Tuberculosis Training Module for Timor Leste National TB Program
Tuberculosis Training Module for Timor-Leste National TB Programme

Developed by: WHO and Timor-Leste NTP

July 2021
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Message from the Hon’ble Health Minister

Tuberculosis is one of the major public health problems in Timor-Leste. In order to address this problem, the National Tuberculosis Control Program (NTP) was established in 2000 through an NGO, Caritas Dili, and was then handed over to the Ministry of Health under the Communicable Disease Control (CDC) department in early 2006.

The NTP is now fully integrated within the Ministry of Health and works in collaboration with international organizations, national and international NGOs. The NTP receives technical support from the World Health Organization (WHO). The program has been successful in adapting to the rapidly changing circumstances whilst following internationally recommended best practices and standards in tuberculosis control. The country is now moving forward from control to end TB by 2030, and therefore it is important for everyone to support this collective vision of ending TB by proper implementation of the national TB guidelines and strategies.

Tuberculosis Training Module for Timor-Leste National TB Programme (2021) has been developed from the fifth edition of the NTP Manual (Revised TB/DR-TB Guidelines) to give health workers knowledge and skills required in manage Drug-Sensitive TB (DS-TB) and Drug-Resistant TB (DR-TB). Health workers include physicians, nurses, midwives, and other health professionals both in public and private sectors. In this module, participant will learn about – 1) Latent TB Infection and TB Preventive Treatment; 2) Drug-Sensitive TB Infection; 3) Drug-Resistant TB Infection; 4) Monitoring and Evaluating Treatment; 5) Treating TB with Comorbidities; and 6) Basics on Recording and Reporting.

I endorse this latest comprehensive TB Training Modules as an official TB training manual of the Timor-Leste Government and recommend it for use for training of all health professionals, along with the revised NTP Manual (Fifth Edition) 2020.

Dr. Olete Maria Feitas Belo, MPH
Honorable Minister of Health,
Democratic Republic of Timor-Leste
Dili, July 2021
Timor-Leste has the 2\textsuperscript{nd} highest TB incidence rate in the WHO South-East Asia Region after North Korea. According to data released by the WHO in 2020, total TB incidence rate in Timor-Leste is 498 per 100,000 population.

The recent Drug Resistance Survey findings revealed that the prevalence of Rifampicin Resistant (RR) TB among new is 0.6\% (95\% CI 0.2-1.3) and previously treated TB cases is 2.7\% (95\% CI 0.5-8.2) in Timor-Leste are lower than in the surrounding countries of South-East Asia Region. The relatively low prevalence of RR-TB in Timor-Leste is an encouraging finding, but gaps remain in obtaining bacteriological confirmation of TB and routine rifampicin testing among bacteriologically confirmed cases. Drug-Resistant TB (DR-TB) is significantly more difficult to treat compared to Drug-Sensitive TB (DS-TB) with a lower success rate and a higher chance of adverse effects during treatment. Because of this, treatment of DR TB needs to be given by highly trained medical personnel, competent in management of the DR TB regimen. Another challenge faced in fighting TB is latent tuberculosis infection (LTBI). It is estimated that the global prevalence of LTBI is 24.8\%. With reactivation rate of 5-10\%, treating LTBI parallel with active TB, is important.

The TB training modules provide the basic information that has to be learnt. Participants should read the module before the webinar/ Training sessions. The course is intended to be conducted in two consecutive days with allocated time of approximately 6 hours each day. Each topic will be delivered in 45–60 minutes. At the end of each day, participants will have a session focused on discussing and answering topic that has not yet been understood.

WHO is committed to support the NTP and the MoH in its efforts to end TB in the country. In this direction, effective training of all health care professionals with the help of the TB Training Modules, 2021, in line with the revised NTP guidelines (Fifth edition), is of paramount importance.

Dr. Arvind Mathur
World Health Organization Representative in Timor-Leste
Dili, July 2021
Acknowledgement from the Director General Health Services

The Ministry of Health, Democratic Republic of Timor-Leste gratefully acknowledges the contributions from Dr. Erlina Burhan, Member-GDG, WHO and an expert on DR-TB management; Dr Debashish Kundu, Technical Officer, Communicable Diseases, WHO Country Office for Timor-Leste, and Dr Vineet Bhatia, Medical Officer (DR-TB), WHO SEARO, for their valuable support and contributions in developing the TB Training Modules, 2021.

Special thanks to the leadership at the Ministry of Health, Mr Constantino Lopez, the NTP Manager and his team in Dili and health professionals across the municipalities who actively participated in five-day intensive in-country TB Modular Training workshop 15 – 17 June 2021.

The final TB Training modules were reviewed by the WHO SEARO TB Unit and the NTP Team lead by Mr Constantino Lopez. The central NTP team provided background information on the NTP and the health system context in Timor-Leste. Dr Vineet Bhatia and Dr Debashish Kundu reviewed and compiled the final TB Training Modules.

The Ministry of Health gratefully acknowledges the financial support provided from the regional green light committee (r-GLC) mechanism of The Global Fund for TB, AIDS and Malaria (GFATM) for supporting development of training modules as per updated TB (and MDR-TB) guideline for the country, and the continued technical support from the World Health Organization (WHO). I am also delighted to know a Pocketbook on NTP Manual has also been developed for the health professionals in Timor-este.

Dr. Odete da Silva Viegas, Dermatologist
Director-General of Health Service
Ministry of Health RDT
Dili, July, 2021
**Background**

Pulmonary Tuberculosis (TB) is one of the deadliest infectious disease in the world with annual mortality reaching 1.6 million globally. Its incidence was as high as 10 million in 2017. Despite the decreasing number of TB cases globally, many nations still suffer from it. Two-third of these TB cases are suffered by developing countries, thereby putting more burden on the already strained national economies.

Timor-Leste has the second highest TB-incidence rate in WHO South-East Asia Region, after Democratic People’s Republic of Korea. According to the data released by WHO in 2018, total TB incidence in Timor-Leste is 498 per 100 000 population. As a comparison, incidence rate in Indonesia is 316 per 100 000, in India 199 per 100 000, and in China 61 per 100 000 population.

One of the biggest challenges in ending TB is the increasing number of Drug-Resistant TB (DR-TB). It is estimated that 3.1% of all TB patients in Timor-Leste is DR-TB or Rifampicin-Resistant TB (RR-TB).

DR-TB is significantly more difficult to treat compared to Drug-Sensitive TB (DS-TB) with lower treatment success rate and higher chance of adverse effect during course of treatment. Treatment of DR-TB, therefore, needs to be given by medical personnel competent in the management of DR-TB regimen.

Another challenge faced in fighting TB is latent tuberculosis infection (LTBI). It is estimated that the global prevalence of LTBI is 24.8%. With reactivation rate of 5 – 10%, treating LTBI, parallel with active TB, is important in eliminating TB.

This training module is designed to give health workers knowledge and skills required in manage DS-TB and DR-TB. Health workers include physicians, nurses, midwives, and other health professionals both in public and private sectors.

**Objectives**

Objectives of this training module are:

- Increase participants basic understanding of TB
- Increase participants knowledge regarding case definition used in managing TB for recording and reporting
- Help participants identify presumptive cases of DS-TB and DR-TB, and who should be screened
- Train participants how to conduct pre-treatment evaluation
- Train participants in designing TB treatment regimen
- Train participants on how to monitor and evaluate TB treatment.

Outcomes

After attending this training, participants are expected to be able to:

- Participants have a clear idea of the current DS-TB, LTBI and DR-TB situation in Timor-Leste
- Participants understand the diagnosis process of DS-TB, LTBI and DR-TB infections and their management
- Participants understand and able to implement the NTB Guidelines, 2020
- Participants can construct effective shorter all oral drug regimen for DR-TB treatment and manage adverse events that may occur
- Participants understand the target population for LTBI screening.

Facilitator guidelines

Target audience

This training module is intended for health workers who are involved in detecting cases and managing patient with pulmonary tuberculosis. The health workers may be physician, nurses, and midwives. This training course will be conducted primarily through webinar lectures with interactive case discussion and hands on training.

Training materials required

1. Internet connection
2. Computer
How will the course be conducted?

The training modules provide the basic information that has to be learnt. Participants should read the module before the webinar session. The course will be conducted in two consecutive days with allocated time of approximately 6 hours each day. Each topic will be delivered in 45–60 minutes. At the end of each day, participants will have a session focused on discussing and answering topic that has not yet been understood.

Example of webinar schedule is given below:

**Day 1**

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<th>Sl. No.</th>
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<th>Topic</th>
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</thead>
<tbody>
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<td>9.30–10.00</td>
<td>Registration</td>
</tr>
<tr>
<td>2</td>
<td>10.00–10.15</td>
<td>Inauguration/ Opening remarks</td>
</tr>
<tr>
<td>3</td>
<td>10.15–11.00</td>
<td>Diagnosis of Tuberculosis (National TB Guidelines, August 2020)</td>
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<tr>
<td></td>
<td></td>
<td>- Case definition</td>
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<tr>
<td></td>
<td></td>
<td>- TB Diagnostic Algorithm</td>
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<td></td>
<td></td>
<td>- Diagnose and treat DS TB</td>
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<td>4</td>
<td>11.00–12.00</td>
<td>Prevent, diagnose, and treat LTBI</td>
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</tr>
<tr>
<td>5</td>
<td>12.00–13.00</td>
<td>Lunch Break</td>
</tr>
<tr>
<td>6</td>
<td>13.00–14.00</td>
<td>Discrepancy between GeneXpert and Culture results</td>
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<td>7</td>
<td>14.00–15.00</td>
<td>Principles of DR-TB Treatment</td>
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<td></td>
<td></td>
<td>All oral Shorter DR-TB Treatment Regimen</td>
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<td>8</td>
<td>15.00–16.00</td>
<td>Discussion/ Questions &amp; Answers</td>
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<td>2</td>
<td>10.45–11.30</td>
<td>Formulating DR-TB regimen: exercise by case illustration</td>
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<td>3</td>
<td>11.30–12.15</td>
<td>Treatment of DR-TB with HIV co-infection, pregnant mothers, children and other special situations</td>
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<td>4</td>
<td>12.15–13.00</td>
<td>Lunch Break</td>
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<td>5</td>
<td>13.00–14.00</td>
<td>Reading ECG:</td>
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<td>- Basics of ECG</td>
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<td></td>
<td>- Identifying adverse event with ECG</td>
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<tr>
<td>6</td>
<td>14.00–14.45</td>
<td>Monitoring and Evaluation; aDSM</td>
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<td></td>
<td>Time</td>
<td>Activity</td>
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<tr>
<td>7</td>
<td>14.45–15.30</td>
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<td>8</td>
<td>15.30–16.15</td>
<td>Discussion/Questions &amp; Answers</td>
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1 Introduction

It is estimated that about one-fourth of the world population is infected with TB. Although majority of them are asymptomatic, they have a real risk of progressing into active TB infection in most cases within 5 years after the initial infection. The progression is multifactorial. However, the most essential factor is the immune status of the patient. Tuberculosis Preventive Treatment (TPT) is elicited in order to combat this, and is currently a significant part of WHO End TB Strategy. Multiple literatures found the efficacy of TPT at around 60--90%.

Despite this promising solution, it is not ideal to globally test for Latent TB Infection (LTBI), since no gold standards exist for diagnosing LTBI, and it is not always cost effective and the public health impact of wide-testing of LTBI remains unknown. In addition to that, fatal adverse drug reactions (ADRs) should always be considered.

WHO provides a comprehensive solution called “Programmatic Management of TB Preventive Treatment” (PMTPT) that offers the complete package of care for patients with LTBI, starting with the identification of LTBI patients, the administration of TPT and monitoring.

Another essential of way preventing TB is BCG vaccination. This is essential in highly endemic areas to prevent the manifestation of severe TB infection, such as Tuberculous Meningitis and Miliary TB, which are especially prevalent among children.

2 Module objectives

1. Identify LTBI cases in the population
   a. Identify the at-risk population
   b. Able to rule out active TB infection using the correct diagnostic procedures
2. Choose the appropriate TPT regimen for LTBI cases
3. Identify infants that require BCG vaccination.
3 Outline

1. Definition of LTBI and TPT
2. Identifying the population at-risk that should receive LTBI treatment
3. Ruling out active TB infection
4. TPT regimens for treating LTBI
5. BCG vaccine.

3.1 Definition of LTBI and TPT

LTBI is where a patient elicits an immune response towards *Mycobacterium tuberculosis*, however, without any clinical manifestations of TB. There may be a risk where LTBI progresses to active TB disease. This is affected by several factors such as the patient’s immune status (whether immunocompromised or not), demographical, environmental and epidemiological aspects that will be further explained in this module. The aim of detecting LTBI in a patient is to administer TPT, and to prevent the disease progression to active TB infection.

TPT is part of the PMTPT, which includes a complete and coordinated set of actions that aim to detect LTBI patients and treat them accordingly.

3.2 Identifying the population at-risk that should receive LTBI treatment

In order to ease implementation of PMTPT, WHO has grouped the patients who are at-risk:

1. **Adults, adolescents, children and infants with HIV**

All adults and adolescents with HIV, who do not have active TB, should receive TPT, regardless of CD4 counts and viral loads measurements, or whether the patient has already received anti-retroviral treatment (ART) or not, or whether the patient has a history of TB infection or not. Children aged above 12 months with HIV should also receive TPT if active TB has been ruled out, even if the patient has no bacteriologically confirmed-TB household contact, considering that Timor-Leste, in general has a high TB transmission setting based on estimated incidence rates. Infants below the age of 12 months should receive TPT if they were found to have pulmonary TB household contact, if further diagnostic procedures have ruled out active TB disease.

2. **HIV-negative with TB-positive household contact**
In all children below the age of 5 years without HIV, they should receive TPT if they were found to have bacteriologically confirmed pulmonary TB contact, and when further diagnostic procedures have ruled out active TB infection. In all persons above the age of 5 years, including adolescents and adults, they should receive TPT if they were found to have contact with a bacteriologically confirmed pulmonary TB patient, and when further diagnostic procedures successfully ruled out active TB infection.

3. Other HIV-negative groups

Patients included in the “other HIV-negative groups” are patients with a history of Diabetes Mellitus (DM), patients undergoing anti-TNF regimen, alcohol users, tobacco users, patients on dialysis, patients undergoing preparation for organ transplant and patients with silicosis. According to WHO, these patients are not recommended to undergo systematic diagnostic testing for LTBI, and not all should receive TPT. They should be treated case-by-case. However, WHO recommends their close monitoring.

3.3 Ruling out active TB infection

Ruling out active TB infection is a very important step in PMTPT. If the TPT were to be given to a patient with active TB infection, it may cause drug-resistance and worsen the patient’s prognosis.

WHO recommends using the “four-symptom screening” method for patients living with HIV (PLHIV) and for patients that had contact with bacteriologically confirmed pulmonary TB patients. The symptoms to screen are cough, fever, weight loss and night sweats. Any one symptom is enough to progress to the next step in the algorithm. Chest radiography, if available, should be performed but is not necessary for this investigation and the unavailability of the chest radiograph should not withhold treatment as the four symptom screening method offers the highest sensitivity among other symptom-based screening methods, and also has a high negative predictive value (NPV). LTBI testing using IGRA or TST is permissible, however, its unavailability should not hinder the administration of TPT. Chest radiography or IGRA/TST are not prerequisites to diagnosing LTBI. Hence this application can be implemented in Timor Leste, of the facility does not have IGRA/TST nor X-Ray, then the unavailability of these diagnostic tools should not hinder the administration of TPT, especially among children and adult contacts of TB patients, and PLHIV.
Fig. 1. Algorithm for screening adults and adolescents living with HIV for TB

Adults and adolescents living with HIV

Screen people with any of the following symptoms of TB:
- Current cough
- Fever
- Weight loss
- Night sweats

No

Assess for contraindications to preventive treatment:

No
- Give preventive treatment

Yes
- Defer preventive treatment (also screen for TB at follow-up)

Yes

Investigate for TB

No

Other diagnosis

Yes

Not TB
- Follow up and consider preventive treatment

TB
- Treat for TB

Screen for TB regularly, at each encounter with a health worker or visit to a health facility

Every adult and adolescent should be evaluated for eligibility to receive ART. Infection control measures should be prioritized to reduce M. tuberculosis transmission in all settings in which care is provided. Chest radiography can be done if available, particularly for people living with HIV in ART, but is not required to classify patients into TB and non-TB groups.

Contraindications include: active hepatitis (acute or chronic), regular and heavy alcohol consumption and symptoms of peripheral neuropathy. History of B and current pregnancy should not be contraindications for starting preventive treatment.
The simplest way to understand the algorithm given in Fig. 1 is by dividing it into two major groups:

1. **HIV positive patients**

   If the patients were found to have symptoms of pulmonary TB the patient should undergo further investigation to detect the presence of active TB. If the result is positive for active TB infection, then the patient should be treated for TB. If the patient is negative, then the patient should receive TPT if there are no contraindications. In HIV patients without pulmonary TB symptoms, the patient should be given TPT if there are no contraindications. If a diagnosis of other than TB is made, then the patient should receive treatment according to the diagnosis.

2. **Household contact with bacteriologically confirmed pulmonary TB patient**

   Investigation for household contacts is simple. WHO recommends to screen for pulmonary TB symptoms. If the contact has any TB symptoms, then the patient should undergo further investigation for active TB infection. If the result is positive, then the patients should be treated for
pulmonary TB. If the result is negative, the person should receive TPT if there are no contraindications. Patients with household contact and without pulmonary TB symptoms should receive TPT if there are no contraindications.

3.4 TPT regimen for treating LTBI

Overall, there are two choices of TPT regimens. The first one is isoniazid monotherapy for a minimum of 6 months (IPT) and the second one is a two-drug combination of rifamycin (rifampicin or rifapentine) with isoniazid for 3 months (either 3HP or 3HR). Research has found the efficacy and the safety profiles of these two combinations very similar. 3HR or 3HP’s shorter duration is a significant advantage compared to 6 months’ IPT because of ease of compliance, and decreased toxicity. The shorter-duration also is a better fit for Timor-Leste’s condition (Table 1).

**Table 1. TPT regimen for LTBI treatment**

<table>
<thead>
<tr>
<th>Drug regimen</th>
<th>Dose per kg body weight</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid alone, daily</td>
<td>Adults, 5 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td></td>
<td>Children, 10 mg (range, 7–15 mg)</td>
<td></td>
</tr>
<tr>
<td>Daily rifampicin alone for 3–4 months</td>
<td>Adults, 10 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td></td>
<td>Children, 15 mg (range, 10–20 mg)</td>
<td></td>
</tr>
<tr>
<td>Weekly rifapentine plus isoniazid for 3 months (12 doses)</td>
<td>Individuals aged &gt; 12 years: Isoniazid: 15 mg Individuals aged 2–11 years: isoniazid: 25 mg Rifapentine: 10.0–14.0 kg = 300 mg 14.1–25.0 kg = 450 mg 25.1–32.0 kg = 600 mg 32.1–50.0 kg = 750 mg &gt; 50 kg = 900 mg</td>
<td>Isoniazid, 900 mg Rifapentine, 900 mg</td>
</tr>
<tr>
<td>Daily isoniazid plus rifampicin for 3 months</td>
<td>Isoniazid: Adults, 5 mg Children, 10 mg (range, 7–15 mg) Rifampicin Adults, 10 mg Children, 15 mg (range, 10–20 mg)</td>
<td>Isoniazid, 300 mg Rifampicin, 600 mg</td>
</tr>
</tbody>
</table>

Which TPT regimen should be used?

1. **People living with HIV**
The 3HP treatment is the most preferred option. If rifapentine is not available, it may be switched to rifampicin, and hence the patient will follow the 3RH regimen. If that is not available, then the patient should be given 6 months’ IPT.

2. **HIV-negative with bacteriologically positive pulmonary TB household contact**
   
   In this group, any patient above two-year old should be given 3HP or 3HR as first-line TPT. If that is not available, then the patient should be given the 6 months’ IPT. If the patient is in this group and is below two-year old, the 3HR treatment is preferred over the 3HP treatment.

3.5 **BCG vaccine**

The BCG vaccine is very effective where TB is highly endemic, such as the case in Timor-Leste. The vaccination protects the population from the more severe forms of TB manifestations such as miliary TB or tuberculous meningitis, which are highly prevalent in children. Therefore, WHO recommends that every infant should be vaccinated with BCG as soon as possible after birth. However, there are several exceptions:

1. **Neonates born by bacteriologically confirmed pulmonary TB mothers**

   The decision to give BCG vaccine in this group is based on medical history. If the mother has active TB infection and has been treated for a minimum of 2 months, the BCG vaccine can be administered, if the neonate does not exhibit any symptoms. If the the mother was treated for active TB infection for less than 2 months, then the neonate should be further investigated for active TB infection. If the neonate is asymptomatic, they should be given the 3RH TPT regimen, and can receive BCG afterwards.

2. **Infants with HIV**

   BCG vaccine should not be used in children who are known to be HIV-positive because of the increased risk, reported from some settings, of severe and often fatal disseminated BCG disease. On the other hand, detecting HIV in an infant is not a simple matter. This potentially serves a problem, where if BCG vaccine is not given, the infant would have a greater risk of developing a severe manifestation of TB infection. Hence, WHO recommends administering the BCG vaccine in neonates given birth by asymptomatic HIV-positive mothers.
What if the BCG vaccine administration is too late (>6 weeks after birth)? Then further investigation to rule out active TB should be carried out, such as determining possible close contacts to people with active TB infection. If there is contact, the neonate should be given 3RH TPT followed by the BCG vaccine after the regimen is finished.

4 Case study

Case 1

Mr X, aged 31 years with a history of productive cough since two months ago comes to the hospital in order to obtain his medications. The patient has been diagnosed with bacteriologically confirmed pulmonary TB one month ago (and is HIV-negative) and is undergoing the second-month DS-TB regimen (RHZE). He came with his family (his wife Mrs Y aged 29 years and two children aged 4 years and 4 months, respectively.

Question

1. Would you diagnose the wife and the two children as LTBI patients? Why or why not?
2. Please explain how would you rule out active TB infection in the patient’s wife and two children?
3. Would you administer TPT to the wife and two children? What are the possible contraindications and which regimen would you give?
4. What education would you give to the family?

Case 2

Mrs A, aged 27 years, just gave birth to her first child, Baby T. However, the mother was diagnosed with bacteriologically confirmed pulmonary TB one month ago, and an unknown HIV status. Baby T instantly cried after birth, APGAR score of 9/10.

Question

1. Would you consider administering the BCG vaccine to Baby T? Please explain your reasons.
2. Would you consider administering TPT to Baby T? If so, which regimen?
3. When should you give the BCG vaccine to Baby T?

References


MODULE II: DRUG-SENSITIVE TB INFECTION

1 Introduction

TB, which is caused by a bacillus belonging to the *Mycobacterium tuberculosis* complex, affects the lung in more than 85% of cases. Pulmonary TB is an infectious disease mostly transmitted via inhalation of infected droplet nuclei discharged into the air when a patient with untreated sputum smear-positive TB coughs or sneezes. Hence, people living with or coming in close contact with a patient who has undiagnosed or untreated infectious TB (in particular, smear-positive) have the risk of being infected. Identifying individuals with presumptive TB who have symptoms of pulmonary TB early in the course of the disease and ensuring their treatment are important to cut the chain of transmission. The most common symptoms of pulmonary TB that one should be aware of are persistent cough for more than two weeks (usually with sputum, sometimes blood-stained or even hemoptysis), fever, chest pain, night sweats, lethargy, lassitude, loss of appetite and weight loss.

The mainstay of TB diagnosis is sputum smear microscopy. Chest radiography, along with the screening for symptoms, can be used subsequently to improve the pre-test probability of diagnostic test. Since 2014, the Xpert MTB/RIF assay had been used as an additional test for diagnosis of non-resistant and resistant forms of TB. Subsequently, the initial diagnostic test using smear-microscopy will gradually be phase out and replaced with molecular test using GeneXpert. Smear microscopy will be used as follow-up examination for the treated TB patients.

The comprehensive treatment of TB, with regard to many aspects, determines its cure rate. WHO has updated its treatment guideline published in 2017 with some revisions. The prescribing of category II regimen is no longer recommended. Therefore, drug-susceptibility testing (DST) should be conducted in patients who require TB treatment to inform the choice of treatment regimen.

2 Module objectives

1. Understand the case definitions of DS-TB
2. Identify persons who need to be screened for TB
3. Understand the diagnosis step of TB
4. Understand the comprehensive treatment of DS-TB, including its monitoring.

3 Identification of patients with presumptive TB

People who live with or come in close contact with undiagnosed and untreated infectious TB (particularly smear-positive) have the risk of being infected. Hence, they should be identified when they have symptoms of TB early in the course of the disease and ensure their treatment.

A TB presumptive case is any person who presents with symptoms or signs suggestive of TB, particularly cough for more than 2 weeks duration or cough of any duration with other symptoms suggestive of PTB and of contact. All TB presumptive cases must be screened for TB and diagnostic procedures followed as per NTP diagnostic algorithms.

3.1 Case definitions

- **Bacteriologically confirmed TB case**: someone from whom a biological specimen is positive for TB bacillus, by smear microscopy or Xpert MTB/RIF or LPA or culture. This case should be registered and reported, regardless of whether TB treatment has started.

- **Clinically confirmed TB case**: someone who does not fulfil the criteria for bacteriological confirmation, but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment.

TB cases are also classified according to anatomical site of disease, history of previous treatment, drug resistance and HIV status (Table 2).
### Table 2. Classification of TB cases

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anatomical site of disease</strong></td>
<td></td>
</tr>
<tr>
<td>Pulmonary tuberculosis (PTB)</td>
<td>Any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree.</td>
</tr>
<tr>
<td>Extrapulmonary tuberculosis (EPTB)</td>
<td>Any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges.</td>
</tr>
<tr>
<td><strong>History of previous TB treatment (patient registration group)</strong></td>
<td></td>
</tr>
<tr>
<td>New patients</td>
<td>Have never been treated for TB or have taken anti-TB drugs for less than 1 month.</td>
</tr>
<tr>
<td>Previously treated patients</td>
<td>Have received 1 month or more of anti-TB drugs in the past.</td>
</tr>
<tr>
<td></td>
<td>Previously treated patients are further classified by the outcome of their most recent course of treatment as follows:</td>
</tr>
<tr>
<td></td>
<td>• <strong>Relapse</strong>: have previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection);</td>
</tr>
<tr>
<td></td>
<td>• <strong>Treatment after failure</strong>: have previously been treated for TB and whose treatment failed at the end of their most recent course of treatment;</td>
</tr>
<tr>
<td></td>
<td>• <strong>Treatment after loss to follow-up</strong>: have previously treated for TB and were declared lost to follow-up at the end of their most recent course of treatment (These were previously known as treatment after default patients).</td>
</tr>
<tr>
<td></td>
<td>• <strong>Other</strong>: have previously treated for TB, but whose outcome after their most recent course of treatment is unknown or undocumented.</td>
</tr>
<tr>
<td><strong>HIV status</strong></td>
<td></td>
</tr>
<tr>
<td>HIV-positive</td>
<td>Any TB case who has a positive result from HIV testing conducted at the time of TB diagnosis or other documented evidence of enrolment in HIV care, such as</td>
</tr>
</tbody>
</table>
enrolment in the pre-ART register or in the ART register once ART has been started.

| HIV-negative | Any TB case who has a negative result from HIV testing conducted at the time of TB diagnosis or up to 6 months before diagnosis. Any HIV-negative TB patient subsequently found to be HIV-positive should be reclassified accordingly. |

3.2 **Intensified (active) case finding**

The *primary objective* of intensified case finding is to *detect active TB early* by reaching out to those at risk or those who do not have easy access to TB services; this can contribute to two ultimate goals, as given below, and help find missing cases:

- To ensure that active TB is detected early and treatment is initiated promptly, reducing the risk of poor treatment outcomes, health sequelae, and the adverse social and economic consequences of TB for the individual. This reduces suffering, the prevalence of TB, and death from TB
- To reduce TB transmission by shortening of the duration of infectiousness. This reduces the incidence of TB infection and consequently contributes to reduced incidence of TB disease.

A *second objective* is to rule out active disease to help identify people who are eligible for treatment of LTBI.

**Passive case-finding** is conducted on four actions:

- a) a person with active TB experiencing and recognizing symptoms
- b) the person presenting to an appropriate health facility
- c) a health-worker correctly assessing whether the person fulfils the criteria for presumptive TB
- d) the successful application of a complete diagnostic algorithm with sufficient sensitivity and specificity.
3.2.1 **Systematic screening for active TB**

More than 50% of bacteriologically pulmonary TB patients detected in prevalence surveys do not report symptoms suggestive of TB (particularly, cough lasting longer than 2--3 weeks). These individuals are less likely to seek care than people with more prominent symptoms. When they do seek care, they are less likely to be diagnosed. PLHIV, young children, elderly people, people with diabetes, and other groups who have compromised immune systems also face a high risk of poor outcomes from TB treatment, including relapse and death. The risk is augmented when diagnosis is delayed.

Systematic screening for active TB may be beneficial for people who do not seek health care, because they do not have or recognise symptoms or perceive that they have a health problem that warrants medical attention. This can be due to the barriers to accessing care, or for other reasons. It may also avail people seeking health care who do or do not have symptoms or signs compatible with TB and who may not be identified by “passive case-finding” as possibly having TB. **Systematic screening for active TB** is defined as the **systematic identification of people with suspected active TB, in a predetermined target group, using tests, examinations or other procedures that can be applied rapidly**, and it is predominantly provider-initiated.

3.2.2 **Target populations for active case finding in Timor-Leste**

Any group of people within which the prevalence or incidence of TB is significantly higher than in the general population are considered as a risk group of TB. TB risk groups have been classified based on the places where they can be reached for screening (Table 3).
Table 3. Classification of TB risk groups

<table>
<thead>
<tr>
<th>Category</th>
<th>TB risk groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community</td>
<td>• Geographical areas with high TB burden and subpopulations with poor access (poor populations, urban slums, remote areas, refugees, homeless, etc.)</td>
</tr>
<tr>
<td>Hospital outpatient and inpatient departments and primary health care centres</td>
<td>• People previously treated for TB</td>
</tr>
<tr>
<td></td>
<td>• People with an untreated fibrotic lesion</td>
</tr>
<tr>
<td></td>
<td>• PLHIV and people attending HIV testing</td>
</tr>
<tr>
<td></td>
<td>• People with diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>• People with chronic respiratory diseases and smokers</td>
</tr>
<tr>
<td></td>
<td>• Undernourished</td>
</tr>
<tr>
<td></td>
<td>• People with gastrectomy or jejunooileal bypass</td>
</tr>
<tr>
<td></td>
<td>• People with an alcohol or drug-use disorder</td>
</tr>
<tr>
<td></td>
<td>• People with chronic renal failure</td>
</tr>
<tr>
<td></td>
<td>• People with immunocompromising treatments</td>
</tr>
<tr>
<td></td>
<td>• Elderly people</td>
</tr>
<tr>
<td></td>
<td>• People in mental health clinics or institutions</td>
</tr>
<tr>
<td>Residential institutions</td>
<td>• Prisoners and prison staff</td>
</tr>
<tr>
<td></td>
<td>• People residing in shelters</td>
</tr>
<tr>
<td></td>
<td>• Other congregate settings (such as the military)</td>
</tr>
<tr>
<td>Immigration and refugee services</td>
<td>• Immigrants from settings with high prevalence of TB</td>
</tr>
<tr>
<td></td>
<td>• People in refugee camps</td>
</tr>
<tr>
<td>Workplaces</td>
<td>• Health care workers</td>
</tr>
<tr>
<td></td>
<td>• Miners or others who are exposed to silica</td>
</tr>
<tr>
<td></td>
<td>• Other workplaces with high prevalence of TB</td>
</tr>
</tbody>
</table>

4 Diagnosis of TB

Initial examination may include screening for symptoms (screening either for cough lasting for longer than two weeks, or any symptom compatible with TB, including cough of any duration, haemoptysis, weight loss,
fever, or night sweats) or screening with chest radiography. If symptom screening is used initially, then chest radiography can be used as a second step to increase the pre-test probability of the subsequent diagnostic test and reduce the number of people who need to undergo further diagnostic evaluation.

The NTP began to implement the Xpert MTB/RIF assay as an additional test for diagnosis of non-resistant and resistant forms of TB. Smear-microscopy as the initial diagnostic test will gradually be phased out, but will be used for follow-up examination. Universal Drug Susceptibility Testing (U-DST) for all notified PTB cases by GeneXpert testing is proposed from 2020 (WHO Rapid Communication January 2020). LPA is used to detect genetic mutations that render *M. tuberculosis* strains resistant to H, R (first-line LPA, FL-LPA), SLIs and FQs (second-line LPA, SL-LPA). As per WHO recommendation, isoniazid (INH) and rifampicin (RIF) need to be tested for smear-positive cases to avoid transmitting the resistant bacilli.

**Diagnostic algorithms**

The U-DST can be completed in a phased manner---initially doing DST for all notified TB patients by June 2020 (Fig. 3) and expanding Xpert Ultra to all presumptive TB cases by 2021.

---

**Fig. 3. Diagnostic Algorithm for Universal DST of all TB cases by June 2020**
4.1 Moving towards U-DST

According to the current WHO recommendations, molecular tests should be used as the initial screening test for TB. The NTP expects that use of smear-microscopy as the initial diagnostic test will gradually be phased out. The proposed U-DST diagnostic algorithm for all presumptive TB cases is given in Fig. 4.

**Fig. 4.** Diagnostic algorithm in areas with universal Xpert MTB/RIF access (U-DST of all presumptive TB cases by 2021)

Key points on the Diagnostic Algorithm (U-DST for all presumptive TB cases):

- Chest X-ray (preferably with artificial intelligence to read the CXRs) should be used as the initial screening test for people at high risk of TB. Vulnerability assessment tool should be used to identify the risk groups for TB
- Molecular tests should be used as the initial diagnostic test for TB
- For any discordance/ambiguity in Xpert Ultra and/or LPA results, perform Liquid Culture (MGIT DST) on the second sample. Also, for any second-line drug resistance, failing regimen, drug
intolerance, or return after interruption (>1 month), perform extended panel of drug testing by MGIT

- The use of smear-microscopy as the initial diagnostic test could be gradually phased out.

### 4.2 Procedures and interpretation of results for Xpert MTB/RIF test

Samples for the Xpert MTB/RIF assay can be collected at all community health centres (CHCs) in sputum cups used for smear microscopy and culture samples. One sputum specimen per patient should be collected. Patients should be instructed and supported in the collection of a good quality sputum specimen for the collection of smear microscopy samples, as described above.

The Xpert MTB/RIF assay provides diagnostic information with respect to the existence of the TB as well as the existence of resistance to rifampicin. The results are reported as in Table 4.

**Table 4. Classification of Xpert MTB/RIF test results**

<table>
<thead>
<tr>
<th>Result</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>MTB detected; rifampicin resistance not detected</td>
</tr>
<tr>
<td>RR</td>
<td>MTB detected; rifampicin resistance detected</td>
</tr>
<tr>
<td>TI</td>
<td>MTB detected, rifampicin resistance indeterminate</td>
</tr>
<tr>
<td>N</td>
<td>MTB not detected</td>
</tr>
<tr>
<td>I</td>
<td>invalid/no result/error</td>
</tr>
</tbody>
</table>

*Note:* Whenever the test result is reported as "TI" or "I", the test should be repeated until a definite outcome can be observed. All retreatment or failure cases with patients with a "T" results should also provide an additional sputum specimen for LPA testing to exclude INH resistance.

Depending on the Xpert® MTB/RIF® test result, the following actions will take place:

- **MTB not detected:** Proceed to solid culture to confirm whether NTM. If still negative, then discard
- **MTB detected:** Proceed with solid culture
- **MTB and RR detected:** Proceed with solid culture and subsequently process for first-line and second-line DST once culture is positive. Second-line DST will also be conducted on all MTB-positive retreatment cases
- **Test invalid:** Repeat testing from the sediment from the sample which has been stored as back up.
4.3 Procedures and interpretation of results for smear microscopy

Smear diagnosis should be performed for all presumptive TB cases until NTP switches to U-DST by molecular diagnosis. The number of specimens required for diagnosis of bacteriologically confirmed PTB is two, which are collected spot and spot on the same day, preferably in early morning, during the initial patient visit.

One specimen positive out of the two is enough to declare a patient as bacteriologically confirmed TB by any methods – Smear Microscopy/GeneXpert.

To obtain good quality sputum specimens and to prevent contamination, health staff must perform certain tasks before, during and after sputum collection as the following:

1. Before sputum collection: the health worker must explain briefly the reasons for sputum collection to the patients. The clinician should fill the laboratory form completely to be sent along with the sputum samples/smears

2. During sputum collection:
   - The person guiding the patient for specimen collection should stand behind and encourage him/her to cough and produce a good quality specimen
   - Whenever possible, sputum should be collected in an open place or well-ventilated room meant for this purpose
   - Patients are usually more comfortable if they are separated from other persons at the time of sputum collection
   - The patient should be given a sputum container with the laboratory serial number written on its side. When the sputum is being collected at a location other than the DMC, it will not be possible to give a laboratory serial number. In such cases, the patient’s name should be written on the side of the container
   - The person collecting the specimen should demonstrate how to open and close the container
   - The patient should be instructed to inhale deeply (2–3 times), cough out sputum from the chest, spit into the container and then close it
• The person collecting the specimen should make sure that no one stands in front of the patient who is trying to cough up sputum. Sputum should not be collected in closed rooms, toilets or poorly ventilated rooms

• When a patient has only coughed up saliva or has not coughed up at least 2 mL of sputum, the patient should be encouraged to repeat the procedure in order to give a good (mucopurulent) specimen

• If the outside of the container is contaminated with sputum, the person collecting the specimen should wipe the container with disinfectant and destroy the material used to clean the container.

3. After sputum collection:

• If the sputum specimens are to be sent immediately to the laboratory, the person should put the container into a special box meant for transport. If the sputum specimens are not being sent immediately to the laboratory, these should be stored at 2--8 degrees C (in a refrigerator) in the referring health facility. As far as possible, the cold chain must be maintained for molecular and culture-based TB diagnosis

• The person should wash their hands thoroughly with soap and water every time they handle specimens

• Patients should be told when to come back to receive the results of sputum examination

• Alternatively, sputum results may be sent to the referring health facility by hand. The laboratory serial number should be clearly written on the side of the sputum container.

5 Treatment of DS-TB

The objective of TB chemotherapy is to achieve a cure rate of at least 90% of all newly detected bacteriologically confirmed TB patients. Some requirements that must be done to attain the adequate therapy are as follows:

1. An appropriate combination of quality assured anti-TB drugs (which would ensure cure)

2. Prescription in the correct dosage

3. All doses to be taken regularly by the patient

4. Prescribed for period of time (to prevent relapse).
WHO recommendations for TB treatment in the latest revision of the treatment guidelines published in 2017 mentioned some points as follows:

- In patients who require TB retreatment, drug-susceptibility testing should be conducted to inform the choice of treatment regimen. Category II regimen should no longer be prescribed.
- Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment.
- In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6--8 weeks should be used.
- In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used.
- A package of treatment adherence intervention may be offered for patients on TB treatment in conjunction with the selection of a suitable treatment administration option.

### 5.1 Drug used for TB treatment by the NTP

The drugs used by the NTP in the treatment of DS-TB are isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E).

The following combinations are used by the NTP:

- Four fixed drug combination tablets (4FDC) in blister packs (R 150 mg + H 75 mg + Z 400 mg + E 275 mg). This is used in the intensive phase of treatment.
- Two fixed drug combinations (2FDC): R150 mg + H 75 mg. This is used in the continuation phase of treatment.

The dosages of drugs are based on the body weight. The recommended dosages for adults per kilogram of body weight for daily therapy are given in Table 5.

### Table 5. Drug dosage for daily regimens for adults (with range)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose and range (mg/kg body weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>5 (4--6)</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>10 (8--12)</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>25 (20--30)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15 (15--20)</td>
</tr>
</tbody>
</table>
5.2 **Standard treatment regimen**

The NTP uses only one standard treatment regimen for drug-sensitive cases, i.e., 2(RHZE)/4(RH). The prefix before the regimen is the number of months and the suffix is the number of doses in a week. Total duration is six months; two months’ intensive phase (IP) and four months’ continuation phase (CP). Drug dosage and number of tablets given for the treatment are according to body weight (Table 6).

**Table 6. Standard treatment regimen for drug-sensitive cases**

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Intensive phase (2 months) daily</th>
<th>Continuation phase (4 months) daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4FDC: (RHZE)</td>
<td>2FDC: (RH)</td>
</tr>
<tr>
<td></td>
<td>(150 mg + 75 mg + 400 mg + 275 mg)</td>
<td>(150 mg + 75 mg)</td>
</tr>
<tr>
<td>30--39</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>40--54</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>55--70</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>&gt;70</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

5.3 **Organization of treatment and its supervision**

1. **Organization of direct observation of treatment (DOT)**

WHO defines DOT as any person observing the patient taking medications in real time. DOT could be a friend, a relative or a lay person who works as a treatment supervisor or supporter. It can be provided at home, in the community, or in a health facility and by trained lay providers or health-care workers. Health staff should discuss any options of facilities for treatment supervision (DOT centres) with the patient and the patient should select the most convenient place and accessible for DOT. To ensure better treatment outcomes, WHO recommends the use of additional adherence interventions. As the technology develops, video observed treatment (VOT) has been approved as a treatment adherence intervention and could replace DOT when the video communication technology is available. VOT can be appropriately organized and operated by the health-care providers and patients.

2. **Package of combined treatment adherence interventions**

WHO, in its most recent TB Treatment Guidelines, notes that treatment supervision only is not always adequate to guarantee better treatment outcomes. Besides, the combination of treatment supervision with other treatment adherence interventions significantly increase the outcomes for TB patients. The
NTP will use a mixture of types of adherence interventions depending on the specific patient situation (Table 7).

**Table 7. Treatment adherence interventions**

<table>
<thead>
<tr>
<th>Treatment adherence intervention</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient education</td>
<td>Health education and counselling</td>
</tr>
<tr>
<td>Staff education</td>
<td>Education, chart or visual reminder, educational tool and desktop aid for decision-making and reminders</td>
</tr>
<tr>
<td>Material support</td>
<td>Food or financial support such as meals, food baskets, food supplements, food vouchers, transport subsidies, living allowance, housing incentives or financial bonus. This support addresses indirect costs incurred by patients or their attendants in accessing health services and, possibly, tries to mitigate the consequences of income loss related to the disease</td>
</tr>
<tr>
<td>Psychological support</td>
<td>Counselling sessions or peer-group support</td>
</tr>
<tr>
<td>Tracer</td>
<td>Communication with the patient, including home visits or via mobile telephone communication such as SMS or telephone (voice) call</td>
</tr>
<tr>
<td>Digital medication monitor</td>
<td>A digital medication monitor is a device that can measure the time between openings of the pill box. The medication monitor can give audio reminders or send SMS to remind a patient to take medications, along with recording when the pill box is opened.</td>
</tr>
</tbody>
</table>

**3. In-patient versus outpatient treatment**

Hospitalization is usually indicated for a few weeks only for seriously ill TB patients, those with complications of TB (e.g., haemoptysis, spontaneous pneumothorax), and for those TB patients with other serious accompanying diseases. During hospitalization, all drugs must be administered under direct observation by the hospital staff.
5.4 Monitoring during treatment of DS-TB

Regular monitoring of TB patients is conducted to assess their response to therapy, facilitate treatment completion and allow the identification and management of adverse events during treatment. Patient should be monitored each month and asked about the persistence or reappearance of symptoms of TB (including weight loss), symptoms of ADRs, or treatment interruptions. A written record of all medications given, bacteriological response and adverse reactions should be maintained for every patient on the TB Treatment Card.

For all PTB patients treated with first-line drugs, sputum smear microscopy is performed at completion of the intensive phase of treatment and at the end of the treatment. Sputum should be collected when the patient is given the last dose of the intensive phase and continuation phase 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 (Fig. 5).

Fig. 5. Follow-up schedule in sputum-positive and -negative TB patients

Among EPTB patients, sputum microscopy recommended only if patients have cough
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 adherence to treatment was poor;
- poor quality of anti-TB drugs;
- doses of anti-TB drugs given were 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.

It is unnecessary, unreliable and wasteful of resources to monitor the patient by chest radiography.

Additional sputum monitoring is needed for new patients whose sputum smear is positive at the end of the intensive phase (Fig. 6). *If the specimen obtained at the end of the intensive phase (month 2) is smear-positive, an Xpert MTB/RIF assay must be performed.* The main purpose of obtaining samples is to detect drug resistance without waiting until the fifth month to change to appropriate therapy.

**Note:** If a patient is found to harbour 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 multidrug resistant TB (MDR-TB) treatment programme.

**Fig. 6. Sputum monitoring by smear microscopy in new PTB patients**

<table>
<thead>
<tr>
<th>Months of treatment</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<td>obtain Xpert</td>
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<td>MTB/RIF a</td>
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<td>obtain Xpert</td>
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<tr>
<td>MTB/RIF b</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Key:**

[========] intensive phase of treatment (HRZE)

[--------] continuation phase (HR)

- Sputum smear examination

a omit if patient was smear-negative at the start of treatment and at 2 months.

b Smear- or culture-positivity at the end of the intensive phase, 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.
5.5 Recording standardized treatment outcomes

The NTP has adopted the most recent revision of the standard recording and reporting system published by WHO. The new treatment outcome definitions make a clear distinction between two types of patients:

- patients treated for DS-TB

Any patient found to have DR-TB and placed on second-line treatment is removed from the DS-TB outcome cohort. This means that management of the standard TB register and of the second-line TB treatment register needs to be coordinated to ensure proper accounting of the outcomes of treatment. All bacteriologically confirmed and clinically diagnosed TB cases should be assigned an outcome from the list (Table 8) except those with RR-TB or MDR-TB, who are placed on a second-line drug regimen.

Table 8. Treatment outcomes for TB patients (both for DS-TB and DR-TB)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failed</td>
<td>A patient whose treatment regimen needed to be terminated or permanently changed(^a) to a new regimen or treatment strategy.</td>
</tr>
<tr>
<td>Cured</td>
<td>A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy, with evidence of bacteriological response(^b) and no evidence of failure.</td>
</tr>
<tr>
<td>Treatment completed</td>
<td>A patient who completed treatment as recommended by the national policy, whose outcome does not meet the definition for cure or treatment failure.</td>
</tr>
<tr>
<td>Died</td>
<td>A patient who died for any reason before starting treatment 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 two 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 those whose treatment outcome is unknown; however, it excludes those lost to follow-up</td>
</tr>
</tbody>
</table>
Treatment success

The sum of cured and treatment completed.

a Reasons for the change include:

- no clinical response and/or no bacteriological response (see note ‘b’);
- adverse drug reactions; or
- evidence of additional drug resistance to medicines in the regimen.

b “Bacteriological response” refers to bacteriological conversion with no reversion.

- “bacteriological conversion” describes a situation in a patient with bacteriologically confirmed TB where at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only), taken on different occasions at least 7 days apart, are negative.
- “bacteriological reversion” describes a situation where at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only), taken on different occasions at least 7 days apart, are positive either after the bacteriological conversion or in patients without bacteriological confirmation of TB.

5.6 Management of treatment interruption

If a patient misses an arranged appointment to receive treatment, the NTP should ensure that the patient is contacted within a day after missing treatment during the initial phase, and within a week during the continuation phase. It is important to find out the cause of the patient’s absence so that appropriate action can be taken to support patient, and treatment can continue.

The management of patients who have interrupted treatment takes into consideration several factors, each of which, if present, will necessitate further caution and probably additional treatment, as follows:

- The patient is found to be smear- or culture-positive upon returning from treatment interruptions
- Interruption occurs in the intensive, rather than the continuation phase
- Interruption occurs early (rather than later) in the continuation phase
- The interruption is of long duration
- The patient is immunocompromised (living with HIV or another condition)
- The patient had poor response to treatment before the interruption
- Drug-resistant disease is known or suspected.

Xpert MTB/RIF should be performed in addition to smear microscopy for all patients returning after treatment interruption.

6 Childhood TB

Treatment of TB in children: The current recommendation for treatment is using FDC drug, with a dosage of 50H/75R/150Z (Table 9).
Children with suspected or confirmed PTB or TB peripheral lymphadenitis who live in settings with low HIV prevalence and/or low prevalence of isoniazid resistance, and children who are HIV-negative, can be treated with a three-drug regimen (HRZ) for 2 months followed by a two-drug regimen (HR) for 4 months (Source: Rapid advice: treatment of tuberculosis in children. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13).

The number of FDC tablets for different weight categories of children is given in Table 10.

Table 9. The dosages of anti-TB medicines to be used daily for the treatment of TB in children

<table>
<thead>
<tr>
<th>Anti-TB drug</th>
<th>Dose and range (mg/kg body weight)</th>
<th>Maximum dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>10 (7–15)</td>
<td>300</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>15 (10–20)</td>
<td>600</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>35 (30–40)</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 10. Number of fixed-dose combination tablets for different weight categories

<table>
<thead>
<tr>
<th>Weight band</th>
<th>Intensive phase</th>
<th>Continuation phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RHZ 75/50/150</td>
<td>RH 75/50</td>
</tr>
<tr>
<td>4–7 kg</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>8–11 kg</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>12–15 kg</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>16–24 kg</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>25 + kg</td>
<td>Adult dosages recommended</td>
<td></td>
</tr>
</tbody>
</table>

7 Extrapulmonary TB

Extrapulmonary TB (EPTB) diagnosis should be supported with relevant investigations and bacteriological examination. Positive contact history of TB is an indication for suspicion of TB when a patient presents with symptoms. Sputum is negative in most cases of EPTB. However, EPTB along with pulmonary lesions is
classified as PTB for reporting purposes. Symptoms and signs of EPTB usually depend on the site involved (Table 11).

7.1 Common symptoms of EPTB

1) Fever (found in up to 80% of all patients)
2) Weight loss
3) Night sweats
4) Loss of appetite.

Table 11. Symptoms of EPTB by site of disease

<table>
<thead>
<tr>
<th>Sites</th>
<th>Symptoms and signs</th>
</tr>
</thead>
</table>
| Pleural           | 1. Pleuritic chest pain  
2. Shortness of breath  
3. Effusions are usually unilateral |
| Lymphatic         | 1. Most common site of extra-pulmonary disease  
2. Usually presents as a painless swelling, most commonly in the neck. Any nodes can be involved  
3. Adenopathy usually occurs in a single lymph node or chain |
| Central nervous system | 1. Headache, altered mental status, nausea and vomiting  
2. Meningeal signs, with characteristic neck rigidity  
3. Paralysis of the oculomotor nerve, leading to strabismus and/or ptosis (drooping/floppy eyelids) and sometimes convulsions |
| Bone and joint    | 1. Most commonly affects the spine and the weight-bearing joints  
2. Insidious onset of joint pain and swelling  
3. Involvement of the cervical vertebrae may signal its presence by pain in the neck and shoulders. It may lead to rigidity of the neck, a cervical cold abscess behind the sterno-mastoid muscle, and more rarely neurological signs leading to progressive tetraplegia. Involvement of the dorsal vertebrae is indicated by localised back pain, deformity of the spine, and in extreme cases an angulated kyphosis (gibbus): the chief risk is spinal cord compression and paraplegia |
| Genitourinary     | 1. Flank pain  
2. Haematuria |
3. Recurrent urinary tract infections
4. Pyuria

<table>
<thead>
<tr>
<th>Abdominal</th>
<th>1. Abdominal pain and swelling</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2. Abdominal tenderness</td>
</tr>
<tr>
<td></td>
<td>3. Ascites</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disseminated</th>
<th>1. Clinical signs: general deterioration, high fever and dyspnoea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2. Other organs may be affected including: pleural effusion, digestive problems, hepatosplenomegaly and sometimes meningeal signs.</td>
</tr>
</tbody>
</table>

8 Case study

1. Mrs N, 36 years old, 40 kg, complained of cough for three weeks, losing appetite, losing 5 kg-weight in two weeks, and malaise. Previously, she never experienced these complaints. She is a housewife and lives with her husband, one daughter and two sons. She lives in a densely populated house with poor sanitation. Her husband, who accompanies her to the clinic, also complains of coughing for a week.

   a. Who is included in the presumptive case?
   b. What examinations should be done to ensure the diagnosis?
   c. Mrs N is bacteriologically confirmed TB then. What aspects should be considered in managing such TB cases?
1 Introduction

Finding a case of drug-resistant TB (DR-TB) needs more effort and time than drug-sensitive TB (DS-TB). Drug resistance (DR) cannot be detected by sputum-smear microscopy examination. This is because both DR-TB and DS-TB are caused by the same organism, *Mycobacterium tuberculosis*, and hence would look the same under the microscope.

The presence of mycobacterium and their resistance to anti-TB drugs must be identified from the sample to establish a definite DR-TB diagnosis. This can be done by growing mycobacterium culture (using either solid or liquid media), confirming it as *M. tuberculosis* complex (MTBc), and then performing DST. Another option is by conducting WHO endorsed rapid molecular test to amplify mycobacterium DNA and detect the mutations associated with DR.

The first method mentioned, the conventional or phenotypic DST, confirms whether the isolated mycobacterium strain replicates in the presence of specific anti-TB drugs or whether the drugs will delay or halt its growth. The presence of growth means the strain is resistant to that specific drug. Molecular or genotypic testing finds mutations associated with DR in the mycobacterium genome. Currently, WHO endorses molecular tests, such as Xpert MTB/RIF and line-probe assay (LPA) for faster confirmation.

After the establishment of DR, the physician in DR-TB management centre determines the appropriate drugs to be included in the patient’s regimen. Regimen design is crucial so that patients with DR-TB take all the appropriate drugs in the regimen correctly to increase the probability of being cured and reduce the risk of an unfavourable outcome. Once patients have been diagnosed with DR-TB, correct treatment represents the best opportunity for them to be cured. This is especially true for patients with MDR/extensively drug-resistant (XDR)-TB that have high mortality rates, even if treated correctly.

Untreated TB patients are usually infectious because they may release tubercle bacilli into the air by coughing and/or sneezing. Close contacts of patients with DR-TB should be evaluated as they may already be infected with a DR strain of TB when they breathe in resistant tubercle bacilli. The
longer that people with DR-TB remain untreated, the greater the probability that they will infect their close contacts, just like people with DS-TB. Early recognition of presumptive cases of DR-TB should be prioritised by every health care facility. It is crucial to detect DR-TB and treat using the appropriate drugs because first-line drugs are no longer effective in treating it. If patients with DR-TB are not detected and treated correctly with second-line medicines, they will have poor treatment outcomes, spread DR-TB in their communities and the resistance of bacilli harboured by such patients may amplify overtime.

2 Module objectives

1. Understand the case definition of DR-TB
2. Identify presumptive cases of DR-TB and who should be screened
3. Conduct pre-treatment evaluation
4. Design DR-TB treatment regimen
5. Investigate close contacts of DR-TB patients.

2.1 Understand the case definition of DR-TB

Cases are classified into categories based on the result of the Xpert MTB/RIF assay and any confirmatory DST results received from the national reference laboratory (NRL).

- **Rifampicin resistance (RR-TB):** resistance to rifampicin detected in the Xpert MTB/RIF assay
- **Isoniazid resistance (HR-TB):** resistance to H (based on DST results from the NTRL)
- **Multidrug resistance (MDR-TB):** resistance to at least both isoniazid and rifampicin (based on DST results from the NRL)
- **Pre-extensively drug resistance (PreXDR-TB):** resistance to any fluoroquinolone in addition to MDR (based on DST results from the NRL)
- **Extensively drug resistance (XDR-TB):** resistance to any fluoroquinolone AND to at least one of the Group A drugs*, in addition to MDR (based on DST results from the NRL).
2.2  Identify presumptive DR-TB cases and risk category factors

2.2.1  Criteria for identifying

Presumptive DR-TB cases are cases fulfilling one of the following criteria:

- TB patients who are contacts of DR-TB
- Previously treated TB patients
- TB patients found positive on any follow-up sputum examination during treatment with first-line drugs
- Paediatric TB non-responders
- New TB patients with HIV coinfection.

The risk factors for DR-TB are divided into high-and low-risk categories.

High risk

- History of unstandardized anti-TB treatment and use of quinolone and second-line injection drug for at least 1 month
- Failed treatment in category 1
- Fail to convert in category 1
- Relapse case in category 1
- Patient returning after loss to follow-up
- Presumptive TB with history of close contact with DR-TB patient
- Coinfection TB-HIV which doesn’t respond, either clinically or bacteriologically, to anti-TB treatment.

For high-risk group, patients should check for rapid molecular test/RMT (Xpert) and if the test revealed:

- TB and rifampicin resistant, then the diagnosis is RR-TB, and hence do first and second-line DST
- TB and rifampicin sensitive, then the diagnosis is DS-TB
- Negative, then the diagnosis is not TB
• Invalid result/error and indeterminate to be re-examined and Xpert to be repeated with the second sputum/specimen collected. If the result is rifampicin resistant do culture and DST. If the result is rifampicin sensitive, then the diagnosis is DS-TB. However, if the result revealed negative, diagnosis is not TB, and if the second result is invalid or indeterminate, Xpert test should not be repeated.

Table 12. Steps to be taken in high-risk groups

<table>
<thead>
<tr>
<th>Result of 1st XPERT</th>
<th>Results 2nd XPERT</th>
<th>Final results</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invalid/no result/error</td>
<td>Rifampicin sensitive</td>
<td>Rifampicin sensitive</td>
<td>DS-TB</td>
</tr>
<tr>
<td>Rifampicin resistant</td>
<td>Rifampicin resistant</td>
<td>Rifampicin resistant</td>
<td>DR-TB</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Other treatment</td>
<td></td>
</tr>
<tr>
<td>Indeterminate</td>
<td>Indeterminate</td>
<td>Therapy by clinical judgement</td>
<td></td>
</tr>
<tr>
<td>Invalid/no result/error</td>
<td>Invalid/no result/error</td>
<td>Invalid/no result/error</td>
<td>Therapy by clinical judgement</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>Rifampicin resistant</td>
<td>Rifampicin resistant</td>
<td>DR-TB</td>
</tr>
<tr>
<td>Rifampicin sensitive</td>
<td>Rifampicin sensitive</td>
<td>Rifampicin sensitive</td>
<td>DS-TB</td>
</tr>
<tr>
<td>Negative</td>
<td>Indeterminate</td>
<td>Therapy by clinical judgement</td>
<td></td>
</tr>
<tr>
<td>Indeterminate</td>
<td>Indeterminate</td>
<td>Therapy by clinical judgement</td>
<td></td>
</tr>
<tr>
<td>Invalid/no result/error</td>
<td>Indeterminate</td>
<td>Therapy by clinical judgement</td>
<td></td>
</tr>
</tbody>
</table>

Low risk
Presumptive DR-TB in **low-risk** category are:

- Presumptive TB
- Children with presumptive TB
- TB in diabetes mellitus
- Presumptive TB with HIV positive.

Steps to be taken by the clinical management committee of DR-TB in low-risk groups for repeating Xpert (Re-examine – Second Xpert) are given in Table 13.

**Table 13. Steps to be taken in low-risk groups**

<table>
<thead>
<tr>
<th>Result of 1st XPERT</th>
<th>Results 2nd XPERT</th>
<th>Final results</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin resistant</td>
<td>Rifampicin resistant</td>
<td>Rifampicin resistant</td>
<td>DR-TB</td>
</tr>
<tr>
<td>Rifampicin sensitive</td>
<td>Rifampicin sensitive</td>
<td>Rifampicin sensitive</td>
<td>DS-TB</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>MTB positive</td>
<td>MTB positive</td>
<td>DS-TB</td>
</tr>
<tr>
<td>Invalid/no result/error</td>
<td>MTB positive</td>
<td>MTB positive</td>
<td>DS-TB</td>
</tr>
<tr>
<td>Invalid/no result/error</td>
<td>Rifampicin resistant</td>
<td>-</td>
<td>Therapy by clinical judgement</td>
</tr>
<tr>
<td>Rifampicin sensitive</td>
<td>Rifampicin sensitive</td>
<td>Rifampicin sensitive</td>
<td>DS-TB</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Other treatment</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>MTB positive, Indeterminate (Rif?)</td>
<td>MTB positive, Indeterminate (Rif?)</td>
<td>DS-TB</td>
</tr>
<tr>
<td>Invalid/no result/error</td>
<td>Invalid/no result/error</td>
<td>Invalid/no result/error</td>
<td>Therapy by clinical judgement</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>Rifampicin Resistant</td>
<td>Rifampicin resistant</td>
<td>DR-TB</td>
</tr>
<tr>
<td>Rifampicin Sensitive</td>
<td>Rifampicin sensitive</td>
<td>DS-TB</td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>Indeterminate</td>
<td>DS-TB</td>
<td></td>
</tr>
<tr>
<td>Indeterminate</td>
<td>Indeterminate</td>
<td>DS-TB</td>
<td></td>
</tr>
<tr>
<td>Invalid/no result/error</td>
<td>Indeterminate</td>
<td>DS-TB</td>
<td></td>
</tr>
</tbody>
</table>
2.3 Conduct pre-treatment evaluation

2.3.1 Pre-treatment evaluation

The initial assessment comprises: a medical examination, sputum smear microscopy, Xpert testing, SL-LPA (if available), culture and DST for first-line (H and R) and second-line (FQs and SLIs) anti-TB drugs, chest X-ray, audiogram, blood tests (creatinine, potassium, glucose, transaminase, blood cell count), pregnancy test for women of childbearing age and HIV testing. An electrocardiogram (ECG) should be performed at treatment initiation and repeated a after 15 days. An initial home visit also needs to be done to verify the address and meet the family members. Since the drugs used for the treatment of DR-TB are known to produce adverse effects (AEs), a proper pre-treatment evaluation is essential to identify patients who are at increased risk of developing such AEs. These include screening for diabetes mellitus, liver disease, drug or alcohol use, mental illness, renal insufficiency, thyroid function, pregnancy and lactation. Those DR-TB presumptive cases, and cases who have a history of high-risk behaviour in relation to HIV infection, a sexually transmitted disease, or any HIV-related opportunistic infection (OI), will be offered a referral to the nearest voluntary counselling and testing centre (VCTC). Management of patients with any of these conditions is likely to vary from the standard practice depending on the condition and may require more intense monitoring. Patients should receive counselling on the nature and duration of treatment, the need for regular treatment, possible side-effects of these drugs, and the consequences of irregular treatment or premature cessation of treatment. It is advisable to involve close family members during the counselling, since family support is an essential component in treatment management. Patients should be advised to report if they experience any unusual problem. Female patients should receive special counselling on family planning. It is preferable to screen all close family contacts of patients for the presence of chest and extrapulmonary symptoms as per NTP norms. A DOT provider (who can either be a health care worker, a community worker, or a community volunteer) should be identified for the patient in consultation with the patient. The DOT centre can be either at a health post or in the community. The DOT provider should be given training for drug administration and to identify possible AEs during treatment, and also the frequency of follow-up.
2.4 Design DR-TB regimen

2.4.1 Deciding on treatment
The DR-TB committee (a DR-TB clinical management committee) will review the patient’s details, including previous treatment history, LPA/DST result, and concurrent illnesses, and decide to treat with a DR-TB regimen. If the committee decides on treatment with a DR-TB regimen, the patient is admitted to the designated in-door facilities (HNGV/Klibur Domin), counselled about the treatment, treatment book is opened and treatment initiated. In the initial 6 months, all-oral DR-TB treatment duration as criteria for failure, and the time point to reduce the frequency of follow-up cultures if the patient is responding well to the treatment regimen.

The NTP is aiming for a fully ambulatory treatment delivery model for all DR-TB patients. However, this requires the availability of facilities for monitoring the patients, which must be ensured by the programme. In the interim, until all of these facilities are available, patients should be admitted into Klibur Domin (DR-TB Centre) for a period of 1 to 3 months.

2.4.2 Drugs used to treat DR-TB and principles of treatment
Following a thorough assessment of relative benefits to harms, recommendations were made for each medicine and published in the revised guidelines on DR-TB treatment\(^1\) in early 2019. Drugs were classified into three groups (Table 14).

\(^1\) WHO consolidated guidelines on drug-resistant tuberculosis treatment, WHO/CDS/TB/2019.3.
Table 14. Grouping of medicines recommended for the treatment of RR-TB and MDR-TB

<table>
<thead>
<tr>
<th>Groups</th>
<th>Steps</th>
<th>Medicines</th>
<th>Abbreviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Include all three medicines in the regimen, if no contraindication</td>
<td>Levofloxacin OR Moxifloxacin Bedaquiline Linezolid</td>
<td>Lfx /Mfx Bdq Lzd</td>
</tr>
<tr>
<td>B</td>
<td>Add one or both medicines</td>
<td>Clofazimine Cycloserine OR Terizidone</td>
<td>Cfz Cs, Trd</td>
</tr>
<tr>
<td>C</td>
<td>Add to complete regimen and when medicines from Groups A and B cannot be used</td>
<td>Ethambutol Delamanid Pyrazinamide Imipenem-cilastatin OR Meropenem Amikacin (OR Streptomycin) Ethionamide OR prothionamide P-aminosalicylic acid</td>
<td>E Dlm Z Imp,Cln, Mpm Am(S) Eto , Pto PAS</td>
</tr>
</tbody>
</table>

**Important notes:**

1. The recommended duration of use for Bdq is 6 months and its use beyond this duration is “off label”
2. Bdq can be used in children 6 years and above
3. Dlm can be used in children 3 years and above
4. Bdq and Dlm can be used together to complete the regimen - such use is to be considered as “off-label”
5. Lzd preferably to be used for the whole duration of treatment or less if not tolerated
6. If DST to Z, E shows susceptibility, can be part of the regimen
7. Imipenem should always be used with Amox-Clv

8. Use Am and S; only to be used, if only susceptible and under close monitoring, preferably in patients who are 18 years or above and when a regimen cannot be designed with sufficient drugs from Groups A and B, and other Group C drugs.

2.4.3 Principles of MDR-TB treatment and regimen construction

The following general principles and precautions related to DR-TB treatment have been taken into account for designing the NTP’s standardized DR-TB regimen in line with WHO’s 2019 DR-TB guidelines:

- It is recommended by WHO that treatment should start with at least four medicines likely to be effective and that at least three agents are continued for the rest of the treatment after bedaquiline is stopped
- Possibly all three Group A agents (Lfx/Mfx, Bdq and Lzd) and at least one Group B agent (Cfz or Cs) should be part of the regimen and if only one or two Group A agents are used, then both Group B agents are to be included in the regimen
- If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it
- Bdq use beyond 6 months is considered as “off label” and it should be case by case keeping in view treatment response and the number of effective drugs on board after Bdq is stopped
- The use of three cardiotoxic drugs (Bdq, Dlm and Cfz) in combination should be with caution and with close monitoring. However, recent data show that combined use of Bdq and Dlm is safe, and QTcF interval with co-administration of both drugs is clinically modest
- The use of Lzd for the whole duration is associated with better treatment outcomes and lower mortality, but is expected to cause toxic effects in a significant number of patients. The neurological toxicity is associated with duration, while hematological toxicity/myelosuppression is dose-related
- For Lzd use in the regimen, baseline assessment by blood CP and neuropathy screening should be done and if contraindicated, should not be part of regimen or, if possible, with the lower dose of 300 mg daily or 600 mg on alternative days.

2.4.4 Standardized RR/MDR-TB treatment regimen and treatment duration

All patients with MDR/RR-TB, including those with additional resistance to fluoroquinolones, stand to benefit from effective all-oral treatment regimens, either shorter or longer, implemented under programmatic conditions:

- MDR/RR-TB patients with extensive TB disease, severe forms of ETB those with resistance to FQ, or who have been exposed to treatment with second-line drugs will benefit from an individualized longer regimen designed using WHO priority grouping of medicines recommended in 2018. Proposed standardized regimen for all-oral longer regimen:

\[ 6_{\text{months}} \text{ Lfx/Bdq/Lzd/Cfz /Z, } 12_{\text{months}} \text{ Lfx/Cs/Cfz.} \]

The following principles for the determination of treatment duration apply:

- A total minimum duration of 18 months depending on the patient’s response
- A treatment duration of 16 months is recommended after culture conversion
- The treatment duration may be modified as per the patient’s response to treatment
- Prolonging BDQ beyond 6 months and total treatment duration longer than 20 months may be considered in patients with additional resistance or late converters, extensive disease, and other risk factors for failure or relapse of treatment.

- For MDR/RR-TB patients without previous exposure to second-line treatment (including bedaquiline) without FQ resistance and no extensive TB disease or severe ETB, the preferred treatment option is a shorter, all-oral, bedaquiline-containing regimen using seven drugs:
Regimen for all-oral shorter treatment is proposed as below:¹

4 - 6 months: Lzd (2 months only)/ BDQ (total 6 months)/ Lfx / Cfz / Z / E (total 6 months)

continued by

5 months: Lfx/ Cfz/ Z/ E.

¹ regimen under operational research condition

Linezolid will only be administered during the first two months. Bedaquiline is included to replace injectables for a duration of six months. Levofloxacin is included to replace moxifloxacin. The total duration of all-oral short treatment is 9–11 months. All treatment should be delivered under WHO-recommended standards, including patient-centred care and support, informed consent when necessary, principles of good clinical practice, active drug safety monitoring and management, and regular patient monitoring to access regimen effectiveness (Fig. 7).

Fig. 7. Exclusion criteria to be followed for shorter, all-oral, bedaquiline-containing regimen

- Preference by the clinician and patient for a longer MDR-TB regimen
- Confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance)
- Exposure to one or more 2nd line medicines in the shorter MDR-TB regimen for >1 month (unless susceptibility to these 2nd line medicines is confirmed)
- Intolerance to medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)
- Pregnancy
- Disseminated, meningeal or central nervous system TB
- Any extrapulmonary disease in PLHIV
- One or more medicines in the shorter MDR-TB regimen not available

2.4.5 Treatment of RR/MDR-TB with additional resistance (Pre-XDR and XDR)

A pre-XDR- and XDR-TB treatment regimen is not for a failing second-line regimen, but when resistance is detected at the start of the treatment.
• If a resistance to a Group A drug is found, the particular drug should never be included into the regimen.

• A drug with high early bactericidal activity, such as linezolid, should be included to protect Bdq and to prevent resistance amplification. Lzd should only be used in the intensive phase because of its toxicity, and its use should be carefully evaluated if given throughout treatment. Possible alternatives are meropenem or imipenem/cilastatin plus amoxicillin/clavulanate. These need an implantable venous access device, which is problematic in most endemic settings. Another possible option is amikacin, if still susceptible.

• A companion drug with bactericidal activity, such as delamanid, should be included to protect the action of the other drugs and to prevent resistance amplification. This is presently an off-label use. Possible alternatives are meropenem or imipenem/cilastatin plus amoxicillin/clavulanate, if available.

• A sterilizing drug, such as clofazimine, to prevent relapse after treatment cessation. In the case of resistance to clofazimine, cycloserine is an option. However, its low sterilizing activity must be taken into account. Pyrazinamide may be added because of its sterilizing activity.

• High-dose isoniazid should also be added in the intensive phase for its bactericidal properties, except in the case of confirmed high H resistance (mainly double katG and inhA mutations or katG deletion).

Prolonged use of bedaquiline with concomitant use of delamanid is considered off-label, as both drugs have been registered to be used for a maximum duration of 24 weeks. Data on the simultaneous use of the two drugs in the same patient remains limited, but the use of the two drugs has proved effective and safe to date. Nevertheless, the risk of creating additional drug resistance with a weak regimen is very real and the proposed approach seems justified. An all-oral individualized regimen is preferred whenever possible.

As an example, a regimen may be composed of as follows:

Bdq-Lzd-Hh-Dlm-Cfz-Z for a total duration of 18–20 months.
In the case of high H resistance:

Bdq-Dlm-Lzd-Cs-Cfz-Z for a total duration of 18--20 months.

2.4.6 Management of INH (Hr)-TB

The significant number of Hr-TB individuals who remain undiagnosed and inappropriately treated cannot be ignored. Moreover, in recent years based on WHO recommendations, most countries (including TLS) are eliminating the Cat. 2 TB treatment and using the following as operational ways to treat patients:

- Patients with a history of previous treatment who have pan-susceptible disease to be treated with first-line drugs
- Patients with mono- or poly-resistance (other than RRTB) should be treated with appropriate regimens
- Patients with RR/MDR-TB should be treated with second-line therapy.

2.4.6.1 Diagnosis of Hr-TB

Hr-TB can be diagnosed using first-line LPA and phenotypic conventional DST to first-line drugs. It has been observed that such cases are now being increasingly reported and early detection of such cases is crucial. The following are suggested to test for Hr-TB;

1. Close contacts of patients who are being treated with mono/poly DR-TB should be tested both by Xpert and by first-line LPA if Xpert shows no RR-TB
2. DS-TB retreatment patients when tested with Xpert and result is TB with no RR, such patient should be tested by LPA first-line
3. In DS-TB non-converters when Xpert shows TB with no RR
4. Clinicians should request testing first-line drugs by liquid/solid DST, where LPA is not available or non-interpretable and patient response to treatment is poor.

Once mono and poly DR--TB (other than RR--TB) is reported, it is also imperative to request SL LPA to exclude resistance to FQs.
2.4.6.2 Treatment of Hr-TB

In line with WHO recommendations, in practice the following situations apply at the field level:

1. Hr-TB is confirmed before TB treatment is started: treatment with the (H)REZ-Lfx is started immediately. If the diagnosis is strongly presumed (e.g. close contacts of a confirmed Hr-TB source case) but results of drug susceptibility testing are still pending, the regimen may be introduced. Should drug susceptibility test results taken at the start eventually show susceptibility to isoniazid, then levofloxacin is stopped, and the patient continues treatment to complete a 2HREZ/4HR regimen.

2. Hr-TB is confirmed after the start of treatment with 2HREZ/4HR regimen: This includes patients who had undiagnosed isoniazid resistance at the start or who developed isoniazid resistance later while on first-line regimen treatment. In such cases, rapid molecular testing for rifampicin resistance must be done (or repeated). Once rifampicin resistance is excluded, a full 6-month course of (H)REZ-Lfx is given. The duration is driven by the need to give levofloxacin for 6 months, which usually implies that the companion first-line medicines are taken for longer than this.

3. If rifampicin resistance is detected, the patient needs to be started on a recommended MDR-TB treatment regimen.

It is imperative to perform Xpert in all mono and PDR cases before enrolling them on treatment. This excludes cases with R, RZ, RZE resistance as such cases require full MDR-TB treatment. Likewise, it is essential to always use Xpert MTB/RIF at months 0, 2 and 3, and if rifampicin resistance is found switch to full MDR-TB treatment.

2.4.7 Drug dosages for Hr-TB regimen

Drug dosages for Hr-TB regimen as per different age groups based on weight bands are given in Table 15.
Table 15. Drug dosages for Hr-TB regimen with 4-drug FDC (RHZE) - Adults

<table>
<thead>
<tr>
<th>Weight bands in adults</th>
<th>4-drug adult FDC RHZE-150/75/400/275*</th>
<th>Levofloxacin 250 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>35–49 kg</td>
<td>3 tablets</td>
<td>3 tablets</td>
</tr>
<tr>
<td>50–64 kg</td>
<td>4 tablets</td>
<td>4 tablets</td>
</tr>
<tr>
<td>65–75 kg</td>
<td>5 tablets</td>
<td>4 tablets</td>
</tr>
</tbody>
</table>

*patients <35 kg may receive 3 tablets/day and patients >75 kg may receive 6 tablets/day if they tolerate this dose.

Table 16. Drug dosages for Hr-TB regimen with 3-drug FDC (RHZ) - Children

<table>
<thead>
<tr>
<th>Weight bands in children*</th>
<th>3-drug pediatric FDC RHZ- 75/50/150</th>
<th>Ethambutol 100 mg</th>
<th>Levofloxacin 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>4–7 kg</td>
<td>tablet</td>
<td>1 tablet</td>
<td>1 tablet</td>
</tr>
<tr>
<td>8–11 kg</td>
<td>2 tablets</td>
<td>2 tablets</td>
<td>2 tablets</td>
</tr>
<tr>
<td>12–15 kg</td>
<td>3 tablets</td>
<td>3 tablets</td>
<td>3 tablets</td>
</tr>
<tr>
<td>16–24 kg</td>
<td>4 tablets</td>
<td>4 tablets</td>
<td>4 tablets</td>
</tr>
</tbody>
</table>

*In children weighing 25 kg or more, the adult schedule shown in the previous section is followed.

If levofloxacin 100 mg dispersible tablet is not available, the 250 mg tablet can be used with 6(H)REZ in children aged 0–14 years, based on a slightly different weight band from the above, as given in Table 17.
Table 17. Drug dosages for Hr-TB regimen for children aged 0–14 years based on weight band

<table>
<thead>
<tr>
<th>Weight</th>
<th>Levofloxacin 250 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>5–6 kg</td>
<td>½ tablet/day</td>
</tr>
<tr>
<td>7–9 kg</td>
<td>¾ tablet/day</td>
</tr>
<tr>
<td>10–15 kg</td>
<td>1 tablet/day</td>
</tr>
<tr>
<td>16–23 kg</td>
<td>1.5 tablets/day</td>
</tr>
<tr>
<td>24–30 kg</td>
<td>2 tablets/day</td>
</tr>
<tr>
<td>31 kg +</td>
<td>Follow adult schedule (up to 1 g/day)</td>
</tr>
</tbody>
</table>

2.4.8 MDR-TB in children

2.4.8.1 Diagnosis

- It may take several weeks from the time a child first presents with signs and symptoms of TB and the receipt of test results, during which time a child’s condition can rapidly deteriorate
- Thus, it is important to consider initiating MDR-TB therapy in the absence of bacteriologic confirmation in line with a consultation with a paediatrician expert in TB/MDR-TB
- GeneXpert and culture in liquid media should be prioritized in children
  - Collecting the respiratory specimen at optimal times is important to enhance the yield, e.g., early morning fasting gastric aspirate, before mobilization; induced sputum after fasting 2–4 hours; expectorated sputum early morning
  - Of note, sputum (induced or expectorated) should be minimum of 3 mL, gastric aspirate 5 mL, gastric lavage 10 mL, BAL 3 mL, nasopharyngeal aspirate 2 mL
  - Extrapulmonary samples that are useful for testing with Xpert for diagnosis in children that can be obtained at any time, e.g., CSF, stool, urine (use of the urinary lipoarabinomannan (LAM) may be a useful test to diagnose TB in children or individuals living with HIV with low CD4 counts)
  - For testing purposes, CSF 2 mL and stool 5 g are enough
• Serosal fluids including pleura, pericardium, peritoneum and synovium may also be helpful in diagnostics, but the bacteriological yield is higher in tissues than fluids.
• TB must be included in the differential diagnosis list of any child with a persistent non-settling cough or fever, weight loss/failure to thrive, or focal findings that are suggestive of TB, such as lymphadenitis, spinal deformities, ascites, and joint effusions. Danger signs of possible meningitis include lethargy/sleepiness, loss of consciousness and seizures.
• MDR-TB in children can either be confirmed (they have clinical TB disease and a sample taken from the child shows MDR-TB) or clinically diagnosed (the child has clinical TB disease and has risk factors for drug resistance).

2.4.8.2 Treatment
• The treatment regimens for children are identical to those for adults
• Use of pediatric formulations where available should be preferred
• For drugs that do not have pediatric formulation, currently available tablets may be cut into fragments and crushed, or capsules may be opened and the contents fractioned. The drugs may be mixed with small amounts of liquid or soft food.
• The treatment regimens for children are as follows:
  
  \[ 6 \text{Lfx/Bdq/E/Cfz}, 12 \text{Lfx/Cs/Cfz} \text{ (>=6 years)} \]
  
  \[ 6 \text{Lfx/Dlm/E/Cfz}, 12 \text{Lfx/Cs/Cfz} \text{ (<6 years)}. \]

2.4.9 DR-TB in pregnant women and women of childbearing age
• Pregnancy is not a contraindication to treatment
• The decision whether or not to treat should be based on an assessment of the risks and benefits for the mother and the fetus
• If treatment is deferred: high risk of serious worsening of the mother’s general condition during pregnancy, increased risk of abortion, low birth weight, and risk of disseminated TB for the baby
• For women of childbearing age:
  ▪ Do pregnancy test before treatment initiation
  ▪ Advise against pregnancy during RR-TB treatment: Encourage the use of contraceptives
  ▪ During treatment follow-up visits:

61
• Always enquire about amenorrhea
• Perform pregnancy tests when needed.
2.4.10 **Dosages of medicines by weight band used in MDR-TB regimens in adults and children**

The dosing of medicines used in second-line MDR-TB regimens in patients as per their weight bands are given in Tables 18--19.

**Table 18.** Dosing of medicines used in second-line MDR-TB regimens in patients older than 14 years

<table>
<thead>
<tr>
<th>Group</th>
<th>Medicine</th>
<th>Weight-based daily dose</th>
<th>Formulation</th>
<th>30–35 kg</th>
<th>36–45 kg</th>
<th>46–55 kg</th>
<th>56–70 kg</th>
<th>&gt;70 kg</th>
<th>Usual daily dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Fluoroquinolones</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Levofloxacin</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>250 mg tab</td>
<td></td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>1.5 g</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>500 mg tab</td>
<td></td>
<td>1.5</td>
<td>1.5</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>750 mg tab</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>400 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>standard dose</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>400 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>high dose</td>
<td></td>
<td>1 or 1.5</td>
<td>1.5</td>
<td>1.5 or 2</td>
<td>2</td>
<td>2</td>
<td>800 mg</td>
<td>as used in the standardized shorter MDR-TB regimen</td>
</tr>
<tr>
<td></td>
<td>Bedaquiline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>400 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 mg tab</td>
<td></td>
<td>4 tabs od for first 2 weeks; then 2 tabs od M/W/F for 22 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td></td>
<td></td>
<td>(&lt;15 y)</td>
<td>(&lt;15 y)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1.2 g</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>600 mg tab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Clofazimine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 mg cap or tab</td>
<td></td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>100 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 mg cap or tab</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>100 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cycloserine or</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>terizidone</td>
<td></td>
<td></td>
<td>10–15 mg/kg</td>
<td>250 mg cap</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Group</td>
<td>Medicine</td>
<td>Weight-based daily dose</td>
<td>Formulation</td>
<td>Weight bands for patients older than 14 years</td>
<td>Usual upper daily dose</td>
<td>Comments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
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<td>--------------------------------------------------------------------------</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ethambutol</td>
<td>15–25 mg/kg</td>
<td>400 mg tab</td>
<td>30–35 kg: 2, 36–45 kg: 2, 46–55 kg: 2, 56–70 kg: 3, &gt;70 kg: 3</td>
<td>3</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Delamanid</td>
<td>50 mg tab</td>
<td>2 bd</td>
<td>30–35 kg: 2, 36–45 kg: 2, 46–55 kg: 2, 56–70 kg: 3, &gt;70 kg: 3</td>
<td>200 mg</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>20–30 mg/kg</td>
<td>400 mg tab</td>
<td>30–35 kg: 3, 36–45 kg: 4, 46–55 kg: 4, 56–70 kg: 4, &gt;70 kg: 5</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>500 mg tab</td>
<td>2 bd</td>
<td>30–35 kg: 3, 36–45 kg: 3, 46–55 kg: 3, 56–70 kg: 4</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Imipenem–cilastatin</td>
<td>0.5 g + 0.5 g vial</td>
<td>2 vials (1 g + 1 g) bd</td>
<td>-</td>
<td>-</td>
<td>To be used with clavulanic acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meropenem</td>
<td>1 g vial (20 ml)</td>
<td>1 vial 3 times per day or 2 vials bd</td>
<td>-</td>
<td>-</td>
<td>To be used with clavulanic acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amikacin</td>
<td>15–20 mg/kg</td>
<td>500 mg/2 ml vial*</td>
<td>30–35 kg: 2.5 ml, 36–45 kg: 3 ml, 46–55 kg: 3 to 4 ml</td>
<td>4 ml 1 g</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Streptomycin</td>
<td>12–18 mg/kg</td>
<td>1 g vial*</td>
<td>Calculate according to the dilution used</td>
<td>1 g</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ethionamide or prothionamide</td>
<td>15–20 mg/kg</td>
<td>250 mg tablet</td>
<td>30–35 kg: 2, 36–45 kg: 2, 46–55 kg: 3, 56–70 kg: 4</td>
<td>1 g</td>
<td>Once daily dose advised but can start with 2 divided doses until tolerance improves</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>p</em>-aminosalicylic acid</td>
<td>8–12 g/day in 2–3 divided doses</td>
<td>PAS sodium salt (4 g) sachet</td>
<td>1 bd 1 bd 1 bd 1 bd 1 to 1.5 bd</td>
<td>12 g</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PAS acid (4 g) sachet</td>
<td>1 bd 1 bd 1 bd 1 bd 1 to 1.5 bd</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Isoniazid</td>
<td>4–6 mg/kg (standard dose)*</td>
<td>300 mg tab</td>
<td>30–35 kg: 2/3, 36–45 kg: 1, 46–55 kg: 1, 56–70 kg: 1, &gt;70 kg: 1</td>
<td>-</td>
<td>100 mg isoniazid tablet can facilitate the administration of certain dosages Pyridoxine given with isoniazid in patients at risk (such as those with HIV, malnutrition)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10–15 mg/kg (high dose)</td>
<td>1.5 1.5 2 2 2</td>
<td>-</td>
<td>Pyridoxine given with isoniazid in patients at risk (such as those with HIV, malnutrition)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clavulanic acid</td>
<td>125 mg tab*</td>
<td>1 bd</td>
<td>30–35 kg: 1, 36–45 kg: 1, 46–55 kg: 1, 56–70 kg: 1, &gt;70 kg: 1</td>
<td>-</td>
<td>Only to be used with carbenemens</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>Medicine</td>
<td>Weight-based daily dose</td>
<td>Formulation</td>
<td>30–35 kg</td>
<td>36–45 kg</td>
<td>46–55 kg</td>
<td>56–70 kg</td>
<td>&gt;70 kg</td>
<td>Usual upper daily dose</td>
<td>Comments</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------</td>
<td>-------------------------</td>
<td>-------------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td>-------</td>
<td>------------------------</td>
<td>-----------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Other medicines</td>
<td>Kanamycin</td>
<td>15–20 mg/kg</td>
<td>500 mg/2 ml vial&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 to 2.5 ml</td>
<td>2.5 to 3 ml</td>
<td>3 to 4 ml</td>
<td>4 ml</td>
<td>4 ml</td>
<td>1 g</td>
<td>M/W/F dosing of aminoglycosides at 25 mg/kg/day may limit toxicity and inconvenience when the injectable agents are used in longer MDR-TB regimens</td>
</tr>
<tr>
<td></td>
<td>Capreomycin</td>
<td>15–20 mg/kg</td>
<td>500 mg/2 ml vial&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.5 ml</td>
<td>3 ml</td>
<td>3 to 4 ml</td>
<td>4 ml</td>
<td>4 ml</td>
<td>1 g</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gatifloxacin</td>
<td>~&lt;sup&gt;c&lt;/sup&gt;</td>
<td>400 mg tab</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>800 mg</td>
<td>Not used in &lt;18 year olds (no quality assured product currently available)</td>
</tr>
<tr>
<td></td>
<td>Thioacetzone</td>
<td>~&lt;sup&gt;c&lt;/sup&gt;</td>
<td>150 mg tab</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>~&lt;sup&gt;q&lt;/sup&gt;</td>
<td>Not used in &lt;18 year olds (no quality assured product currently available)</td>
</tr>
</tbody>
</table>

(<15 y) = follow the separate dose schedule for patients younger than 15 years of age; bd = two times a day; cap = capsule; g = gram; im = intramuscular; iv = intravenous; kg = kilogram; ml = millilitre; mg = milligram; M/W/F = Monday, Wednesday, Friday; soln = solution; susp = suspension; tab = tablet

<sup>a</sup> Dosages were established by the Guideline Development Group for the WHO treatment guidelines for rifampicin- and multidrug-resistant tuberculosis. 2018 update and the WHO Global task force on the pharmacokinetics and pharmacodynamics (PK/PD) of TB medicines and other drugs. They are based on the most recent reviews and best practices in the treatment of MDR/RR-TB. For certain agents the dosages were informed by pharmacokinetic modelling results based on the principle of allometric scaling (Anderson BL, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol 2008;48:303–32). Due to the pharmacokinetic properties of certain medicines the doses proposed may exceed the mg/kg/day ranges shown here in order to achieve blood concentrations similar to target levels in an average adult patient. In patients <30 kg follow the schedule for <15 year olds unless otherwise indicated. If multiple dose options are given for one weight band select the lower or higher option depending on whether the patient is at the lower or higher limit of the body weight range. Dosing more closely to the target mg/kg/day should be aimed for, and is more feasible with oral or parenteral fluids and when solid forms of different dosages are available. Fractioning of tablets into halves or less should be avoided, if possible. Therapeutic drug monitoring is advised when the dose is at the upper and lower ends of the range to minimize the adverse therapeutic consequences of over- and under-exposure, respectively (especially for injectable agents, linezolid and fluoroquinolones).

<sup>b</sup> Clinicians may decide to exceed these values in particular cases to improve therapeutic effect.

<sup>c</sup> No weight-based dosing is proposed.

<sup>d</sup> Unless there is risk of toxicity, the high dose may be used if antimicrobial levels may be lowered because of pharmacokinetic interactions, malabsorption or other metabolic reasons or if the strain has low-level drug resistance.

<sup>e</sup> Weight-based daily dose is for 6 or 7 days/week administration (M/W/F scheduling may permit higher dosing). Volumes shown may differ by preparation. Streptomycin may be diluted in three different ways. For iv use, the volume may be increased.

<sup>f</sup> In the 2018 WHO treatment guidelines, these agents are either no longer recommended (kanamycin, capreomycin), only recommended as a companion agent (amoxicillin/clavulanic acid) or not included because of lack of data from the latest analysis on longer MDR-TB regimens in adults (gatifloxacin, isoniazid and thioacetzone).

<sup>q</sup> Only available in combination with amoxicillin as co-amoxiclav (e.g. 500 mg amoxicillin/125 mg clavulanic acid fixed dose combination). It is given with each dose of carbapenem, either as 125 mg bd or 125 mg 3 times daily.
**Table 19.** Dosing of medicines used in second-line MDR-TB regimens in patients under 15 years
Dosing of medicines used in second-line MDR-TB regimens by weight band in patients under 15 years

<table>
<thead>
<tr>
<th>Group</th>
<th>Weight bands among patients not yet 15 years</th>
<th>Usual upper daily dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5–6</td>
<td>7–9</td>
<td>10–15</td>
</tr>
<tr>
<td><strong>A</strong> Fluoquinolones</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–20 mg/kg</td>
<td>100 mg dt</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>250 mg tab</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10–15 mg/kg</td>
<td>100 mg dt</td>
<td>0.8</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>400 mg tab</td>
<td>2 ml</td>
<td>3 ml</td>
</tr>
<tr>
<td>Bedaquiline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100 mg tab</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 mg/kg od in &lt;16 kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 mg/ml susp</td>
<td>4 ml</td>
<td>6 ml</td>
</tr>
<tr>
<td></td>
<td>600 mg tab</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10–12 mg/kg od in &gt;15 kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B Clofazimine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–5 mg/kg</td>
<td>50 mg cap or tab</td>
<td>1 alt days</td>
<td>1 alt days</td>
</tr>
<tr>
<td></td>
<td>100 mg cap or tab</td>
<td>M/W/F</td>
<td>M/W/F</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycloserine or terizidone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–20 mg/kg</td>
<td>125 mg mini capsule</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>250 mg cap</td>
<td>4–5 ml</td>
<td>5–6 ml</td>
</tr>
<tr>
<td>C Ethambutol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–25 mg/kg</td>
<td>100 mg dt</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>400 mg tab</td>
<td>3 ml</td>
<td>4 ml</td>
</tr>
<tr>
<td>Group</td>
<td>Weight bands among patients not yet 15 years old*</td>
<td>Usual upper daily dose*</td>
<td>Comments</td>
</tr>
<tr>
<td>-------</td>
<td>-------------------------------------------------</td>
<td>-------------------------</td>
<td>----------</td>
</tr>
<tr>
<td></td>
<td>5–6</td>
<td>7–9</td>
<td>10–15</td>
</tr>
<tr>
<td>C</td>
<td>50 mg tab</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>30–40 mg/kg</td>
<td>150 mg dt</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>400 mg tab</td>
<td>0.5</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>500 mg tab</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Imipenem-clavulanic acid</td>
<td>-</td>
<td>0.5 g + 0.5 g vial</td>
<td>-</td>
</tr>
<tr>
<td>Meropenem</td>
<td>20–40 mg/kg</td>
<td>1 g vial (20 ml)</td>
<td>2 ml</td>
</tr>
<tr>
<td>Amikacin</td>
<td>15–20 mg/kg</td>
<td>500 mg/2 ml vial</td>
<td>0.4 ml</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>20–40 mg/kg</td>
<td>1 g vial</td>
<td>Calculate according to the dilution used</td>
</tr>
<tr>
<td>Ethionamide or prothionamide</td>
<td>15–20 mg/kg</td>
<td>125 mg dt (ethionamide)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>250 mg tab</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>P-aminoosalicylic acid</td>
<td>200–300 mg/kg in 2 divided doses</td>
<td>PAS acid (4 g) sachet</td>
<td>0.5–0.75 g bd</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PAS sodium salt (4 g) sachet</td>
<td>0.5–0.75 g bd</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PAS sodium salt 60% (9.2 g) SACHET</td>
<td>1.5 g bd</td>
</tr>
<tr>
<td>Group</td>
<td>Weight bands among patients not yet 15 years old*</td>
<td>Usual upper daily dose*</td>
<td>Comments</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------------------------------------</td>
<td>-------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>15–20 mg/kg (high dose) 50 mg/5 ml soln</td>
<td>8–10 ml 15 ml 20 ml 4 ml</td>
<td>300 mg isoniazid</td>
</tr>
<tr>
<td></td>
<td>100 mg tab</td>
<td>1 1.5 2 3 4 4 (14 y)</td>
<td>Pyridoxine is always given with high-dose isoniazid in children (12.5 mg od in &lt;5 y olds and 25 mg od in &gt;4 y olds)</td>
</tr>
<tr>
<td>Clavulanic acid</td>
<td>250 mg amoxicillin/62.5 mg clavulanic acid/5 ml susp</td>
<td>2 ml 3 ml 5 ml 8 ml 10 ml (14 y)</td>
<td>Only to be used with carbapenems</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>15–20 mg/kg 500 mg/2 ml vial</td>
<td>0.4 ml 0.6 ml 0.8–1 ml 1.2–1.5 ml 2.0 ml</td>
<td>(&gt;14 y) (&lt;14 y) 1 g</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>15–20 mg/kg 500 mg/2 ml vial</td>
<td>0.4 ml 0.6 ml 0.8–1 ml 1.2–1.5 ml 2.0 ml</td>
<td>(&gt;14 y) (&lt;14 y) 1 g</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>400 mg tab</td>
<td>– – – – – –</td>
<td>Not used in &lt;18 y olds (no quality assured product currently available)</td>
</tr>
<tr>
<td>Thiacetazone</td>
<td>– – – – – –</td>
<td>– – – – – –</td>
<td>Not used in &lt;18 y olds (no quality assured product currently available)</td>
</tr>
</tbody>
</table>

(>14 y) = follow the separate dose schedule for patients older than 14 years of age; alt = alternate; bd = two times a day; cap = capsule; dt = dispersible tablet; g = gram; im = intramuscular; iv = intravenous; kg = kilogram; ml = milliliter; mg = milligram; M/W/F = Monday, Wednesday, Friday; soln = solution; susp = suspension; tab = tablet

* Dosages were established by the Guideline Development Group for the WHO treatment guidelines for rifampicin- and multidrug-resistant tuberculosis, 2018 update and the WHO Global task force on the pharmacokinetics and pharmacodynamics (PK/PD) of TB medicines and other experts. They are based on the most recent reviews and best practices in the treatment of MDR/RR-TB. For certain agents the dosages were informed by pharmacokinetic modelling results based on the principle of allometric scaling (Anderson BI, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu
Due to the pharmacokinetic properties of certain medicines the doses proposed may exceed the mg/kg/day ranges shown here in order to achieve blood concentrations similar to target levels in an average adult patient. In patients > 30 kg follow the schedule for > 14 year olds unless otherwise indicated. If multiple dose options are given for one weight band select the lower or higher option depending on whether the patient is at the lower or higher limit of the body weight range. Dosing more closely to the target mg/kg/day should be aimed for, and is more feasible with oral or parenteral fluids and when solid forms of different dosage are available. Fractioning of tablets into halves or less should be avoided if possible. Therapeutic drug monitoring is advised when the dose is at the upper and lower ends of the range to minimize the adverse therapeutic consequences of over- and under-exposure respectively (especially for injectable agents, linezolid and fluoroquinolones). Clinicians may decide to exceed these values in particular cases to improve therapeutic effect.

Dissolving in 10 ml of water may facilitate administration in patients in lower weight-bands and avoids fractioning solid formulations, although bioavailability is uncertain (use of dispersible tablets is preferred if available).

In individuals > 44 kg a dose of 600 mg od is proposed.

May be used in children 3–5 years of age. Giving half a 50 mg adult tablet in these children does not result in the same blood levels observed in trials using the special 25 mg paediatric tablet. Bioavailability may further be altered when the 50 mg tablet is split, crushed or dissolved.

Weight-based daily dose is for 6 or 7 days/week administration (M/W/F scheduling may permit higher dosing). Volumes shown may differ by preparation. Streptomycin may be diluted in three different ways. Dosing closer to the upper limit of the mg/kg/day is more desirable. For iv use, the volume may be increased.

In the 2018 WHO treatment guidelines, these agents are either no longer recommended (kanamycin, capreomycin), only recommended as a companion agent (amoxicillin/clavulanic acid) or not included because of lack of data from the latest analysis on longer MDR-TB regimens in adults (gatifloxacin, isoniazid and thioacetzone).

Only available in combination with amoxicillin as co-amoxiclav. Only to be used with carbapenems, in which case they are given together, e.g. 125 mg bd or 125 mg 3 times daily in the 24–30 kg weight band.

See the text of the 2019 WHO Consolidated Guidelines on DR-TB Management for more details on the use of medicines.
2.4.11 Monitoring during treatment of patients diagnosed with Xpert MTB/RIF

- Molecular tests, including Xpert MTB/RIF, are not suitable for patient monitoring, as these tests also detect DNA from nonviable bacilli.

- Follow-up of TB patients diagnosed with GeneXpert will be done by smear microscopy as described in the relevant chapters of treatment monitoring for specific types of patients.

2.5 Investigate contacts of DR-TB patients

2.5.1 Management of contacts of MDR-TB patients

- A close contact of an MDR-TB patient is someone who has been exposed to infection with drug-resistant *M. tuberculosis* by sharing air space with a patient who has confirmed MDR-TB.

- Close contacts are defined as people living in the same household or spending multiple hours a day together with the patient in the same indoor living space. They can be family members, colleagues, friends, roommates and neighbours.

- All close contacts of MDR-TB cases should be identified through contact tracing and those who are symptomatic will be evaluated for active TB.

- Special attention needs to be paid to children.

- The TB screening will include a complete clinical examination, an Xpert MTB/Rif test of a sputum sample or other relevant specimen, and a chest X-ray. If the Xpert MTB/Rif result is RR, the patient must be sent to the nearest MDR Unit.

- Screening of contacts of MDR-TB patients should be an ongoing process. Asymptomatic contacts need to be screened at diagnosis, at the end of the intensive phase, and at the end of treatment. Contacts should also receive appropriate health information and education regarding TB and MDR-TB.

- Preventive therapy is recommended for contacts of MDR-TB patients (see module 1).
Case 1 – medical history

• Mr. H, 27 years old, 48 kg, diagnosed with pulmonary TB with positive smear on early January 2021. Patient was started on standard TB drug (2RZHE / 4 RH) on 15 January 2021.

• At the end of intensive phase (11 March 2021), patient was complaining of persistent cough, bloody sputum, and still losing weight. Sputum smear at 11 March 2021 intensive phase was positive.

• Patient have no history of contact with preXDR / XDR TB patient. No history of consuming levofloxacin.

Case 1 – Laboratory examination

• GeneXpert test on 11 March 2021 was positive, rifampicin resistant

• LPA test on 11 March 2021:
  • Rifampicin resistant
  • Isoniazid resistant
  • No resistance tofloroquinolone and SLI drug

What drug regimen is suitable for this patient?
Case 2 – medical history

• Mrs. F, 26 years old, 42 kg, with history of persistent cough of 1 month with occasional bloody sputum. Diagnosed with pulmonary TB with positive smear on 29 May 2020. Patient have history of consuming Levofloxacin prescribed by local doctor (patient does not remember the dosage and the duration)
• Patient have no history of contact with preXDR / XDR TB patient.
• Patient is sexually active and have not had menstruation in the last 2 months

Case 2 – Laboratory examination

• GeneXpert: rifampicin resistant
• LPA:
  • Rif resistant
  • INH resistant
  • FQ resistant
  • Kanamycin sensitive

What drug regimen is suitable for this patient?
MODULE IV: MONITORING AND EVALUATING TREATMENT

1 Introduction

Active TB drug-safety monitoring and management (aDSM) is a method of detecting, recording and reporting adverse event using systematic clinical and laboratory assessment of patients on TB treatment. aDSM applies to patients on treatment with: (i) new anti-TB drugs; (ii) novel MDR-TB regimens; or (iii) XDR-TB regimens. The recording and reporting activities of ADSM primarily target the serious adverse events (SAEs) as a basic requirement. The appropriate and timely management of ADRs is an integral component of ADSM and patient care.

Doing ADSM is of paramount importance since it ensures patient safety. ADSM is also useful in helping health programmes to prevent and manage ADRs and improve patient’s quality of life.

Implementing ADSM may require a lot of effort involving various sectors. ADSM is best to be initiated using a top-down approach, starting at the national level and progressing down to the health facilities treating the patient.

Key activities of ADSM are:

- **Active and systematic clinical and laboratory assessment during treatment** to detect drug toxicity and AEs
- **All AEs detected should be managed in a timely manner** in order to deliver the best possible patient care
- **Standardized data should be systematically collected and reported for any detected SAE** to be used in the future.

During the initial period at the DR-TB management centre, patients start DR-TB treatment, and are monitored closely for early detection and management of adverse events, while receiving education and information about the disease and its treatment. When a patient tolerates the medicines, treatment may be decentralised (or transferred) to a local health facility, or the patient may continue treatment at the DR-TB management centre. If a patient’s treatment is
decentralised, the patient receives treatment at his or her local health facility or from a community treatment supporter for the remainder of the regimen.

In other countries, DR-TB treatment can be fully ambulatory, meaning that both the intensive and the continuation phase take place at a local health facility near the patient’s home or with assistance from a community treatment supporter. In both situations, the patient continues to have monthly sputum examinations and is also evaluated monthly by the physician at the DR-TB management centre.

To provide patient-centred DOT, the health worker coordinates a place and time convenient to both the patient and the health worker or a community-based treatment supporter at a local health facility. At each visit, the health worker:

- greets the patient and asks about any AEs and other problems since the last visit
- administers treatment, including watching that the medicines are swallowed and giving the injection
- records the treatment observed and the date on the second-line TB treatment card
- notes immediately whether treatment has been interrupted and takes action, such as tracing the patient and encouraging the patient to resume treatment
- establishes and maintains a supportive relationship with the patient.

The first-line anti-TB medicines used to treat DS-TB are efficacious and tolerable, whereas the second-line medicines used to treat DR-TB may be less efficacious and cause more AEs. The AEs occur mainly during the first few months of treatment. However, very SAEs are uncommon. Some AEs are self-limiting and resolve after a short time; others can be treated with medicines to alleviate the patient’s symptoms. All AEs must be swiftly and effectively managed or treated until the patient develops a tolerance for these effects or until the AEs resolve. Reducing the dose of a medicine, or withdrawing or replacing it should occur only as the last possible course of action. For patients who have resistance to multiple medicines so that only a few medicines can be used, stopping any of these medicines may result in treatment failure.
2 Module objectives

1. Understand the key activities of ADSM
2. Identify the AEs, their management and monitoring of TB drugs
3. Understand the reporting of AEs.

3 Identification and management of AEs

3.1 Adverse events

Adverse event is defined by the International Conference on Harmonization (ICH) as any untoward medical occurrence in a subject administered by a medicinal (investigational or non-investigational) product. It does not necessarily have a causal relationship with the treatment. Thus, AE can be any unfavourable and unintended sign (including an abnormal finding), symptom or disease temporally associated with the use of a medicinal product, though not related to that medicinal product. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition or abnormal results of diagnostic procedures including laboratory test abnormalities.

3.2 Adverse drug reaction

Adverse drug reaction (ADR) is any untoward medical occurrence considered associated with use of a specific drug/s. It can be serious (as defined above) or non-serious (does not fulfil the criteria for serious ADR).

3.3 Serious adverse event

A serious adverse event (SAE) is any untoward medical occurrence that:
- results in death
- life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is a suspected transmission of any infectious agent via a medicinal product
- is medically important.

3.4 Monitoring AE

The flow chart for monitoring AE is given in Fig. 8.
3.5 Management of AEs

AE should be monitored and recorded routinely by the treatment provider. Timely, accurate and complete reporting and analysis of AEs are required to be reported under the programme to ensure the protection of patients. The broad principles of AEs management are as follows:

- if AE is mild continuing the treatment regimen and manage with ancillary drugs, if needed
- in case of SAEs the offending drug/s should be stopped and then can be reintroduced at a lower dose or withdrawn permanently
- an essential component of the management is psychosocial support, which can be provided through patient education by treatment provider and patient support groups.
### 3.5.1 Symptom-based approach to manage side-effects of DS-TB drugs

#### Table 20. Managing side-effects of anti-TB drugs

<table>
<thead>
<tr>
<th>Side-effects</th>
<th>Drug(s) responsible</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin rash with or without itching</td>
<td>Streptomycin, isoniazid, rifampicin, pyrazinamide</td>
<td>Stop responsible drug(s) and refer to clinician urgently</td>
</tr>
<tr>
<td>Jaundice (other causes excluded), hepatitis</td>
<td>isoniazid, pyrazinamide, rifampicin</td>
<td>Stop anti-TB drugs</td>
</tr>
<tr>
<td>confusion (suspect drug induced acute liver failure if there is jaundice)</td>
<td>most anti-TB drugs</td>
<td>Stop anti-TB drugs</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>
<tr>
<td><strong>Minor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia, nausea, abdominal pain</td>
<td>pyrazinamide, rifampicin, isoniazid</td>
<td>Continue anti-TB drugs, check drug doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>give drugs with small meals or just before bedtime and advise patients to swallow pills slowly with small sips of water. If symptoms persist or worsen, or there is protracted vomiting or any sign of bleeding, consider the side-effects to be major and refer to clinician urgently.</td>
</tr>
<tr>
<td>Joint pains</td>
<td>pyrazinamide</td>
<td>Aspirin or non-steroidal anti-inflammatory drug, or paracetamol pyridoxine 50–75 mg daily (3)</td>
</tr>
<tr>
<td>Burning, numbness or tingling sensation in the hands or feet</td>
<td>Isoniazid</td>
<td></td>
</tr>
<tr>
<td>Drowsiness</td>
<td>Isoniazid</td>
<td>reassurance. Give drugs before bedtime.</td>
</tr>
<tr>
<td>Orange/red urine</td>
<td>Rifampicin</td>
<td>reassurance. Patients should be told when starting treatment that this may happen and is normal</td>
</tr>
<tr>
<td>Flu syndrome (fever, chills, malaise, headache, bone pain)</td>
<td>intermittent dosing of rifampin</td>
<td>change from intermittent to daily rifampicin administration (3)</td>
</tr>
</tbody>
</table>
3.5.2 Symptom-based approach to manage side-effects of anti TB drugs during DR-TB treatment

AEs are more frequent in patients on second-line TB treatment than with first-line drugs and are the main cause of treatment interruption. Good counselling at the beginning of the treatment and careful monitoring and management are the basis of patient adherence. During the first baseline visit, comorbidities that are associated with a high risk of AEs, such as diabetes, kidney and liver failure, malnutrition, HIV infection, excessive alcohol, and drug use, etc., should be identified and recorded. The underlying causes of AEs should be identified and treated. AEs are classified according to their severity (Table 21).

Table 21. Grading of the severity of adverse events during DR-TB treatment

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1: Mild</td>
<td>Mild or transient discomfort without limitation of normal daily activities; no medical intervention or corrective treatment required.</td>
</tr>
<tr>
<td>Grade 2: Moderate</td>
<td>Mild to moderate limitation of normal daily activities; minimal medical intervention or corrective treatment required.</td>
</tr>
<tr>
<td>Grade 3: Severe</td>
<td>Marked limitation of normal daily activities; medical intervention and corrective treatment required; possible hospitalization.</td>
</tr>
<tr>
<td>Grade 4: Life-threatening or permanent injury</td>
<td>Extreme limitation of normal daily activities; medical intervention and corrective treatment required, almost always in a hospital setting.</td>
</tr>
</tbody>
</table>

Ref: 2008 ANRS* scale for the gradation of the severity of adverse events in adults.

*Agence Nationale pour la Recherche sur le SIDA et les hépatites (National AIDS and Hepatitis Research Agency), Paris, France.

Grade 1 AEs need only be noted in the patient’s card, whereas Grade 2 AEs require medical intervention with ancillary drugs, of which the most frequently used are detailed in Table 22.

Table 22. Frequently used ancillary drugs during DR-TB treatment

<table>
<thead>
<tr>
<th>Therapeutic class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Antidiarrhoeals</td>
<td>Loperamide</td>
</tr>
<tr>
<td>Antiemetics</td>
<td>Metoclopramide (or metopimazine) and ondansetron</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Cetirizine (or diphenhydramine)</td>
</tr>
<tr>
<td>Antiulcer drugs</td>
<td>Cimetidine (or ranitidine) and omeprazole</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Prednisolone, hydrocortisone</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs (NSAIDs)</td>
<td>Acetylsalicylic acid and ibuprofen</td>
</tr>
</tbody>
</table>
Vitamins and mineral supplements | Pyridoxine (vitamin B6). Potassium and magnesium.
---|---

These drugs should be stocked and available at all times in TB treatment units where patients with drug-resistant TB are being treated.

Serious AEs (SAEs), which are either life-threatening or could cause permanent damage (degrees 3 and 4), should be managed by an experienced clinician who will identify the drug suspected, reduce dosage, or discontinue its use and replace it with an equivalent drug if the drug needs to be definitively discontinued.

Changing a regimen drug should be considered only as a last resort after any attempt to manage AEs with ancillary drugs has failed.

Symptoms-based approach for TB drugs AEs

**Gastro-intestinal disorders**

1. **Nausea and vomiting**

   Suspected drugs: Pto/Eto, PAS, H, E, Z, Cfz, Bdq.

   - Toxicity of the Pto/Eto on the gastric mucosa.
   - Possible risk of hypokalaemia.

   **Treatment:**
   
   1. Rehydration using oral rehydration solution (ORS).
   2. Recommend taking a light meal before medication.
   3. Prescribe metoclopramide 10-20 mg 30 minutes before drug intake.
   4. If vomiting persists, prescribe ondansetron 2–8 mg 30 minutes before drug intake.
   5. Divide Pto/Eto dose into morning and evening provided DOT is ensured (dose dependent effect; higher doses better tolerated by most patients in the evening).
   6. For patients concerned about possible nausea, prescribe diazepam 5 mg 30 minutes before medication.

2. **Gastritis**

   Suspected drugs: Pto/Eto, PAS.

   **Treatment:**
   
   1. Recommend taking a light meal before medication.
   2. Absorption of FQs is reduced by drugs containing cations, such as magnesium and aluminium (and sucralfate) (high reduction); iron (moderate reduction); calcium, zinc (and multivitamins) (low reduction).
3. Prescribe omeprazole 20-40 mg in the evening (2 hours before or 3 hours after medication).

3. Diarrhoea
Suspected drugs: PAS, Pto/Eto.

Treatment:
1. Encourage patient to tolerate mild diarrhoea.
2. Encourage fluid intake.
3. Treat diarrhoea with no complications (no blood in the stools, no fever) with loperamide 4 mg, followed by 2 mg after each bowel movement up to a maximum of 10 mg in 24 hours.
4. Check potassium levels and hydration status in case of severe diarrhoea.

4. Hepatotoxicity
Suspected drugs: Z, H, Pto/Eto, Bdq, PAS, Lzd, FQ (very rarely).
- Symptoms: nausea, vomiting, abdominal pain, jaundice.

Management:
1. Pay attention to medical history (viral hepatitis, HIV infection, alcohol use, etc).
2. If ALT, AST ≤5 times the upper limit of normal and there is no jaundice, continue treatment and treat nausea and vomiting.
3. If ALT, AST >5 times the upper limit of normal and/or jaundice (bilirubin > 3 mg/dL), stop all drugs and assess the transaminases every week; if they return to 2 times the upper limit of normal, reintroduce the least hepatotoxic drugs (Am, E, Mfx, Cfz) and check transaminase levels. Then, reintroduce hepatotoxic drugs in the following order: Pto/Eto, H and Z and monitor transaminase levels every 3 days. Check transaminase values after introducing each drug.
4. If drug reintroduction leads to the return of hepatotoxicity, remove the culprit drug from the treatment and replace it by another if this is an essential drug. Do not replace H and Z.
5. Monitor transaminase levels monthly.

Kidney disorders
1. **Nephrotoxicity**

Suspected drugs: Km, Am, Cm, E, Z, Cs.

- Higher risk if intensive phase is prolonged.

Treatment:

1. Close monitoring of creatinine (and potassium) every week or every 2 weeks.
2. Adequate hydration.
3. If creatinine clearance <90 ml/min, prescribe Am 2-3 times per week at 12-15 mg/kg; give E and Z, 3 times/week. If creatinine clearance remains <60 ml/min despite dose reduction to 2-3 times/week, stop the injectable drug and replace it with Dlm or Lzd. Give E and Z, 3 times/week.
4. If Dlm is not available or if Lzd is contraindicated, consider Bdq.

**NB:** in case of increase in creatinine levels, severe malnutrition or advanced age, renal functions are determined by calculating creatinine clearance using the Cockroft-Gault formula:

\[
\text{Cl} \text{ Cr} = (140-\text{age}) \times \text{Weight} \times k \div \text{Cr}
\]

- Cl Cr: estimation of the creatinine clearance in ml/min;
- Cr: creatinine levels in µmol/l;
- Age: age in years;
- Weight: in kg; k coefficient (1.23 for men and 1.04 for women).

Note: Creatinine conversion from µmol/L to mg/dL: mg/dL = µmol/L /88.4.

**Table 14:** Stages of kidney disease according to creatinine clearance levels

<table>
<thead>
<tr>
<th>Stage of chronic kidney disease</th>
<th>Creatinine clearance (ml/min)</th>
<th>Action on TB drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 Normal</td>
<td>≥ 90</td>
<td></td>
</tr>
<tr>
<td>Stage 2 Mild</td>
<td>60–89</td>
<td>2–3 times per week</td>
</tr>
<tr>
<td>Stage 3 Moderate</td>
<td>30–59</td>
<td>Stop the injectable and switch to Dlm or Lzd or Bdq</td>
</tr>
<tr>
<td>Stage 4 Severe</td>
<td>15–29</td>
<td></td>
</tr>
<tr>
<td>Stage 5 Terminal</td>
<td>&lt; 15</td>
<td></td>
</tr>
</tbody>
</table>
2. Electrolyte imbalance

Suspected drugs: Cm, Km, Am.

- Hypokalaemia: K⁺ <3.5 mEq/l.
- Hypomagnesaemia: Mg²⁺ <1.5 mEq/l.
- Hypokalaemia may be refractory if the concurrent hypomagnesaemia is not corrected.
- Higher risk if intensive phase is prolonged.
- Vomiting, diarrhoea and diuretics may cause electrolyte imbalance.
- Risk of QTc prolongation (check ECG).
- Electrolyte imbalances are reversible upon discontinuation of the injectable drug (however, this might take weeks or months!).
- Hypokalaemia and hypomagnesaemia are often asymptomatic.
- Symptoms of moderate intensity: fatigue, myalgia, cramps, weakness of the lower limbs, somnolence, confusion.
- Symptoms associated with severe electrolyte loss: tetany, paralysis and severe arrhythmias.

Treatment:

1. Encourage dietary intake of potassium (bananas, oranges, tomatoes, chocolate ...).
2. Check for signs of dehydration among patients with vomiting and diarrhoea. Start oral or IV rehydration.
3. Consider potassium supplementation: oral slow-release tablets of potassium chloride 1200–3600 mg daily in 2–3 divided doses (600 mg = 8 mEq).
4. In case of severe hypokalaemia: KCl IV: 10 mEq/h (10 mEq KCl will raise serum potassium by 0.1 mEq/l).
5. If potassium levels are low, check magnesium levels (if this is not possible, consider empirical treatment with magnesium in all cases of hypokalaemia with magnesium gluconate at 1000 mg twice a day).
6. Prescribe spironolactone 25 mg/day in refractory cases.
7. Check ECG for QTc prolongation.

Neurological disorders

1. Peripheral neuropathy

Suspected drugs: Lzd, Cs, H, FQs, SLIs, Pto/Eto, E.

- Check for possible comorbidities: diabetes, HIV, alcohol abuse, hypothyroidism, malnutrition.
- No formal contraindications to anti-TB treatment in case of comorbidities.

Treatment:

1. Pyridoxine 100–200 mg/day (maximum dose 100 mg/day in pregnant women).
2. Amitriptyline 25–50 mg in the evening (maximum dose 150 mg/day in three doses).
3 Carbamazepine 100–400 mg x 2/day (follow-up and monitoring of transaminases).

2. **Optic neuritis**

Suspected drugs: Lzd, E.

- Serious, irreversible if medication is not immediately discontinued.

Treatment:

1. Immediate discontinuation of Lzd and/or E.

3. **Seizures**

Suspected drugs: Cs, H, FQs.

Treatment:

1. Discontinue Cs, the drug likeliest to be responsible.
2. Always check creatinine levels in patients with sudden onset of seizures. Compromised renal function may cause increased serum concentrations of Cs.
3. Begin anti-convulsive treatment (carbamazepine, phenytoin or valproic acid).
4. Replace Cs by Pto/Eto (or PAS) if not previously used in a failed regimen.

**Osteoarticular disorders**

1. **Arthralgia**

Suspected drugs: Z, FQs, Bdq.

Treatment:

- Prescribe NSAIDs: ibuprofen 600 mg 3 times/day.
- Rest the joint.
- Symptoms generally diminish with time and without any intervention.

2. **Tendinitis (Achilles’ tendon)**

Suspected drugs: FQs (all).

Treatment:
1. Prescribe NSAIDs: ibuprofen 600 mg 2–3 times a day.
2. Rest the joint.
3. Tendon rupture is more probable among patients with diabetes and among the elderly, but rare among patients with MDR-TB.
4. If significant inflammation persists, discontinue FQ use and replace with Bdq.

**Dermatological disorders**

1. **Itchiness, skin rashes and allergic reactions**

Suspected drugs: all.

Steps to take:

1. Symptoms generally resolve spontaneously in the first few weeks.
2. In case of dryness of the skin, use moisturizing cream.
3. Prescribe antihistamines (diphenhydramine 25–50 mg or cetirizine 5–10 mg before medication).
4. Prescribe corticosteroid ointments.
5. Prescribe oral prednisolone in low doses (10–20 mg/day) if there is no improvement.
6. Identify and discontinue the drug in question only in case of serious AEs (e.g., Stevens Johnson syndrome and Lyell’s syndrome).

**Thyroid disorders**

1. **Hypothyroidism**

Suspected drugs: Pto/Eto+PAS, Pto/Eto, PAS.

- Reversible at the end of the treatment.
- If thyroid stimulating hormone (TSH) levels increase, assess symptoms of hypothyroidism.
- If TSH >1.5–2 times upper limit of normal, initiate treatment.

Treatment:

- Levothyroxine 100–150 µg/day in adults; 75–100 µg/day in young adults;
  50 µg/day in elderly people (> 65 y); 25 µg in case of serious cardiovascular disease.
- Reassess TSH levels after 1–2 months and adjust levothyroxine dosage accordingly.

**Metabolic disorders**
1. Hypoglycaemia and hyperglycaemia

Suspected drugs: Gfx, Mfx.

• Reversible at the end of treatment.
• Good glucose control is important during treatment.
• Higher risk with Gfx than with Mfx.

Treatment:

1. Treat hypoglycaemia and hyperglycaemia as needed.
2. Stop Gfx, replace with Mfx and monitor glycaemia.

2. Lactic acidosis

Suspected drug: Lzd.

• Build-up of lactates in the body, which results in an excessively low pH in the blood.
• Consequence of mitochondrial toxicity.
• Monitor with blood test (arterial or venous).
• Symptoms: abdominal pain, nausea, vomiting, rapid deep breathing, general weakness.

Treatment:

1. Stop Lzd and replace with another drug with similar characteristics (e.g., imipenem or meropenem + clavulanic acid).

Haematological disorders

1. Bone marrow aplasia

Suspected drug: Lzd.

Treatment:

1. Discontinue Lzd immediately in case of severe medullar aplasia (Grade 3) of the white or red blood cells, or platelets.
2. Consider blood transfusion in case of severe anaemia.
3. Consider possible causes of haematological disorders unrelated to Lzd.
4. Reduce Lzd dosage (300 mg/day or 600 mg thrice a week instead of 600 mg/day) if the aplasia resolves and check complete blood count.

Psychiatric disorders
1. Depression

Suspected drugs and conditions: psychological and socio-economic conditions, Cs, H, FQs.

Treatment:

1. Assess psychological and socio-economic conditions.
2. Discontinue Cs, which is the drug most likely to cause depression.
3. Always check creatinine levels in patients with sudden onset of depression. Impaired renal functions can raise Cs serum concentrations.
4. If moderate or severe symptoms persist, initiate anti-depressant treatment with fluoxetine, amitriptyline or similar drugs. Do not administer these in conjunction with Lzd (risk of serotonin syndrome).
5. Replace Cs with Pto/Eto (or PAS) if not previously used in a failed drug regimen.

2. Psychosis

Suspected drugs: Cs, H, FQs.

Treatment:

1. Discontinue Cs, which is the drug most likely to be responsible.
2. Always check creatinine levels in patients with sudden onset of psychosis. Impaired renal function can raise Cs serum concentrations.
3. If moderate or severe symptoms persist, initiate antipsychotic treatment with haloperidol.
4. Replace Cs with Pto/Eto (or PAS) if not previously used in a failed regimen.

Cardiac disorders

1. QTc interval prolongation

Suspected drugs: FQs, Bdq, Dlm, Cfz, Mfx prolongs QTc more than Lfx and Gfx.

Treatment:

1. Repeat ECG and confirm QTc prolongation.
2. Take note of conditions such as diarrhoea, vomiting, use of diuretics, alcohol and ancillary drugs (ondansetron at high dose).
3. Check potassium, magnesium and calcium levels and maintain normal electrolyte levels (refer to electrolyte loss in the section on renal disorders).
4. If QTc < 500 ms, continue Mfx or Bdq or Dlm and perform ECG once a week.
5 If QTc ≥ 500 ms, temporarily hold all drugs prolonging QT and replace Mfx with Gfx or high-dose Lfx (if Gfx is not available) after normalization.

6 If QTc still ≥ 500 ms, consider discontinuing Cfz and refer to cardiologist wherever possible.

7 If QTc still ≥ 500 ms, consider discontinuing Bdq and/or Dlm.
MODULE V: TREATING TB WITH COMORBIDITIES

1 TB in PLHIVs

PLHIVs are at increased risk of getting infected with TB. TB is the leading preventable cause of death among PLHIVs. Among treated TB patients, death rates are higher in HIV-positive than in HIV-negative patients. Case-fatality is higher in PLHIVs 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.

All PLHIVs should be regularly screened for TB and vice versa, using a clinical symptom-based algorithm consisting of current cough, fever, weight loss or night sweats at the time of initial presentation for HIV care and at every visit to a health facility or contact with a health care worker afterwards. Adults and adolescents living with HIV, who report any one of the symptoms of current cough, fever, weight loss or night sweats, may have active TB and should be evaluated for TB and other diseases. Screening for TB is important regardless of whether they have received or are receiving TPT or ART. Similarly, children living with HIV who have any one of the following symptoms – poor weight gain, fever or current cough or contact history with a TB case – may have TB and should be evaluated for TB and other conditions.

It is important for patient living with HIV to be started on TB treatment as soon as possible, followed by co-trimoxazole, and initiation of ART. In principle, regimen used in treating TB in PLHIV is the same with people without HIV (2RHZE/4RH). In people newly diagnosed with TB and HIV, ART should be initiated only after 2 weeks of TB drug regimen and not more than 8 weeks after TB drug regimen is started, regardless of CD4 cell count. In PLHIVs, DOT is generally need to be implemented more carefully as PLHIV need to consume large number of tablets everyday and tend to experience more side-effect compared to people without HIV.

Early use of ART is also recommended for TB patients living with HIV who also receive medication with second-line anti-TB regimens for DR-TB. Rifampicin reduces drug levels of both NNRTIs and protease inhibitors through induction of the cytochrome P450 liver enzyme system.
Efavirenz should be used in preference to nevirapine when rifampicin is needed for treatment of TB.

Occasionally, patients with HIV-related TB may experience a temporary exacerbation of symptoms, signs or radiographic manifestations of TB after beginning TB treatment. This paradoxical reaction occurs in HIV-infected patients with active TB and is thought to be a result of immune restitution due to the simultaneous administration of ARV and TB medication (IRIS Syndrome). Symptoms and signs may include high fever, lymphadenopathy, expanding intra-thoracic lesions and worsening of chest radiographic findings. The diagnosis of a paradoxical reaction should be made only after a thorough evaluation has excluded other aetiologies, particularly TB treatment failure. For severe paradoxical reactions prednisone (1–2 mg/kg for 1–weeks, then gradually decreasing doses) may be used. Both anti-TB treatment and ART should be continued even there is an exacerbation of symptoms.

2 TB with diabetes mellitus

Diabetes mellitus (DM) is a strong risk factor for TB. It is also associated with worse TB treatment outcome. Furthermore, the presence of diabetes may enhance adverse reactions to anti-TB drugs, particularly renal impairment and peripheral neuropathies. Diabetes should be closely monitored and treated throughout the duration of anti-TB treatment.

It is essential to screen all TB patients for diabetes (and vice versa) and manage them appropriately. Regimen used in TB-DM is similar to patient without DM, provided blood glucose is controlled appropriately.

The algorithm for screening TB and DM is provided below.
Screening for TB in DM patients

ALL REGISTERED DM PATIENTS

SCREEN FOR TB
Do the patients have one of the following symptoms for at least two weeks: cough?/fever? Drenching night sweat? Unexplained weight loss?

Refer to TB clinic for TB work up (based on national guideline)
Is TB diagnosed?

YES
- Start TB management according to national guideline: Be aware of poor treatment outcome
- Continue DM management: Be aware of poor blood sugar control
- Education and counselling: TB & DM treatment adherence and psychological support
- Regularly follow-up for both TB and DM

NO
- FOLLOW-UP: According DM schedule OR come back early if TB symptoms present
- Continue DM management
- Check for TB symptoms at each follow-up: Is TB suspected?

Screening for DM in TB patients

ALL REGISTERED TB PATIENTS

DO GLYCEMIC TEST
Do patients have FBS ≥ 126mg/dl OR RBS (at least 2 hours after meal) ≥ 200mg/dl?

Refer to DM clinic for DM work up (based on national guideline)
Is DM diagnosed?

YES
- Start DM management according to national guideline: Be aware of poor blood sugar control
- Continue TB management: Be aware of poor TB treatment outcome
- Education and counselling: TB & DM treatment adherence and psychological support
- Regularly and strictly follow-up

NO
- FOLLOW-UP: According to TB schedule. Repeat glycemic test every 2 months OR if DM symptoms present
- Do patients have FBS ≥ 126mg/dl OR RBS (at least 2 hours after meal) ≥ 200mg/dl?

YES
- Start/Continue TB management according to national guideline
- Adherence to TB medications

NO
- Continue TB management:
  - Stop smoking, stop alcohol drinking, do physical exercise, healthy diet
  - Be aware of DM symptoms
  - Adherence to TB medications
3 TB with malnutrition

Malnutrition is an important risk factor for TB. Studies have shown that malnourished TB patients have higher risk of loss to follow-up and poor outcomes. Timor-Leste has one of the highest rates of malnutrition in the world, with 46% of children under five suffering from chronic malnutrition. The number of undernourished people in the country has remained constant around 300,000.

Malnourished children and adults should be screened for TB under active and passive case-finding efforts and linked with nutritional support programme. The nutritional status of all notified TB patients should be assessed (by measuring MUAC or BMI) and those with malnutrition should be provided nutritional support. Advocate for extending the existing nutritional support programme (for mothers and children) to TB patients also.
4 TB and smoking

There are now considerable evidences linking smoking and TB. Smoking interferes with TB treatment at every stage of the disease. It increases the risk of LTBI, culture conversion, sputum smear positivity, cavitary disease, treatment delay, treatment default, poor treatment outcomes, and transmission of the disease. Smokers also tend to have higher bacillary load compared to non-smokers.

National TB programme should encourage integration between tobacco control and TB control whenever possible. Detailed instruction for helping patient stop smoking is outside the scope of this training module, however physician should always encourage TB patients to stop smoking using ABC method (Ask, Brief advice, Cessation support) since smoking cessation is vital in determining TB treatment outcome.

5 TB patient with liver and renal disorder

Some TB patient may present with liver or renal disorder as comorbidities, interfering with normal standard regimen. Patient with liver disorder may use the alternative regimen below:

Two hepatotoxic drugs (rather than the three in the standard regimen):

- months of isoniazid and rifampicin, plus ethambutol (until or unless isoniazid susceptibility is documented);
- 6–9 months of rifampicin, pyrazinamide and ethambutol.

Liver function should be monitored monthly during treatment.

In patient with renal disorder, 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). While receiving isoniazid, patients with severe renal insufficiency or failure should also be given pyridoxine in order to prevent peripheral neuropathy.
MODULE VI: RECORDING AND REPORTING

Maintenance of accurate records and registers of patients and programme activities and reporting data to the municipality/central unit are essential for proper monitoring and management of the NTP. NTP records and reports are standardized and provide the required information for managing the programme effectively.

The following standardized records are to be used in the NTP:

<table>
<thead>
<tr>
<th>Forms</th>
<th>Registers</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Referral slip</td>
<td>• TB laboratory register</td>
</tr>
<tr>
<td>• Laboratory request form for specimen</td>
<td>• TB register</td>
</tr>
<tr>
<td>Examination</td>
<td>• LTBI register</td>
</tr>
<tr>
<td>• Contact tracing and TPT forms</td>
<td>• Presumptive TB register</td>
</tr>
<tr>
<td>• TB treatment card</td>
<td>• Vulnerability assessment register with</td>
</tr>
<tr>
<td>• DR-TB treatment card</td>
<td>scoring</td>
</tr>
<tr>
<td>• Patient’s TB identity card</td>
<td>• Referral and feedback TB register</td>
</tr>
<tr>
<td>• DR-TB patient identity card</td>
<td>• Stock register</td>
</tr>
<tr>
<td>• Referral/Transfer form for treatment</td>
<td>• Culture and DST laboratory register</td>
</tr>
<tr>
<td>• Referral/Transfer form for treatment of</td>
<td>• Second-line TB treatment register</td>
</tr>
<tr>
<td>DR-TB</td>
<td></td>
</tr>
<tr>
<td>• TB-HIV forms</td>
<td></td>
</tr>
<tr>
<td>• TB-Diabetes screening forms</td>
<td></td>
</tr>
</tbody>
</table>

1 Referral/Transfer form for treatment

The Referral/Transfer form for treatment is kept at all health facilities. The medical officer of the diagnostic health facility which refers patients for treatment (both DS-TB and DR-TB) to other peripheral health facilities must complete the top half of the form which includes the patient characteristics. Once the patient arrives, the receiving unit fills in the bottom half of the form and sends it back to the referring unit. Information regarding referral of patients should also be noted in the TB notification register.

The Referral/Transfer form is to be used when transferring registered patients currently under treatment from one reporting unit to another. If a patient is being ‘Transferred Out’, a Referral/Transfer form and a copy of the TB treatment card will be sent from the “transferring unit”, i.e., referring health facility/Transferring unit to the “receiving unit”, i.e., health facility/transferring unit where the patient will receive further treatment. The first part of the form contains information about the patient, her/his disease, treatment details and address of the transferring unit. This information should be used to
complete a new TB treatment card for the patient, who should be reregistered as a “transfer in” case in the receiving unit. When the patient has reported to the receiving unit, the bottom part of the form is completed by the receiving unit and returned to the transferring unit. This is to communicate patients’ follow up examination results at the end of the intensive phase and the treatment outcome to the transferring unit.

All NTP forms and registers with a focus on strengthening municipality and sub-district level reporting are annexed (Transition Plan to DHIS 2 TOOL).

**Drug Sensitive (DS)-TB**

**Quarterly Reports**

1. Quarterly reports from municipality level, including quarterly reports on contacts and vulnerability assessment - CF, TO, PMR, DLS – TB and DR-TB drugs, TB-HIV, TB-Diabetes
2. Quarterly reports from CHC level, including quarterly reports on contacts and vulnerability assessment - CF, TO, PMR, DLS – TB and DR-TB drugs, TB-HIV, TB-Diabetes

**Registers**

1. Municipality level – 2 Registers: TB and LTBI registers
2. Sub-municipality level – 5 Registers: 1) Duplicate TB & 2) LTBI registers; 3) Lab register; 4) Presumptive TB register; 5) Vulnerability assessment register
3. Referral feedback register: HNGV and Maubisse Referral Hospital

**Treatment Card and Transfer Form**

**Integrated Municipality & Referral Hospital TB Centres:** Baucau, Maliana, Oecusse and Suai

**Drug Resistant (DR) - TB**

**Quarterly Reports**

1. Quarterly reports from municipality level,
2. Quarterly reports from CHC level.

**Register: DR-TB register and PMDT treatment card**

**TB presumptive register**

This register is used in those health facilities that identify TB presumptives, collect sputum and make smear fixation, or collect Xpert MTB/RIF samples. The smears or Xpert MTB/RIF samples are sent to the designated microscopy or diagnostic centre (DMC/DDC) for smear microscopy or Xpert MTB/RIF testing. It is important to note down the complete address of all TB presumptives in the TB presumptive register.
**Request for examination of biological specimen for TB**

This is the standard form that accompanies a biological sample sent to a laboratory for smear microscopy, culture, Xpert MTB/RIF or DST. The form includes culture and DST as the NTP will make these services available at the national level in the future.

If analyses of several types of specimen (e.g., sputum and other fluids) are requested a separate request form should be used for each specimen.

If multiple analyses (e.g., culture and DST on the same sputum sample) are requested the results should be sent from the laboratory to the requestor as they become available, rather than waiting until all test results are confirmed.

The requestor completes the upper portion of the form including basic demographic and contact details of the patient being tested. Depending on the type of analysis required, the requestor also fills in the date of sample collection in the lower part of the form.

The lower part of the form is used to communicate results back to the facility that requested the tests using a standardized notation. The person responsible for the test result must be clearly identified.

**Laboratory register for smear microscopy and Xpert MTB/RIF**

This register can be used for both sputum-smear microscopy and Xpert MTB/RIF examinations.

If more than one specimen is being tested in the course of investigation of the same patient, as is commonly the case when serial sputa are tested using microscopy, the results are recorded on the same line. This also applies if both direct sputum smear microscopy and Xpert MTB/RIF examinations are carried out for the same patient with presumptive TB. If a patient is tested again during another diagnostic episode (e.g., if a patient with presumptive TB has a negative initial test and presents again with symptoms after a few months), the test results are registered in a new row. Results of tests undertaken for monitoring of patients on treatment are likewise entered in separate rows.

**Laboratory register for culture, Xpert MTB/RIF and drug susceptibility testing**

This register will be used for the national reference laboratory. The method of diagnostic testing (culture or Xpert MTB/RIF) is indicated in the first two columns under “Type of examination”.

If more than one specimen is being tested in the course of the investigation of the same patient, as is commonly the case when serial sputa are tested using microscopy, the results are recorded on the same line. This also applies if both direct sputum smear microscopy and Xpert MTB/RIF examinations are carried out for the same patient with presumptive TB. If a patient is tested again during another diagnostic episode (e.g., if a patient with presumptive TB has a negative initial test and presents again with symptoms after a few months), the test results are registered in a new row. Results of tests undertaken for monitoring of patients on treatment are likewise entered in separate rows.
**District TB register**

The district TB register is intended primarily for recording the data needed to monitor district performance, using indicators and reports about TB patients. It is also commonly used to summarise testing results and treatment decisions in order to determine whether basic diagnostic and treatment guidelines are correctly implemented. No information that is beyond this monitoring scope should be included in the register.

The register should contain the records of all patients diagnosed with TB and eligible for TB treatment, including those diagnosed with RR-TB or MDR-TB, regardless of whether treatment was actually started. All of these cases are notifiable and should be included in the summary case notification reports sent to higher levels. The registration date is the date on which the BMU decides that a patient has TB and is eligible for treatment.

Bacteriological examination before the start of treatment (“month 0”) now allows for the registration of results from an Xpert MTB/RIF test. Space is provided for recording whether the case is RR-TB or MDR-TB. Both smear and culture results can be recorded.

**Second-line TB treatment register**

The second-line TB treatment register is intended primarily to keep a record of those data that are important for generating indicators and reports of patients on second-line regimens for RR-TB or MDR-TB. In contrast to the district register, it is restricted to patients who have actually started on a second-line TB treatment regimen. This register is also commonly used to follow, at a glance, the adequacy of testing and treatment decisions.

The second-line TB treatment register should be updated regularly from the individual second-line TB treatment cards and from laboratory registers. Patients are recorded in the register consecutively by *date of registration*. A patient’s date of registration is the day when health staff enter him or her in the register; however, in some countries it may be the date when the review panel decided to register the patient for second-line treatment.

Bacteriological examination before the start of treatment (“month 0”) allows for the registration of results from an Xpert MTB/RIF test.

**TB treatment card**

The TB treatment card is filled as soon as the diagnosis of TB is made and when the treatment is initiated. It is kept at the health facilities where the patient receives treatment (either at the TB clinic, district hospital, CHC, PHC, Health post, etc.). For patients who have to be given treatment at the sub-centre or village level by a multi-purpose worker, a duplicate card is made and given to the most peripheral health staff directly supervising drug administration of the patient. In case a duplicate is used, the information is periodically transferred on to the main card. The ‘TB-responsible staff’ at the health facility transfers the relevant data, particularly the results of bacteriological examinations, from the treatment card to the TB register.
**TB patient identity card**

This card is completed as soon as the diagnosis of TB is made and while treatment is initiated. It is kept by the patient. The most important information in this card is the date of starting treatment, the regimen being used, and the drugs to be consumed under direct observation of the health worker, and the information on observation and collection of drugs at the health facility during the continuation phase. Appointment dates for collection of drugs during the continuation phase and follow-up examinations are entered on the reverse side of the card.

**PMDT treatment card**

This card is a key instrument for the DOT provider administering the drugs daily to the patient. When a patient starts a Category IV treatment, the DOT provider should fill in the treatment card. The card should be updated daily, ticking off the administration of drugs. It is the source from which to complete and periodically update the Category IV register. When or if the patient moves (for example from a specialized hospital to his/her district of origin for follow-up) the card, or a copy of the card, must follow the patient. A copy of this card may be used as a notification form and to inform about final outcome of treatment.

**2. Report forms**

**Quarterly report on TB case registration in the district**

This is the standard aggregated report of cases as recorded in the district register and of laboratory activity as recorded in the laboratory register.

The categories of cases in the report are stratified by whether they are bacteriologically confirmed or clinically diagnosed, by site of disease and by previous history of treatment. For all incident cases (new and relapses), a breakdown by age group and sex is requested. The form also captures the yield of bacteriological tests among patients with presumptive TB tested, and the yield of HIV testing among TB cases tested.

Among HIV-infected cases, the numbers on ART and CPT during the quarter are recorded.

**Quarterly report on TB treatment outcomes in the district**

This is the standard quarterly report used to monitor treatment outcomes for all TB cases that have not been started on second-line treatment.

The report enumerates the treatment outcomes of patients registered (i.e., recorded in the district register) in the quarter that ended 12 months previously. For example, if this report is completed at the close of the second quarter data are compiled on patients registered in the second quarter of the previous calendar year.
This report **excludes**:

- Patients who were transferred in from another BMU;
- Patients who were found to have RR-TB or MDR-TB and who were started on a full MDR-TB treatment regimen (i.e., were moved to the second-line treatment register).

The report **includes** TB/HIV activities as this allows the NTP to update the data it has previously collected in the quarterly report on TB case registration in the basic management unit.

**Quarterly report on PMDT TB case finding**

This is the standard aggregated report of DR-TB cases as recorded in the PMDT register. The report is provided in two parts, one for all patients diagnosed and a second for all patients put on treatment.

**Interim report for MDR treatment**

Each quarterly cohort defined by the date of the start of PMDT registration should have an interim or preliminary outcome report after the initial months of treatment depending on the treatment regimen. This report should be prepared by the PMDT treatment coordinator based on the PMDT treatment register. Since reporting at the end of treatment is very late (after two or even three years), preliminary results are desirable for all cohorts.

**Quarterly PMDT treatment outcome report**

This is the standard quarterly report used to monitor treatment outcomes for all TB cases that have been started on second-line treatment. Reporting periods vary depending on the type of treatment regimen.

**Quarterly report on programme management**

This is completed at the district level by the DTC and sent to the national level. This report indicates the status of programme performance and the stock of drugs and logistics in the district.

Reports are completed by the staff at the district level on the first week of each quarter and sent to the national level. The data have to be analyzed at the district level. Remedial actions must be initiated immediately at the district level where the technical and managerial indicators have not been achieved. Reports and district-wise analysis must be sent to the central level NTP.
3 Transmission of reports

All sub districts have to submit reports on case-finding, smear conversion, results of treatment and programme management to the DTC. The DTC will compile the sub-district reports to generate the district level reports. The reports are:

- Quarterly report on case finding
- Quarterly report on sputum conversion
- Quarterly report on treatment outcome registered 12–15 months earlier
- Quarterly report on programme management.

These reports are to be completed in duplicate by each district TB coordinator; one copy will be sent to the central TB unit and the other retained for their records. The dates for analysing the results of the treatment (treatment outcomes) of patients who started treatment during a particular quarter are as shown in the example below:

<table>
<thead>
<tr>
<th>Start of treatment</th>
<th>Date of analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st January to 31st March 2020</td>
<td>1st week April 2021</td>
</tr>
<tr>
<td>1st April to 30th June 2020</td>
<td>1st week July 2021</td>
</tr>
<tr>
<td>1st July to 30th September 2020</td>
<td>1st week October 2021</td>
</tr>
<tr>
<td>1st October to 31st December 2020</td>
<td>1st week January 2021</td>
</tr>
</tbody>
</table>

4 Process of recording and reporting

When a TB presumptive is identified at a health facility, his/her name will be entered in the TB presumptive register. Then the laboratory form for sputum examination and Xpert MTB/RIF is completed to refer the patient for bacteriological investigation. In the designated microscopy or diagnostic centre, the name of the patient is entered in the laboratory register. When the physician decides the category of treatment for a patient who is diagnosed as having TB, the treatment card and patient identity card are prepared.

If the patient is diagnosed at the district CHC, the particulars are entered in the TB register on the same day and the TB number is allotted. If the patient is diagnosed in the sub-district, the address is verified, the patient is put on treatment at the CHC/HP and the registration is done during the supervisory visit of the DTC.
The treatment card is maintained at the CHC or health post where the patient is diagnosed. If the patient is to be treated in a health post or by a community volunteer, a duplicate card will be prepared and given to the DOT provider to record the DOT.

Treatment cards are organized at drug distribution centres according to the day of scheduled observation and the phase of treatment (intensive phase or continuation phase). When the patient swallows the medication under direct observation in this manner, the cards of patients who do not present for treatment will be apparent on the same day, and appropriate action for their retrieval can be taken. The health staff records the drug administration at the time of intake by the patient.

In cities (Dili and Baucau) diagnosis is also made in hospitals, where microscopy and treatment administration are done by hospital staff. After the doctor decides on the category of the patient, the treatment card and patient identity card are prepared, and the patient is registered in the TB register (by the visiting district TB coordinator) and allotted a TB number. The doctor explains the treatment schedule and refers the patient to the district CHC near his/her residence for DOT. When the DOT provider is a community volunteer, he/she will be given a duplicate treatment card together with the patient’s drugs.
# Adverse Event Reporting Format

<table>
<thead>
<tr>
<th>Patient’s Name:</th>
<th>Age: _ _</th>
<th>Sex:</th>
<th>PMDT No:</th>
<th>Date: _ / _ / _ _ _ _</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address:</td>
<td></td>
<td></td>
<td>Height (cm):</td>
<td>Weight (Kg):</td>
</tr>
<tr>
<td>Type of TB:</td>
<td></td>
<td></td>
<td>Type of Drug Resistance:</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td></td>
<td></td>
<td>RR/MDR-TB</td>
<td>RR/MDR + FQ/SLI</td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td></td>
<td></td>
<td>H mon/poly</td>
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</tr>
</tbody>
</table>

## Current regimen:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Date/Month/Year since the drug was started</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
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<tr>
<td>INH</td>
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<tr>
<td>Pyrazinamide</td>
<td></td>
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<tr>
<td>Ethambutol</td>
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<tr>
<td>Bedaquiline</td>
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<tr>
<td>Linezolid</td>
<td></td>
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<tr>
<td>Moxifloxacin</td>
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<tr>
<td>Levofloxacin</td>
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<tr>
<td>Clofazimine</td>
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<tr>
<td>Capreomycin</td>
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<tr>
<td>Cycloserine</td>
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<tr>
<td>Ethionamide</td>
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<tr>
<td>PAS</td>
<td></td>
<td></td>
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<tr>
<td>Delamanid</td>
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<tr>
<td>Streptomycin</td>
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</tbody>
</table>

## Details of the event:

Date of onset: __/__/____  Time of onset: __:__

(Describe the details related to the event)

## Type of Serious Adverse Event:

Death  □  Life threatening  □  Hospitalization  □  Permanent Disablity  □  Congenital anomaly  □
<table>
<thead>
<tr>
<th>Outcome of the event</th>
<th>Date of outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovered/resolved</td>
<td></td>
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<tr>
<td>Recovered/resolved with sequelae</td>
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<tr>
<td>Fatal</td>
<td></td>
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<tr>
<td>Recovering/resolving</td>
<td></td>
</tr>
<tr>
<td>Not recovering</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
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</tbody>
</table>

### Causality Assessment (to be done by ADSM Committee)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Certain</th>
<th>Probable</th>
<th>Possible</th>
<th>Unlikely</th>
<th>Not assessable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
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<tr>
<td>Streptomycin</td>
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### Results of other lab tests done

<table>
<thead>
<tr>
<th>Test</th>
<th>Date</th>
<th>Result</th>
<th>Test</th>
<th>Date</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum Smear</td>
<td></td>
<td>ALT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sputum Culture</td>
<td></td>
<td>AST</td>
<td></td>
<td></td>
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<tr>
<td>Xpert MTB/RIF</td>
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<td>Lactic acid</td>
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<tr>
<td>LPA</td>
<td></td>
<td>Lipase</td>
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<tr>
<td>HIV</td>
<td></td>
<td>Bilirubin</td>
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<td>CD4</td>
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<td>ESR</td>
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<td>Hb</td>
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<td>WBC</td>
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<td>Creatinine</td>
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<td>B.Urea</td>
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<td>B. Glucose</td>
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<td>HbA1c</td>
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<td>TSH</td>
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<td>S. Potassium</td>
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<td>S Calcium</td>
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<td>S. Magnesium</td>
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<td>CXR</td>
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<td>ECG</td>
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