from confirmed AFB positive sputum samples. The smears are then dried, fixed with heat and stored in a slide box.

7. QUALITY CONTROL OF STAINED SPUTUM SMEARS

The laboratory technician in charge of the Microscopy Centre should keep all AFB positive and negative smears for external quality control. The laboratory supervisor re-examines a proportion of the stained AFB positive and AFB negative smears as part of external quality control. The re-examination of the smears can be done either at the regional reference laboratory or at the respective microscopy centre during laboratory supervisory visits. Re-examination of stained sputum smears at the microscopy centre is the best option as it offers the laboratory supervisor the opportunity to discuss discrepant slides with the laboratory technicians and provide specific
recommendations. The laboratory technicians should implement the recommendations and make appropriate changes.

The supervisor can also specifically examine negative diagnostic slides of patients who have been placed on treatment, and follow-up slides from patients whose initial smears were positive. These two types of slides are more likely to contain errors (false-negative results).

**SUPERVISORY CHECK LIST FOR MICROSCOPY CENTRES**

**NTPS TO REVISE THE CHECK LIST FOR MICROSCOPY CENTRES**

The Senior Laboratory Technologist/Laboratory Technician responsible for the supervision of Sputum Microscopy Centres, should always complete the supervisory check list on every visit and leave a copy of the completed check list at the microscopy centre for record

**SUPERVISORY CHECK LIST**

Laboratory ________________ District_____________ Region____________

Laboratory Supervisor_______________ Date______________

Laboratory Technician/Laboratory Assistant in-charge___________________

**GENERAL ASPECTS**

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<thead>
<tr>
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<td>Laboratory supplies and reagents</td>
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<td>Laboratory equipment</td>
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<td>Laboratory safety measures</td>
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**Laboratory supplies out of stock**

__________________________________________
__________________________________________
TECHNICAL ASPECTS

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<th>Fair</th>
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<td>Smear preparation</td>
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<td>Examination procedures</td>
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<tr>
<td>Recording and reporting of results</td>
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<tr>
<td>Storage of slides for quality control</td>
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<tr>
<td><strong>Proportion of positive smears per month</strong></td>
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<td><strong>TB CULTURE</strong></td>
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<td>Number of specimens submitted for culture</td>
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<td>Date of receipt of culture results</td>
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Recommendations

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Corrective measures taken

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Name and signature of supervisor                      Date

_______________________________________________________________

Name and signature of laboratory technician/technologist    Date