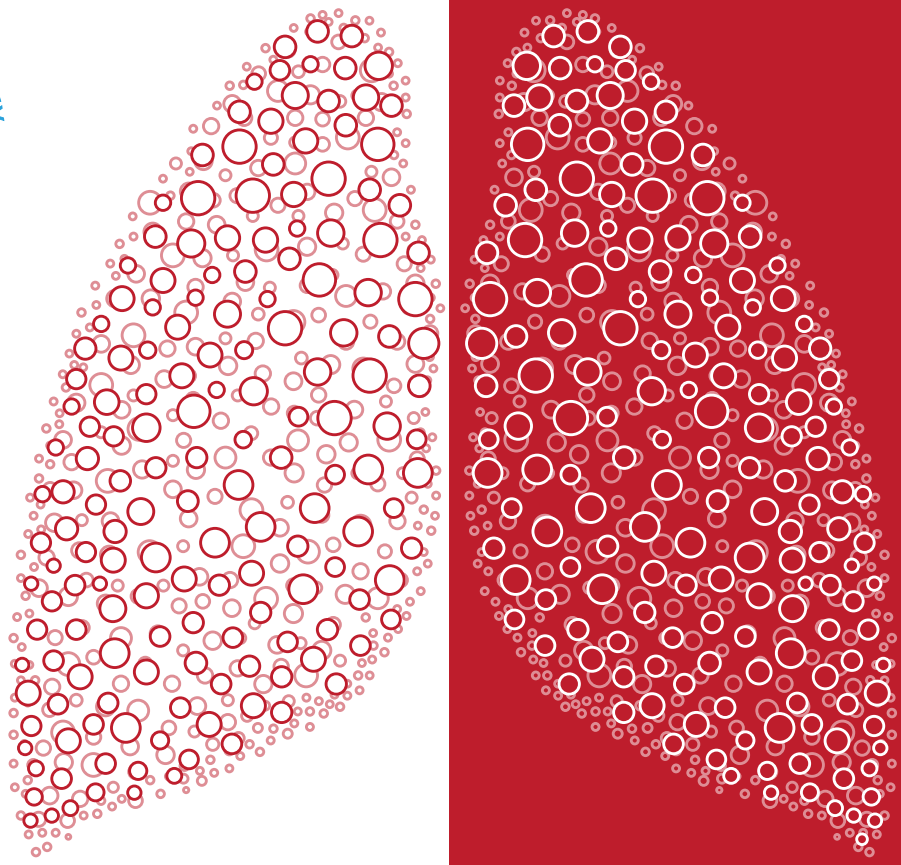
PAKISTAN CHEST SOCIETY



DIAGNOSIS & MANAGEMENT OF DRUG-SUSCEPTIBLE

TUBERCULOSIS

A NATIONAL CLINICAL GUIDELINE

MARCH, 2020

NATIONAL CLINICAL GUIDELINES

ON

"DIAGNOSIS & MANAGEMENT OF DRUG-SUSCEPTIBLE TUBERCULOSIS"

PREPARED BY:

PAKISTAN
CHEST SOCIETY
STRIVING FOR PULMONARY CARE

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Message By The President Pakistan Chest Society (PCS)

Consumption, phthisis and the White Plague are the terms used to refer to tuberculosis. It is caused by Mycobacterium Tuberculosis. Despite initial success with discovery of anti-tuberculous chemotherapy it is still hard to conquer. The 1.3 million deaths attributed to TB each year makes TB the ninth most prolific cause of death globally and renders TB only second to HIV with regards to infectious disease-related mortality.

Tuberculosis is a major public health problem. Pakistan ranks 5th amongst high burden tuberculosis countries. As per WHO Global Tuberculosis report 2019, incidence of Tuberculosis in Pakistan is 265/100000. In the year 2018, out of 562000 a total of 3690610 cases were notified. The remaining cases may be treated by General practitioners as is the usual practice in Pakistan or small chunk may be the real missing cases. The contributing factors for high rates of TB are delay in diagnosis, inadequate treatment regimen, poor supervision leading to the irregular intake of drugs, and not proper follow-up. These factors may result in treatment failure, relapse, and the emergence of MDR TB and Extensively Drug-Resistant TB (XDR TB). Tuberculosis is historically regarded as the disease of poverty, so malnutrition, poor housing, and unhygienic conditions contribute to the spread and exacerbation of the disease.

The aim of TB treatment is to cure the individual patient which in turn will help to prevent the spread of the disease. Other areas of case management should also be kept in mind like education and counseling, home visits, patient reminders etc. Generally, the Directly Observed Therapy (DOT) should be used for the treatment of patients with all forms of TB disease.

In order to achieve uniformity in TB treatment across all service providers, it is mandatory to develop and validate TB guidelines. The Pakistan Chest Society (PCS) has always been at the forefront of the war against TB and formulated the first "Guidelines for Management of Tuberculosis" in March 2002. The guidelines were updated in 2011 and were later adopted by the National Tuberculosis Program (NTP) as the National Guidelines for TB control. The third edition of guidelines was published in March 2018. The current document is the fourth edition of the guidelines, which have been modified to bring it in consonance with the Programmatic Management of The National Tuberculosis Control Program. The WHO “Definitions and reporting framework for tuberculosis-2013 revision” and "Treatment of Tuberculosis Guidelines 2017" have been consulted to update these guidelines.

Latest development in TB research has been incorporated in this updated comprehensive guidelines along with the state-of-the-art information and day to day clinical practice knowledge of drug susceptible TB for the general practitioners, physicians, pulmonologists,

postgraduates, TB program related medical staff, policy makers / politicians and donor agencies. These guidelines will encourage service providers to adopt standardized practices. To get rid Pakistan of TB, it is of utmost importance that every effort should be made by those involved in the management of Tuberculosis to adhere to the standardized recommendations and ensure the enrolment of every patient in the National tuberculosis control program. I remind all the stake holders of the need to work towards controlling TB, we can do it together.

Prof. Dr. Nisar Ahmed Rao
Chairman, TB Guidelines Working Group
President, Pakistan Chest Society (Centre)

Introduction

Tuberculosis is an infectious, chronic granulomatous disease caused in the vast majority of cases by Mycobacterium Tuberculosis**. The discovery of MTB was announced on 24th March, 1882 in a meeting.**The organism was identified by Robert Koch on 24th March 1882. This day is now commemorated as 'world TB day' throughout world every year.

Tuberculosis is one of the major public health problems in Pakistan.

Pakistan has the world's 5th highest number of people falling ill with TB each year - TB incidence in 2018 in Pakistan has been reported as 265/100,000 by WHO. Pakistan had a burden of 562,000 TB cases in 2018. Pakistan notified 36,0472 TB cases in 2018 which is 64% of the total burden. Only India, Indonesia, China and the Philippines have more cases. While the Eastern Mediterranean has only 8% of the global burden, Pakistan is responsible for 75% of it. However, only 369,000 cases were notified in 2018, meaning that 193,000 – over one third - were not notified. This was especially true of the elderly, and of men. Treatment Success rate of TB cases in Pakistan is 93%.

Despite the fact the Pakistan has achieved high Treatment success rates among notified TB cases(more than 90%), low detection rates remain a formidable challenge. Pakistan still misses one third of tB Cases mainly because of access issue, stigma, sub optimal awareness and associated out of pocket burden on patinets.

WHO estimates that 44,000 Pakistani citizens died from TB in 2018, the highest number from any infectious disease.

Tuberculosis is the 7th largest cause of lost years of life in Pakistan, behind the major causes of death in infants and children, and ischemic heart disease. WHO estimates that 44,000 Pakistani citizens died from TB in 2018, the highest number from any infectious disease. Tuberculosis is the 7th largest cause of lost years of life .

Pakistan is also estimated to have 5th highest prevalence of multidrug-resistant TB with 4.2% MDR-TB in new Pulmonary TB cases and 16% in retreatment TB case. In 2018 there were an estimated 28,000 multi-drug resistant (MDR-TB) cases, but only 11% were diagnosed and put on treatment. 3177 DR TB patients were put on treatment though number of Gen Expert Machines have increased many folds in the country. GenXpert is a rapid molecular test approved by WHO for the rapid diagnosis of MTB and detection of Rif Resistance.

Although high case detection rates have been achieved in the country under NTP, cure of cases of active tuberculosis is the key to effective control of the disease. Prompt early diagnosis and appropriate treatment of tuberculosis patients reduces sufferings and prevents death from tuberculosis. The purpose of these guidelines is to help doctors and related health workers in the identification of presumptive TB cases, diagnosis and treatment of a TB patient and to underline their important of 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 of 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. Nontuberculous 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, do 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 in 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 people with the active respiratory disease. Tiny droplets thus created dry rapidly, attach themselves to fine dust particles and smallest of them may remain suspended in the air for several hours. The number of infectious droplets projected into the atmosphere by a patient when coughing (3500) or sneezing (1 million). Only those particles that are less than 10 microns in diameter reach the pulmonary alveoli and result in the infection of individual. 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. This stage is usually asymptomatic; however, in some rare cases, hypersensitivity reactions may occur.

In the absence of treatment and of immune deficiency, the risk is estimated at 05 to 10 % in the 10 years following primary infection and 05% for the reminder of the individual's lifetime. A smear positive patient who is not treated can infect 10 individuals per year for an average duration of infectiousness of 02 years before becoming non-infectious (due to spontaneous cure or death), so a smear positive patient can infect 20 people during his /her life time and create 02 cases of tuberculosis, at least one of which will be infectious. As long as at least one new case of tuberculosis is created by each existing case, the disease is maintained in the community.

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 Defenses:

- 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 will be as follow:

- 50-60% will die (case fatality ratio for untreated TB);
- 20-25% will cure (spontaneous cure);
- 20-25% will still be 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 anti-retroviral) is almost always fatal. Even on anti-retroviral, the CFR is higher than in non-HIV infected patients.

Factors Modifying TB Epidemiology

There are four major factors that influence TB epidemiology: socioeconomic development, TB treatment, HIV infection and 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 industrialized 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 industrialized 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. 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)
- Extra pulmonary 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 hyper vascularisation 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 localization (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 resent 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 localization, which should be searched for whenever EPTB is diagnosed or suspected.

1. **Lymph NodeTuberculosis**

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 lympadenothapy 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 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 micro or 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 (fever, 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 well-equipped hospitals.

8. Cutaneous Tuberculosis

The clinical presentation of cutaneous tuberculosis is chronic, painless, non-pathognomonic lesions, ranging from small papule 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 and MTB Gene Xpert for children with suspected pulmonary TB who are old enough to produce a sputum sample. Gastric lavage is useful if child is not expectorating. 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 when meninges are involved
- Backache with or without loss of function in lower limbs when there is spinal involvement. Gibbus may be presenting feature in some patients.
- Abdominal pain, diarrhea 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. Trial for TB treatment should not be considered 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, bones, meninges etc.

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 Followup 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

Treatment Outcomes for Drug-susceptible TB Patients (Excluding Patients Treated for Rifampicin Resistant i.e. RR-TB or MDR-TB)

Table-1: Treatment Outcomes

Outcome	Definition
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of Cured treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion
Treatment completed	A TB patient who completed treatment without evidence of failure BUT with no Treatment completed 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.
Treatment Failed	ATB patient whose sputum smear or culture to positive of month 5 or later during treatment.
Died	ATB patient who dies for any reason before starting or during the course of treatment

Lost to Follow-up	ATB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more
Not Evaluated	ATB patient for whom no treatment outcome is assigned. This includes cases Not evaluated "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.
Treatment Success	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 referred to Drug- resistant TB clinic for further evaluation and management. These cases are excluded from the main TB cohort when calculating treatment outcomes and included only in the second-line TB treatment cohort analysis

Classification Based on Drug Resistance:

Cases are classified 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 second-line injectable drugs (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.

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 Approach

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. Mycobacterium tuberculosis has a minimum doubling time of 14.7 hours.

Shortcomings of smear microscopy are that it cannot distinguish Mycobacterium tuberculosis from Non-Tubercular Mycobacteria (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 HIV co-infection, and those with 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.

Mycobacteria are “acid and alcohol fast bacilli” (AAFB), often shortened to “acid fast bacilli” (AFB). The waxy coat of mycobacteria retains an aniline dye (e.g. carbol fuchsin) even after discoloration with acid and alcohol.

Table-2: Grading of Sputum AFB smear Microscopy Results

AFB SMEAR MICROSCOPY		
Number of bacilli seeing in a smear.	RESULT REPORTED	
No AFB	Per 100 oil immersion fields	0
1-9 AFB	Per 100 oil immersion fields	Exact number of AFB
10-99 AFB	Per 100 oil immersion fields	+
1-10 AFB	Per oil immersion fields	+ +
> 10 AFB	Per oil immersion fields	+ + +

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 and 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.

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. 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.

Automated Real Time PCR (Xpert MTB/RIF):

The X-pert MTB/RIF is the only WHO-recommended Rapid Molecular Diagnostic Test that simultaneously detects TB and resistance to rifampicin in less than two hours. GeneXpert is currently the only fully automated cartridge based real-time DNA based test. It is more sensitive than microscopy and with detection limit of 136 (MTB/Ml of sputum) and thus has

a high sensitivity in smear-negative tuberculosis. The sensitivity of the Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, United

States) for detecting TB is similar to that of solid culture (88% when compared with liquid culture as a reference standard). The specificity is also high (99%) Sensitivity of a single X-pert MTB/RIF test in smear-negative/ culture-positive patients is reported to be 72.5% and increased to 90.2% when three samples are tested.

The Xpert MTB/RIF Ultra assay has a higher sensitivity than the Xpert MTB/RIF assay, particularly in smear-negative, culture- positive specimens and in specimens from HIV-positive patients. It has at least as good accuracy for detecting rifampicin resistance. However, as a result of the increased sensitivity, the Xpert MTB/ RIF Ultra assay also detects non-replicating and non-viable bacilli, particularly in patients with a recent history of TB, which reduces the overall specificity of the Xpert MTB/RIF Ultra assay in high-burden settings. Nonetheless, in low burden settings and when testing specimens to diagnose EPTB and pediatric TB, false positive results were not a major concern.

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. Identification of TB bacilli by Xpert MTB/RIF only requires 131 colony forming units per ml of sputum. It detects both live and dead bacteria. 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/RIEF 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 99.7 and specificities 98.5% for smear-positive, culture-positive samples, and 76.1% and 98.8% 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. However, the sensitivity of the Xpert test in pleural fluid is low.

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.

Line Probe Assays (LPA)

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 (NAAT) 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.

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 turnaround 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 however, recommended when the smear microscopy results are negative and still TB is suspected. Patients with tuberculosis have varied radiological pattern like alveolar infiltrates, cavitation which may be single or multiple, military shadow, consolidation, collapse of segment, lobe or lung etc. It may even be normal in endobronchial tuberculosis. It is often

difficult to detect the difference between old healed lesions of fibrosis and active 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. CT scan is helpful in the diagnosis of TB abdomen, pelvis etc. MRI can be useful in specific clinical conditions like Pott's disease and CNS TB.

Ultrasound

Ultrasound is useful in confirming pleural effusions and septations. Ultrasound is extremely useful in pericardial 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 (ileocecal region) is also suggestive of abdominal TB.

Tests to Detect Latent Tuberculosis

1. Interferon Gamma Release Assays (IGRAs)

These in vitro tests of cellular immunity to detect interferon gamma. 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 sensiti ve test in HIV co-infected. In addition, IGRAs remain expensive and are not routinely used in resource-constrained settings.

2. 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- BCG 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: It is useful test to detect AFB by microscopy, culture and MTB Gene Xpert especially in children. It also has high yield in adult TB suspects who are not expectorating.

Bronchoscopy (Bronchial wash/ biopsy): for AFB smear/ culture, MTB Gene Xpert and biopsy should also be sent for histopathology. It is recommended in selected cases.

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.

Pleural fluid Examination /pleural biopsy: DR (Protein, LDH, CELL CLOUNT, DLC), ADA. Yield of microscopy (AFB Smear), Xpert / MTB Rif Assay, AFB culture is low in TB pleural effusion so not routinely recommended. Pleural biopsy for AFB culture and histopathology (chronic granulomatous inflammation with caseous necrosis) is mainstay of diagnosis in suspected Tuberculous Pleural disease.

Pleural Fluid Markers for Tuberculosis:

Pleural Fluid Adenosine Deaminase Level: With lymphocytic exudative pleural effusion and high ADA levels (> 40 U/L) tuberculosis should be the first possibility. ADA represents the sum of two isoenzymes (ADA1 and ADA2). ADA1 is ubiquitous in all cells, including lymphocytes and monocytes, whereas ADA2 is found only in monocytes. Analysis and determination of these isoenzymes have shown that increase in ADA with tuberculous pleurisy is due to increase in ADA2 and that ADA1 / ADAp ratio improves performance in terms of sensitivity, specificity and efficacy (100%, 92-97%, and 98%, respectively). ADA level < 40 U/L virtually excludes tuberculosis in lymphocytic pleural effusion.

Plural Fluid Interferon Gamma Levels: Pleural fluid interferon gamma levels are also elevated with tuberculous pleuritis. Pleural fluid interferon gamma levels are more efficient than ADA levels in differentiating tuberculous pleural effusion. Pleural fluid interferon gamma levels up to 3.7 IU/mL has a sensitivity of 98% and a specificity of 97% in detecting tuberculous pleural effusion, through it is not widely available in Pakistan.

Urine LAM Test:

The urine lipoarabinomannan (LAM) is especially helpful in cases where the smear result is negative in a probable TB patient and also in severely ill patients, from whom it is difficult to physically collect sputum.

Owing to suboptimal sensitivity and specificity, currently this test is not suitable as a general screening or diagnostic test for TB. However it has demonstrated good sensitivity in seriously ill HIV infected individuals, especially in those with low CD4 counts.

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.

AN ILLUSTATED APPROACH TO THE DIAGNOSIS OF PRESUMPTIVE PULMONARY TUBERCOLOSIS

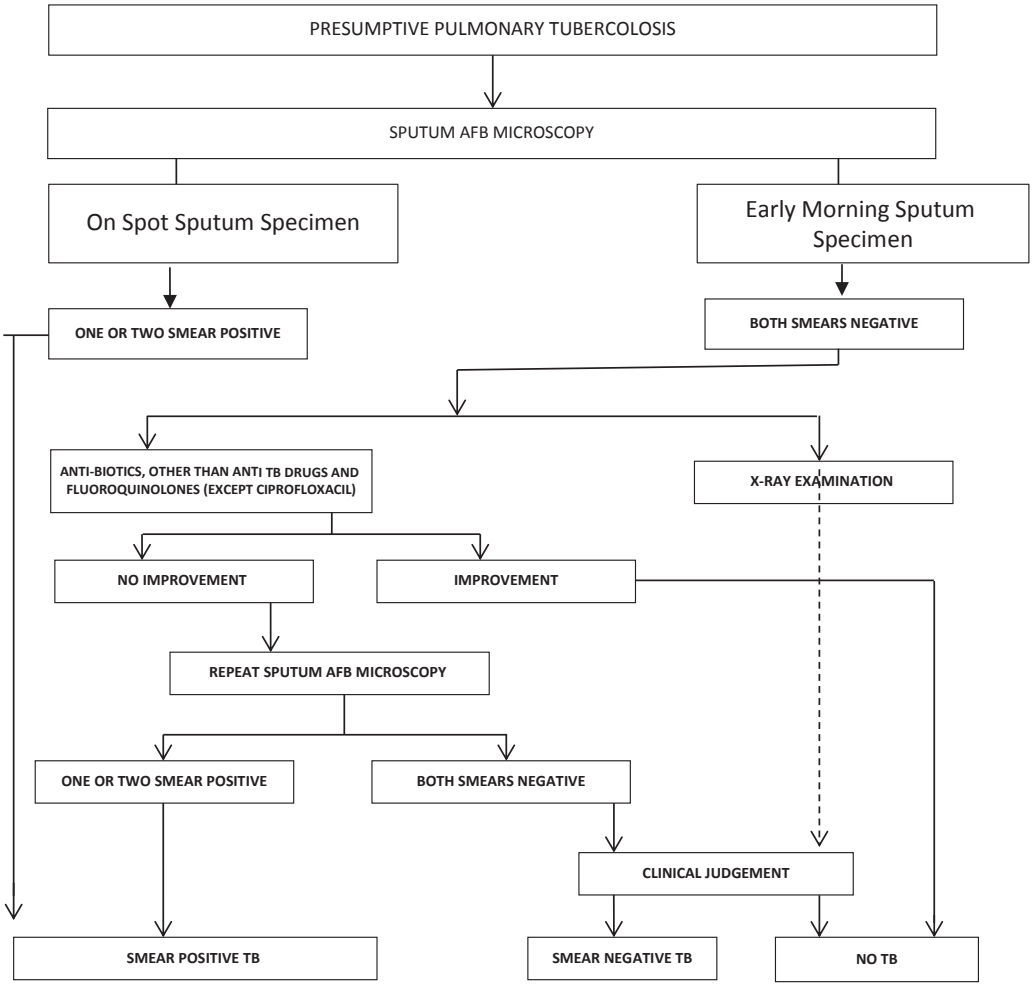

Figure-1 Diagnostic Algorithm for Presumptive Pulmonary Tuberculosis

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/disease in 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 programs should have component of health education for hygienic and healthy living. Psychological support in the form of counseling sessions or peer-group support would be helpful.

School health examinations and Tuberculosis awareness programs 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, schoolteacher, 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 i.e. 6 months for new, previously treated patients or patients with unknown previous TB treatment history (provided rifampicin resistance is not detected on Xpert /MTB Rif assay in the latter group). 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: 30-39kg 40-54kg 55kg 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 have 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 at regular, uninterrupted supply of all essential anti-TB drugs
4. A regular, uninterrupted (DOT) by watching patient ingest anti-TB drugs
5. A monitoring system for program supervision and evaluation.

Categorization of Patients for Treatment

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.

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 administered on daily basis for 6 months.

This regime is not consistent in with WHO recommendation and National Guidelines but keeping high INH resistance in view ,HRE has been recommended in continuation phase 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.

Table-3: Regimen Dosages With Fixed-Dose Combinations in Adults

Patient Body weight (kg)	Initial Intensive Phase Daily (2 months)	Continuation Phase Daily (4 months)
	HRZE (75+150+400+275)	**HRE** (75+150+275)
30-39	2	2
40-54	3	3
55-70	4	4
>70	5	5

*Applies only with high level of isoniazid resistance in TB patients, and where isoniazid drug susceptibility testing is not done (or results are unavailable) before the continuation phase begins.

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.

Table-4: Monitoring During Treatment

Perform Sputum Exam	Treatment Regimen 6 Months
At the end of the intensive phase	The end of 2nd month
During the continuation phase	The start of 5th month
At the end of treatment	The end of the 6th month

Monitoring Timeline for New Patients

Table-5: Treatment Monitoring Calendar Month 1st 2nd 3rd 4th 5th 6th Start x End x X

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. 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 fluooroquinolone-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-6: When to End Intensive Phase and Start Continuation Phase of Treatment

If	Next Step
At the end of the 2nd month patient's sputum smear- negative (true for vast majority).	Start in continue with the continuation phase treatment as planned until the end of regimen.
At the end of 2nd month patient's sputum smear positive.	Do Xpert/MTB Rif assay If RR not detected. START continuation face treatment If RR detected than refer to PMDT site for Management of DR TB.
At the start of 5th month patient's is sputum smear negative.	Continue with the treatment as planned.
At the start of the 5th month patient's sputum smear positive.	Do Xpert /MTB Rif assay send AFB culture and sensitivity. If RR not detected, re-register patient as treatment failure, RESTART ATT as Re-treatment case. Obtain result of sensitivity test for further management. If RR detected, then refer to PMDT site for Management of DR TB.
At the end of 06 months patient is sputum smear- negative.	Patient is considered cured, if last sputum not done, declare treatment completed.
At the end of 06 months patient is sputum smear positive.	Follow the same steps as at the start of 5th month if sputum smear positive.

2. Re-Treatment Cases:

All smear positive cases identified as "failures", "Treatment after lost to follow up" and "relapses" should be classified as "re-treatment cases".

The current category II regimen (2 HRZES/1HRZE/5HRE) should no longer be prescribed and drug susceptibility testing should be conducted to determine the choice of treatment.

Therefore, after registration as re-treatment case and before starting treatment all TB cases eligible re-treatment regimen will be tested on Xpert to exclude RR, it is preferable also to determine Isoniazid resistance status if possible by LPA. The recommended regimen is 3HRZE/5HRE if no resistance is determined. If rifampicin resistance is present than these patients are referred to PMDT unit for further drug susceptibility testing and treated accordingly.

TABLE-7: Treatment Regimen in new & Retreatment Cases

Sr.		Intensive	Continuation
1	New TB case smear+ & - cases	2HRZE	4HRE
2	Bacteriologically confirmed Retreatment cases	3HRZE	5HRE

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

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

3. Re-Treatment Failure:

This is a group of patients 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 who have completed the full course of re- treatment regimen. This group is considered as DR TB suspect and should be referred to PMDT unit. All close contacts are to be traced and evaluated for tuberculosis.

Duration of Chemotherapy

It is recommended for 6 months for New cases and 8 months for smear +ve retreatment cases with no rifampicin resistance on Xpert/MTB Rif assay.

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 and Bone Tuberculosis longer duration for up to 9 to 12 months treatment regimens are recommended. It is better to seek opinion from concerned specialist to ensure a proper completion of ATT treatment.

Additional Points in Extra-Pulmonary TB Management

Unless drug resistance is suspected, adjuvant corticosteroid treatment is recommended for TB meningitis and pericarditis.

In tuberculous meningitis, Ethambutol should be replaced by Streptomycin. Surgery should be reserved for the 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.

Tuberculous Pleural Effusion

TB pleural effusion may be asymptomatic if small. When the effusion is large, dry cough and shortness of breath may be present. Sputum production 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.

Tuberculous Pericardial Effusion

Tuberculous pericardial effusion present with chest pain, shortness of breath, oedema of the lower limbs and sometimes ascites. There may be associated systemic symptoms like fever, malaise, night sweats etc. 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 well-equipped hospitals.

Cutaneous Tuberculosis

The clinical presentation of cutaneous tuberculosis is chronic, painless, skin lesions, ranging from small papule and erythema to large tuberculomas. The diagnosis is based on skin biopsy

Management in Cases of Treatment Interruptions:

In patients who have had treatment interruptions, the reason for the interruption, such as medication stock-outs, adverse effects from medicines or need for greater patients / provider education should be addressed. The recommended treatment for this group of patient's is as follows.

TABLE-8: Management plan of patients with interrupted treatment

Length of interruption	Do a smear?	Result of smear	Do Xpert?	Result Xpert	Register again as	Treatment
Length of treatment			<1 month			
<2 weeks	No	-	No	-	-	Continue on same treatment for new case
2-8 weeks	No	-	No	-	-	Start again on treatment for new case
>8 weeks	Yes	Positive	Yes	MTB+RR- MTB+RR+	*Treatment after lost to follow-up	Start on treatment for new case Ref to PMDT
		Negative	Yes	MTB+RR– MTB+RR+ MTB ND	*Treatment after lost to follow-up	Start on treatment for new case Ref to PMDT Send for culture & wait for result
Length of treatment			>1 month			
<2 weeks	No	-	No	-	-	Continue on same treatment for new case
2-8 weeks	Yes	Positive	Yes	MTB+RR- MTB+RR+		Start again on same treatment for new case Ref to PMDT
		Negative	Yes	MTB+RR– MTB+RR+ MTB ND		Start again on same treatment for new case, Ref to PMDT Send for Culture, Send for culture,& wait for result
>8 weeks	Yes	Positive	Yes	MTB+RR- MTB+RR+	*Treatment after lost to follow-up	Start on treatment for previously treated case & send sample for DST Ref to PMDT
		Negative	Yes	MTB+RR– MTB+RR+ MTB ND	*Treatment after lost to follow-up	Start on treatment for previously treated case & send sample for DST Ref to PMDT Send for culture,& wait for result

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.

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 spread of disease through droplet infection.

Patients should 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, start of 5th and end of 6th month of 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)

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 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.

Anti-Tuberculosis Drugs

The first line anti TB drugs (FLD) consists of Isoniazid (H), Rifampicin(R), Pyrazinamide (Z) 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 use of Rifampicin for disease other than mycobacterium disease should be discourages.

Table-9: Anti-TB Drugs - Mechanisms of Action

Rifampicin	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
Isoniazid	A bactericidal drug active against all populations of TB bacilli Highly bactericidal against replicating tubercle bacilli. Kills 90% during first few days of treatment
Pyrazinamide	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
Ethambutol	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

Table-10: Clinical information about essential Anti-TB drugs

Rifampicin (R)	
Form	150 mg and 300 mg capsule
Administration Remarks	Must always be administered in combination with other anti- mycobacterial agents Should be given at least 30 minutes before meal
Dosage	10 mg/kg (8-12 mg/kg) daily Maximum 600 mg daily
Adverse Reaction	Gastrointestinal intolerance, Hepatitis, Cholestasis, Hepatic enzyme induction, drug interactions
Contraindication	Hepatic dysfunction, Known hypersensitivity to Rifamycins

Isoniazid (H)	
Forms	50 mg syp, 100 mg, 300 mg tablets, 50 mg in 2 ml injection
Administration Remarks	Taken orally. Injections reserved for critically ill patients
Dosage	5 mg/kg (4-6 mg/kg) daily Maximal dose is 300 mg daily
Adverse Reaction	Hepatic dysfunction, Skin rashes, Neurotoxicity

Pyrazinamide (Z)	
Forms	500 mg tablets
Administration Remarks	Highly effective during the first 2 months of therapy
Dosage	25 mg/kg (20-30 mg/kg) daily
Adverse Reaction	Hepatitis, Hyperuricaemia, Rash
Contraindication	Hepatic dysfunction, Known hypersensitivity

Ethambutol (E)	
Forms	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	Ocular toxicity
Contraindication	Pre-existing optic neuritis from any cause, Renal impairment, Inability to report like in young children visual disturbances Known hypersensitivity

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:

Table-11: Major Side Effects and Likely Causative Drugs

Major Side Effects	**Like Causative Drugs**
Skin Rash	INH
Jaundice	Isoniazid, Rifampicin, Pyrazinamide
Visual Impairment	Ethambutol
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	Like 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

Adverse drug reactions are more common in HIV-positive than in HIV-negative TB patients. Most reactions occur in the first 2 months of treatment. Since rifampicin reduces the effective of the oral contraceptive pill so advise a woman to use another form of contraception wherever indicated. Moreover, refer patients with severe drug reactions to specialist centres.

MANAGEMENT OF ADVERSE DRUG REACTIONS:

Gastrointestinal: (Hepatotoxicity/Drug Induced Liver Injury DILI)

Clinical Presentation:

Nausea, vomiting, abdominal pain & tenderness right upper abdomen, jaundice, hepatic enlargement, impaired LFTs

Causative Agents: INH, Rifampin, Pyrazinamide

Routine Monitoring for Hepatotoxicity: Patients < 35 years old, without a history of hepatic disease and with normal baseline LFTs: follow-up LFTs are not required unless the patient becomes symptomatic.

However patient > 35 years old, daily alcohol consumption, history of hepatic disease or abnormal baseline LFTs: They may require LFTs every 4-6 weeks.

Management in Adults:

Of the first-line anti TB drugs, isoniazid, pyrazinamide and rifampicin can all cause liver damage (drug-induced hepatitis). In addition, rifampicin can cause asymptomatic jaundice without evidence of hepatitis. It is important to try to rule out other possible causes before deciding that the hepatitis is induced by the TB regimen.

The management of hepatitis induced by TB treatment depends on:

- whether the patient is in the intensive or continuation phase of TB treatment
  the severity of the liver disease

- the severity of the TB and
- the capacity of the health unit to manage the side-effects of TB treatment

Asymptomatic Patients with an increase in ALT from baseline:

if the increase in ALT is < 3 times upper limit of normal (rifampin competes with bilirubin for elimination resulting in increased serum bilirubin initially; bilirubin levels usually return to normal with continued therapy): continue the current regimen and monitor for symptoms of liver dysfunction

For Asymptomatic Patients, if the serum transaminases increases > 5 times upper limit of normal: hold ATT until levels return to baseline.

Symptomatic Patients: (see "clinical presentation")

Hold all drugs and obtain LFTs

If LFTs are within the normal ranges, refer to the Management of Nausea/Vomiting section.

If LFTs are elevated, hold drugs until symptoms resolve and the transaminases decreases to < 2 times upper limit of normal

SEQ (streptomycin, ethambutol, fluoroquinolone) should be started if drug therapy cannot be held due to the patient's serious clinical condition

Re-challenge the patient after resolution of signs and symptoms by adding one by one drug to the regimen every 4 days, starting with rifampicin, followed by INH, then Pyrazinamide.

if signs and symptoms recur with re-challenge, discontinue the responsible drug and modify the regimen and/or duration of therapy as required.

Alternative regimens depend on which drug is implicated as the cause of the hepatitis. If rifampicin is implicated, a suggested regimen without rifampicin is 2 months of isoniazid, ethambutol and streptomycin followed by 10 months of isoniazid and ethambutol. If isoniazid cannot be used, 6–9 months of rifampicin, pyrazinamide and ethambutol can be considered. If pyrazinamide is discontinued before the patient has completed the intensive phase, the total duration of isoniazid and rifampicin therapy may be extended to 9 months. If neither isoniazid nor rifampicin can be used, the non-hepatotoxic regimen consisting of streptomycin, ethambutol and a fluoroquinolone should be continued for a total of 18–24 months. Reintroducing one drug at a time is the optimal approach, especially if the patient's hepatitis was severe. National TB control programmes using FDC tablets should therefore stock limited quantities of single anti-TB drugs for use in such cases. However, if the country's health units do not yet have single anti-TB drugs, clinical experience in resource-limited settings has been successful with the following approach, which depends on whether the hepatitis with jaundice occurred during the intensive or the continuation phase of TB treatment with

isoniazid, rifampicin, pyrazinamide and ethambutol: once hepatitis has resolved, restart the same drugs EXCEPT replace pyrazinamide with streptomycin to complete the 2-month course of initial therapy, followed by rifampicin and isoniazid for the 6-month continuation phase once hepatitis has resolved, restart isoniazid and rifampicin to complete the 4-month continuation phase of therapy.

GASTROINTESTINAL ADVERSE EFFECTS (Nausea/Vomiting)

Rule out other causes of nausea and vomiting: Consider measuring liver function tests to rule out drug induced hepatic dysfunction (refer to "Hepatotoxicity" section,).

If the TB medications are the likely cause of the patient's nausea/vomiting, follow the management plan.

The following describes a stepwise approach to the management of nausea and vomiting:

Always check for danger signs associated with nausea and vomiting:

- Signs of dehydration (thirst, dry mouth, sunken eyes, low blood pressure)
- Serum electrolytes if vomiting
- Signs of hepatitis (jaundice, right-sided abdominal pain)
- Ask if there is any blood in the vomit and melena, if so, address possible bleeding ulcers

For all patients, nausea and vomiting should be aggressively treated with a three-phase approach:

First Phase - Adjust Drug Administration Without Lowering Doses:

- Administer drugs causing nausea at night.
- Encourage the patient: nausea and vomiting often improve over the first weeks and may resolve entirely with time.

Second Phase - Administer Anti-Emetics:

- Start with metoclopramide PO: 10 mg 30 minutes before anti-TB drugs, maximum 15 mg twice daily. Do not use metoclopramide if neurological problems develop.
- If symptoms persist, metoclopramide can be continued with the addition of ondansetron or promethazine:

ondansetron PO: 8 mg twice daily (30 minutes before anti-TB drugs). Ondansetron can increase the QT interval and it is recommended to avoid this drug in patients taking medicines that significantly increase the QT interval.

If ondansetron is not available: promethazine PO: 25 mg 30 minutes before anti-TB drugs. If necessary, the dose of promethazine may be increased to 50 mg 3 times daily.

Third Phase - Reduce the Dose or Stop Temporarily the Drug: (Expert Consult)

- If absolutely necessary, stop all anti-TB drugs until symptoms resolve.

Notes:

- Ondansetron is serotonin 5-HT3 receptor antagonist with strong anti-emetic properties. A number of other anti-emetics from this class exist and sometimes a patient may respond better to one than another.
- Omeprazole decreases the acid production in the stomach is also useful in the treatment of nausea (20 mg at bedtime, and if not effective, 20 mg twice daily for 1 to 2 months – longer if necessary).
- In any of the phases, if there is excessive anxiety over the nausea caused by medications, consider adding benzodiazepine (e.g. diazepam 5 mg PO) 30 minutes prior to giving the medications. This can help a condition called "anticipation nausea". Once nausea is improved, stop the diazepam. The treatment must be short as benzodiazepines can cause dependence and tolerance. Do not give diazepam for longer than 2 weeks.

<u>GASTROINTESTINAL ADVERSE EFFECTS (Diarrhea)</u>

Clinical Presentation

3 loose bowel movements per day

Causative Agents

Rifampin, isoniazid, pyrazinamide.

Management:

Rule out other causes of diarrhea.

Withhold drugs until diarrhea resolves

Restart drugs one at a time every 4 days

Begin with drugs that are least likely to cause diarrhea

Consider crushing pills/capsules and administering.

If diarrhea recurs when one particular drug is added to the regimen, consider discontinuing the causative agent and adding other TB drugs and/or extending the duration of treatment

If diarrhea occurs with multiple drugs, consider separating medication administration times

Different drugs in the regimen should be administered several hours apart

Do not split doses for individual drugs (possible exception: ethionamide)

example: administer INH 300mg in the morning and rifampin 600mg in the evening

If diarrhea continues and an alternate regimen cannot be utilized, consider the addition of an antimotility agent

loperamide (Imodium®)

Adult dose: 4mg x 1, then 2mg after each loose stool (maximum dose=16mg/d)

Day 2 and subsequent days: 0.1mg/kg/dose after each loose stool (dose should not exceed the day 1 dose for each age/weight group)

Adsorbents (kaolin-pectin, polycarbophil) should not be prescribed because decreased absorption of the TB drugs may occur

ARTHALGIAS (Joint Pain)

Arthralgias Type 1

Causative Agents

pyrazinamide>>ethambutol>isoniazid

Clinical Presentation

Pain and tenderness of joints: fingers, shoulders, knees, etc. (usually mild)

Management

TB medications do not require discontinuation

Low dose nonsteroidal anti-inflammatory agents (NSAIDS) can be used for pain relief as needed, if symptoms persist, consider referral for rheumatologic evaluation

Arthralgias Type 2 (Gouty Arthritis)

Causative Agents

pyrazinamide>>ethambutol

Clinical Presentation

Symptoms: pain, tenderness and swelling of joints: fingers, shoulders, knees, etc.
Symptoms are usually severe

Signs: elevated serum uric acid concentrations

Management

TB medications usually do not require discontinuation

If acute swelling is present, the affected joint should be aspirated and examined for urate crystals to confirm the diagnosis of acute gouty arthritis.

Therapy:

1. Nonsteroidal anti-inflammatory agents include:

Indomethacin 50mg tid-qid until pain relief, then 25mg tid-qid Ibuprofen 800mg tid
Naproxen 750mg x1, then 250mg q 8 hour

   a) Colchicine is an alternative to NSAIDS
      1) dose: 0.5-1.2 mg x1, then 0.5-0.6 mg q 1-2 hours until joint pain is relieved, or nausea, vomiting or diarrhea occurs
      2) pain usually resolves after 4-8 mg cumulative dose
      3) maximum dose: 8mg
   b) A steroid taper may be required for severe attacks

2. Recurrent episodes may occur while the patient remains on pyrazinamide or ethambutol.
   a) consider using prophylactic colchicine
      1) 0.6mg one to two times daily
      2) continue until causative agent is discontinued

Consider referral for rheumatologic evaluation for acute gouty arthritis attacks.

<u>Peripheral Neuropathy:</u>

Causative Agents:

INH>>>ethambutol

Clinical Presentation

Prickling, tingling or burning sensation of the fingers and/or toes, usually occurs in a stocking glove distribution.

Management

Peripheral neuropathy is uncommon if the patient is receiving pyridoxine (vitamin B6) along with ATT. If peripheral neuropathy develop, it can be treated with pyridoxine 100-200mg po q day while the patient is receiving INH

Optic Neuritis (vision)

Causative Agents

Ethambutol >>INH

Clinical Presentation

Blurred vision (decrease in the "sharpness" of objects), "spots" present in patient's field of vision, red/green color blindness

Management

Discontinue drug

DERMATOLOGIC (SKIN) ADVERSE EFFECTS:

Mild Hypersensitivity (Immune) Reactions

There may be two different types of mild flashing the reactions.

Reaction-1

Flushing and / or itching of skin with or without rash; usually involves the face and scalp; may cause redness/ watering of the eyes; usually occur 2 to 3 hours after drug ingestion.

Reaction-2

Flushing and / or itching of the skin with or without rash; PLUS, hot flashes, palpitations, headache and /or increased blood pressure, occurs immediately often ingestion of certain foods (see below); usually resolves within 2 hours.

Causative Agents

Reaction -1: Rifampicin, pyrazinamide.

Reaction-2: Isoniazid + tyramine containing foods (cheese, red wine) or certain fish (tuna, skipjack).

Management

Reaction-1: Flushing is usually mild and resolves without therapy. If flushing is bothersome to the patient, an antihistamine may be administered to treat or prevent the reaction.

Reaction-2: Advise patient not to ingest foods listed above while receiving INH.

MODERATE/SEVERE HYPERSENSITIVITY (IMMUNE) REACTIONS

Patient may present with hives (raised, itchy skin) with or without fever.

Causative Agents

INH < Rifampicin < PZA < Ethambutol < Streptomycin

Management

Discontinue all drugs until reaction resolves. Identify the causative drug by rechallenging (restarting) each drug every 4th day according to the following:

Table-12 Drug Re-challenge protocol

Drug Rechallenge protocol			
Drug	Challenging Dose		
	DAY 1	**DAY 2**	**DAY 3**
Isoniazid (least likely)	50mg	300mg	300mg
Rifampicin	75mg	300mg	Full dose
Pyrazinamide	250mg	01 Gm	Full dose
Ethambutol	100mg	500mg	Full dose

For example begin the re-challenge with INH 50mg on day 1, if allergic reaction does not occur after the day 1 dose, increase the INH to 300mg q day. Continue to add drugs in the order and doses specified on the table every 4 days. If the reaction is severe with challenge dose then do not use that drug.

TREATMENT REGIMENS IN SPECIAL SITUATIONS

HIV and Tuberculosis

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/mm3 or less.
- ART should be deferred in pulmonary TB patients whose CD4 cell count exceeds 350 cells/mm3 provided that there is no other stage 3 or 4 event. Patients whose CD4 count at TB diagnosis exceeds 350 cells/mm3 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 throughout 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) than 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 neither the treatment is reinstituted 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 7 million people died from tobacco use in 2017 and tobacco use is estimated to be responsible for 16% of deaths among men and 7% of deaths among women each year. In 2017, there were an estimated 10 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)

Table-13 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
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. Treatment of DR TB is under-taken 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.

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