

# PCS GUIDELINES

## Diagnosis & Management of Drug-susceptible Tuberculosis

**A National Clinical Guideline**

2017

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## **Introduction**

Tuberculosis causes a great deal of ill health and an enormous burden on the population of low-income countries. The tuberculosis situation, like many other developing countries is very serious in Pakistan. It is one of the major public health problems in Pakistan. Pakistan ranks 5<sup>th</sup> among TB high burden countries worldwide which together accounts for 56% of the global total.

As per WHO estimates, Total cases of tuberculosis reported in 2016 in Pakistan were 366061 out of them new and relapse cases were 356390 and retreatment were 8091(excluding relapse registered in 2015) with prevalence of 397 per 100,000 population and incidence of 268 rate per 100,000 population and the majority of the cases are in productive age group. Pakistan is also estimated to have 6<sup>th</sup> highest prevalence of multidrug-resistant TB with 4.2% MDR-TB in new cases and 16% in retreatment TB cases.

Although high case detection rates have been achieved in the country under NTP, the delay in diagnosis, unsupervised inappropriate and inadequate drug regimens, poor follow up and lack of social support program for high risk populations are some of the reasons for not reaching the target cure rates and emergence of Drug Resistant forms of Tuberculosis. Our country has currently annual death rate of 24 per 100,000\* people attributed to Tuberculosis. We have achieved 50% mortality rate reduction in 2015 as compared with 1990.

Cure of cases of active tuberculosis is the key to effective control of the disease. Proper treatment of tuberculosis patients reduces suffering and prevents death from tuberculosis. The purpose of these guidelines is to help doctors and related health workers in the identifications of TB suspects, diagnosis and treatment of a TB patient and to underline their important or essential role in the control of Tuberculosis in the community. These guidelines have been prepared to develop a consensus management of tuberculosis preferably in programmatic settings in line with International Standards in Tuberculosis Care.

## **What is Tuberculosis?**

Tuberculosis is an infectious bacterial disease caused by *Mycobacterium tuberculosis* which most commonly affects the lungs. Mycobacteria are small rod-shaped bacilli that can cause a variety of diseases in humans. There are three main groups:

1. *Mycobacterium tuberculosis* complex: this group includes *M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti*, and *M. canetti*. They all can cause “tuberculosis” in humans. The vast majority of tuberculosis is caused by *M. tuberculosis*, with the other organisms being relatively rare. Their treatment is similar (*M. bovis* is innately resistant to pyrazinamide and *M. africanum* is resistant to thioacetazone). This guide only addresses disease caused by *Mycobacterium tuberculosis* complex.
2. *Mycobacterium leprae* causes leprosy.
3. Non tuberculous mycobacteria (NTM): this group includes all the other mycobacteria that can cause diseases in humans. NTM sometimes can cause clinical manifestations (in the lungs, skin, bones, or lymph nodes) similar to those of tuberculosis. Most NTM exist in the environment, are not usually spread from person to person and are often non-pathogenic in persons with intact immune system or healthy lung tissue.

All mycobacteria are classical acid-fast organisms and are named so because of their ability to retain stains used in evaluation of tissue or sputum specimens (Ziehl-Neelsen stain).

*M. tuberculosis* multiplies more slowly and causes disease weeks or even months to years after infection. *M. tuberculosis* is a strictly aerobic bacterium. It therefore multiplies better in pulmonary tissue (in particular at the apex, where oxygen concentration is higher) than in the deeper organs.

## **How Does Tuberculosis Develop?**

Tuberculosis is transmitted from person to person via droplets from the throat and lungs of people with the active respiratory disease. A healthy person might be infected by inhaling these tiny particles and developing a primary complex in the lungs. Infection with *Mycobacterium tuberculosis*, in most healthy people, often causes no symptoms since the person’s immune system acts to wall off the bacteria. However, in some people the tuberculosis bacteria will spread from the primary lung lesion to other parts of the body via the blood stream and lymphatics or by direct extension, and in this way may affect any organ.

## **Evolution of TB infection and disease in humans**

When a person inhales infectious droplets containing *M. tuberculosis*, most of the larger droplets become lodged in the upper respiratory tract (nose and throat), where infection is unlikely to develop. However, smaller droplet nuclei may reach the small air sacs of the lung (the alveoli), where infection may begin.

## **Primary infection**

After transmission, *M. tuberculosis* multiplies slowly, in most cases in the terminal alveoli of the lungs (primary focus) and in the lymph nodes of corresponding drainage areas: this represents the primary infection. The primary focus and related hilar lymphadenopathy form the primary complex. In one to two

months, due to the action of lymphocytes and macrophages (cellular immunity), the primary focus will be contained and encapsulated with a central zone of parenchymal necrosis (caseous necrosis). It is at this moment that specific TB immunity appears, and a positive skin reaction to tuberculin is observed<sup>4,5</sup>. This stage is usually asymptomatic; however, in some rare cases, hypersensitivity reactions may occur.

Note: A small area of granulomatous inflammation will occur in the alveoli, which is not usually detectable on chest X-ray unless it calcifies or grows substantially. It is called a primary focus.

In the majority of cases (90 to 95% of non-HIV infected patients), the pulmonary lesions gradually heal. In 5 to 10% of the cases, the pulmonary lesion will progress to active disease either by gradual progression and/or spread via lymphatics or blood or by reactivation (often many years later) of primary or secondary lesions.

### **Active TB**

Before immunity is established, bacilli from the primary infectious focus or from a near-by lymph node can be transported and disseminated throughout the body via the lymph system or the bloodstream. Secondary foci containing bacilli can be born this way, particularly in the lungs, lymph nodes, serous membranes, meninges, bones and kidneys. As soon as an immune response is mounted, most of these foci spontaneously resolve. Yet, a number of bacilli may remain latent in the secondary foci for months or even years. Different factors can reduce immunity (e.g. HIV infection) and lead to reactivation of the bacilli and their multiplication in one or more of these foci. This reactivation or progression of the primary or secondary foci results in “active TB disease”. While active TB may occur after months or years without clinical signs following primary infection, it is estimated that half of the cases of active TB appear in the year following infection.

### **Risk factors for developing active TB**

The risk depends on a number of factors including those that lead to a weakened immune system, damaged lungs, or the intensity and duration of exposure:

#### **Host immune defences:**

- HIV infection (risk multiplied by 20-40);
- Diabetes mellitus (risk multiplied by 3-5);
- Malnutrition;
- Prolonged therapy with corticosteroids (such as prednisolone) and other immuno - suppressive therapies;
- Certain types of cancer (e.g., leukaemia, Hodgkin's lymphoma, or cancer of the head and neck);
- Severe kidney disease;
- Alcoholism;

- Substance abuse;
- Age:
  - Young children (children under 5 have twice the risk and higher risks are observed for those under 6 months);
  - Persons over sixty years have 5 times the risk;
- Pregnancy.

**Conditions that damage the lung:**

- Tobacco smoking;
- Silicosis.

**Intensity of exposure (number of inhaled bacilli):**

- Contagiousness of the source;
- Environment and proximity in which the exposure took place;
- Duration of exposure;
- Residents and employees of high-risk congregate setting.

**Prognosis**

TB is a severe and often deadly disease without treatment. After 5 years without treatment, the outcome of smear-positive pulmonary TB (PTB) in HIV-negative patients is as follows:

- 50-60% die (case fatality ratio for untreated TB);
- 20-25% are cured (spontaneous cure);
- 20-25% develop chronic smear-positive TB.

With adequate treatment, the case fatality ratio (CFR) often falls to less than 2 to 3% under optimal conditions. Similar CFRs are seen with untreated EPTB and smear-negative PTB, with an equivalent fall in CFR with adequate treatment. Untreated TB in HIV-infected patients (not on antiretrovirals) is almost always fatal. Even on antiretrovirals, the CFR is higher than in non-HIV infected patients.

## **FACTORS MODIFYING TB EPIDEMIOLOGY**

There are four major factors that influence TB epidemiology: (1) socioeconomic development; (2) TB treatment; (3) HIV infection; and (4) BCG vaccination.

### **Socioeconomic development**

In European countries, the incidence and specific mortality of TB have diminished by 5 to 6% per year since 1850. This progressive improvement dates back to before the era of vaccination and antibiotics and was correlated with socioeconomic development (improvement of living conditions, nutritional status of populations, etc.). TB is a disease of the poor: over 95% of cases occur in resource-constrained countries and in poor communities. In industrialised countries, TB generally affects the most disadvantaged social groups.

### **TB treatment**

Diagnosing and initiating effective treatment in a patient early in the course of their TB disease, before they can infect many people, is considered the most effective preventive measure against TB. Effective treatment substantially reduces or eliminates disease transmission from smear-positive patients in less than one month after initiation of treatment. Since the introduction of anti-TB treatment, a rapid reduction of the annual risk of infection (ARI) has been observed in many industrialised countries, with the infection risk diminishing by approximately 50% every 5 to 7 years during this period. This tendency was observed in countries having a BCG vaccination programme, as well as, in those without one. This reduction of the risk of infection is a direct consequence of detection programmes, diagnosis and treatment.

### **HIV infection**

Immunodeficiency induced by HIV infection is a major risk factor for progression of TB infection and has a dramatic impact on the epidemiology of TB. While the lifetime risk of TB disease after infection is approximately 10%, patients infected both with HIV and *M. tuberculosis* have an approximate risk of 10% annually. Approximately 12 to 14% of TB cases in the world are at present among HIV patients. The African region accounts for 82% of the TB cases among HIV patients. The impact of HIV on TB epidemiology can only increase with the spread of the HIV epidemic in Asia, where two-thirds of the world's *M. tuberculosis*-infected population lives.

### **BCG vaccination**

The effect of BCG vaccination is controversial. Two notions may be distinguished: the effectiveness of BCG at an individual level and the epidemiological impact of this vaccination. Effectiveness of BCG at an individual level Even though results of controlled surveys are contradictory (efficacy ranging from 0 to 80%), it is acknowledged that BCG, if administered before primary infection (as is done in the practice of giving it at birth), confers a protection of 40 to 70% for a period of approximately 10 to 15 years<sup>13,14,15,16</sup>. Protection from the severe forms of TB in children (miliary and meningitis) is estimated at 80%. Epidemiological impact of vaccination The analysis of public health statistics of some

European countries has shown that BCG vaccination reduces the number of active TB cases in vaccinated subjects as compared to those unvaccinated. Models demonstrate that even moderately effective vaccines could have a significant effect on reducing tuberculosis epidemics if they can be coupled with moderate to high treatment rates. Despite some protection of the BCG vaccination, the impact of BCG vaccination on TB transmission and the TB epidemic is generally considered quite minimal and more effective vaccines are needed.

### **Other factors**

Other modifying factors include infection control measures and isoniazid preventive therapy for latent TB. The degree to which the TB epidemiology is affected by these measures is not known.

### **Anatomical Sites of Tuberculosis**

For the purpose of registration and treatment TB is divided in two broad categories i.e 1. Pulmonary TB.  
2. Extra Pulmonary TB.

#### **Pulmonary Tuberculosis:**

Tuberculosis affects the lungs in more than 80% of cases. Pulmonary tuberculosis in adults is often sputum smear-positive and therefore highly infectious. Smear negative cases are 7-10 times less infectious than smear positive cases.

#### **Extra-Pulmonary Tuberculosis:**

Affects various organs such as lymph nodes, pleura, pericardium, bones and joints, genito-urinary tract, the nervous system, intestines, skin and many other parts of the body. Diagnosis is often difficult and should preferably be made by Specialists using specific diagnostic tools to confirm the diagnosis.

Clinical presentation of Tuberculosis

- Pulmonary tuberculosis (PTB)
- Extrapulmonary tuberculosis (EPTB)
- Disseminated or miliary tuberculosis
- Clinical presentation in HIV-infected patients
- Summary of clinical presentations of tuberculosis

## **Pulmonary tuberculosis (PTB)**

Certain signs of PTB are quite typical: prolonged cough (lasting more than 2 weeks) and sputum production, while others are less so: weight loss, anorexia, fatigue, shortness of breath, chest pain, moderate fever, and night sweats. Haemoptysis (blood in sputum) is a characteristic sign present in about one third of patients. All these signs are variable and evolve in a chronic, insidious manner. History taking and questioning the patient are therefore of the utmost importance.

Advanced forms and complications are not uncommon. These include:

- Respiratory insufficiency due to extensive lesions and destroyed lungs;
- Massive haemoptysis due to large cavities with hypervascularisation and erosion of vessels;
- Pneumothorax due to the rupture of a cavity in the pleural space.

In an endemic area, the diagnosis of PTB is to be considered, in practice, for all patients who have experienced respiratory symptoms for more than 2 weeks.

## **Extrapulmonary tuberculosis (EPTB)**

Starting from a pulmonary localisation (primary infection), *M. tuberculosis* can spread to other organs during a silent phase, generally at the beginning of the infection. Active TB can develop in many other parts of the body, in particular lymph nodes, meninges, vertebrae, joints, kidneys, genital organs and the abdominal cavity. EPTB forms can develop at any age. Young children and HIV infected adults are more susceptible. EPTB forms present with a variety of clinical characteristics. However, a common characteristic is the insidious evolution with gradual deterioration of the physical condition. Furthermore, there is a lack of response to symptomatic or non-tuberculosis anti-infective treatments. EPTB may be associated with a pulmonary localisation, which should be searched for whenever EPTB is diagnosed or suspected.

### **1. Lymph node tuberculosis**

Lymph node TB is a common presentation particularly in certain areas of Asia, where it represents up to 25% of TB cases. This form is more common in children and HIV infected patients. The presentation of lymph node tuberculosis is non-inflammatory adenopathies, cold and painless, single or multiple, usually bilateral, evolving in a chronic mode towards softening and fistulisation. Cervical lymphadenopathy is most frequent, followed by axillary and mediastinal forms. Diagnosis is mainly clinical, however fine needle aspiration can be done if the diagnosis is in question. Adenopathies usually disappear in less than 3 months after treatment initiation. Paradoxical reactions may be observed at the beginning of treatment (appearance of the lymph node getting worse with abscesses, fistulas or other lymph nodes appearing) and often a change in the treatment is not needed.

Differential diagnosis includes malignancies (lymphoma, leukaemia, ear/nose/throat tumours, Kaposi sarcoma) and other infections (bacterial, viral, non-tuberculosis mycobacteria, toxoplasmosis, HIV infection, syphilis, African trypanosomiasis).

## 2. Tuberculous meningitis

Meningitis due to tuberculosis is most common in children below 2 years of age 5 and in HIV-infected adults. Headaches, irritability, fever, and an altered mental status accompany the beginning of the disease, often in a variable manner, which is progressive in nature. The meningeal syndrome (stiff neck, hypotonia in infants, photophobia and headache) is present in most cases. Vomiting may be present. The impairment of the third cranial nerve is a sign that can accompany TB meningitis (oculomotor paralysis). The main differential diagnoses are other forms of meningitis where the cerebrospinal fluid (CSF) is clear – viral/fungal meningitis or incompletely treated bacterial meningitis are the most common. TB meningitis is a medical emergency, and any delay in diagnosis/treatment may result in irreversible neurological sequelae.

## 3. Tuberculosis of bones and joints

Tuberculosis of bones and joints is mostly found in children, probably because of better vascularisation and oxygenation of osteo-articular structures during growth.

**Arthritis:** Often arthritis due to TB is a chronic monoarthritis, starting insidiously, with little or no pain and accompanied by joint destruction. The joints most often affected are the hips, knees, elbows and wrists. Half of the patients with TB arthritis have PTB at the same time.

**Osteitis:** This is the less frequent presentation of TB of the bones. It may be a primary osteitis or an osteitis complicating arthritis. It affects long bones and is occasionally accompanied by cold abscesses. Like arthritis, it is distinguished from common bacterial infections by the contrast of slight symptoms and the extent of destruction detected by radiography.

**Spondylodiscitis (TB of the spine or Pott's disease):** TB of the spine affects vertebrae and disks, bringing about destruction and deformation of the spine. A missed diagnosis of thoracic or cervical spinal TB can result in paralysis. Dorsal localisation is the most frequent followed by lumbar and lumbosacral areas. Localised pain may precede the appearance of the first radiological anomalies (destruction of an inter-vertebral disk) by several months. A para-vertebral cold abscess may accompany osteo-articular lesions, yet neurological signs may complicate them. The diagnosis is often made based on the clinical history and X-ray, as biopsy and culture is difficult to perform in resource-constrained settings. Deterioration of physical condition and prolonged and insidious clinical history of osteitis or arthritis are in favour of TB aetiology as opposed to bacterial osteomyelitis or brucellosis. The patient may have a history of not responding to broad-spectrum antibiotics. months. A para-vertebral cold abscess may accompany osteo-articular lesions, yet neurological signs may complicate them.

## 4. Genitourinary tuberculosis

Renal involvement is frequent and may be asymptomatic for a lengthy period of time, with a slow development of genitourinary signs and symptoms including: dysuria, urinary frequency, nocturia, urgency, back and flank pain, abdominal pain, tenderness/swelling of the testes or epididymitis and haematuria. General physical condition is preserved most of the time with only about 20% of patients having constitutional symptoms.

Diagnosis is suspected in the presence of pyuria (white blood cells in the urine) and microor macroscopic haematuria, which does not respond to broad-spectrum antibiotics. Examination of the urine aids in diagnosis

In women, genital tract contamination can also happen by a haematogenous path. Abdominal pain, leucorrhoea and vaginal bleeding are variable, non-specific signs of genital tract tuberculosis. Extension may be found in the peritoneum with resulting ascites. The presenting complaint leading to the diagnosis of genitourinary disease is often sterility. In men, genital localisation is secondary to renal localisation. It is manifested most often by epididymitis with scrotal pain.

### **5. Abdominal tuberculosis**

Abdominal TB commonly presents as ascites resulting from the peritoneal localisation of the infection. The frequency of chronic ascites in tropical regions, with its many different causes, makes this relatively uncommon form of TB a common diagnostic challenge. Diagnosis is assisted greatly by examination of the ascitic fluid via paracentesis.

Besides ascites, clinical symptoms are non-specific: abdominal pain, diarrhoea and constitutional symptoms (feve night sweats, malaise, weight loss). The ascites may mask weight loss.

### **6. Tuberculous pleural effusion**

TB pleural effusion by itself is often asymptomatic, especially if less than 300 ml. When the effusion is large, shortness of breath may be present. Sputum production and cough may only be present if there is also pulmonary involvement, which is common. Constitutional symptoms such as fever, weight loss, night sweats, anorexia and malaise may also be present. This form of TB is more frequent in young adults. Diagnosis is assisted by examination of the pleural fluid via paracentesis.

### **7. Tuberculous pericardial effusion**

Clinical signs of a tuberculous pericardial effusion include: chest pain, shortness of breath, oedema of the lower limbs and sometimes ascites. The clinical examination may show pericardial friction rub, raised jugular pressure and tachycardia. The radiography and ultrasounds are key elements for diagnosis. Pericardiocentesis may be necessary in the event of acute heart failure resulting in haemodynamic compromise. It must be performed by experienced personnel in wellequipped hospitals.

### **8. Cutaneous tuberculosis**

The clinical presentation of cutaneous tuberculosis is chronic, painless, non-pathognomonic lesions, ranging from small papula and erythema to large tuberculomas. The diagnosis is based on culture from a biopsy.

## **Disseminated or miliary tuberculosis**

Miliary TB is a generalised massive infection characterized by diffusion of bacteria throughout the body. The disease may manifest as a miliary pattern or very small nodular shadows (“millet seeds”) in the lungs. It can occur immediately after primary infection or during reactivation of a latent site; it is thought to occur during haematological spread.

The classic acute form is mostly found in children, young adults and HIV patients. The presentation can be either abrupt or insidious, marked by a progressive deterioration of the patient’s physical condition. The clinical picture is often completed within one to two weeks and is characterized by a profoundly altered physical condition, marked wasting, headaches and constant high fever. Discrete dyspnoea and coughing suggest a pulmonary focus; however, lungs can often be clear on auscultation. A moderate hepatosplenomegaly is occasionally found. Certain forms of miliary TB evolve in a subacute fashion over several months. Given this non-specific clinical picture, typhoid fever and septicaemia should be considered in a differential diagnosis.

Diagnosis of miliary TB is confirmed by chest X-ray. When feasible, fundoscopy would reveal choroidal tubercles. Generally, sputum smear examination is negative. When there is no possibility of obtaining chest X-rays, the lack of response to broad-spectrum antibiotics is an argument in favour of miliary TB. In children, the risk of meningeal involvement is high (60-70%). Lumbar puncture should be routinely performed if miliary TB is suspected. The tuberculin skin test is more likely to be falsely negative than in any other form of TB. Miliary TB is a medical emergency.

## **Clinical presentation in HIV-infected patients**

TB is a leading cause of HIV-related morbidity and mortality, and it is one of the main opportunistic diseases. According to the WHO clinical staging of HIV/AIDS, HIV patients with pulmonary TB are in clinical stage III and HIV patients with extrapulmonary TB are in clinical stage IV.

In the early stages of HIV infection, when the immune system is functioning relatively normally, the clinical signs of TB are similar to those in HIV-negative individuals. As the immune system deteriorates in later stages of the disease, the patterns of TB presentation become increasingly atypical, with pulmonary smear-negative, disseminated, and extrapulmonary TB forms becoming more common. These cases are more difficult to diagnose and have a higher fatality rate than smear-positive cases.

HIV patients with PTB tend to experience more fever and weight loss compared to those who are HIV-negative. Yet, these patients suffer with less coughing and haemoptysis due to lesser inflammation and cavity formation. Smear microscopy is more often negative.

In HIV adult patients, the most common non-pulmonary forms of TB are lymphadenopathy, pleural effusion, pericarditis, meningitis, as well as, miliary (disseminated) TB. In HIV infected children, miliary TB, TB meningitis and diffuse lymphadenopathy are the most common non-pulmonary forms. PTB is also present in patients with EPTB. Immune reconstitution inflammatory syndrome (IRIS) is a clinical presentation of TB in patients starting antiretroviral therapy.

## **Tuberculosis in Children**

The diagnosis of TB in children relies on careful and thorough assessment of all the evidence derived from a careful history, clinical examination and relevant investigations, e.g. Tuberculin Skin Testing, Chest X-ray (CXR) and Sputum smear microscopy. Most children with TB have pulmonary TB. Although bacteriological confirmation of TB is not always possible, it should, nevertheless, be sought whenever possible, e.g. by sputum microscopy for children with suspected pulmonary TB who are old enough to produce a sputum sample. Newer diagnostics techniques like PCR and IGRA have an emerging role in diagnosis. A trial of treatment with anti-TB medications is not recommended as a method to diagnose TB in children. Treatment is same as for adults with parental supervision in DOTS programme. Regimens including Ethambutol are best avoided in children younger than five years.

### **When should Tuberculosis be suspected?**

The most common symptom of pulmonary tuberculosis is persistent cough usually productive of two weeks or more for which no cause has been found. The other associated symptoms may be fever, loss of appetite, weight loss, tiredness, night sweats, chest pain, shortness of breath and hemoptysis. The suspicion of tuberculosis is much more likely to be correct in patients with the above-mentioned symptoms and history of close contact with a smear-positive tuberculosis patient. For extra-pulmonary tuberculosis, symptoms depend on the organ involved. Tuberculosis should be suspected in the differential diagnosis of any patients with the following symptoms for example:

- Cough and shortness of breath with pleural or pericardial effusions.
- Swelling, occasionally with pus discharge when lymph nodes are affected.
- Joints pain and swelling.
- Headache, fever, neck stiffness and confusion in possible tuberculous men
- Backache with or without loss of function in lower limbs when there is Gibbu and spinal involvement.
- Abdominal pain, diarrhoea or ascites with abdominal involvement.
- Infertility when genital organs are affected.

## DEFINITIONS

Tuberculosis should be defined accurately for registration and programmatic management.

**Presumptive Tuberculosis:** Any person who presents with symptoms or signs suggestive of Tuberculosis (previously known as TB suspect). The most common symptom of pulmonary TB is a productive cough for more than 2 weeks, which may be accompanied by other respiratory symptoms (shortness of breath, chest pains, hemoptysis) and/or constitutional symptoms (loss of appetite, weight loss, fever, night sweats, and fatigue).

**Case of tuberculosis:** A definite case of TB (defined below) or one in which a health worker (clinician or other medical practitioner) has diagnosed TB and has decided to treat the patient with a full course of anti-TB treatment.

Note. Any person given treatment for TB should be recorded as a case. Incomplete “trial” TB treatment should not be given as a method for diagnosis.

**Bacteriologically confirmed TB case:** is one from whom a biological specimen is positive by smear microscopy, culture or by a newer method such as Xpert MTB/RIF assays (GeneXpert) or molecular line probe assay. All such cases should be notified, regardless of whether TB treatment has started.

**Clinically diagnosed TB case:** is one who does not fulfill 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. This definition includes cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extra pulmonary cases without laboratory confirmation.

Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

Bacteriologically confirmed or clinically diagnosed cases of TB are also classified according to: –

- Anatomical site of disease
- History of previous treatment
- Drug resistance
- HIV status.

### Classification based on anatomical site of disease

**Pulmonary tuberculosis (PTB):** This refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree.

Miliary TB is classified as PTB because there are lesions in the lungs. Tuberculous intra-thoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extrapulmonary TB.

A patient with both pulmonary and extrapulmonary TB should be classified as a case of PTB.

**Extrapulmonary tuberculosis (EPTB):** This refers to 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

### **Classification based on history of previous TB treatment (patient registration group)**

Classifications based on history of previous TB treatment are slightly different from those previously published.

They focus only on history of previous treatment and are independent of bacteriological confirmation or site of disease

**New patients:** who have never been treated for TB or have taken anti-TB drugs for less than 1 month.

**Previously treated patients:** who have received 1 month or more of anti-TB drugs in the past. They are further classified by the outcome of their most recent course of treatment.

**Relapse patients:** who 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).

**Treatment after failure patients:** are those who have previously been treated for TB and whose treatment failed at the end of their most recent course of treatment.

**Treatment after loss to follow-up patients:** have previously been 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.) Other previously treated patients are those who have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.

**Patients with unknown previous TB treatment history:** do not fit into any of the categories listed above.

New and relapse cases of TB are **incident** TB cases.

### **Classification based on HIV status**

**HIV-positive TB patient** refers to any bacteriologically confirmed or clinically diagnosed case of TB 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 enrolment in the pre-ART register or in the ART register once ART has been started.

**HIV-negative TB patient** refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a negative result from HIV testing conducted at the time of TB diagnosis. Any HIV-negative TB patient subsequently found to be HIV-positive should be reclassified accordingly.

**HIV status unknown TB patient** refers to any bacteriologically confirmed or clinically diagnosed case of TB who has no result of HIV testing and no other documented evidence of enrolment in HIV care. If the patient's HIV status is subsequently determined, he or she should be reclassified accordingly.

## Treatment outcome definitions

The new treatment outcome definitions make a clear distinction between two types of patients

- Patients treated for drug-susceptible TB
- Patients treated for drug-resistant TB using second-line treatment (defined as combination chemotherapy for drug-resistant tuberculosis which includes drugs other than those in Group 1).

The two groups are mutually exclusive. Any patient found to have drug-resistant TB and placed on second line treatment is removed from the drug-susceptible 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.

## Treatment outcomes for TB patients (excluding patients treated for RR-TB or MDR-TB)

All bacteriologically confirmed and clinically diagnosed TB cases should be assigned an outcome from this list except those with RR-TB or MDR-TB, who are placed on a second-line drug regimen.

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

Patients found to have an RR-TB or MDR-TB TB strain at any point in time should be started on an adequate second-line drug regimen. These cases are excluded from the main TB cohort when calculating treatment outcomes<sup>1</sup> and included only in the second-line TB treatment cohort analysis. If treatment with a second-line drug regimen is not possible, the patient is kept in the main TB cohort and assigned an outcome from among those in table above

**Classification based on drug resistance** (adopted from WHO 2014 DR TB companion handbook)  
Cases are classified in different types based on drug susceptibility testing (DST) of clinical isolates confirmed to be *M. tuberculosis*:

**Mono-resistance:** resistance to one first-line anti-TB drug only.

**Poly-resistance:** resistance to more than one first-line anti-TB drug, other than both isoniazid and rifampicin together

**Multidrug resistance (MDR):** resistance to at least both isoniazid and rifampicin.

**Extensive drug resistance (XDR):** resistance to any fluoroquinolone, and at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance.

**Rifampicin resistance (RR):** resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, in the form of mono-resistance, poly-resistance, MDR or XDR.

- Poly-/mono-resistant TB without rifampicin resistance. Some of these cases may have second-line anti-TB drugs added to their treatment. These patients should be treated in the program registered in separate ENRS as per program protocols.
- XDR-TB (confirmed or presumptive). Patients maybe started on XDR-TB treatment on the basis of a laboratory diagnosis or, in its absence, because of significant risk.
- Patient based on previous H/O treatment (registration group): New, previously treated, Relapse patients, Treatment after failure, Treatment after lost to follow up, other previously treated, patients with unknown previous TB treatment history.

#### **Definitions of Conversion & Reversion:**

The terms “conversion” and “reversion” of culture as used here are defined as follows

- **Conversion (to negative):** culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion.
- **Reversion (to positive):** culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining Treatment failed, reversion is considered only when it occurs in the continuation phase.

#### **Treatment Outcomes for RR-TB/MDR-TB/XDR-TB patients treated using second-line treatment Cured:**

- Treatment completed as recommended by the national policy (minimum 20 months with 18 months past culture conversion) without evidence of failure AND 3(three) or more consecutive cultures taken at least 30 days apart are negative after the intensive phase

- For the purpose of declaring cure, the patient should have three consecutive negative cultures reported by the end of treatment, ensuring that cultures are done as per national policy.
- If there is one positive culture by the end of treatments, this positive culture should be followed by 3 negative cultures Treatment completed.

**Treatment completed** as recommended by the national policy (minimum 20 months 18 months past culture conversion) without evidence of failure BUT no record that three consecutive cultures taken at least 30 days apart are negative after the intensive phase.

**Treatment failed** Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of:

- Lack of conversion by the end of the intensive phase, or
- Bacteriological reversion in the continuation phase after conversion to negative, or
- Evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or
- Adverse drug reactions (ADRs).

**NOTE:**

- If an MDR TB patient has 4 positive cultures and is on month 6 of treatment, it is suggested to repeat DST to SLDs and act accordingly as per result. Please note that there may be a delayed response to treatment in XDR-TB patients.
- In case of reversion in continuation phase repeat DST to SLDs, continue with treatment and decide as per further response to treatment and in the light of result of DST.
- On the basis of baseline DST results there is only adjustment in treatment as per DST pattern and not to be declared failure.

**Died:** A patient who dies for any reason during the course of treatment

**Lost to follow-up:** A patient whose treatment was interrupted for 2 consecutive months or more.

**Not evaluated:** A patient for whom no treatment outcome is assigned. (This includes cases “transferred out” to another treatment unit and whose treatment outcome is unknown)

**Treatment success:** The sum of cured and treatment completed

- For Treatment failed, lack of conversion by the end of the intensive phase implies that the patient does not convert within the duration of intensive phase applied by the program.
- If no specific duration is defined, an 8-month cut-off is proposed.
- For regimens without a clear distinction between intensive and continuation phases, a cut-off 8 months after the start of treatment is suggested to determine when the criteria for Cured, Treatment completed

and Treatment failed start to apply provided that the patient had at least 18 months of treatment past culture conversion.

The sum total of Cured and Treatment completed is commonly used as an indicator of favorable outcome, or Treatment success. The outcome Cured is restricted to pulmonary bacteriologically confirmed TB cases only.

### **Latent Tuberculosis Infection (LTBI)**

Latent Tuberculosis Infection (LTBI) is defined as exposure and infection of an individual by Mycobacterium Tuberculosis without clinical signs of disease. LTBI is associated with less than 10% chances of developing overt Tuberculosis over a period of 10 years. It is diagnosed best by Interferon Gamma Release Assays (IGRA) and less accurately by Tuberculin Skin Testing (TST).

# DIAGNOSIS OF TUBERCULOSIS

## TB CASE FINDING APPROACHES

Currently the case detection rate CDR in Pakistan is about 64 %. This means that more than 200,000 TB cases are missed annually in Pakistan against estimated 600,000 incident cases. About 74% of the "missed cases" exist in 10 countries and Pakistan stands third among these countries and contribute 7% of the globally missed TB cases.

To improve tuberculosis control, patient with active TB disease must be diagnosed quickly and treated immediately. Passive case finding approaches were used mostly for TB case finding in the past however now NTP recommends using active case finding approaches in certain population to enhance case finding. Main difference between two approaches is described below.

## PASSIVE TUBERCULOSIS CASE FINDING

Relies on patients seeking medical help because they feel unwell, Examination is recommended of:

- Presumptive TB cases (cough >two weeks or with relevant symptoms) who present themselves at health facilities
- Patient with radiological examination of the chest showing an abnormality consistent with Tuberculosis.

Passive case finding is likely to delay the diagnosis and treatment of tuberculosis and increases *M tuberculosis* transmission

## ACTIVE TUBERCULOSIS CASE FINDING

Where health workers seek out and diagnose individuals with TB mainly in the communities who have not sought care on their own initiative- The ultimate goal of active TB case finding is to reduce TB transmission in the community through improved case detection and reduction in diagnostic delays. Active tuberculosis case finding is recommended among

- Household contacts of all pulmonary TB patients
- Marginalized population e.g. Urban slums
- High vulnerable population prisons and institutes
- Internally displaced population
- Patients with positive HIV status

## **DIAGNOSTIC TOOLS FOR TUBERCULOSIS**

### **AFB SMEAR MICROSCOPY**

Mycobacteria are distinguished from other micro-organisms by thick lipid-containing cell-walls that retain biochemical stains despite decolourisation by acid-containing reagents (so-called 'acid-fastness'). Sputum smear microscopy allows a rapid, inexpensive and reliable identification of patients with pulmonary tuberculosis (PTB) where there are more than 5000 bacilli/ml of sputum.

Shortcomings of smear microscopy are that it cannot distinguish *Mycobacterium tuberculosis* from NTM, nor viable from non-viable organisms, or drug-susceptible from drug-resistant strains. Also smear sensitivity is further reduced in patients with extra-pulmonary TB, those with HW-co-infection, and those with disease due to non-tuberculous mycobacteria (NTM). However, in areas of high TB prevalence, positive smears have a very high probability of being *M. tuberculosis*.

The reliability of sputum microscopy depends on the quality of sputum collection. Sputum produced on early morning often shows a higher concentration of *M. tuberculosis*. Importantly, the reliability of sputum microscopy depends on the proper preparation and interpretation of slides. Thus, laboratory technicians must be properly trained and quality control checks must be regularly carried out in a supervising laboratory.

It is recommended that all patients presumptive of PTB should submit at least two sputum specimens. Studies have shown that, when collection and examination techniques are correctly conducted, about 80% of sputum smear-positive patients are found during the first sputum examination and over 15% more during the second. Successive, repeated examinations yield fewer positives. Usually, a first sample is collected at the time of the consultation when the patient is identified as a suspected TB case. A second sample is collected in the early morning the day after the initial consultation (and the patient brings the sample to the health facility if it is collected at home).

In order to limit the number of visits to the health facility, "frontloaded microscopy" (also referred to as 'same day' or 'spot-spot' microscopy) can be performed. Two sputum specimens are collected one hour apart. This strategy has shown similar results to the standard strategy over two days (spot-morning-spot) in terms of diagnostic yield.

### **Conventional light microscopy**

Ziehl-Neelsen (ZN) light microscopy performed directly on sputum specimens is suitable for all laboratory service levels, including peripheral laboratories at primary health care centers or districts hospitals. In general, one ZN microscopy centre per 100,000 populations is sufficient; however, expansion of ZN microscopy services should also take into account the location and utilization of existing services, urban/rural population distribution, and specimen transport mechanisms.

### **Conventional fluorescent microscopy**

Fluorescence microscopy is on average 10% more sensitive than ZN microscope. Conventional fluorescent microscopes require technical expertise and capital and running costs is considerably higher. Conventional fluorescent microscopy is therefore recommended at intermediate laboratory level where more than 100 smears are examined per day.

**Light-emitting diode (LED) fluorescent microscopy:** LED microscopes are cost effective as require less power, are able to run on batteries, the bulbs have a very long half-life. WHO evaluation (2007) confirmed the diagnostic accuracy of LED microscopy compared to conventional fluorescent microscopy, and superior efficiency of LED over conventional ZN microscopy. It is therefore recommended that conventional fluorescence microscopy be replaced by LED microscopy and that LED microscopy be phased in as an alternative for conventional ZN light microscopy in both high and low-volume laboratories.

### **Culture and species identification**

Mycobacterial culture and identification of *M. tuberculosis* provide a definitive diagnosis of TB and is the gold standard for diagnosis. It can detect far lower numbers of AFB, the detection limit being around 10-100 organisms per ml and thus can detect cases earlier (often before they become infectious). Culture also provides the necessary isolates for conventional DST. Moreover, culture makes it possible to identify the mycobacterial species. It therefore seems that, for the diagnosis of tuberculosis, both the sensitivity and the specificity of culture methods are better than those of smear microscopy as well as X-pert MTB/Rif assay. However, it is not considered for use as an initial diagnostic test because it demands more resources, is technically complex and requires infrastructure of biosafety laboratory for processing and requires a much longer wait of 2-6 weeks for results (1-2 weeks on liquid culture media and 4-8 weeks on solid culture media) than both the X-pert MTB/Rif test and sputum-smear microscopy, both of which can provide final test results in less than 1 day.

Solid and liquid culture methods are suitable for Regional /Provincial and National reference laboratories (or regional laboratories in large countries). Usually, one culture laboratory is adequate to cover 500,000 - 1 million populations. Solid culture methods are less expensive than liquid culture systems, but results are invariably delayed due to the slow growth of mycobacteria. Liquid culture increases the case yield by 10% over solid media, and automated systems reduce the diagnostic delay to days rather than weeks. Liquid systems are, however, more prone to contamination and the manipulation of large volumes of infectious material mandates appropriate and adequate biosafety measures.

Culture should play a bigger role in diagnosis and patient follow-up due to the limited value of direct microscopy for:

- Confirmation of failure cases;
- To obtain Culture isolates for conventional DST.
- Diagnosis of EPTB;
- Confirmation of smear negative TB when the diagnosis is in doubt;

- Distinction between *M. tuberculosis* complex and NTM;
- Monitoring treatment and outcome evaluation for patients on second-line anti-TB drugs.

Once there is growth on either a solid or liquid media, the organism must be identified. There are a number of ways to identify *M. tuberculosis*. The tests can be phenotypic (the most common being the niacin test) or genotypic (which use DNA analysis, Section 3.4). Given the complexities associated with phenotypic identification, genetic tests are preferred. The drawback is their cost. Nonetheless, laboratories performing cultures, at a minimum, should be able to conduct identification tests for *M. tuberculosis* that follow international guidelines.

### **Phenotypic drug susceptibility tests (DST)**

Phenotypic DST determines if a strain is resistant to an anti-TB drug by evaluating the growth (or metabolic activity) in the presence of the drug. The laboratory performing phenotypic DST should be specialised in mycobacterial cultures, reliable and subject to external quality assessment, often by a supranational laboratory or national reference laboratory. The reliability of DST varies from one drug to another. For Group 1 anti-TB drugs, DST is very reliable for rifampicin and isoniazid but less so for pyrazinamide and much less for ethambutol. DST for aminoglycosides, polypeptides and fluoroquinolones have been tested in different laboratories and shown to have relatively good reliability and reproducibility. DST to other second-line drugs (para aminosalicylic acid, ethionamide and cycloserine) is much less reliable and reproducible.

### **Molecular techniques**

- Automated real time PCR (Xpert MTB/RIF)
- Line probe assays (LPA)

Molecular (or genotypic) tests can be used to diagnose TB through the amplification of nucleic acids (DNA or RNA). They are also used to detect drug resistance through identifying genetic mutations (drug-resistant alleles) in the bacterium responsible (genotypic DST). So far two types of assays and platforms have been developed.

#### **1 Automated real time PCR (Xpert MTB/RIF)**

The Xpert MTB/RIF assay is a new test that is revolutionizing tuberculosis (TB) control by contributing to the rapid diagnosis of TB disease and drug resistance. The test is based on real-time PCR, targeting specific nucleic acid sequences in the *M. tuberculosis* complex genome, while also simultaneously providing information about the most common mutations related to rifampicin resistance. Thus this test

simultaneously detects *Mycobacterium tuberculosis* complex (MTBC) and resistance to rifampin (RIF) in less than 2 hours. In comparison, standard cultures can take 2 to 6 weeks for MTBC to grow and conventional drug resistance tests can add 3 more weeks. The information provided by the Xpert MTB/RIF assay aids in selecting treatment regimens and reaching infection control decisions quickly. In contrast to other techniques (in vitro culture, DST and conventional molecular techniques) the Xpert MTB/RIF can be used in peripheral laboratories and does not require sophisticated equipment or highly-skilled personnel. It is a highly automated test (only 3 manual steps required), which is run in a closed system with one cartridge per sample. Thus, it is less prone to contamination than other PCR-based tests. Each instrument can process 4 samples at one time, with a processing time of just under 2 hours. Higher capacity machines processing 16 samples at one time are also made available. The performances of this test are almost similar to that of the culture. Published results have shown that for PTB detection, the assay has sensitivities of 98% for smear-positive, culture-positive samples, and 72% for smear-negative, culture-positive samples (sensitivity can reach 90% if the test is repeated 3 times).

The test Xpert MTB/RIF also has good sensitivity (80%) and excellent specificity (> 98%) when performed on cerebrospinal fluid, lymph node material and gastric fluid. Because of its excellent performance, its quick turn around time and its ease of use, this test should be used as an initial diagnostic test in HIV-infected patients and when multidrug-resistant TB (MDR-TB) or TB meningitis are suspected, in both adults and children. It can also be used for diagnosis of lymph node TB. As the sensitivity of the Xpert test in pleural fluid is low, its use is not recommended.

The sensitivity for the detection of rifampicin resistance compared with conventional DST on culture is 97.6%. The test has a high negative predictive value, therefore, non rifampicin resistant results can be considered to be true susceptible. However Xpert MTB/RIF does not eliminate the need for conventional microscopy, culture and DST, which are required to monitor treatment progress and to detect resistance to drugs other than rifampicin.

## **2 Line probe assays (LPA) (this topic need expert review to include or exclude)**

To date no fully automated LPA exist. These molecular tests can only be performed by specialized laboratories with strict quality assurance procedures in place.

There are a number of different molecular assays available:

- Conventional Nucleic Acid Amplification (NAA) amplifies *M. tuberculosis*-specific nucleic acid sequences with a nucleic acid probe, enabling direct detection of the bacillus. The current NAA tests available show a lower sensitivity than culture and therefore, are not recommended for the diagnosis of TB. They are also too labour intensive to be implemented for routine diagnosis in most laboratories.
- Two molecular techniques are commercially available:

**1 Hain assays:** GenoType® MTBDR*plus* assay and GenoType®MTBDR*sl* (Hain Lifescience GmbH, Nehren, Germany).

The GenoType® MTBDR*plus* assay has been shown to be good at detecting rifampicin resistance but less so for isoniazid resistance among smear positive patients. The GenoType®MTBDR*sl* assay can detect resistance to fluoroquinolones and injectables drugs with a reasonable specificity.

**2 The INNO-LiPA Rif. TB® line probe assay** (Innogenetics, Belgium).

The GenoType® MTBDR*plus* assay can identify mutations on the KatG or on the InhA genes:

- Mutation on KatG gene corresponds to resistance to high-dose isoniazid;
- Mutation on InhA gene corresponds to resistance to both isoniazid and ethionamide, but not necessarily to high-dose isoniazid. The GenoType®MTBDR*sl* assay can be used as a triage test on smear-positive patients to guide the initial treatment in extensively drug-resistant TB (XDR-TB) suspects while awaiting confirmatory results from conventional phenotypic testing. However, LPA assays cannot be used as replacement tests for conventional phenotypic second-line anti-TB DST.

These molecular methods have the advantage of giving fast results, within a few hours, for smear-positive patients (referred to as direct testing, because the sputum can be directly tested). For smear negative patients, a primary culture is needed prior to testing (referred to as indirect testing because a culture first has to be grown from the patient's sputum).

In order to benefit from the short turn around time of these tests, good logistical support is required for sample transportation to the reference laboratory with timely return of results. The main constraints remain the high cost, high infrastructure requirements, high level of technical training and the risk of cross-contamination.

### **Radiological Methods:**

- X ray chest
- Ultrasound

#### **X ray chest**

Chest X-ray is a non-specific investigation for TB. In national programmes, it is not routinely indicated in sputum smear-positive patients because of limited resources. Chest X-ray is considered as an additional diagnostic tool given its limitations of nonspecificity. It is often difficult to detect the difference between old healed lesions of fibrosis and active TB. They are rarely conclusive and can only complete the clinical presentation and history to constitute a body of arguments suggestive of TB. Chest X-ray is however recommended when the smear microscopy results are negative and still TB is suspected. It is particularly useful where the proportion of bacteriologically unconfirmed TB (i.e. smear microscopy or Xpert MTB/RIF negative) is likely to be high; for example, in populations with a high incidence of TB.

However chest X-rays are valuable tools for the diagnosis of pleural and pericardial effusions, especially at the early stages of the disease when the clinical signs are minimal. The X-ray showing an enlarged heart is a key element for diagnosis of pericardial TB. Chest X-ray is essential in the diagnosis of miliary TB. It shows small characteristic nodular infiltrations disseminated in both pulmonary fields. Another use of radiography includes examination of the joints and bones when TB is suspected. Special Radiography, including the use of computerized tomography scans (CT scans) and MRI can be useful only in specific clinical conditions like Pott's disease CNS TB.

### **Ultrasound**

Ultrasound is useful in confirming pleural effusions. Ultrasound is extremely useful in pericardial TB as it can document that an effusion is the cause of an enlarged heart seen on chest X-ray. It is moderately useful in diagnosing abdominal TB, whereby documenting multiple enlarged lymph nodes on an abdominal ultrasound is consistent with TB, however, multiple enlarged lymph nodes can be seen in other diseases, especially in lymphoma, leukemia, and HIV. Bowel wall thickening (ileocaecal region) is also suggestive of abdominal TB.

### **Interferon gamma release assays (IGRAs)**

These in vitro tests of cellular immunity detect interferon. Individuals who were once exposed to M. tuberculosis complex have lymphocytes in their blood that maintain memory for the priming TB antigen. Addition of TB antigen to blood in vitro results in rapid stimulation of memory T lymphocytes and release of interferon gamma, which is a specific marker of activation of the immune response. IGRAs have the advantage that there is no cross reactivity with prior BCG vaccination and with most environmental mycobacteria. However, overall, they offer little advantage over conventional skin testing and may be a less sensitive test in HIV co-infected. In addition, IGRAs remain expensive and are not routinely used in resource-constrained settings.

### **Tuberculin Skin Test (TST)**

TST e.g Mantoux Test has limited value in the diagnosis of TB, especially in high prevalence countries. A "Positive" tuberculin test does not in itself confirm the diagnosis of TB. At the same time a "Negative" tuberculin test does not exclude active tuberculosis. TST is, however, important in non-GCG vaccinated children under 5 years of age where a positive test is more likely to reflect recent infection with tuberculosis and a much higher risk of developing disease.

### **Invasive Investigations**

**Fasting gastric lavage:** Useful technique for microscopy of AFB especially in children.

**Bronchoscopy (BAL / Safe Brush microscopy):** for culture, histopathology, PCR, IGRA), where relevant and available. Therefore not recommended for routine use.

**Pleural fluid examination:** (microscopy, chemistry, culture, histopathology, PCR, IGRA, ADA) is mainstay of diagnosis in suspected Tuberculous Pleural disease.

**Tissue FNAC/ Biopsy:** Fine needle aspiration for microscopy for AFB and Cytology and tissue biopsy for culture and histopathology have diagnostic role in special conditions.

### **Other nonspecific tests**

#### **ESR**

Sedimentation rate is almost always higher but this examination is very non-specific. A normal sedimentation rate makes TB less likely but still possible. Therefore ESR has no role in the diagnosis and in monitoring a patient with tuberculosis.

#### **C-reactive protein**

C-reactive protein is also generally increased but this test also is very non-specific.

#### **Serological diagnosis of TB**

Commercially available rapid blood tests for “serological diagnosis of TB” like e.g Mycodot assay, ICT TB, are unreliable and ineffective methods and are not recommended for clinical use.

# Management of Drug Sensitive TB

## Health education

Public awareness programs for early detection and effective treatment of TB plays important role in control of disease in any country.

Following measures are recommended for practice at all levels of health care delivery.

General public should be taught the importance of early attendance at a health facility for those with chest symptoms, especially cough persisting for two weeks or more.

Patients with these symptoms should present themselves for an examination to the nearest doctor or chest clinic/hospital.

Efforts should be made to make people aware of the nature of tuberculosis, so as to know that it is a curable disease with adequate treatment, but if not treated properly it may result in infection of other people, or disability and death of the individual.

Tuberculosis is considered as stigma in many communities in our country. Social support services, poverty eradication programmes should have component of health education for hygienic and healthy living. Psychological support in the form of counselling sessions or peer-group support must should be atrated.

School health examinations and Tuberculosis awareness programmes should be started.

Public private partnership has shown tremendous overall benefit and it should be encouraged at all levels. Good communication between a tuberculosis patient and the health care provider who treats him is also very important.

Supervised treatment by the health care workers or trained volunteers is an essential component of Tuberculosis control and the health care provider should make utmost efforts to ensure completion of treatment by the patient till the cure has been achieved.

Printed material for guidance of patients and their social contacts should be used in all communities.

Print and electronic media should be used for advocacy and education.

Modern communication sources including mobile telephone communication such as SMS or telephone (voice) call. Digital medication monitor is a device that can measure the time between openings of the pill box can be used. The medication monitor can give audio reminders or send SMS to remind patient to take medications, along with recording when the pill box is opened.

## **Principles of Chemotherapy**

### **Basis of Treatment**

The basis of treatment of tuberculosis is chemotherapy. It is also one of the most efficient means of preventing the spread of tuberculosis microorganisms. The requirements for adequate chemotherapy are;

- An appropriate combination of anti-tuberculosis medications to prevent the development of resistance to those medications;
- A correct Weight Based dosage, Regular administration and swallowing of each dose under DOT. Directly observed therapy (DOT) may be ensured by a daily visit to the health facility by the patient or through a treatment supporter (a respected member of the community e.g. Imam, school teacher, community leader) who would visit the patient at his house daily for administering the drugs.
- In educating the patients and their relatives on the importance of regular drug intake, DOT and treatment completion must be emphasized.
- A Full course of treatment regimen to prevent relapse of the disease after the completion of treatment.

### **DOSAGE AND DURATION OF ANTI-TB DRUGS:**

It is very important to treat TB with the correct dosage of recommended drugs for a specified period (6 months for new case and 8 months for re-treatment case of TB). Anti-TB drugs are not effective if they are not given in the correct dose and according to the weight group of the patient. If the dose prescribed is less than the recommended dose, the TB bacteria will not be killed and they may become resistant to the drugs. If the dose is higher than recommended, the drugs may cause severe toxic effects. To simplify the drug prescription process, the following three pretreatment weight groups have been suggested in adults: • 30 –39 kg • 40-54kg • 55 kg or more The number of tablets differs only if patients fall in different weight categories otherwise it remains same for all the patients within the same range of any given weight category.

Patient weight should be monitored each month, and dosages should be adjusted if weight changes from one weight band to another. The number of drugs prescribed is determined by the category of the TB patient and phase of the treatment (intensive or continuation). The dosage (number of tablets) of each drug is determined by weight of the patient at the time of diagnosis. Anti-TB drugs may need to be temporarily suspended or stopped in case of severe drug intolerance or toxicity. :

### **Directly Observed Treatment Short Course (DOTS)**

WHO recommends a strategy for TB control called DOTS (Directly Observed Treatment, Short-course). DOTS is a comprehensive strategy which ensures cure to a majority of patients presenting to health services. The DOTS strategy for TB control is based on the widespread use of simple technology and good management practices integrated into an existing network of health services. Its integration into existing services allows the DOTS strategy to reach a majority of the population in any country. DOTS has been determined to be the most cost-effective strategy for TB control. The success of the DOTS strategy depends on the implementation of a five-point package which consists of:

1. Government commitment to a National Tuberculosis Programme (NTP).
2. Case detection through case finding by sputum smear microscopy examination of TB suspects in general health services, with priority given to detecting infectious cases.
3. Standardized short-course chemotherapy (SCC) for at least all smear-positive TB cases under proper case management conditions – health personnel or trained volunteer “directly observed treatment” (DOT) by watching patient ingest anti-TB drugs
4. A regular, uninterrupted supply of all essential anti-TB drugs
5. A monitoring system for programme supervision and evaluation

### **Categorization of Patients for treatment**

In order to ensure appropriate treatment to a TB patients, it is of paramount important to categorize them in light of the history of previous anti TB treatment. It is mandatory to ask the patient about history of anti TB in the past before starting treatment. The guidelines recommend 3 categories of patients;

1. New cases
2. Retreatment cases
3. Retreatment failures

### **Duration of Chemotherapy**

The modern strategy of TB treatment is based on standardized short-course chemotherapy regimens of;

6 months duration for New cases and

8 months for Re-treatment cases.

Duration & regimen of treatment for patients who have failed the retreatment regimen depends on the culture & sensitivity report. Such patients should be referred to a Drug Resistant TB centre (PMDT site). In special circumstances like TB Meningitis longer duration for up to 9 to 12 months treatment regimens are recommended. Chemotherapy should Not be stopped or interrupted unless severe drug intolerance or toxicity occurs necessitating a special management by a specialist to ensure a proper completion of ATT treatment.

### **Drugs and Regimens**

Tuberculosis treatment should be started after a firm diagnosis has been made. TB patients should receive a full course of treatment according to their weight, specific regimens and specified duration and no ATT drugs should be given on a trial basis. TB patients can be categorized into 3 major groups:

1. New Cases
2. Re-Treatment Cases
3. Re-Treatment failures

## 1. New Cases

Patients who have never received treatment for tuberculosis or taken it for less than one month. This group includes the following:

- Smear positive pulmonary tuberculosis.
- Smear negative pulmonary tuberculosis.
- Extra-pulmonary tuberculosis.

The treatment for this group of patients should be 6 months short course chemotherapy (SCC).

### **Initial Intensive Phase:**

**2HRZE**, i.e. Isoniazid, Rifampicin, Pyrazinamide and Ethambutol administered under direct observation (DOT) daily for 2 months.

### **Continuation Phase:**

**4HRE** i.e. Isoniazid, Rifampicin and Ethambutol daily for 4 months.

Thus this regimen is 2HRZE/4HRE and administered on daily basis for 4 months.

This regime is in compliance with WHO recommendation and has been implemented based on country expert opinion.

WHO recommends that in populations with known or suspected high levels of isoniazid resistance new TB patients should receive HRE as therapy in the continuation phase as an acceptable alternative to HR.

## **SPUTUM EXAMINATION**

Sputum smear examination is the key follow-up examination, and treatment decisions are based on sputum smear results of the patient. At least one sputum sample, preferably a morning sample should be examined on each follow-up visit.

### **Monitoring during Treatment**

<b>Perform Sputum Exam</b>	<b>Treatment regimen 6 months</b>
At the end of the initial phase	The end of 2nd month
During the continuation phase	The start of 5h month
At the end of treatment	The end of the 6th month

## Monitoring Timeline for New patients

Treatment monitoring calendar						
Month	1st	2nd	3rd	4th	5th	6th
Start					X	
End		X				X

When the patient has completed the initial intensive phase of two months, first follow up sputum test is done, and continuation phase will start irrespective of sputum smear result. Similarly for smear negative cases initial intensive phase (HRZE) is administered for two months. Sputum smear is done at the end of 2 month, if smear is negative, the continuation phase will start. However if sputum smear is positive, this does not necessarily mean failure or emergence of resistance and will be tested on X-pert and if test result is Mycobacterium detected but RR not detected patient, continuation phase will start. Additionally, patient's management plan should be reviewed and supervision and support should be enhanced. Proper dosage should be recalculated. Sputum positive at this stage does not necessarily mean failure or emergence of resistance. During the continuation phase, isoniazid, rifampicin and ethambutol (HRE) are administered daily for four months.

Note: Rifampicin-containing regimens should be taken under direct observation.

In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing is not recommended in both the intensive and continuation phases of therapy and daily dosing remains the recommended dosing frequency.

(In patients with drug-susceptible pulmonary TB, 4-month fluoroquinolone-containing regimens (4MfxHRZ, 4MfxRZE, or 2MfxRZE + 2(Mfx+RFP), 2MfxRZE/4(Mfx+RFP) should not be used and the 6-month rifampicin-based regimen 2HRZE/4HR remains the recommended regimen.)

### Table: when to end intensive phase & start continuation phase of treatment

If	Next Step
At the end of the 2nd month patients sputum smear-negative (true for vast majority)	Start & Continue with the continuation phase treatment as planned until the end of regimen
At the end of the 2nd month patient is sputum smear-positive	Do Xpert/MTB Rif assay . If RR not detected. START continuation phase treatment. If RR detected then refer to PMDT site for Management of DR TB.
At the start of the 5th month patient is sputum smear-positive	Declare treatment outcome as New Case- CAT –I treatment failure Do drug susceptibility test Re-register patient as treatment failure Start retreatment regimen as treatment failure Obtain result of sensitivity test For further management refer protocol for Previously treated case- CAT II
At the start of the 5th month patient is sputum smear-negative	Continue with the treatment as planned until the end of regimen
At the end of the 6th month patient	Patient is considered cured, If last sputum not done, declare

is sputum smear-negative	treatment completed
At the end of the 6th month patient is sputum smear-positive	Follow the same steps as at the start of 5th month if sputum smear – positive

## 2. Re-Treatment Cases

In patients who require TB retreatment, the current category II regimen (2HRZES/1HRZE/5HRE) should no longer be prescribed and drug-susceptibility testing should be conducted to inform the choice of treatment. Therefore after registration as re-treatment case & before starting treatment, all TB cases eligible for re-treatment regimen will be tested on **X-pert to exclude RR**, it is preferable also to determine isoniazid resistance status. Standard first-line treatment regimen (2HRZE/4HR) is to be repeated if no resistance is documented. If rifampicin resistance is present then these patients are referred to PMDT unit for further drug susceptibility testing and treated as MDR cases.

All smear-positive cases identified as “failures”, “treatment after lost to follow up” and “relapses” should be classified as “retreatment” cases. In patients who have had treatment interruption, the reason for the interruption, such as medication stock-outs, adverse effects from medicines or need for greater patient/provider education should be addressed.

The recommended treatment for this group of patients is 8 months as follows:

### Initial Intensive Phase:

**3HREZ:** i.e. Rifampicin, Isoniazid, Pyrazinamide and Ethambutol for 3 months.

### Continuation Phase:

**5HRE:** i.e Rifampicin, Isoniazid and Ethambutol for a period of 5 months

In settings where rapid molecular-based drug-susceptibility testing results are not routinely available to guide the management of individual patients, these patients may receive the retreatment regimen containing first-line drugs 2HRZES/1HRZE/5HRE if data show low or medium levels of MDR in the area or if such data are unavailable.

### Monitoring during Treatment:

#### SPUTUM EXAMINATION

Sputum smear examination is the key follow-up examination, and treatment decisions are based on sputum smear results of the patient. At least one sputum sample, preferably a morning sample should be examined on each follow-up visit.

Perform Sputum Exam	Treatment regimen 8 months
At the end of the initial phase	The end of 3rd month
During the continuation phase	The end of 5th month
At the end of treatment	The end of 8thmonth

## Monitoring Timeline for CAT II patients

Treatment monitoring calendar

Month	1st	2nd	3rd	4th	5th	6th	7th	8th
End of			X		X			X

**Table: when to end intensive phase & start continuation phase of treatment in Retreatment TB cases**

If	Next Step
At the start of first month patient is sputum smear-positive	Register patient for Previously treated case- CAT II Do Xpert/MTB Rif assay before start of treatment If R resistant refer to the DR TB management unit If R sensitive, Start intensive Phase (2RHZE+5RHE).
At the end of the 3rd month patients sputum smear-negative (true for vast majority)	Start continuation phase treatment until the end of regimen
At the end of the 3rd month patient is sputum smear-positive	Repeat Xpert/MTB Rif assay / X-pert test- if DST available send specimen for DST also. If X-pert report as RR, refer patient to PMDT site for management If RR not detected start continuation phase of re-treatment.
At the end of the 5th month patient is sputum smear-Negative	Continue continuation phase until the end of regimen
At the end of the 5th month patient is sputum smear-positive	Declare Treatment outcome Previously treated case- CAT-II TREATMENT FAILURE Declare DR presumptive case and refer patient to PMDT site for management
At the end of the 8th month patient is sputum smear-negative	Declare treatment outcome “ CURE”, If last sputum not done, declare treatment completed
At the end of the 8th month patient is sputum smear-positive	Declare Treatment outcome Previously treated case- CAT-II TREATMENT FAILURE Declare DR presumptive case and refer patient to PMDT site for management

**Remember:** Never add a single drug if the patient is not responding well to treatment.

**Follow-up:** Subsequent relapse is rare when patients complete the prescribed course of chemotherapy. They should be told to report for re-examination if symptoms recur.

### 3. Re-treatment Failure:

This is a group of patient who during the re-treatment regimen are found to be smear positive in the fifth month of the treatment regimen or a case of relapse of having completed the full course of re-treatment regimen. This group is considered as DR TB suspect and their sputum should be collected for culture and drug sensitivity testing at the outset and a special treatment regimen is designed and instituted with combination of second line anti TB drugs pending the receipt of bacteriological results. All patients have to be referred to DR TB management centers and registered with NTP DR Registry as suspects. All close contacts are to be traced and evaluated for tuberculosis.

### **Treatment of extrapulmonary TB**

Pulmonary and extrapulmonary disease should be treated with the same regimens. Note that some experts recommend 9–12 months of treatment for TB meningitis given the serious risk of disability and mortality, and 9 months of treatment for TB of bones or joints because of the difficulties of assessing treatment response. Unless drug resistance is suspected, adjuvant corticosteroid treatment is recommended for TB meningitis and pericarditis.

In Tuberculous meningitis, Ethambutol should be replaced by Streptomycin. Although sometimes required for diagnosis, surgery plays little role in the treatment of extrapulmonary TB. It is reserved for management of late complications of disease such as hydrocephalus, obstructive uropathy, constrictive pericarditis and neurological involvement from Pott's disease (spinal TB). For large, fluctuant lymph nodes that appear to be about to drain spontaneously, aspiration or incision and drainage appear beneficial.

### **COUNSELING AND EDUCATION OF TB PATIENTS**

Proper counseling and education of TB patients along with chemotherapy is of utmost importance. Patients should be counseled that tuberculosis (> 95%) is curable if the right drugs are taken for the right duration. The patients should be explained that incomplete treatment may lead to drug resistance, which is an extremely difficult form of tuberculosis to treat.

Most TB patients (about three in four) are poor and illiterate, so numerical explanation of six/eight month treatment should be supplemented by sign-posting the treatment duration in terms of the month when the patient is expected to complete the treatment.

Some patients may develop symptoms related to the side effects of TB drugs. These symptoms may range from mild nausea to severe jaundice. The education of patients helps them to detect and take action concerning these side effects promptly. Patients should be advised to consult staff at the health facility if itching of the skin, jaundice, vomiting, impaired vision etc. is noticed.

Patients should cover their mouths when they cough. This will reduce the chances of spreading the spread of disease through droplet infection. Patients do not need to cover their mouth when they are not coughing.

Patients should not spit close to other people. Spit into a container and then bury it or put it into the drain. TB bacteria are not spread by sharing dishes, plates, clothes, or through sexual contact. This is an important message, because it helps to prevent social exclusion of TB patients by avoiding unnecessary separation of his/her household belongings and activities.

Patients are required to visit the health Care Facility at the end of the 2nd, /5<sup>th</sup> and 6th for new case while 3rd,5th & 8th month for previously treated case of treatment.

It is important to verify that patients have clearly understood the messages provided by asking specific questions. The patient should be given an opportunity to share his/her concerns with the care provided and the care provided should also do everything possible to deal with these concerns.

## **MANAGING CONTACTS**

Contacts are people who have been sharing the same living premises and the daily life activities with the patient. It is important to identify contacts, of a patient with sputum smear positive pulmonary tuberculosis, and manage them in order to reduce the risk of missing cases and continued transmission of TB to other family members. Priority is assigned in screening contacts that had frequent, prolonged and close contact with the patient during the infectious period, in an enclosed environment. This may include all people living in the same household or dwelling, close relatives and friends, and close work colleagues who share the same indoor small work area on daily basis.

All child contacts till 5 years must be examined for symptoms and BCG scar. The management of contacts consists of the following two steps.

1. Identifying and Retrieving Contacts All the household members should be considered to be Contacts. All household members irrespective of age and gender need be assessed and those who need further screening at the health Care Facility should be identified.

- All children less than 5 years of age should be brought to the BMU /TB Care Facility for further assessment and management. The children below 5 year of age found not suffering from any symptoms are put on INH prophylaxis therapy (IPT). The INH is prescribed in a dosage of 5mg/kg and is given for a period of 6 months. Child breast- fed by sputum smear-positive mother would continue breast feed and is protected by prescribing INH in same dosage for six months and is given BCG, if not already given.

Adults and children (older than 5 years of age) with symptoms suggestive of tuberculosis i.e. cough > two weeks, weight loss, fever etc. should be asked to visit the BMU/ TB Care Facility at their earliest convenient date. The significance of screening all Contacts should be explained to the patient and the patient should be given a list of the household members who need to visit the BMU /TB Care Facility. The patient should also be requested to encourage the household members to get screened.

## **DIRECTLY OBSERVED TREATMENT**

It is very important to explain the importance of “direct observation” to the patient and help the patient to identify an acceptable and affordable means of supervising his/her treatment. Direct observation of all patients taking Rifampicin (throughout whole period of treatment of new and previously treated cases)

## IDENTIFYING & MANAGING SIDE EFFECTS

Screening for side effects of anti-tuberculosis drugs is essential part of follow-up at Health Care Facility. There are two main types of side effects of anti-tuberculosis drugs, major and minor side effects.

**Major Side Effects:** are those that give rise to serious health hazards. In this case, discontinuation of anti-tuberculosis drugs is mandatory and the patient should be referred to a hospital specialist. TB drugs can cause the following major side effects:

### MAJOR SIDE EFFECTS LIKELY CAUSATIVE DRUGS

Major side effects	Likely causative drugs
Skin rash	Thiacetazone, Streptomycin
Deafness	Streptomycin
Dizziness	Streptomycin
Jaundice	Isoniazid, Rifampicin, Pyrazinamide
Visual Impairment	Ethambutal
Shock	Rifampicin
Purpura	Rifampicin

**Minor Side Effects:** Minor side effects cause only relatively little discomfort. They often respond to symptomatic or simple treatment but occasionally persist for the duration of drug treatment. In this case, anti-tuberculosis treatment should be continued and symptomatic treatment added. TB drugs can cause the following minor side effects:

Minor side effects	Likely causative drugs
Anorexia, nausea, abdominal pain	Rifampicin
Joint pain	Pyrazinamide
reddish change in urine colour	Rifampicin
Burning sensation in feet	Isoniazid,
Itching of skin	Isoniazid, Rifampicin, Pyrazinamide,

## ANTI TUBERCULOSIS DRUGS

The first line anti TB drugs ( FLD) used in the treatment of tuberculosis consists of Isoniazid (H), Rifampicin(R), Pyrazinamide (Z), Streptomycin (S) and Ethambutol (E). Most of the above drugs are available in combined preparations. Only fixed drug combination (FDC) of proven bioavailability according to WHO recommended strengths should be used. The bioavailability should be assessed for all 2, 3 or 4 drugs in the FDC, according to the WHO protocol at a WHO recommended site. The quality should be the prime consideration in selecting the Anti-TB drugs. Drugs should be manufactured to GMP (Good Manufacturing Practice) standards. The use of Rifampicin or Streptomycin, for disease other than mycobacterium disease should be carefully evaluated and used only for very specific indications.

## ANTI-TB DRUGS – MECHANISMS OF ACTION

<b>Rifampicin</b>	A bactericidal drug active against all populations of TB bacilli Semi-synthetic, macrocyclic antibiotic inhibiting nucleic acid Synthesis Potent bactericidal action and potent sterilizing effect against tubercle bacilli
<b>Isoniazid</b>	A bactericidal drug active against all populations of TB bacilli Highly bactericidal against replicating tubercle bacilli Kills 90% during first few days of treatment
<b>Pyrazinamide</b>	A bactericidal drug active against certain populations of TB bacilli Particularly active in acid intra cellular environment and in areas of acute inflammation Active in acid environment against bacilli inside macrophages Synthetic analogue of nicotinamide with weak bactericidal, but potent sterilizing activity against M.tuberculosis
<b>Streptomycin</b>	A bactericidal drug active against certain populations of TB bacilli Active against rapidly multiplying extra-cellular TB bacilli
<b>Ethambutol</b>	A synthetic, bacteriostatic drug active against M. tuberculosis and other mycobacteria. Used in combination with other more powerful drugs to prevent emergence of resistant bacilli

## CLINICAL INFORMATION ABOUT ESSENTIAL ANTI-TB DRUGS

<b>Rifampicin (R)</b>	
Forms	150 mg and 300 mg capsule
Administration Remarks	<ul style="list-style-type: none"> <li>• Must always be administered in combination with other anti-mycobacterial agents</li> <li>• Should be given at least 30 minutes</li> </ul>

Dosage	<ul style="list-style-type: none"> <li>• 10mg/kg ( 8–12 mg/kg) daily</li> <li>• Maximum 600mg daily</li> </ul>
Adverse Reaction	<ul style="list-style-type: none"> <li>• Gastrointestinal intolerance</li> <li>• Hepatitis/Cholestasis</li> <li>• Hepatic enzyme induction/ drug interactions</li> </ul>
Contraindication	<ul style="list-style-type: none"> <li>• Hepatic dysfunction</li> <li>• Known hypersensitivity to Rifamycins</li> </ul>

<b>Isoniazid (H)</b>	
Forms	<ul style="list-style-type: none"> <li>• 50 mg, 100 mg, 300 mg tablets</li> <li>• 50 mg in 2 ml injection</li> </ul>
Administration Remarks	<ul style="list-style-type: none"> <li>• Taken orally</li> <li>• Injections reserved for critically ill patients</li> </ul>
Dosage	<ul style="list-style-type: none"> <li>• 5 mg/kg (4–6 mg/kg) daily</li> <li>• Maximal dose is 300 mg when given daily</li> </ul>
Adverse Reaction	<ul style="list-style-type: none"> <li>• Hepatic dysfunction</li> <li>• Skin rashes</li> <li>• Neurotoxicity</li> </ul>
Contraindication	<ul style="list-style-type: none"> <li>• Hepatic dysfunction</li> <li>• Known hypersensitivity</li> </ul>

<b>Pyrazinamide (Z)</b>	
Forms	500 mg tablet
Administration Remarks	<ul style="list-style-type: none"> <li>• Highly effective during the first 2 months of therapy</li> </ul>
Dosage	<ul style="list-style-type: none"> <li>• 25 mg/kg (20–30 mg/kg) daily</li> </ul>
Adverse Reaction	<ul style="list-style-type: none"> <li>• Hepatitis</li> <li>• Hyperuricaemia</li> <li>• Rash</li> </ul>

Contraindication	<ul style="list-style-type: none"> <li>• Hepatic dysfunction, Known hypersensitivity</li> </ul>
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<b>Streptomycin (S)</b>		
Forms	•	1.0 g ampoule injections
Administration Remarks	•	Given by intramuscular
	•	Streptomycin is an
		antibiotic with bactericidal activity against TB bacilli
Dosage	•	15 mg/kg (12–18 mg/kg) daily
	•	In patients over age 60, 500-mg daily
Adverse Reaction	•	Vestibular damage
	•	Hypersensitivity
	•	Nephrotoxicity
Contraindication	•	Pre-existing auditory nerve impairment
	•	Renal impairment
	•	Myasthenia gravis
	•	Pregnancy
	•	Known hypersensitivity

<b>Ethambutol (E)</b>		
Forms	•	100 mg, 250 mg, 400 mg tablets
Administration Remarks	•	Used in combination with other anti-TB drugs to prevent the emergence of resistant strains
Dosage	•	15 mg/kg (15-25 mg/kg) daily

Adverse Reaction	<ul style="list-style-type: none"> <li>• Ocular toxicity</li> </ul>
Contraindication	<ul style="list-style-type: none"> <li>• Pre-existing optic neuritis from any cause</li> <li>• Renal impairment</li> <li>• Inability (young children, Unconscious patients) to report visual disturbances</li> <li>• Known hypersensitivity</li> </ul>

### **Treatment regimens in special situations**

WHO recommends testing for HIV testing for all TB patients in all settings including low prevalence countries. Where possible and clinically warranted it should be considered. If HIV positive when available, CD4 cell counts should be a factor in the decision on ART initiation in TB patients as follows:

- ART is recommended for all people infected with HIV and diagnosed with TB whose CD4 counts are 350 cells/mm<sup>3</sup> or less.
- ART should be deferred in pulmonary TB patients whose CD4 cell count exceeds 350 cells/mm<sup>3</sup> provided that there is no other stage 3 or 4 event. Patients whose CD4 count at TB diagnosis exceeds 350 cells/mm<sup>3</sup> should be re-evaluated 8 weeks after starting TB therapy and again when TB treatment is completed.
- ART is recommended for all people living with HIV diagnosed with extrapulmonary TB, regardless of the CD4 count.
- Co trimoxazole is recommended to be added to all cases through out the treatment period. Only specialized centers should undertake treatment of such cases.

### **Pregnancy and breastfeeding**

Women of childbearing age should be asked about current or planned pregnancy before starting TB treatment. A pregnant woman should be advised that successful treatment of TB with the standard regimen is important for successful outcome of pregnancy. With the exception of streptomycin, the first line anti-TB drugs are safe for use in pregnancy: streptomycin is ototoxic to the fetus and should not be used during pregnancy.

A lactating female who has TB should receive a full course of TB treatment. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to the baby. Mother and baby should stay together and the baby should continue to breastfeed and she should cover her face with mask/veil to avoid breathing over the infant. After active TB in the baby is ruled out, the baby should be given 6 months of

isoniazid preventive therapy, followed by BCG vaccination. Pyridoxine supplementation is recommended for all pregnant or breastfeeding women taking isoniazid.

### **Liver disorders**

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

In patients with unstable or advanced liver disease, liver function tests should be done at the start of treatment, if possible. If the serum alanine aminotransferase level is more than 3 times normal before the initiation of treatment, the following regimens should be considered. More unstable or severe the liver disease is, the fewer hepatotoxic drugs should be used.

Possible regimens include:

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

- \_ 9 months of isoniazid and rifampicin, plus ethambutol (until or unless isoniazid susceptibility is documented);

- \_ 2 months of isoniazid, rifampicin, streptomycin and ethambutol, followed by 6 months of isoniazid and rifampicin;

- \_ 6–9 months of rifampicin, pyrazinamide and ethambutol.

- **One hepatotoxic drug:**

- \_ 2 months of isoniazid, ethambutol and streptomycin, followed by 10 months of isoniazid and ethambutol.

- **No hepatotoxic drugs:**

- \_ 18–24 months of streptomycin, ethambutol and a fluoroquinolone.

Expert consultation is advisable in treating patients with advanced or unstable liver disease. Clinical monitoring (and liver function tests, if possible) of all patients with pre-existing liver disease should be performed during treatment.

“In tuberculous patients with drug induced hepatitis, the treatment should be stopped if the ALT is more than 5 times normal in the absence of symptoms and 3 times normal in the presence of symptoms suggestive of hepatitis. If the TB situation is serious enough to continue ATT (like in TBM, tuberculous pericarditis or tuberculous spine) then any one of the above mentioned regimens (with two or one hepatotoxic drugs) should be continued.

In less serious situations, treatment can be halted till hepatic functions have returned to normal and then either the treatment is reinstated or any of the two above mentioned regimens (with two or one hepatotoxic drugs) can be started”.

### **Renal failure and severe renal insufficiency**

The recommended initial TB treatment regimen for patients with renal failure or severe renal insufficiency is 2 months of isoniazid, rifampicin, pyrazinamide and ethambutol, followed by 4 months of isoniazid and rifampicin. 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. Because of an increased risk of nephrotoxicity and ototoxicity, streptomycin should be avoided in patients with renal failure. If streptomycin must be used, the dosage is 15 mg/kg, two or three times per week, to a maximum of 1 gram per dose, and serum levels of the drug should be monitored.

### **TUBERCULOSIS & TOBACCO**

Both tobacco smoking and tuberculosis are major global public health problems. Globally, nearly 6.4 million people died from tobacco use in 2015 and tobacco use is estimated to be responsible for 16% of deaths among men and 7% of deaths among women each year. In 2012, there were an estimated 8.6 million new tuberculosis cases and 1.3 million tuberculosis-related deaths worldwide. Smoking is common in the 22 countries categorized by the World Health Organization (WHO) as high-burden countries for tuberculosis – which together account for more than 80% of all tuberculosis cases. The burden of smoking among patients with tuberculosis is poorly defined in most countries.

An understanding of the epidemiological relationship between smoking and tuberculosis is important because both smoking and tuberculosis cause extensive morbidity and mortality worldwide. Furthermore, tobacco smoking amplifies the negative impact of TB. Compared with those who have never smoked, it is estimated that people who smoke have approximately twice the risk of both *Mycobacterium tuberculosis* infection and active tuberculosis. There is now a growing body of evidence on the impact of smoking on treatment outcomes among patients with active tuberculosis.

In short there is a strong association between smoking and TB as

- Smoking substantially increases the risk of tuberculosis (TB) and death from TB

- More than 20% of global TB-related burden may be attributable to smoking
- Controlling the tobacco epidemic will help control the TB epidemic
- Smoking is a risk factor for TB, independent of alcohol use and other socioeconomic risk factors
- Smoking increases the risk of TB disease by more than two-and-a-half times
- Smoking increases severity of disease with more cavity lesions and greater likelihood of hospitalization.
- Smoking is associated with poorer adherence to anti-TB medicines
- Smoking leads to a higher risk of relapse after the initial treatment and the development of multi-drug resistance TB
- Smokers have a higher treatment default rate, and are also more likely to transmit TB to others

### **Recommended Policies to Combat Tobacco and TB**

Control tobacco everywhere, but especially where people are at risk of TB infection

Coordinate national TB and tobacco control programmes

Train TB healthcare workers in delivering behavioural support (counseling) to TB patients who smoke

Register TB patients' tobacco use in TB surveillance tools (e.g. TB03 forms) and offer them behavioural support (counseling) and treatment for tobacco addiction

Promote and enforce smoke-free policies, particularly where TB services are delivered

Offer tobacco cessation support to those health workers who smoke themselves

Integrate brief tobacco interventions (5 'A's and the 5 'R's) into TB control programme activities

Implement smoking cessation procedures through PAL (the Practical Approach to Lung Health)

### **Public Health-Oriented Actions to Combat Tobacco and TB**

TB control programmes can support tobacco control by promoting policies to:

- Apply price and tax increases
- Provide protection from exposure to tobacco smoke
- Ban tobacco advertising, promotion and sponsorship
- Regulate the packaging and labelling of tobacco products
- Raise public awareness of tobacco risks

- Treat tobacco dependence

(These and other recommendations are featured in the WHO Framework Convention on Tobacco Control)

### Patient-Oriented Actions to Combat Tobacco and TB

The 5 'A's	The 5 'R's
ASK TB patients about their tobacco use	RELEVANCE ensure TB patients know their treatment will be more effective if they quit smoking
ADVISE them to quit	RISKS – point out all the risks of continuing to smoke including the risk of TB relapses
ASSESS their willingness to attempt to quit	REWARDS – educate the TB patient about the many other benefits of quitting smoking
ASSIST in their attempt to quit	ROADBLOCKS – ask the TB patient to identify obstacles to quitting smoking
ARRANGE follow up with them	REPETITION – continue to encourage the TB patient to quit smoking

### Drug resistant Tuberculosis

DR-TB is confirmed through laboratory tests that show that the infecting isolates of *Mycobacterium tuberculosis* grow in vitro in the presence of one or more anti-tuberculosis drugs. Four different categories of drug resistance have been established:

- **Mono-resistance:** resistance to one antituberculosis drug.
- **Poly-resistance:** resistance to more than one first line antituberculosis drug other than both isoniazid and rifampicin.
- **Multidrug-resistance:** resistance to at least isoniazid and rifampicin.
- **Extensive drug-resistance:** resistance to any fluoroquinolone, and at least one of three injectable second-line drugs (capreomycin, kanamycin and amikacin), in addition to multidrug-resistance.

Culture and DST guide the therapy in DR TB cases. Where DST facilities are not readily available empiric DR TB regimen should be started. An empiric regimen for MDR TB should be started in cases where DST results are not available on the basis of moderate or high level of suspicion (clinical assessment levels). An empiric regimen is to be designed using the following classes of anti tuberculosis drugs.

Treatment of DR TB is undertaken essentially under the Programmatic Management of Drug resistance TB (PMDT) sites these are specialized centers and having facilities of management of this serious disease with highly specific treatment regimen which is not only prolonged and very expensive but also has high rate of drug adverse reactions.

### **SCREENING OF DRUG RESISTANT TB: PRESUMPTIVE CASES:**

The use of X-pert / MTB Rif has been recommended as a first diagnostic testing for screening to the following high risk groups (DR-TB presumptive cases).

#### **1. ALL PREVIOUSLY TREATED TB CASES:**

All TB cases (AFB SS +ve or clinically diagnosed) with history of previous ATT should be tested for X-pert at month zero of enrolment. This includes:

- Treatment Failure New Case (Cat-I)
- Treatment Failure Previously Treated Case (Cat-II)
- Relapse after New Case (Cat-I)
- Relapse after Previously Treated Case (Cat-II)
- Treatment after loss to follow up New Case (Cat-I)
- Treatment after loss to follow up Previously Treated Case (Cat-II)
- Other Previously treated Case

#### **2. SYMPTOMATIC CONTACTS OF DR-TB PATIENT:**

All household and workplace symptomatic contacts of DR-TB patients should be screened for drug resistance. Specimen from these individuals should be processed for AFB smear and then the specimen is referred for X-pert MTB/RIF assay irrespective of smear results.

### **C. TB PATIENTS UNDER TREATMENT WHO FAIL TO CONVERT AT THE END OF INTENSIVE PHASE**

- B+ive patient on New Case (Cat-1 who fail to convert at the end of month #2 of treatment.
- B+ive patient on Previously Treated Case (Cat- II who fail to convert at the end of 3 months.

- B-ive Patient who is reported AFB smear positive at the end of intensive phase

Comprehensive First and second line DST: All patient who are reported rifampicin resistant on Xpert/MTB Rif assay should be referred to DR treatment site and specimen should be referred to quality assured DST laboratory for comprehensive first and second line DST before start of treatment .

If patient is reported rifampicin sensitive on X-pert MTB/Rif assay but is clinically considered at high risk of DR (e.g. Cat-II-failure), patient may be referred for phenotypic drug susceptibility testing as small number of rifampicin resistant are not detected by X-pertMTB/RIF assay Reporting pattern and interpretation of results of X-pert MTB Rif

**REPORT DR-TB RISK ASSESSMENT, INTERPRETATION and ACTION based on**

**Xpert / MTB Rif assay**

	REPORT	DR-TB RISK ASSESSMENT	INTERPRETATION	ACTION
1	MTB Detected Rif resistance NOT detected	No previous history of ATT	Definite TB case NO Rifampicin resistance	Start New Case treatment Cat-I
		History of previous ATT	Definite TB case NO Rifampicin resistance	Start Previously Treated Case Treatment Cat- II
		History of Cat-II Failure	Definite TB case No Rifampicin resistance	Start Previously Treated Case Treatment Cat- II And transport sample/Refer patient for pheno DST
2	MTB Detected  Rifampicin Resistance Detected	No previous history of ATT	Definite TB case with Rifampicin resistance	Repeat X-pert MTB/Rif assay – If -RR Not detected - start on FLD- New Case treatment Cat-I -RR detected Reg and start on SLD
		History of previous ATT	Definite TB case with Rifampicin resistance	Refer patient to DR Treatment site enroll Patient on SLD and send specimen for FL and SL DST.
3	MTB NOT detected		MTB Not detected but TB not excluded	Culture / clinical evaluation diagnosis

## INTERPRET CULTURE AND DST (R/H) RESULTS

Results, if	Interpretation	Further action
◆ DST – resistance to R and H, with smear positive or negative and culture positive (or result awaited, if rapid DST in-use)	DR-TB patient	◆ Register, further assess, and put patient on DR-TB treatment
◆ DST – susceptible to R and/or H, with smear positive or negative & culture positive (or result awaited, if rapid DST in-use)	TB but not DR-TB	◆ Manage as non-DR TB (e.g. re-treatment or mono-drug resistant TB)

## CONCLUSIONT

The above guidelines are to be followed under a programmatic approach with DOTS protocol. Failure and default cases are to be dealt with under the specific guidelines detailed in National Drug Resistance Tuberculosis Guidelines. All cases must be registered and followed.

# ANNEXURES

## TREATMENT TABLETS

### Fixed Dose Combinations (FDCS)

FDCs have the advantage of improving patient compliance. With FDC the prescription errors are likely to be less frequent because dosage recommendations are straight forward and adjustment of dose according to patient's weight is easier. The number of tablets to ingest is smaller, which makes patients more adherent to treatment. Fixed dose combination drugs have also some disadvantages. If prescription error occurs and excess dose is prescribed, toxicity of all drugs will increase. Similarly under dose prescription will lead to sub inhibitory concentrations of all drugs favoring development of drug resistance. FDC drugs also cannot be continued once there is side effects to anyone companion drug, which justify. Always calculate dosage according to weight of the patient. Use of separate drugs is advised in case of weight-dosage discrepancy with FDCs. Any FDCs with Rifampicin must have a certificate of bioavailability by a WHO recommended reference laboratory.

### NEW CASES: (FDCS)

<b>PATIENT BODY</b>	<b>Initial Phase</b>	<b>Continuation Phase</b>
<b>WEIGHT (KG)</b>	<b>02 Months</b>	<b>04 Months</b>
	<b>R H Z E</b>	<b>H R</b>
30-39	02 tablets	1
40-54	03 Tablets	1.5 Tablets
55 & above	04 Tablets	02 Tablets

(RHZE) R= 150 mg+ H= 75mg+ Z= 400mg+ E= 275. (HR) H= 150mg+ R= 300mg

R= Rifampicin H= Isoniazid Z= Pyrazinamide E= Ethambutol

**NEW CASES: 2 FDC and Separate Drugs**

INITIAL INTENSIVE PHASE				Continuation Phase
Weight of patient	Daily During First 2			Daily During next 4 months
	HR	Z	E	HR
30-39	1	2	1.5	1.5
40-54	1.5	3	2	2
55 & above	2	4	3	2

(HR) H= 150mg+ R 300 mg, (Z) = 400mg Tab. (E) = 400mg Tab. R= Rifampicin H= Isoniazid Z= Pyrazinamide E= Ethambutol

**RE-TREATMENT CASES: (FDCS)**

Patient body Weight (kg)	Initial Phase for 3 months			Continuation Phase
	2 Months		1 Months	05 Months
	S	RHZE	RHZE	HRE
30-39	500mg	02 tablets	02 tablets	02 tablets
40-54	750mg	03 Tablets	03 Tablets	03 Tablets
55 & above	750mg	04 Tablets	04 Tablets	04 Tablets

(RHZE) R= 150 mg, H= 75mg, Z= 400mg, E= 275. (RHE) R=150mg+H=75mg+E=275mg

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

**Re-TREATMENT CASES: 2 FDC and Separate Drugs**

INITIAL INTENSIVE PHASE				Continuation Phase		
Daily during first 3 months				Daily During next		
				5 months		
Weight of patient (pretreatment weight)	S (first 2 months only)	H R	Z	E	H R	E
30-39	500mg	1	2	1.5	1	1.5
40-54	750mg	1.5	3	2	1.5	2
55 & above	750mg	2	4	3	2	3

(HR) = H 150mg, R 300mg (Z) = 400mg Tab. (E) = 400mg Tab.

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