



Manual for the Prevention, Diagnosis, Treatment, Care, and Control of Tuberculosis in Belize

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FOREWORD

Tuberculosis is an infectious disease that affects about one third of the world's populace. Tuberculosis is considered one of the world's deadliest diseases. The World Health Organization (WHO) reported over 1.4 million TB deaths and an estimated 10.4 million new (TB incident) TB cases in 2015.

Tuberculosis is strongly related to the influences of existing Social Determinants of Health mostly social inequality, cultural, ethical, legal and labor issues. The TB Epidemic has significant negative effect on the economic development of our country and as part of the social determinants of health, poverty, malnutrition and loss of wages due to increased unemployment can dramatically increase the incidence of TB among the poorest sector of society who lack adequate access to healthcare and live under inhumane conditions.

In Belize, as in other parts of the world the highest prevalence of TB is seen in the active and productive members of society. To decrease the burden and impact of this disease there is a need to intensify action against TB through active and multi-sectorial participation as the Ministry strengthens its program to provide effective treatment and diagnostic tools for equal health care for those with TB.

One of the more important objectives of the National Tuberculosis Programme is to ensure the availability of highly effective Anti-Tuberculosis drugs for those affected and to ensure adherence, treatment completion and cure. This activity can only be achieved by constant monitoring of treatment of those affected. The program entity is responsible for monitoring of adverse effects associated with some of the anti-tuberculosis medications, adherence, treatment completion and surveillance of defaulters and drug resistance.

The Ministry of Health's purpose is to accelerate access to comprehensive TB Treatment and Care for Belizeans with Tuberculosis with the goal to reduce the burden of this disease through the delivery of efficient and effective TB services. Another important call is for the strengthening of surveillance in regards to drug resistance patterns that have come to light, it is therefore imperative that such activities of culture and drug sensitivity be done routinely by the program in collaboration with the national laboratory.

Tuberculosis efforts must be holistic and multi sectorial as we strive in our efforts and paths to achieve zero new infections and zero deaths associated to Tuberculosis. In light that the Ministry of Health is a present recipient of Global fund the implementation of such project depicts the efforts of our staff to improve diagnostic capacity and services to those affected and to ensure that as much support is delivered cautiously and effectively.

Sincerest gratitude to all those who have strived in making this a reality and work for the benefit of our fellow Belizeans.

Hon. Pablo Marin

Minister of Health

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Lead Author

Francis Morey, MD, MPH (Deputy Director of Health Services, National tuberculosis Coordinator)

Collaborating Authors

- Marvin Manzanero, MD (Director of Health Services-Ministry of Health Belize)
- Keisha Westby, MD

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List of Abbreviations

3TC	Lamivudine
ADRs	Adverse Drug Reactions
AFB	Acid Fast Bacilli
AIDS	Acquired Immune Deficiency Syndrome
Am	Amikacin
Amx-Clv	Amoxicillin-Clavulanate
ART	Antiretroviral therapy
ARV	Antiretroviral
AZT	Zidovudine
Bdq	Bedaquiline
BCG	Bacilli Calmette Guerin
BHIS	Belize Health Information System
BMI	Body Mass Index
CARPHA	Caribbean Public Health Authority
CEM	Cohort Event Monitoring
Cfz	Clofazimine
Cm	Capreomycin
CNS	Central Nervous System
CPT	Cotrimoxazole Preventative Therapy
Cs	Cycloserine
CSF	Cerebrospinal fluid
CXR	Chest X-ray
Dlm	Delamanid
DST	Drug Sensitivity Test
DTB	Disseminated TB Disease
DOTS	Directly Observed Therapy Short-Course
DST	Drug susceptibility testing
EFV	Efavirenz
EMB/E	Ethambutol
EPTB	Extra-Pulmonary Tuberculosis
Eto	Ethionamide
FDC	Fixed Dose Combinations
FEFO	First expiry, first out
FNA	Fine needle aspiration
FTC	Emtricitabine
Gfx	Gatifloxacin
HAART	Highly Active Anti-Retroviral Therapy
Hh	High dose Isoniazid
HIV	Human Immunodeficiency Virus
IGRA	Interferon Gamma Release Assay
INH/H	Isoniazid

Ipm	Imipenem
IPT	Isoniazid preventive therapy
IRIS	Immune Reconstitution Inflammatory Syndrome
ISTC	International Standards for Tuberculosis Care
Km	Kanamycin
Lfx	Levofoxacin
LTBI	Latent Tuberculosis Infection
Lzd	Linezolid
MAC	Mycobacterium Avium Complex
MDG	Millennium Development Goal
MDR	Multidrug resistant
MDR-TB	Multidrug-resistant tuberculosis
Mfx	Moxifloxacin
MOH	Ministry of Health
MOTT	Mycobacterium Other Than Tuberculosis
Mpm	Meropenem
MTB	Mycobacterium tuberculosis
NAP	National AIDS Programme
NNRTI	Non-nucléoside reverse transcriptase inhibitor
NsRTI	Nucleoside reverse transcriptase inhibitor
NGO	Non-Governmental Organization
NTP	National Tuberculosis Programme
PAHO	Pan American Health Organization
PAS	Para-amino salicylic acid
PCR	Polymerase chain reaction
PPD	Purified Protein Derivative
PHC	Primary Health Care
PI	Protease inhibitor
PMTCT	Prevention of mother-to-child transmission
PTB	Pulmonary Tuberculosis
Pto	Prothionamide
PZA	Pyrazinamide
RIF/R	Rifampicin
RR	Rifampicin Resistance
S	Streptomycin
sADR	Suspected Adverse Drug Reactions
SR	Spontaneous Reporting
TB	Tuberculosis
TDF	Tenofovir Disoproxil Fumarate
TMP	Trimethoprim
Trd	Terizidone
TSR	Targeted Spontaneous Reporting

TST	Tuberculin skin Test
TU	Tuberculin units
VCT	Voluntary counseling and testing
WHO	World Health Organization
WRDT	WHO Rapid Diagnostic Test
XDR	Extensively drug resistant
XDR-TB	Extensively drug resistant tuberculosis
Z	Pyrazinamide

1. Tuberculosis Epidemiology, Transmission, and Pathophysiology

1.1 Tuberculosis Epidemiology

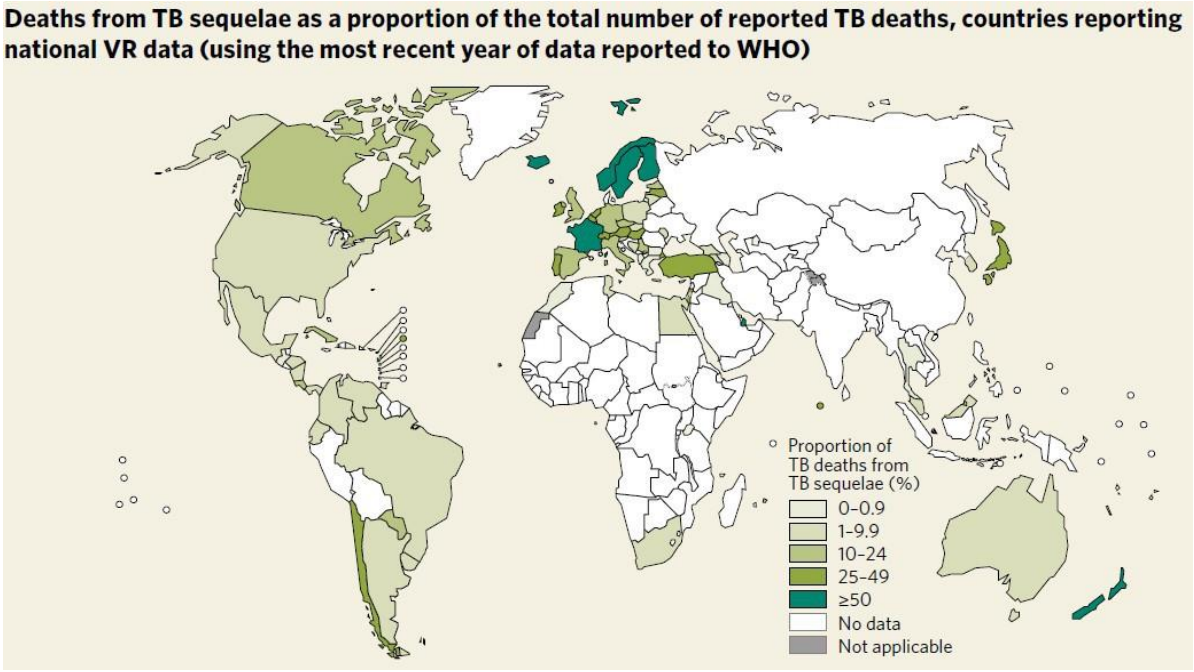
Global Tuberculosis surveillance and reporting has improved enormously in the last 2-3 years resulting in larger Tuberculosis (TB) epidemic figures. This has also been marked by a steady decline in TB associated deaths because of improved access to health services and effective standardized treatment regimens.

In 2015, there were an estimated 10.4 million new (incident) TB cases worldwide, of which 5.9 million (56%) were among men, 3.5 million (34%) among women and 1.0 million (10%) among children. People living with HIV-accounted for 1.2 million (11%) of all new TB cases.

In 2015, there were an estimated 480 000 new cases of multidrug-resistant TB (MDR-TB) and an additional 100 000 people with rifampicin-resistant TB (RR-TB) who were also newly eligible for MDR- TB treatment.

There were an estimated 1.4 million TB deaths in 2015, and an additional 0.4 million deaths resulting from TB disease among people living with HIV. TB associated mortality fell by 22% between 2000 and 2015, however TB remained one of the top 10 causes of mortality worldwide in 2015.

Figure 1.1 Global TB Deaths as a Proportion of Total Number of Reported TB Deaths



Source: WHO Global Tuberculosis Report 2016

Tables 1.1. and 1.2 figures show the burden of Tuberculosis disease in Belize and the PAHO region of the Americas for 2015. Successful NTP's rely heavily on accurate data and interpretation of what the data represents so that appropriate interventions may be formulated.

Table 1.1 WHO/PAHO Region of the Americas TB Burden Statistics

Estimates of TB Burden, 2015			
	Number (thousands)	**Rate (per 100 000 population)**	
Mortality (excludes HIV + TB)	19 (17-20)	1.9 (1.8-2)	
Incidence (includes HIV + TB)	268 (250-287)	27 (25-29)	
Incidence (HIV+TB only)	32 (29-35)	3.2 (2.9-3.5)	
Incidence (MDR/RR/TB)	11 (10-12)	1.1 (1-1.2)	
Estimated TB Incidence by Age and Gender (thousands), 2015			
	0-14 years	**>14 years**	**Total**
Females	13 (11-15)	88 (76-100)	101 (87-115)
Males	13 (11-15)	155 (141-169)	168 (152-183)
Total	26 (23-28)	243 (232-253)	268 (250-287)
TB Case Notifications, 2015			
Total cases notified			230 519
Total new and relapse			217 081
- % with known HIV status			82%
- % pulmonary			85%
- % bacteriologically confirmed among pulmonary			77%

Source: Adapted from the WHO Tuberculosis Report 2016

Table 1.2 is a snapshot of the overall burden of Tuberculosis in Belize. Generally, there was a higher incidence of Tuberculosis cases among males compared to females. The presence of multi-drug resistant Tuberculosis (MDR-TB) presence a major concern and challenge for control of the disease in the country. One of the major aims of the National Tuberculosis Program (NTP) is to prevent the emergence of MDR-TB in the country, while ensuring successful treatment of patients with drug susceptible tuberculosis (TB).

Table 1.2 Snapshot of TB rates in Belize, 2015

Estimates of TB Burden, 2015		
	Number (thousands)	**Rate (per 100000 population)**
Mortality (excludes HIV+TB)	<0.01 (<0.01-<0.01)	2.4 (2.4 – 2.4)
Mortality (HIV+TB only)	<0.01 (<0.01-0.01)	0.85 (0.04-2.9)
Incidence (includes HIV+TB)	0.09 (0.077-0.1)	25 (21-29)
Incidence (HIV+TB only)	0.021 (0.018-0.024)	5.8 (5 – 6.8)
Incidence (MDR/RR-TB)	0.01 (<0.01-0.012)	2.8 (2.4-3.3)

Estimated TB Incidence by age and gender (thousands), 2015			
	0-14 years	**>14 years**	**Total**
Female	<0.01 (<0.01-<0.01)	0.019 (<0.01-0.03)	0.027 (0.015 – 0.035)
Male	<0.01 (<0.01-<0.01)	0.06 (0.047-0.073)	0.063 (0.049 – 0.077)
Total	0.01 (<0.01-0.013)	0.079 (0.072-0.087)	0.09 (0.077-0.1)

1.2 Etiology of Tuberculosis

Tuberculosis is a communicable infectious disease caused by the bacillus ***Mycobacterium tuberculosis*** (MTB). It can produce silent (latent TB infection), or as the progressive, active TB disease.

Mycobacterium Tuberculosis (MTB) retains red color after Ziehl-Neelsen staining with carbol-fuchsin despite washing with acid–alcohol; thus, it also called acid-fast bacilli (AFB). On culture, ***M. tuberculosis*** grows slowly, doubling about every 20 hours (this is slow compared with gram-positive and gram-negative bacteria, which double about every 30 minutes).

There are several mycobacterium bacilli species found in living organisms all known as the Mycobacterium Tuberculosis complex (MTBC); a genetically related group of mycobacterium species that cause Tuberculosis in human beings and other living things.

The Mycobacterium Tuberculosis Complex (MTBC) includes the following bacilli species:

- *Mycobacterium bovis & Mycobacterium bovis BCG*
- *Mycobacterium africanum*
- *Mycobacterium microti*
- *Mycobacterium canetti*
- *Mycobacterium caprae*
- *Mycobacterium pinnipedii*
- *Mycobacterium mungi & Mycobacterium orygis*

1.3 Transmission of Tuberculosis

Tuberculosis (TB) is transmitted when a person with active TB disease of the lungs; coughs, sneezes or spits causing droplet nuclei containing the bacilli to be expelled into the air and inhaled by another person.

Transmission occurs mostly indoors, where there is poor ventilation and the droplets stay airborne for long hours. MTB is killed quickly by sunlight, but may survive in the dark for hours. The risk of transmission of infection from a smear-negative patient is low, and even lower in those with Extra- Pulmonary tuberculosis (EPTB).

1.3.1 Factors Determining Transmission of Tuberculosis

Susceptibility: an individual with a weak immune system has a higher risk of transmission.

Infectiousness: the more the number of tubercle bacilli a person with TB disease expels into the air, the more infectious they are.

Environmental factors: these affect the concentration of M. Tuberculosis organisms; the more droplet nuclei in the air, the more probable that M. Tuberculosis will be transmitted.

Space: Exposure in small, enclosed spaces with inadequate local or general ventilation that results in insufficient dilution or removal of infectious droplet nuclei

Exposure: The longer the duration of exposure, the higher the risk for transmission

Frequency of exposure: The more frequent the exposure to an infectious person, the higher the risk of transmission

1.4 Tuberculosis Infection and Disease

Note: Infection is the acquisition of a microbe, and evidence of infection documents the presence of a microbe in an individual. Infection only results in disease when the host-microbe interaction produces sufficient damage to disrupt normal homeostasis and/or to become clinically apparent.

1.4.1 Tuberculosis infection: means that Mycobacterium Tuberculosis (MTB) are in the body but immune system is keeping them under control. People who have Latent TB infection (LTBI) are NOT infectious and do NOT have active TB disease.

1.4.2 Tuberculosis Disease: A person with a weak immune system allows rapid multiplication of the bacilli to occur and the person begins to present signs and symptoms of active TB disease. The most infectious forms of tuberculosis are TB of the lungs and the larynx.

1.5 Risk Factors for Tuberculosis

1.5.1 Risk factors for TB Infection

- **Location and Place of Birth:** Individuals born in area of high TB incidence and prevalence have a higher risk for Tuberculosis infection.
- **Age:** TB infection is most common in early adulthood (25-44-year-old age group) mostlikely due constant exposure and workplace risk.
- **Gender:** differences between males and females begin to show with increasing age; males being at a higher risk than females.

1.5.2 Risk Factors for TB Disease

Once a person has TB infection, the lifetime risk for progression to active TB disease is estimated to be at 10%. The following factors increase a person's risk of developing active TB disease:

- **Co-infection with HIV:** HIV lowers the strength of the immune system, thus making it easier for Tuberculosis causing Mycobacterium bacilli to multiply and cause disease.
- **Extremes of age:** children below 5 years of age (underdeveloped immune system) and adults' above 65 years of age have 2-5 times the risk of TB disease
- **Recent TB infection (within the past 2 years):** this person can reactivation of the disease and develop signs and symptoms of active TB disease.
- **Substance abuse (crack cocaine, alcohol, tobacco)**
- **Certain medical conditions:** these increase risk of TB disease due to their effect on the immune system.
  - Diabetes mellitus
  - Silicosis
  - Certain types of cancer (e.g., leukemia, Hodgkin's disease, or cancer of the head and neck)
  - Severe kidney disease (Chronic Renal Failure, Hemodialysis)
  - Low body weight (BMI 10% or more below ideal)
  - Solid Organ transplant
- Use of immunosuppressive agents: these reduce overall strength of the immune system e.g.
  - Prolonged therapy with corticosteroids (>15mg daily for over 4 weeks)
  - Chemotherapeutic agents for cancer
  - Anti-rejection drugs for organ transplant, tumor necrosis factor alpha antagonists

- Other factors that increase risk for TB disease
  - Homelessness
  - Migrants from countries with high TB prevalence
  - Overcrowded habitation
  - Institutionalized persons: prisons, geriatric homes, correctional facilities

1.6 Pathogenesis of Tuberculosis

A primary infection occurs on first exposure to the TB bacilli; inhaled droplet nuclei end up at the terminal alveoli of the lungs, where they multiply forming the *Ghons focus* (***radio dense area on the chest radiograph, evidence of stable granulomas***). This focus and the lymphatic system that drains the bacilli to the hilar lymph nodes forms the primary complex, and can travel via the circulatory system to any part of the body. An immune response may occur 4-6 weeks after the primary infection. Hence the Tuberculin Skin Test (TST) positivity would be the only evidence of infection. For others, the weakened immune system may not fight the infection and the individual may develop disease in a few months.

M. tuberculosis can evade/resist the immune responses of a person. It inhibits the initial immune response activities by releasing immunosuppressive chemicals that slow down host immune function; any defects in the host immune system make it likely that *M. tuberculosis* will not be controlled and that active disease will occur.

1.7 Primary and Post-Primary Tuberculosis

A person with no symptoms of TB but is Tuberculin Skin Test (TST) positive (90% of cases) is usually described as Latent TB Infection, has **primary TB.**

Post primary TB: This occurs after a latent period of months or years after primary infection. This is due to re-infection or reactivation of a focus due to alterations in immune system response. The dormant bacilli now multiply rapidly, triggered by the weakened immune system (e.g. HIV infection).

Re-infection is when a person that has had a previous infection, acquires a new one (smear positive). In adults, we see cavitary lesions, upper lobe infiltrate fibrosis, progressive pneumonia, and endobronchial localization.

Table 1.3 Post Primary Tuberculosis Signs

- Hypersensitivity Reactions e.g.
  -Dactylitis
  -phlyctenular conjunctivitis
  -erythema nodosum
- Pulmonary and pleural complications, TB pneumonia, effusion, lobar collapse (bronchial)
- Disseminated Tuberculosis
  -Cervical Lymphadenopathy
  -Meningitis
  -Pericarditis
  -Miliary Disease

Rapid development to intrathoracic disease is more common in children than in adults (intrathoracic lymphadonepathy and lung infiltrates)

1.8 Common Sites of Tuberculosis

1.8.1 Pulmonary tuberculosis: occurs in the lungs (85%). (Cavities, upper lobe infiltrate, fibrosis, progressive pneumonia).

1.8.2 Miliary tuberculosis: results from widespread blood-borne dissemination of TB bacilli, due to a recent primary infection, into the blood vessels. Symptoms; may include anorexia, weight loss, malaise, and fever. The X- ray findings are characteristic (miliary pattern).

1.8.3 Extra-pulmonary Tuberculosis (EPTB) occurs in places other than the lungs (central nervous system, spine, lymph nodes, pericardium, and pleura). (Table 1.4)

Table 1.4: Common Pulmonary and Extra-Pulmonary TB Sites and Symptoms of Disease

Pulmonary Tuberculosis (PTB)	**Extra-Pulmonary Tuberculosis (EPTB)**
Site (s)	**Site (s)**
-Lung	-Kidney -Spine -Larynx -Male/female Genital Tract (less commons) -Adrenal Gland (less common) -Skin (less common - lupus vulgaris, miliary, tuberculids)
Symptoms	**Symptoms**
-Cough (especially if lasting for 3 weeks or longer) with/without sputum production -Coughing blood (hemoptysis) -Chest pain -Loss of appetite -Unexplained weight loss -Night sweats -Fever, fatigue	-TB of the kidney may cause blood in urine -TB Meningitis may cause headaches/confusion -TB of the spine may cause back pain -TB of the larynx may cause hoarseness -Loss of appetite -Unexplained weight loss -Night sweats, fever, fatigue -Lymphadenopathy, pericarditis

1.9 Effects of HIV on Tuberculosis Disease

HIV infection is the strongest single risk factor for active TB infection and disease. As CD4+ lymphocytes multiply in response to the mycobacterial infection, HIV multiplies within these cells and selectively destroys them; in turn the TB-fighting lymphocytes are depleted. This results in HIV-infected patients at 100 times the risk of active TB compared with HIV-negative people.

As mycobacteria spread throughout the body, HIV replication accelerates in lymphocytes and macrophages. HIV-infected patients who are infected with TB deteriorate more rapidly unless they receive antimycobacterial chemotherapy. HIV increases the risk for developing TB disease from 10% to > 50% over the course of their lifetime, related to the degree of immunosuppression (CD4 count). TB disease can develop at any stage during HIV disease.

A person who has HIV infection can become infected with M. tuberculosis (includes exogenous reinfection) and then rapidly develop TB disease. Additionally, the presence of other infections, including TB, activates the immune system, resulting in increased HIV replication and subsequent accelerated progression of HIV disease. Tuberculosis is a disease that can co-exist with other conditions and therefore physicians must have the knowledge and skill to differentiate and rule out other underlying illnesses. (Table 1.5)

Table 1.5: TB Differential Diagnosis

Differential Diagnosis	Guide to Correct Diagnosis
• Pulmonary Bacterial and Fungal Infections: - Bacterial pneumonia, lung abscess - Pneumocystis jirovecii, other mycobacteria - Nocardiosis, Cryptococcosis - Histoplasmosis, Coccidiodomycosis	• Lack of response to antibiotics • Abscess with fluid level on CX Ray • Microbiological study of sputum • Bronchial lavage • Serology for mycosis
• Bronchiectasis (Congenital or Acquired)	• Large amount of purulent sputum in the mornings
• COPD (chronic obstructive lung disease) • Peri-emphysematous Pneumonia	• Risk factor(smoking) • Chronic and progressive dyspnea • Wheezing
• Lung Cancer	• Risk factor (smoking)
• Interstitial Lung Diseases (Idiopathic or Secondary), including Sarcoidosis	• CT scan • Bronchoscopy, biopsy
• Pulmonary Cystic Diseases	• CT scan, biopsy
• Heart Failure	• Symptoms of heart failure (dyspnea, orthopnea, paroxysmal nocturnal dyspnea, hemoptysis, edema, epigastric discomfort from hepatic congestion)

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2. WHO Tuberculosis Case Definitions

Tuberculosis (TB) data collection is part of the health information management system of Belize. The major goals of systematic and accurate data collection on TB are to:

- Ensure high-quality patient care, and continuum ofcare;
- Information-sharing with patients and transfer of information between healthfacilities;
- Aid staff in providing adequate services to individual patients;
- Allow managers at different levels in the National TB programme (NTP) to monitorprogramme performance in a standardized and internationally comparable way;
- Provide the basis for programmatic and policy development.

For data to be comparable within and between NTPs, standard definitions of key concepts captured by NTP information systems need to be used. The World Health Organization (WHO), TB case definitions are based on the level of certainty of the diagnosis and whether laboratory confirmation is available.

2.1 Presumptive TB Case

Any person who presents with symptoms or signs suggestive of TB (prolonged cough > 2weeks, plus respiratory symptoms, shortness of breath, chest pains, hemoptysis) loss of appetite, weight loss, fever, night sweats, fatigue. (***used to be called TB Suspect***)

2.2 Case Definitions of Tuberculosis

2.1.1 A Bacteriologically Confirmed TB case: is a patient who has positive smear microscopy test, culture or WHO-approved Rapid Diagnostic Tests (WRDT) such as Xpert MTB/RIF. All suchcases should be notified, regardless of whether TB treatment hasstarted.

2.1.2 A Clinically Diagnosed TB case: is one who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. This definition includescases diagnosed based on 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 can also be classified by:

- Anatomical site of TB disease
- History of previous TB treatment
- Drug resistance
- HIV status of the patient

2.3 Classification Based on Anatomical Site of Tuberculosis (TB) Disease

2.3.1 Pulmonary Tuberculosis (PTB): refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. Tuberculous intra-thoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extrapulmonary TB.

2.3.2 Miliary TB is classified as PTB because there are lesions in the lungs. A patient with both pulmonary and extra-pulmonary TB constitutes a case of pulmonary TB.

2.3.3 Extra-pulmonary Tuberculosis (EPTB): refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges.

- Therefore, tuberculosis intrathoracic lymphadenopathy (mediastinal and/or hilar), or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitute a case of extra- pulmonary TB.
- It also depends on the site or sites that have the most severe form of the disease. EPTB case with several sites affected depends on the site representing the most severe form of disease.
- Of note, EPTB is considered WHO clinical stage 4 for HIV infection and relateddisease.

Diagnosis of EPTB should be based on;

i. One culture-positive specimen confirmed with M. tuberculosis

ii. Histological specimen; or (i.e. granulomatous inflammation and /or AFB).

iii. Strong clinical evidence consistent with active EPTB and a decision to treat with a full course of tuberculosis chemotherapy.

NOTE: EPTB can only be diagnosed by culture or any newer method to be defined as a definite case of TB.

2.4 Classification Based on Previous TB Treatment

Classifications based on history of previous TB treatment focuses only on history of previous treatment and are independent of bacteriological confirmation or site of disease. (**See *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis*, First Edition WHO 2014**).

2.1.3 New patients: have never been treated for TB or have taken anti-TB drugs for <1 month.

2.1.4 Previously treated patients: 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 oftreatment.

2.4.2.1 Relapse patients: 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 byreinfection).

2.4.2.2 Treatment after failure patients: are those who have previously been treated for TB and whose *treatment failed*. Treatment failure is a positive AFB or culture at the end of fifth month of thestandard treatment regimen.

2.4.2.3 Treatment after loss to follow-up patients: have previously been treated for TB and were declared *lost to follow-up* at the end of their most recent course of treatment. (These were previously known as *treatment after default* patients.) Lost to Follow Up (abandoned): Patient who received at least 1 month of treatment and who interrupted treatment for at least 2 months.

2.4.2.4 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 orundocumented.

- 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 TBcases.

Note: Patients whose sputum is smear positive at the end of (or returning from) subsequent course of treatment are no longer defined as chronic and should be defined by the outcome of their most recent treatment: failure, relapse or default.

2.5 Classification Based on HIV Status

2.5.1 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.

2.5.2 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.

2.5.3 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.

2.6 Classification Based on Drug Susceptibility

Cases are classified in categories based on drug susceptibility testing (DST) of clinical isolates confirmed to be *M. tuberculosis:*

2.6.1 Monoresistance: resistance to one first-line anti-TB drug only.

2.6.2 Polydrug resistance: resistance to more than one first-line anti-TB drug (other than both isoniazid and rifampicin).

2.6.3 Multidrug resistance: resistance to at least both isoniazid and rifampicin.

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

2.6.5 Rifampicin resistance: resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, whether monoresistance, multidrug resistance, polydrug resistance or extensive drug resistance.

These categories are not all mutually exclusive; when enumerating rifampicin-resistant TB (RR-TB), multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) are also included.

2.7 GeneXpert/RIF for the Diagnosis of Pulmonary Tuberculosis and Rifampicin Resistance (WHO Recommendations)

In a move to increase and improve the diagnosis of active TB disease WHO recommends the use of rapid diagnostic test such as the Xpert/MTB/RIF technology which is more sensitive and diagnoses the presence of MTB compared to smear microscopy which detects MTB and other mycobacteria and cannot differentiate between them.

The Xpert also improves early diagnosis for tuberculosis in the presence of possible drug resistant strains as it detects drug resistant TB for rifampicin and can be used as a proxy for MDR-TB. This RDT would provide a result in a period of 2-4 hours, depending on how fast the sample is received and processed, and is also more sensitive than smear microscopy for detection of TB, HIV-associated TB. Sensitivity is similar to solid Lowenstein Jenssen (LJ) culture. Specificity is closer to 100%.

2.7.1 Strong Recommendations for Use:

- Xpert MTB/RIF should be used rather than conventional microscopy, culture and DST as the initial diagnostic test in adults presumed to have MDR-TB or HIV-associated TB (high-quality evidence).
- Xpert MTB/RIF should be used rather than conventional microscopy, culture and DST as the initial diagnostic test in children presumed to have MDR-TB or HIV-associated TB (very low-quality evidence).

2.7.2 Conditional Recommendations (recognizing major resource implications)

- Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in all adults presumed to have TB (high-quality evidence).
- Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in all children presumed to have TB (very low-quality evidence).
- Xpert MTB/RIF may be used as a follow-up test to microscopy in adults presumed to have TB but not at risk of MDR-TB or HIV associated TB, especially in further testing of smear-negative specimens (high-quality evidence).

2.7.3 Groups of Patients Recommended for Gene X-pert testing (Algorithm 1)

i. Retreatment cases classified /defined as (failure, return after loss to follow-up, return after relapse).

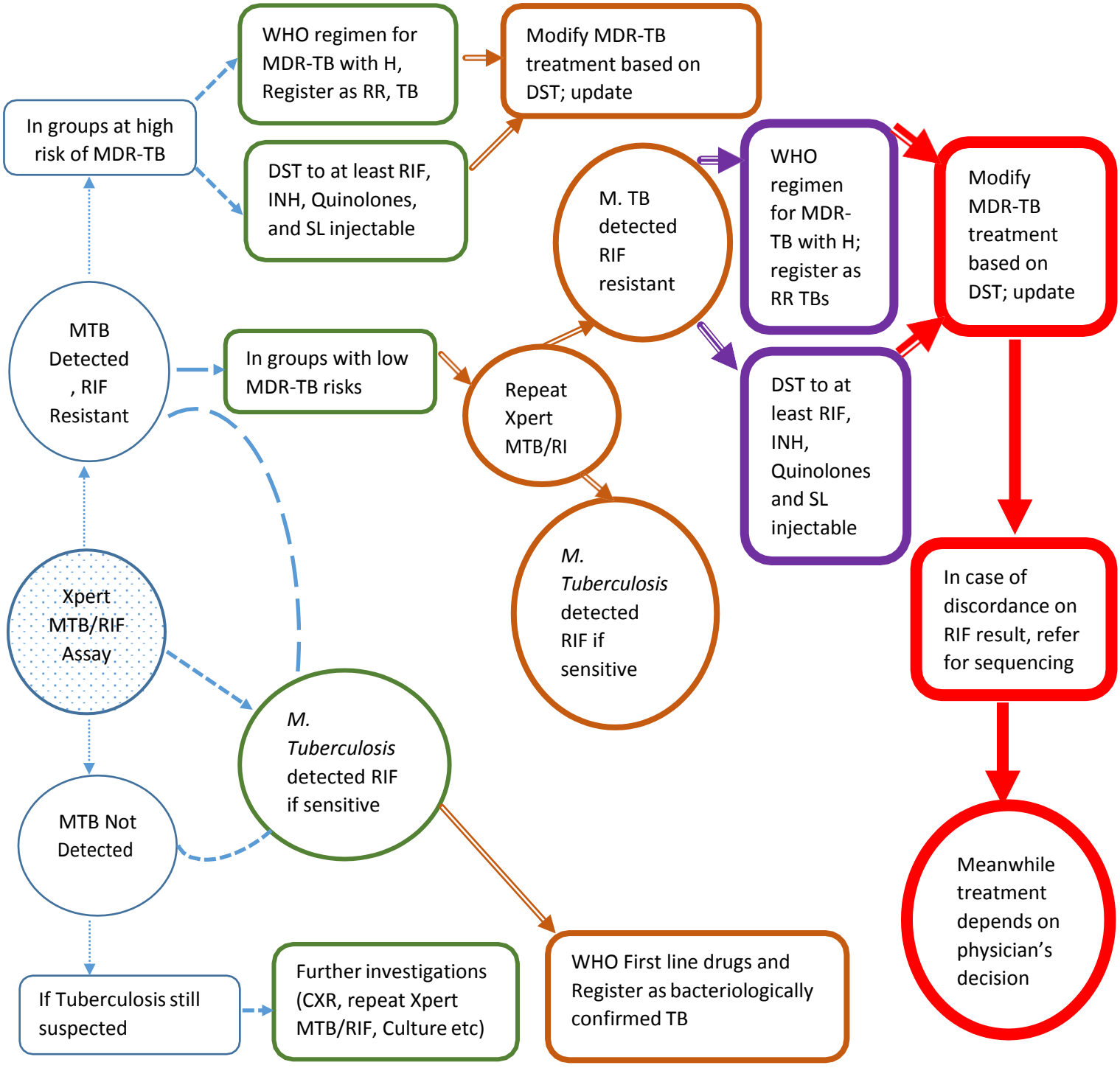
ii. Xpert MTB/RIF should be used as the initial diagnostic test rather than conventional microscopy, culture and DST in all persons living with HIV (and all persons with immunosuppressed conditions) who have signs or symptoms of TB, in persons who are seriously ill and suspected of having TB regardless of their HIV status, and in those whose HIV status is unknown but who present with strong clinical evidence of HIV infection in settings where there is a high prevalence of HIV or among members of a risk group for HIV.

iii. This group includes all individuals suspected of having TB (adults and children). Xpert MTB/RIF may be used as an initial diagnostic test for TB

-Ideally all pulmonary TB patients need to be tested through GeneXpert, searching for *Mycobacterium Tuberculosis* (MTB) and Rifampicin Resistant TB.

-Gene Xpert is useful only for Diagnosis of *Mycobacterium Tuberculosis* (MTB) and Rifampicin Resistance (RR); it is not useful for bacteriological follow up, due to its high sensitivity.

Figure 2: Algorithm for Testing Sputum Samples for Drug Sensitivity via GeneXpert Rifampicin (WHO Recommendation)



2.8 The Belize Health Information System

This electronic patient care health information system should be now the most important reporting tool as it records patient information collected in the system. This includes:

- Name, Age, Gender
- Address, Contact Details
- TB patient's diagnostic category (Laboratory Results and Clinical Details)
- Results of initial and follow-up sputum smear examinations
- Treatment regimen, drug doses
- Initial and follow-up body weight
- Medication history data.

2.9 Treatment Outcomes Definitions

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

The two groups are mutually exclusive. Any patient found to have drug-resistant TB and placed on second-line treatment is removed from the drug-susceptible TB outcome cohort. This means that management of the standard TB register and of the second-line TB treatment register needs to be coordinated to ensure proper accounting of the outcomes of treatment.

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

Table 2.1 Treatment outcomes for TB patients (excluding patients treated for RR-TB or MDR-TB) *(adapted from WHO guidelines)*

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

Patients found to have an RR-TB or MDR-TB strain at any point in time should be started on an adequate second-line drug regimen. These cases are excluded from the main TB cohort when calculating treatment outcomes1 and included only in the second-line TB treatment cohort analysis. If treatment with a second-line drug regimen is not possible, the patient is kept in the main TB cohort and assigned an outcome from among those in table 2.1.

Table 2.2 Outcomes for RR-TB/MDR-TB/XDR-TB Patients Treated Using Second-Line Treatment

Outcome	Definition
Cured	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Treatment Completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Treatment Failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: − lack of conversion by the end of the intensive phase, or − bacteriological reversion in the continuation phase after conversion to negative, or − evidence of additional acquired resistance to fluoroquinolonesor second-line injectable drugs, or − adverse drug reactions (ADRs).
Died	A patient who dies for any reason during treatment.
Lost to Follow-up	A patient whose treatment was interrupted for 2 consecutive months or more.
Not Evaluated	A patient for whom no treatment outcome is assigned. (This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown)
Treatment Success	The sum of cured and treatment completed

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

-The terms "conversion" and "reversion" of culture are defined as follows:

Conversion (to negative): culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion.

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

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3. Case Finding and Diagnosis

All Clinicians must think of active TB disease in a person with symptoms of the disease or abnormal chest X-ray lesions typical of tuberculosis. Late diagnoses of tuberculosis increases risk of transmission and mortality from TB.

3.1 Active and Passive Case Finding

Active case-finding: this can be carried out in several ways. For example, unreported cases of TB disease can be identified through active laboratory and pharmacy audits, follow-up of close contacts of smear-positive patients and of high risk groups, e.g., HIV-positive individuals, respiratory symptomatic persons.

Passive case-finding: based on the referral of symptomatic individuals who seek treatment at a care facility. It includes creating a referral system between HIV and TB diagnostic and treatment centers.

Sites where opportunities for case-finding exist:

- TB chest clinics
- Hospitals (public)
- Other public health clinics
- HIV voluntary counseling and testing (VCT) sites
- Prevention of mother-to-child transmission (PMTCT) clinics
- Correctional institutions, prisons, and jails
- Drug treatment centers
- HIV care facilities
- Private medical facilities
- Occupational health facilities
- Long-term care facilities and shelters

Presumptive TB Case: Anyone with symptoms of TB must be suspected of having TB and be evaluated for the disease. The presence of a chronic cough lasting more than 2-weeks has served as the criterion for defining suspected TB. **(2013 WHO definitions presumed TB)**

3.2 Steps in Diagnosing Tuberculosis (TB)

3.2.1 Medical History: The medical history is essential for the diagnosis and classification of TB, it provides information on the infectious period, and is useful for the contact investigation. It includes social, family, medical and occupational information on the patient, and the following as well:

i. Known exposure to a person who has infectious TB
ii. Symptoms of TB disease and onset
iii. Previous treatment for TB infection or TB disease
iv. Risk factors for developing the disease, and other medical conditions that might impact therapy

3.2.2 Signs and Symptoms of PTB

3.2.2.1 Respiratory symptoms of Pulmonary Tuberculosis (PTB)

- Persistent (productive or non-productive) cough for more than two weeks or more,
- Chest pain when coughing or breathing.
- Shortness of breath
- Bloodstained sputum or hemoptysis

3.2.2.2 Systemic Symptoms of Pulmonary Tuberculosis disease (pulmonary or extra-pulmonary):

- Weight loss
- Loss of appetite
- General malaise and fatigue
- Fever
- Night sweats

Symptoms of EPTB depend on the part of the body that is affected by the disease. (Lymph nodes, pleura, larynx, meninges, genitourinary and intestinal tract, bone, spinal cord, eye and skin)

3.2.3 Bacteriologic Examination (Sputum Smear Microscopy)

A confirmative diagnosis of tuberculosis is done by culturing *M. tuberculosis* complex from a clinical specimen or through use of molecular-based test methods (e.g., nucleic acid amplification, Gene Expert). Microscopic examination of stained sputum is easily accessible and available, and is essential in the diagnosis of tuberculosis. Importance of AFB microscopy:

- It is the most rapid method for determining if someone has tuberculosis
- It identifies persons who are at greatest risk for dying from the disease
- It identifies the most likely transmitters of infection.

In Belize, we recommend that three sputum samples should be collected, in two consecutive days, from patients suspected of having PTB (The first specimen should be "spot- first patient encounter, early morning, spot") and sent for AFB smear Microscopy and Gene Xpert. Clinical discretion can be used depending on the patient's clinical state or sputum productivity.

EPTB is seen frequently in the HIV population. Obtaining specimens for bacteriological examination from EPTB sites may be more difficult. EPTB specimens that may be sent for AFB smear microscopy, culture and other histopathological examination include any of the following:

- Broncho-alveolar lavage
- Aspirated fluid from pleura, stomach or another site
- Biopsied tissue from lung, peripheral lymph node or other site where TB is suspected
- Blood or urine or cerebro-spinal fluid (Visualizing AFB is rare and hence culture is needed).

3.2.4 Culture of Sputum and Identification of MTB

Culture and identification for M. tuberculosis should be performed as part of the diagnostic investigation, some criteria for culture includes:

- Patients meeting the criteria for sputum smear negative PTB or EPTB
- Childhood tuberculosis
- HIV positive TB suspect
- Symptomatic patients at risk for MDR-TB
- Currently in or history of having lived in a prison, jail or correctional facility
- History of exposure or previous treatment to MDR-TB
- History of residence in areas with high MDR-TB prevalence
- Patients who are defaulters or failing treatment prior to a change in regimen.
- All initial positive TB cultures
- Positive cultures from patients who are failing treatment, defaulters or relapse

3.2.5 Drug Susceptibility Testing (DST)

Mortality due to drug resistant TB has been on the increase, with the greatest risk among patients who have HIV/TB co-infection, TB Relapse and Treatment Failure.

WHO recommends the following:

- NTPs undertake DST at the start of TB therapy in all HIV-positive TB patients, to avoid mortality due to unrecognized drug-resistant TB

- NTP's use of rapid DST in sputum smear-positive persons living with HIV
- If the country is introducing DST, but does not yet have the resources to test all HIV-positive TB patients, initial policy should be to target DST at the start of TB treatment for patients with previously treated TB, who are very likely to be multidrug-resistant. This group includes patients whose prior TB treatment has failed, who have relapsed or who are returning from default.

3.2.6 Radiographic Examination

Chest X-rays support the diagnosis of tuberculosis when combined with the clinical presentation; however, other conditions can show chest X-ray abnormalities that resemble TB. A chest x-ray increases the likelihood of TB disease in a person who has only one of three sputum smears that are positive or who has persistent TB symptoms with negative sputum smears;

- Checking for lung abnormalities in people who have symptoms of TB disease especially in the HIV- infected;
- Evaluating persons with a newly identified positive reaction to the tuberculin skin test (TST)
- Evaluating localization and extent of lesions.

Radiographic abnormalities suggestive of tuberculosis should prompt doctors to directly investigate possible tuberculosis by indicating (sputum smear microscopy, and culture examination. (Table 3.1).

Table 3.1: Radiographic presentation of active/inactive TB

Radiographic presentations suggestive of active PTB include- • Acute upper lobe pneumonia • Unresolving pneumonia • Cavitation, cavitary lesion • Pleurisy, pleural effusion • Lung infiltrate, especially in the upper lung zones
Radiographic presentations suggestive of previous or presumed inactive PTB include: • Apical fibrosis • Upper lobe fibronodular abnormality • Pleural (fibro) calcification • Upper lung zone bronchiectasis • Thoracoplasty or partial pneumonectomy • Healed primary lesion (Ghons' focus / complex)

3.3 Diagnosing TB in the Sputum Smear Negative Patient

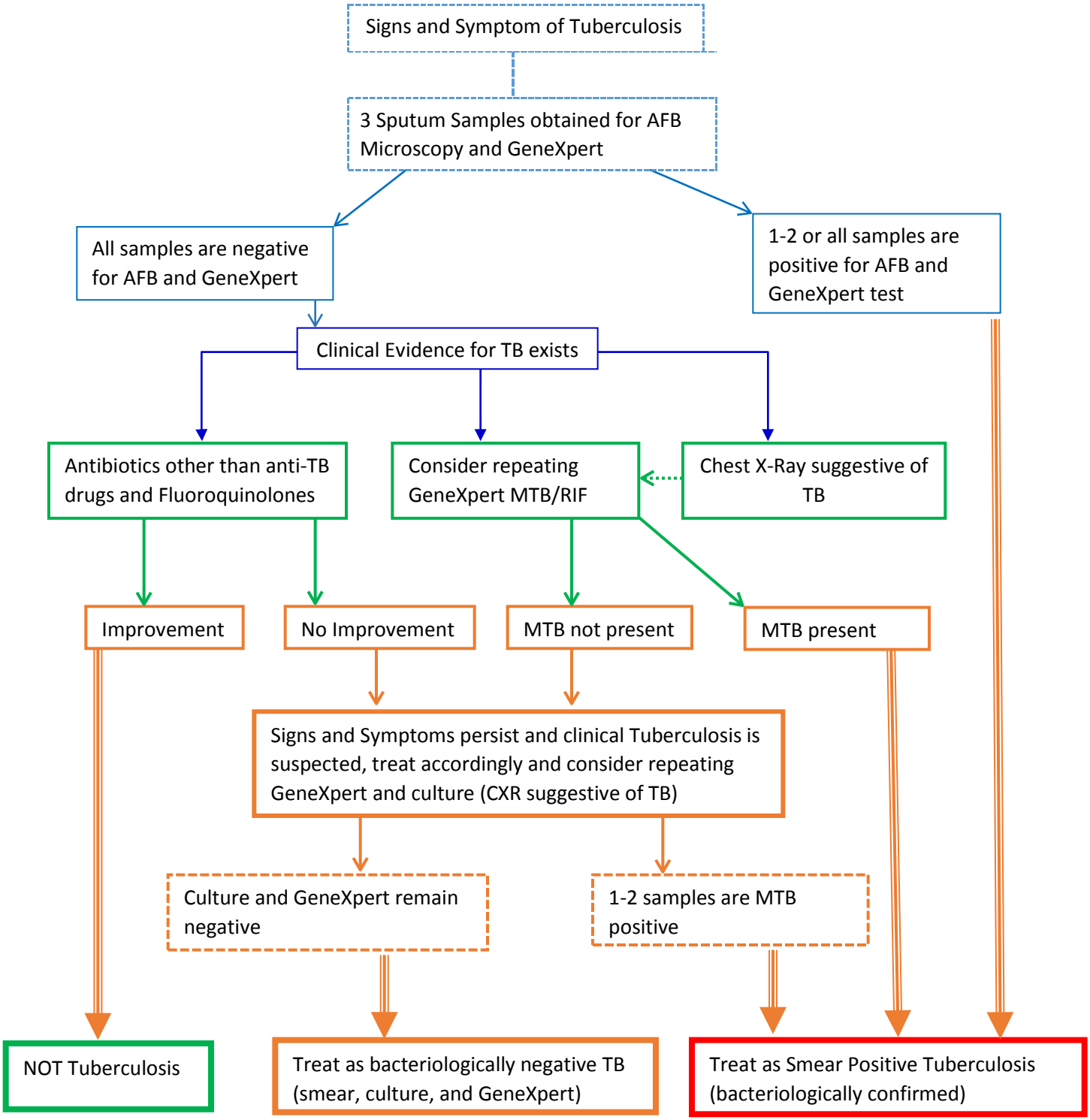
"Sputum smear-negative tuberculosis" presents a difficult diagnostic situation. TB suspect and patients with HIV Co-infection may present with negative smear microscopy, in this situation the use of GeneXpert MTB/RIF is mandatory. (see Figure 3)

i. Patients with HIV and tuberculosis frequently have negative sputum smears

ii. Differential diagnosis includes *Pneumocystis jirovecii pneumonia*, bacterial and fungal respiratory infections

iii. Extra pulmonary sites are more common

Figure 3: Algorithm for the Diagnosis of TB in ambulatory HIV Negative Individuals Presumed Pulmonary Tuberculosis.



3.3.1 Diagnosis of sputum smear negative and Xpert negative PTB should be based on the following criteria

- At least two negative sputum smears and one Xpert negative result
- Cultures must be attempted
- HIV test expedited
- Chest X-ray consistent with TB (Radiographic presentations suggestive of active PTB)
- Lack of response to broad spectrum non-anti TB antibiotic.
- Thorough physical exam

Culture:

Sputum microscopy is the first bacteriological diagnostic test of choice, but when needed and available, all sputum smears whether positive or negative should include culture (in smear negative TB or with HIV patients). Sputum culture results may not be available at an early date until after treatment has been started, however treatment must be continued if TB is highly suspected.

Cases with clinical diagnosis of Extra-pulmonary TB (EPTB): All smear negative specimens in patients with diagnosis of EPTB should be sent for culture and identification of MTB/MOTT; include CSF specimens for Xpert and Culture testing, due to the severity of disease. Bacteriological confirmation is more difficult for extra pulmonary TB than pulmonary TB, as few AFB can be obtained and AFB microscopy from these sites is infrequent. e.g. pleural fluid and CSF only yields 5 to 10% of cases. Hence due to low yield in microscopy both culture and histopathological examination of tissue specimens are needed by biopsy e.g. (lymph nodes for diagnosing EPTB).

3.4 Diagnosis of Extra-Pulmonary Tuberculosis: Presentations and Investigations

3.4.1 Pleural Tuberculosis: Tuberculosis pleural effusions tend to be free flowing in the early stage, but with time it may be localized. Symptoms include cough, often non-productive, fever, and pleuritic chest pain. Dyspnea, chills, sweats, weight loss and malaise occur with advancing disease of the parenchyma. Diagnosis ideally is made through culture of the tubercle bacilli from pleural fluid. Radiographic findings include moderate unilateral effusion or massive fluid collections.

3.4.2 Lymphatic Tuberculosis: Tuberculosis lymphadenitis, also known as "scrofula". is particularly common in the posterior cervical and supraclavicular group of lymph nodes. In immunocompromised individuals and children, mediastinal, peri-bronchial, and para-tracheal lymph node involvement is more commonly seen as part of primary disease. The disease is indolent with gradual, painless enlargement of the node(s) over several weeks to months. Patients typically present with a unilateral, painless, non-tender neck mass. Over time the overlying skin

may become shiny, pink to red and warm to touch, lymph nodes may become fluctuant and drain spontaneously with sinus tract formation. Investigations include excisional lymph node biopsy for AFB and histology or fine needle aspiration (FNA) biopsy for AFB smear and culture and other routine investigation (history, HIV, TST, CXR, etc.).

3.4.3 Genitourinary Tuberculosis: Renal tuberculosis may present with asymptomatic sterile pyuria, hematuria, dysuria, flank pain resembling acute pyelonephritis. Diagnostic investigations include urine for AFB smear and culture (3-5 first morning urine samples); FNA biopsy for histology as well as AFB smear and culture may be indicated; radiologic procedures such as intravenous pyelography, ultrasonography or computed tomography may be useful when available; routine TB workup should be included (history, TST, CXR, etc.).

3.4.5 Genital Tuberculosis: may present with mass lesions of the testes or epididymis in men, frequently without fever or other systemic complaint. Females may present with infertility, pelvic pain, and menstrual disturbances, excessive menstrual loss, amenorrhea, and post- menopausal bleeding. Diagnosis entails culture, biopsy of mass lesions for histological and cultural studies. Other procedures include uterine curettage, cervical biopsy, laparoscopic biopsy to obtain a diagnosis in women with suspect genital TB.

3.4.6 Disseminated Tuberculosis: Is the involvement of two or more non-contiguous organs with TB or the presence of tuberculosis bacteremia. This form is more commonly seen in children and immunosuppressed individuals. Symptoms include fever, weakness, anorexia, and weight loss. Chest radiography is a critical element in the diagnosis of disseminated TB.

3.4.7 Tuberculosis of the spine (Pott's disease): TB of the spine can result in long-term physical disability. Patients may experience pain over a localized area, usually over the lower thoracic, lumber, and lumbar sacral vertebrae. In children and adolescents, the thoracic vertebrae are most often affected; in adults, the lumbar vertebrae are more commonly involved.

3.4.8 TB of the Central Nervous System (CNS): includes TB meningitis and brain tuberculoma. If not diagnosed early and treated, this form can be fatal or cause permanent disability. Early symptoms include malaise, headache, anorexia, nausea and vomiting. It may also include low grade fever, neck stiffness, cranial nerve palsies and seizures as the TB progresses. At presentation, the cerebrospinal fluid (CSF) is often clear and the pressure normal. CSF glucose levels are lower than serum glucose levels with an increase in cells and protein.

3.4.9 Tuberculosis pericarditis: may presents as constrictive pericarditis. Investigations include echocardiogram, pericardiocentesis and pericardial biopsy in addition to the routine TB workup history, TST, CXR etc.

3.5 Tuberculosis Infection Control and Tools to Assess Infection Control at Institutions

TB infection control involves a combination of measures that aim to minimize the risk of TB transmission within at risk groups and populations. The foundation of infection control is earlyand rapid diagnosis, and proper management of TB patients. TB infection control requires and complements implementation of core activities in TB control, HIV control and health-systems strengthening.

It should be part of the national infection control guidelines and policies as this targets airborne infections. Increased transmission of TB may occur in healthcare (clinics and hospitals) and congregate settings (e.g., prisons, jails, and military barracks) where people with TB and HIV are frequently crowded together. Evidence that some patients with MDR-TB and HIV may be highly infectious presents added urgency to ensuring adequate infection control measures are in place to protect against TB transmission in settings where these patients may be seeking care.

Addressing TB infection control requires action at the national and subnational level to provide managerial direction, and at facility level to implement TB infection control measures. The 2009 *WHO Policyon TB Infection Controlin Health-Care Facilities, Congregate Settingsand Households* (http://whqlibdoc.who.int/publications/2009/9789241598323_eng.pdf) outlines 6 key activities to guide Ministries of Health in establishing the managerial framework necessary for the implementation of TB infection control at facility level. Measures to reduce transmission can be classified as "managerial," "administrative," "environmental," and "personalprotective".

3.5.1 Measures to Reduce TB Transmission at Facility Level

Managerial control measures form the framework for establishing and implementing the other three control measures. Managerial activities ensure political commitment and leadership at both national and facility levels.

- **Administrative control measures should include:**

i. Development and maintenance of systems for early recognition, diagnosis, and treatment of TB suspects (particularly those with PTB). Development of a facility Infection Control Plan and designation of an Infection Control Officer with responsibility for implementation of the plan.

ii. Policies and procedures for separation of PTB suspects from others until a diagnosis is confirmed or excluded.

iii. TB Infection control training and annual updates forstaff.

iv. Preparation and/or display of TB information for patients and the public related to its transmission, treatment and prevention.

- **Environmental control measures should include:**
  i. Maximizing natural ventilation to help reduce TB transmission indoors (e.g., open windows to promote cross ventilation and "stack effect" [see Figure 4], use of fans where air may be stagnant)
  ii. Whenever possible, capitalize on sunlight which is a natural source of ultraviolet light and can kill TB bacilli
  iii. Designate an appropriate location for sputum collection in an adequately ventilated booth or out in the open air, away from other people

- **Personal protection should include:**
  i. Provide accessible, acceptable, confidential voluntary HIV counseling and testing
  ii. Protect HIV-positive persons from possible exposure to TB (e.g., transfer of an HIV-infected worker from medical wards where patients with infectious TB are admitted)
  iii. Provide isoniazid preventive therapy if indicated
  iv. Provide a face mask for the TB patient or presumed TB patient to wear when moving within the hospital

Note: The Ministry of Health Recommends that each institution develops an Infection Control Plan for Tuberculosis. This will serve to assist the institutions in quality control and assurance measures that are essential in the elimination of nosocomial infections. See **tables 3.2, 3.3, and 3.4** for forms that can be used to assess infection control practices at health institutions; which can then lead to appropriate infection control policies.

Figure 4: Promoting natural ventilation.

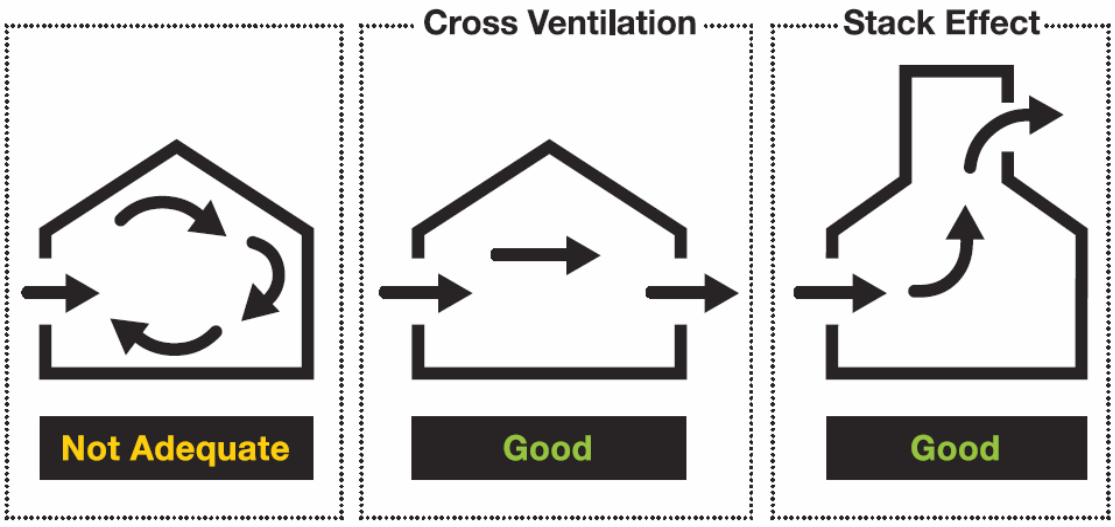


Table 3.2: TB Background Information Sheet

Background Information for the TB Register

1. Do you have a copy of the most recent National Annual TB Report? _____

Information on questions 2-3 should be available at the district or provincial health department

2. What was the number of TB cases in your district or province during the last year? _____
3. What was the incidence of TB in your district or province compared to the national average?

____*information on questions 4-8 should be available in the facility TB Register*

4. How many smear-positive TB patients were diagnosed in your facility last year? _____
5. How many smear-negative TB patients were diagnosed in your facility last year? _____
6. How many extra-pulmonary TB patients were diagnosed in your facility last year?

_____

7. How many were retreatment cases? _____
8. Of those TB retreatment patients, how many were HIV-positive?____How many had MDR TB? ____

Background Information from the Laboratory

9. What diagnostic tests for TB are available on site? Smear_____Culture____Chest X-Ray_____
10. How long does it take to get a Smear result?_____Culture Result?_____Chest X-Ray result? _____
11. How long does it take to get a patient on TB therapy after test results are received? _____
12. Does the Laboratory maintain a current log of results?_____Is there a backlog of results that have not been entered? ____

Background Information on Facility and Services

13. Do patients sometimes stay in the facility for more than 24 hours? _____
14. How many patients received care for any reason in your facility last year? _____
15. How many patients were on ART in your facility? _____
16. How many patients on ART were diagnosed with TB? _____

Background Information on Health Care workers

17. Does your facility conduct high-risk procedures such as bronchoscopies, and autopsies? _____
18. Are high-risk procedures conducted in specially ventilated rooms with 6-12 air exchanges per hour?

___

19. Do you have a routine TB screening program for health care workers?_____If yes, is this information being collected on a routine basis?_____

Table 3.3: Facility Risk Assessment Form Modified for Program Evaluation

Name of the Health Facility	
Address	
Telephone Number	
Date Assessment Completed	Baseline:____ 6-month F/U: ___
Name and Position of Person(s) Completing Assessment	
Level of Facility	District Provincial Health Center Dispensary
Type of Facility Public Private Faith-based	**Services Provided:** ART TB General OPD

Table 3.4: Facility TB Infection Control Risk Assessment Tool

Managerial

	Yes	No	Verified*	Comments
1. The National Infection Control Policy is available on-site.				
2. An infection control practitioner or nurse has been assigned to carry out infection control in the facility				
3. An Infection Control Committee/Team has been designated at this site.				
4. A written site-specific infection control (IC) plan has been written and is available to staff.				
5. The infection control plan contains a statement of endorsement by the facility manager.				
6. A TB IC risk assessment is completed at least annually.				
7. Facility design and patient flow has been assessed for the best use of space and ventilation.				
8. All patients with TB disease are managed on directly observed therapy (DOTS) per the national guidelines.				
9. TB IC practices are monitored daily.				
10. There is a facility reporting system for all patients diagnosed with TB and referred for treatment in accordance with national policies.				
11. TB IC training for all staff has been done and documented at least annually.				
12. Information on TB IC is available for all patients and visitors and is offered by staff.				
13. Operational research to improve TB IC measures is conducted at this site.				
14. An Occupational Health program is in this facility.				

Administrative

	Yes	No	Verified*	Comments
1. Patients are routinely asked about cough when entering the facility.				
2. Patients that are coughing are separated from others and "fast tracked" to a clinician.				
3. A "Cough Monitor" or other designated person gives cough etiquette guidance and assists with separation and triage.				
4. Signage for cough etiquette is present in the clinic.				
5. Supplies are available to coughing patients (tissues, cloths, masks, trash bins, etc).				
6. Sputum samples are collected in a designated area and away from others.				
7. Processing of sputum samples is expedited in the lab. There is a tracking mechanism to monitor turn-around time of lab results.				
8. There is a tracking mechanism to monitor turn-around time of patients within the healthcare facility.				
9. Staff receive an evaluation for TB at least annually				
10. A confidential log is kept of all staff that are diagnosed with TB disease.				
11. Staff are offered an HIV test annually and offered ART if they are positive.				

Environmental

	Yes	No	Verified*	Comments
1. Staff monitors natural and/or mechanical airflow daily (especially in waiting rooms, sputum collection rooms if available, and at least one exam room).				
2. Health care workers that assist during sputum collection take precautions.				
3. Regular cleaning and maintenance of directional and extractor fans is conducted.				
4. Servicing documentation is maintained and is available for review				
5. Signage is in place to keep doors and windows open when feasible				
6. If UV lighting is used, routine cleaning and maintenance is conducted and documentation logs kept.				
7. Patient waiting areas are out-of-doors or have good cross-ventilation.				

Personal Protective Equipment (PPE)

	Yes	No	Verified*	Comments
1. Surgical masks are available and worn by coughing patients.				
2.N-95 or FFP2 respirators are readily available and used by staff.				
3.Staff has been trained on proper fit of respirators and documentation of training is available.				

*Site visit team verifies the information that was initially reported by the facility team by writing "Y" for "yes" and "N" for "no" in the space provided, as appropriate. If "No", note in the "Comment" section what the actual on site situation is.

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4. Standard Treatment Regimens

Proper management of Tuberculosis ensuring successful treatment outcomes for all patients reduces the burden of the disease on government resources and the general population.

4.1 Objectives of Tuberculosis Treatment

i. To rapidly reduce the number of actively growing bacilli in the patient; thus, reducing disease severity and associated mortality and its transmission to the general populace

ii. To eradicate persisting bacilli thus preventing relapse and achieving long term cure

iii. To prevent development of drug resistant species of the bacilli during treatment

The standard of care for initiating treatment of TB disease is four-drug therapy. Treatment with a single drug can lead to the development of a bacterial population resistant to that drug.

4.2 Essential Anti-Tuberculosis Medicines

Table 4.1 is a list of essential medicines used in the management of Tuberculosis (**WHO Essential Medicines List 2015**). These medicines are also available as fixed dose combinations for the purposes of reducing pill burden and thus improving adherence to treatment.

Table 4.1: Doses of First-line Anti-tuberculosis drugs in Adults and Children

Drug	**Recommended dose in mg/kg body weight (range)/daily**	**3 times weekly dosage (e.g. Mon/Wed/Fri)**
Isoniazid (INH, H)	-Children: **10-15 mg/kg (300mg/day)** -Adults: **5mg/kg (max. 300mg/day)**	- Children: - Adults: **15mg/kg, max. 900 mg/dose**
Rifampicin (RIF, R)	-Children: **10-20 mg/kg** -Adults: **10mg/kg (max. 600mg/day)**	- Children: —— - Adults: **10mg/kg, max. 600 mg/dose**
Pyrazinamide (PZA, Z)	-Children: **30-40mg/kg** (max. 2000mg/day) -Adults: **25mg/kg (max. 2000mg/day)**	- Children: —— - Adults: **35mg/kg, max. 3000mg/dose**
Ethambutol (EMB, E)	-Children: **20mg/kg (15-25mg/kg), max. 1000mg/day** -Adults: **15mg/kg (max. 1600mg/day)**	- Children: **30mg/kg (25- 35mg/kg)** - Adults: **30mg/kg, max. 2400mg/dose**
Streptomycin (SM, S)	-Children & adults: **15mg/kg (12-18mg/kg), max. 1000mg/day**	- Children & adults: 1**5mg/kg (12-18mg/kg)**

- Daily dose recommendations for children as determined following review of existing pharmacokinetic studies and in consultation with pediatric pharmacology and TB experts www.who.int/selection_medicines/committees/subcommittee/2/TB.pdf
- -RIF dosages at the higher ranges may be preferable for children under 10 kilograms, and children with HIV infection or malnutrition
- -The recommended dose of Ethambutol is higher in children (20mg/kg), than in adults (15mg/kg) because the pharmacokinetics are different (peak serum concentrations are lower in children than adults receiving the same mg/kg dose). Although it was omitted from treatment regimens for children in the past due to the difficulty in monitoring its toxicity, as it is related to optic neuritis in young children, being safe at a dose of 20mg/kg range being (15-20mg daily).
- -Streptomycin should be avoided when possible in children because the injections are painful and irreversible auditory nerve damage may occur. The use of streptomycin in children is mainly reserved for the first 2 months of treatment of TB meningitis. Streptomycin should also be avoided in patients with renal failure because of increased risk of nephrotoxicity and ototoxicity. If streptomycin must be used, decrease frequency to two or three times per week, and monitor serum levels of the drug. Some sources recommend reduction of streptomycin dose to 10mg/kg/day (max. 750 mg/day) in patients >59 years of age. Patients weighing less than 50 kg may not tolerate doses above 500–750 mg daily (WHO Model Formulary 2015. www.who.int/selection_medicines/list/en/)

Source: Adapted from Tuberculosis Coalition for Technical Assistance. International Standards for Tuberculosis Care (ISTC), 3rd Edition. Tuberculosis Coalition for Technical Assistance, The Hague, 2014. (adjust year)

4.3 Fixed-dose combination tablets (FDCs)

The WHO strongly recommends the use of fixed-dose combination tablets.

ADVANTAGES of Fixed Dose Combinations;

i. Reduces prescription errors because dosage recommendations are straight forward and adjustment of dosage per weight is easier
ii. Reduced pill burden which impacts positively on adherence
iii. Decreases chance of acquired drug resistance due to patient self-selection of drugs when DOT not used

DISADVANTAGES of Fixed Dose Combinations;

i. The use of fixed-dose combination tablets does not obviate the need for separate drugs for a minority of cases that develop drug toxicity, intolerance or resistance.

Table 4.2: Recommended Strengths of FDC formulations of Essential Anti-TB

Drugs	Forms	Strength
Rifampicin+Isoniazid+Pyrazinamide+ethambutol	tablet	R-150mg + H-75 mg + Z-400mg + E-275mg
Rifampicin+Isoniazid+Pyrazinamide	tablet	R-150mg + H-75 mg + Z-400mg R-60 mg + H-30mg + Z-150 mg (Pediatrics)
Rifampicin + isoniazid	tablet	R-300mg + H-150mg
Intermittent use thrice weekly Rifampicin + Isoniazid	tablet	R-150mg + H-150 mg R-60mg + H-60mg (Pediatrics)

Table 4.2 and 4.3 shows that irrespective of whether the cut-off weight for changing from three tablets to four in the proposed four-drug FDC is at 50 kg or 55 kg, therapeutic efficacy is maintained because the mg/kg doses would be kept between the maximum and minimum recommended limits always. For individuals weighing below 50 kg or 55 kg the dose would be 3 tablets,.> 55 kg it would be 4 tablets. Children weighing >10 kg, the dose would be one dispersible tablet per 5 kg body weight. For lower body weights, the tablet dose would be halved and administered per 2.5 kg increments as appropriate.

Table 4.3: WHO Recommended Dosages for Adults using Fixed Dosage Combinations

Weight (Kg)	Initial Phase (2-months)		Continuation Phase (4-months)		Continuation Phase (6-months)
	EHRZ (daily)	HRZ (daily)	HR (daily)	HR (x3 weekly)	EH (daily)
30-37	2	2	2	2	1.5
38-54	3	3	3	3	2
55-70	4	4	4	4	3
≥71	5	5	5	5	3

4.4 Treatment of New Cases (presumed to be drug susceptible)

Treatment for PTB is for a period of 6 months, an initial (intensive) phase lasting 2 months and a continuation phase usually lasting 4-6 months. The initial phase consists of isoniazid, rifampicin, pyrazinamide and ethambutol, with rapid killing of tubercle bacilli. Infectious patients become non- infectious within about 2 weeks. Symptoms improve and most patients with sputum smear-positive TB become smear-negative within 2 weeks. The continuation phase of 4 months includes Isoniazid and Rifampicin and has a sterilizing effect, eliminating remaining bacilli.

Presumed or Known Drug Susceptible TB: The NTP recommends the 6-month treatment regimen that included rifampicin throughout (2HRZE/4HR).

TB medicines must be administered before breakfast (fasting), as rifampicin absorption decreases with fatty food consumption.

4.5 Treatment of New TB Patients With HIV

WHO recommends that TB patients with known positive HIV status and all TB patients living in HIV prevalent settings should receive daily treatment during all the treatment.

Table 4.4: Treatment Regimen for a New Patient

New patients	TB regimen initial phase	TB regimes continuation phase
New patient- presumed or known drug susceptible	2HRZE	4HR (3 times weekly)
New patient- presumed or known drug susceptible, HIV positive	2HRZE	7HR (daily)

4.5.1 Previously Treated Patients and Multidrug Resistance (MDR)

Previous treatment for TB is a strong determinant of drug resistance and of MDR. Prompt identification of MDR and initiation of MDR treatment with the second-line drugs gives a better chance of cure and prevents the spread of further resistance. The NTP abides by WHO MDR-TB treatment guidelines on-specific drug resistance data on failure, relapse and default patient groups to determine the levels of MDR.

The approach to the initiation of retreatment depends on (or if) DST results are routinely available for the individual patient. The NTP relies on CARPHA's ability and timeliness to report such existence, and that of the INDRE Mexican National Reference Laboratory in the near future.

4.5.2 Re-treatment Cases

Previously treated TB patients include those patients treated as new cases for more than one month who are now smear- or culture-positive (failure, relapse, return after default). Retreatment cases have a higher likelihood of drug resistance, which may have been acquired through inadequate prior chemotherapy. The standard treatment regimen should be given (2HRZE/4HR) and Gene Xpert testing and Culture with DST should be carried out. Obtaining specimens for conventional culture and DST should not delay the start of therapy. Empiric regimens should be started promptly, if the patient is seriously ill to avoid clinical deterioration, decreasing infectiousness, halting transmission.

Treatment of Extra-pulmonary TB (EPTB) and special situations are treated with the same first line drugs as PTB.

TB meningitis: 12 months with Streptomycin instead of Ethambutol in the initial phase is the recommended regimen of choice. Steroids are used in pericardial and meningeal TB.

TB Bone/Joint: 9 months is recommended.

4.6 Treatment of Tuberculosis on Special Populations

4.6.1 Treatment for Pregnant Women (See Standard Regimen)

Pregnant women and their fetus are at great risk with untreated tuberculosis. Isoniazid, rifampicin and ethambutol are safe for administration during pregnancy. Streptomycin is contraindicated during pregnancy because it is too toxic (causes deafness) to the baby. It is important to explain to a pregnant woman that successful treatment of TB with the recommended standardized regimen is important for a successful outcome of pregnancy.

4.6.2 Treatment for Breastfeeding Women

A woman who is breastfeeding and has TB should receive a full course of anti-TB treatment on a timely and proper way to prevent transmission of tubercle bacilli to her baby. All the anti-TB drugs are compatible with breastfeeding and a woman taking them can safely continue to breastfeed. The mother and baby should stay together and be breastfeed in the normal way, receiving prophylactic INH for at least 6 months beyond the time that the mother is non-infectious. SUSPEND BCG of the newborn until the end of INH prophylaxis once active TB has been ruled out.

4.6.3 Treatment for Women on the Oral Contraceptive Pill

Rifampicin interacts with the oral contraceptive pill, decreasing the efficacy of the pill, and increasing the risk of pregnancy. A woman who usually takes the oral contraceptive pill and is on rifampicin has two options;

- After consultation with a physician, she could take an oral contraceptive pill containing a higher dose of estrogen (50mcg)
- Or use another form of contraception (e.g. barrier method) to supplement oral contraceptive use

4.6.4 Treatment for Patients with Liver Disorders

Isoniazid, Rifampicin and Pyrazinamide are all associated with hepatitis. Rifampin is the least likely of the three to cause hepatocellular damage, although it is associated with cholestasic jaundice. Pyrazinamide is the most hepatotoxic. Patients with the following conditions can receive the usual short-course chemotherapy regimens if there is no clinical evidence of chronic liver disease, as toxicity may be more common if it exist:

i. Hepatitis virus carriage,
ii. A history of acute hepatitis,
iii. Excessive alcohol consumption.

4.6.5 Established Chronic Liver-disease; Hepatotoxic drugs

Note: Patients with liver disease should NOT receive pyrazinamide. Therefore, recommended regimens are the following:

- Intensive Phase: 2 months SHRE/ Continuation Phase: 6 months HR

or

- Intensive Phase: 2 months SHE/Continuation Phase: 10 HE (**Note:** Do not give pyrazinamide to patients with liver disease)

Drug Regimen with no risk of hepatotoxicity contains 18-24 months of streptomycin, Ethambutol and Levofloxacin

4.6.6 Acute Hepatitis (e.g. acute viral hepatitis)

Suspend TB treatment until the acute hepatitis has resolved. Use the combination of Streptomycin, ethambutol and Levofloxacin. In cases when it is necessary to treat TB during acute hepatitis, the combination of streptomycin and ethambutol up to maximum duration of 3 months is the safest option until the hepatitis has resolved. The patient can then receive a continuation phase of 6 months' isoniazid and rifampicin (6 HR).

4.6.7 Treatment of Patients with Renal Failure

Isoniazid and rifampicin are metabolized by the liver; therefore, these drugs may be given in normal dosage to patients with renal failure. In severe renal failure, patients should receive pyridoxine with isoniazid to prevent peripheral neuropathy.

PZA is also metabolized by the liver but its metabolites (pyrazinoic acid and 5-hydroxy-pyrazinoic acid) may accumulate in patients with renal insufficiency. EMB is about 80% cleared by the kidneys and may accumulate in patients with renal insufficiency, therefore, a longer interval between doses of PZA and EMB with three times a week administration is recommended in patients with impaired renal function. Dosing of these agents when creatinine clearance is < 30ml /minute or the patient is on hemodialysis should be as follows;

- **Pyrazinamide:** 25-35mg/kg po thrice weekly [DOSAGE AFTER DIALYSIS]
- **Ethambutol:** 15-25 mg/kg po thrice weekly [DOSAGE AFTER DIALYSIS]
- **Streptomycin:** it is excreted by the kidney and should be used with caution or avoided in patients with renal disease. Where facilities are available, streptomycin serum drug levels should be monitored and interval adjustment made (12-15mg/kg 2 to 3 times/week) for creatinine clearance < 30ml/minute. The safest regimen to be administered in patients is:

• Intensive Phase – 2 months HRZ & Continuation Phase – 4 months HR

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5. Adherence and Monitoring Throughout Treatment

Achieving treatment completion and cure of tuberculosis requires close monitoring of the patient throughout treatment by various healthcare workers from the public and private sectors. The treating physician should coordinate the treatment regimen with the public health nurse, outreach workers, ensuring the delivery of treatment and care to the TB patient by directly observed treatment strategy (DOTS). These healthcare providers can be involved also in contact investigation activities (social workers, correctional facility or jail nurses, school nurses).

5.1 Directly Observed Treatment Strategy (DOTS) and Implementation

The DOTS strategy is the most effective strategy for controlling tuberculosis, it is the administration of a standardized, rifampicin-based regimen. Non-adherence to anti-tuberculosis treatment is well known to be the most common cause of treatment failure, relapse, and the emergence of drug resistance, the use of DOT is highly regarded as one of a range of measures to facilitate adherence and successful completion of treatment. DOT provides assurance that the prescribed medications have been taken, allowing to see if the patient gets better or not. Because there is regular contact between the patient and the treatment supporter, adverse drug effects and other complications can be identified quickly and managed appropriately.

5.1.1 The five elements of DOTS include:

i. **Political commitment with increased and sustained financing:** Clear and sustained political commitment by national governments is crucial if basic DOTS and the Stop TB Strategy are to be effectively implemented. Political commitment is needed to foster national and international partnerships, which should be linked to long-term strategic action plans prepared by NTPs such as Belize's National Strategic Plan for TB 2015-2018.

ii. **Case detection through quality-assured bacteriology:** Bacteriology remains the recommended method of detecting TB, by using sputum smear microscopy, Xpert MTB/RIF and then culture and drug susceptibility testing (DST).

iii. **Standardized treatment, with supervision and patient support:** In order to achieve adequate TB control, it is important to standardize the treatment regimen across the country for all adult and pediatric TB cases – sputum smear-positive, smear-negative, and extra-pulmonary. Supervised treatment, such as DOT, helps patients to take their drugs regularly and complete treatment, thus achieving cure and preventing further transmission and the development of drug resistance.

iv. **An effective drug supply and management system:** For DOTS to be successful, an uninterrupted and sustained supply of quality-assured anti-TB drugs is necessary.

v. **Monitoring and evaluation system, and impact measurement:** It is essential to establish a reliable monitoring and evaluation system with regular communication between the central and peripheral levels of the health system. Therefore, we have standardized records of individual patient data, including information on treatment outcomes, which are then used to compile quarterly treatment outcomes in cohorts of patients. In the case of Belize, we have the electronic (Belize Health Information System (BHIS) in which patient information is gathered, thus the importance of healthcare personnel's adequate and timely use of this tool. This data, when compiled and analyzed, can be used at the facility level to monitor treatment outcomes, to identify local problems as they arise, and at provincial or national level to ensure consistently high-quality TB control across geographical areas, and nationally and internationally to evaluate the performance of each country. Regular program supervision should be carried out to verify the quality of information and to address performance problems.

Directly Observed Therapy (DOT) has been shown to significantly improve outcomes in most TB patients. However, there are some high priority situations where DOT needs to be applied:

Table 5.1 Priority Situations for the use of Directly Observed Therapy

i. Positive sputum smears
ii. Delayed culture conversion (sputum obtained at/after completion of intensive-phase therapy is culture positive
iii. Treatment failure
iv. Relapse
v. Drug resistance
vi. Homelessness
vii. Current or prior substance abuse
viii. Use of intermittent dosing
ix. HIV Infection
x. Previous non-adherence to therapy
xi. Children and adolescents
xii. Mental, emotional or physical disability
xiii. Resident at correctional or long term care facility
xiv. Previous treatment for active or latent tuberculosis

5.1.2 Clinical Response Monitoring

Patient monitoring and treatment supervision are two separate functions. Patient monitoring is necessary to evaluate the response of the disease to treatment and to identify adverse drug reactions. To judge response to treatment with PTB we must use sputum smear microscopy.

Having a positive sputum smear at completion of five months of treatment defines treatment failure, indicating the need for drug susceptibility and initiation of a retreatment regimen. Continuous radiographic assessments, are unreliable for evaluating response to treatment. Similarly, clinical assessment can be unreliable and misleading in the monitoring of patients with pulmonary tuberculosis. In patients with EPTB and in children, clinical evaluations may be the only available means of assessing the response to treatment.

Two sputum specimen should be collected for smear microscopy at each follow-up appointment. One ("spot") sample should be collected at the time the patient comes in to the clinic or health center and another sputum sample should be collected early the next morning and brought to the clinic/health center, laboratory. Specimens collected should be transported to the laboratory for testing as soon as possible after collection. If a delay is unavoidable, the specimens should be refrigerated or kept in a cool location. Ideally, sputum cultures, as well as smears, should be performed for monitoring.

TB culture and drug susceptibility testing is particularly important when sputum smears remain positive after completion of the initial phase to ensure early identification of unrecognized drug resistance. If present, the treatment regimen can be modified appropriately without waiting until the 5th month (the month when patients remaining sputum smear-positive can first meet the definition for treatment failure). Note that treatment failure is also declared if a patient is found to harbor MDR- TB at any point in time during treatment. Even if eventually full drug susceptible, a positive culture in the fifth month of treatment confirms poor response and further investigation and intervention should follow.

In Belize physicians and public health nurses have been advised that when such patient is seen, efforts must be prioritized in informing the NTP for immediate follow-up and samples should be taken for Culture and DST to be sent to CARPHA/INDRE with coordination of the laboratory staff and CML.

5.1.3 Recommendations to follow along with Annex F for smear microscopy in new and retreatment cases

i. If smear remains positive at the end of initial phase (end of month 2) and the patient has no initial Xpert test done, indicate Xpert testing and TB culture with DST. If culture is positive, MODIFY treatment regimen per drug resistance profile or DST result. If resistance to INH and RIF identified, record as treatment failure, as MDR-TB and seek expert consultation.

ii. If smear remains positive at month 5, indicate Xpert and culture with DST. If smear or culture is positive and DST results are in, patient should be re-registered as a treatment failure and appropriate retreatment regimen must be initiated. Evaluation for non-adherence should be conducted.

Delay in sputum smear conversion can occur due to several factors including

- Poor supervision and patient non-adherence
- Extensive cavitation and large initial bacillary load
- Comorbid conditions interfering with adherence, absorption, or will response to treatment
- Inadequate therapy due to the presence of unrecognized drug-resistant MTB
- The AFB seem are due to Mycobacterium other than tuberculosis (MOTT) (in the presence or absence of TB)
- The mycobacteria remaining visible by microscopy may represent non-viable organisms

When patients fail to show bacteriological and clinical improvement on treatment:

- careful review of the patient's support and supervision should be done with prompt intervention when indicated
- Patient treatment records should be reviewed with the responsible healthcare worker
- Reasons for any treatment interruptions or lack of adherence should be addressed.

5.2 Bacteriological monitoring of New and Retreatment PTB patients

Non-MDR/XDR retreatment only.

i. Modify treatment regimen as needed if drug resistance identified on DST result. If resistance to INH and RIF identified, seek expert consultation, send isolate for second-line DST, and initiate appropriate MDR-TB regimen

ii. If smears remain positive at end of initial phase, obtain Xpert and TB culture. If culture is positive and DST are back, modify treatment regimen if drug resistance is identified on DST result. If resistance to INH and RIF identified, record as treatment failure, send isolate for second-line DST, seek expert consultation and initiate appropriate MDR-TB regimen

The following clinical markers of response to treatment should be monitored and documented for both new and retreatment patients:

i. Sputum smear (and culture) examination results

ii. Weight at initiation of treatment, then monthly records done until end of treatment

iii. Review and documentation of TB symptoms from time of diagnosis until symptoms resolve and treatment is finished.

In the WHO treatment guideline 3rd ed., patients with positive smears at the end of the 2nd month (intensive phase) received an extra month of intensive phase before proceeding to the continuation phase. Extending the intensive phase for patients that remained smear-positive after 2 months meant they would receive an additional month of rifampicin. After review of all existing data, the WHO Guideline committee for the revised treatment guidelines (4th edition) determined there was sufficient evidence to justify continuing to recommend this practice for regimens containing 6 months of rifampicin.

Note: In Belize, the NTP continues to recommend the extension of the one-month treatment of HRZE in the intensive phase for individuals with a positive sputum test at the end of the second month. The NTP also recommends strongly that an Xpert test be done and or culture with DST be done URGENTLY, if there has been no evidence of lack of adherence.

5.2.1 Criteria for Discharge of the TB Patient from the Hospital

For the TB patient admitted to hospital, collect the first follow-up sputum after two weeks of anti- tuberculosis treatment. Discharge from hospital, irrespective of AFB results, may be considered if the following can be documented:

- Clinical improvement noted by decrease in symptoms
- Social capacity and other support systems capacity are in place to ensure successful continuation of treatment as an outpatient

If the above criteria cannot be documented, retain and reassess the patient again in another two weeks. At a minimum, this includes collection of sputum for AFB smear and clinical assessment. If clinical improvement is not observed within four weeks, continue anti-tuberculosis treatment and initiate further evaluation.

5.2.1 Monitoring the Extra pulmonary TB patient

In patient with EPTB and in children, clinical evaluation (including weight and symptom monitoring) is the usual means of assessing response to treatment.

5.3 Interrupters and Patients after lost to follow up (previouslydefaulters)

Attempts to contact patients who have missed an arranged appointment to receive treatment should be made promptly. The management of such patients must take into consideration multiple factors. Each of these factors, if present, will necessitate more caution and erring on the side of additional treatment.

- The patient is returning to treatment after default.
- Interruption occurs in the intensive rather than the continuation phase
- Interruption occurs early in the continuation phase (rather than later)
- Long duration of treatment interruption
- The patient is immune compromised (living with HIV or another condition)
- The patient had poor response to treatment before the interruption
- Drug-resistance is known or suspected

Culture and drug susceptibility testing should be performed upon the return of patients who meet the definition for loss to follow-up. If laboratory capacity permits, additional patients returning after treatment interruption should also have specimens obtained and culture and drug susceptibility testing done.

5.3.1 Management of Interruptions based on Time Point

The clinician taking care of a patient whose treatments have been interrupted has the decision to either restart the course or continue as originally intended.

The earlier the break in treatment and the longer the its duration, the more serious the effect and the greater need to restart treatment. Continuous treatment is more important in the intensive phase when bacillus population is still high and risk of drug resistance development is highest. During continuation phase bacillus burden is smaller and thus the main goal is to kill persistent organisms.

Table 5.2: Management of Treatment Interruptions

Time Point of Interruption	Details of Interruption	Approach
During Intensive Phase	Lapse <14 days in duration	Continue treatment to complete planned total number of doses (if all doses are completed within 3 months)
	Lapse ≤14 days in duration	Restart treatment from the beginning
During Continuation Phase	Received ≥80% of doses and sputum was AFB smear negative on initial testing	Further therapy may not be necessary
	Received ≥80% of doses and sputum was AFB smear positive on initial testing	Continue therapy until all doses are completed
	Received <80% of doses and accumulative lapse is <3 months in duration	-Continue therapy until all doses are completed (full course), unless consecutive lapse is greater than 2 months. -If treatment cannot be completed within recommended time frame for regimen, restart therapy from the beginning (ie restart intensive phase, to be followed by continuation phase)
	Received <80% of doses and lapse is ≥3 months in duration	Restart therapy from the beginning, new intensive and continuation phases (ie, restart intensive phase, to be followed by continuation phase)

5.4 Monitoring, and Managing of Adverse Drug Reactions

Prompt recognition and appropriate management of adverse drug reactions is essential in patients with tuberculosis. Toxicity and hypersensitivity reactions may require stopping the causative drug or all drugs; however, changes to the recommended regimen should be done only after careful evaluation. Some drug-induced side effects can be averted with proper management. Isoniazid-induced peripheral neuropathy may present as numbness, tingling or burning sensation of the feet and occurs more commonly in:

- Pregnant women
- Persons with certain comorbidities (HIV co-infection, malnutrition, diabetes, chronic liver disease, or renal failure
- Persons who abuse alcohol

These patients should receive pyridoxine 10-25 mg daily with their anti-tuberculosis drugs.

Patients having drug side effects should be promptly referred for evaluation to identify the offending drug, to minimize interruptions in treatment and/or unnecessary cessation of important first-line drugs. Physicians and nurses responsible for the management of patients being treated

for tuberculosis should be familiar with the common adverse reactions associated with drug therapy and the related management.

Table 5.3 shows a symptoms-based approach to the most common adverse effects of the essential anti-tuberculosis drugs. Adverse effects are classified as minor or major. In general, a patient who develops minor adverse effects should continue the TB treatment. The patient also receives symptomatic treatment. If a patient develops a major side-effect, the treatment or the offending drug is stopped and the patient should be urgently referred to a clinician or healthcare facility for further assessment and treatment. Patients with major adverse reactions should be managed in a hospital.

Table 5.3: Common Adverse Reactions to the First-Line Anti-Tuberculosis Drugs

Drug	Adverse Reactions	Monitoring	Comments
Isoniazid (INH, H)	-Hepatitis -Peripheral neuropathy -Hypersensitivity reactions -Drug interactions (phenytoin and carbamazepine)	Liver function tests (LFTs) if known or suspected liver disease or other hepatotoxic drugs used concurrently	Hepatitis risk increases with age, alcohol use, & concurrent use of other hepatotoxic drugs. Recommend supplementation with pyridoxine in patients with nutritional deficiency, medical conditions associated with peripheral neuropathy (i.e., diabetes, chronic renal failure/dialysis, HIV) and during pregnancy.
Rifampicin (RIF, R)	-Hepatitis -Flu-like illness (usually only with intermittent administration) -Thrombocytopenia -Drug-interactions (many including oral contraceptives and ARVs')	Baseline CBC; monitor drug concentrations of interacting medications; LFTs if indicated	Significant interactions with methadone, oral contraceptives, & other drugs. Educate patients about normal discoloration of body fluids.
Pyrazinamide (PZA, Z)	-Hepatitis, Hyperuricemia -Arthralgia -Gastrointestinal symptoms very common	Baseline uric acid; LFTs if indicated	Adjust dosing 3 times weekly when creatinine clearance is <30ml/minute.
Ethambutol (EMB, E)	- Retrobulbar neuritis (dose related)	Baseline and monthly visual acuity test and color discrimination	Adjust dosing to 3 times weekly when creatinine clearance is <30ml/minute
Streptomycin			

Note: all drugs may cause rash, nausea, and fever. *For information on managing drug interactions in HIV-related tuberculosis, see www.cdc.gov/tb/tb_hiv_Drugs/default.htm

Tuberculosis treatment should be withheld if transaminase levels exceed three times the upper limit of normal if associated with symptoms, and five times the upper limit of normal if the patient is asymptomatic.

Table 5.4: Symptom-based approach to managing side-effects of anti-TB drugs

Side-effects	Drug(s)	Management
Minor		**Continue anti-tuberculosis drugs, check drug doses**
Anorexia, nausea, abdominal pain	-Pyrazinamide -Rifampicin -Isoniazid	Give drugs with small meals or just before bedtime. If symptoms persist or worsen, or there is protracted vomiting, icterus or signs of bleeding, consider the side effect to be major and refer to clinician urgently
Joint pains	Pyrazinamide	Aspirin or non- steroidal anti-inflammatory drug
Burning, numbness or tingling sensation in the hands or feet	Isoniazid	Pyridoxine 50-75 mg daily
Drowsiness	Isoniazid	Reassurance
Orange/red urine	Rifampicin	Reassurance. Patients should be told when starting treatment that this commonly happens and is normal
Flu Syndrome (fever, chills, malaise, headache, one pain)	Intermittent dosing of Rifampicin	Change from intermittent dosing of Rifampicin to daily Rifampicin dosing.
Major side effects		**Stop offending drug and refer to clinician immediately**
Skin rash with or without itching	S, H, R, E, Z	Stop anti-tuberculosis drugs
Deafness (no wax on auroscopy)	Streptomycin	Stop streptomycin; use ethambutol
Dizziness (vertigo and nystagmus)	Streptomycin	Stop streptomycin; use ethambutol
Jaundice (other causes excluded), hepatitis	H, Z, R	Stop anti-tuberculosis drugs
Confusion (suspect drug-induced acute liver failure if jaundice present)	Most anti-tuberculosis drugs	Stop anti-tuberculosis drugs
Visual impairment (other causes excluded)	Ethambutol	Stop ethambutol
Shock, purpura, acute renal failure	Rifampicin	Stop rifampicin
Decreased urine output	Streptomycin	Stop streptomycin

Source: Adapted from WHO Treatment of Tuberculosis, Guidelines, Fourth edition, 2009

Table 5.5: Standard Approach to Re-Introduction of Anti-Tuberculosis Medicines after a Reaction.

Day	Drug
1	INH-25mg
2	INH-50mg
3	INH-100mg
4	INH-300mg
5	INH-300mg + R-150mg
6	INH-300mg + R-3000mg
7	INH-300mg + R-450mg
8	INH-300mg + R-600mg depending on weight
9	INH-300mg + R-600mg + E-400mg
10	INH-300mg + R-6000mg + E-800mg
11	INH-300mg + R-600mg + E 1.2g (weight dependent)
12	INH-300mg + R-600mg + E 1.2g + Z 500mg
13	INH-300mg + R-600mg + E 1.2g + Z 1.0g
14	INH-300mg + R-600mg + E 1.2g + Z 1.5g
15	INH-300mg + R-600mg + E 1.2g + Z 2.0g (weight dependent)

The dose is gradually increased over 3 days. This procedure is repeated, adding in one drug at a time. A reaction after adding a drug identifies that drug as the one responsible for the reaction.

Table 5.5 is an example of the steps that can be taken to reintroduce a drug after an adverse drug reaction event. A clinician may decide to suspend treatment until adverse event has subsided, and then reintroduce the anti-TB drugs slowly. This process should not take longer than 15 days.

5.4.1 Management of Drug-induced Hepatitis

The 3 most offending and toxic drugs to the liver are INH, PZA, and RIF, rarely ethambutol.

Note: rule out other possible causes of the hepatitis before deciding that is drug-induced and modifying the TB regimen.

The management of drug-induced hepatitis 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 side effects of TB treatment

If the hepatitis is thought to be caused by the anti-tuberculosis drugs, stop all drugs. If the patient is severely ill with TB and it is considered unsafe to stop anti-tuberculosis treatment, the regimen should be changed to a **non-hepatotoxic regimen consisting of streptomycin, ethambutol, and**

Levofloxacin. If the patient is not severely ill, TB treatment should be withheld until liver function tests have returned to normal and clinical symptoms (e.g., nausea, abdominal pain) have resolved. If it is not possible to perform liver function tests; wait an extra 2 weeks after the jaundice and upper abdominal tenderness has disappeared before recommencing TB treatment.

Once drug-induced hepatitis has resolved, reintroduce the same drugs one at a time every 3-7 days starting with rifampicin (as it is the least likely to cause hepatotoxicity and is the most effective agent) then isoniazid. Serum transaminases and bilirubin should ideally be checked immediately prior to initiation of each drug. In patients who experienced jaundice but who are tolerating the reintroduction of rifampicin and isoniazid, it is advisable to avoid pyrazinamide.

Alternative regimens depend on which drug is implicated as the cause of the hepatitis.

- If rifampicin is implicated, a suggested regimen without rifampicin is two months of isoniazid, ethambutol and streptomycin followed by 10 months of isoniazid and ethambutol (2HES/10HE)
- If isoniazid cannot be used, 6 to 9 months of rifampicin, pyrazinamide and ethambutol can be considered
- If pyrazinamide is discontinued before the patient has completed the intensive phase, then 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. Consultation should be sought in these situations.

- Introducing one drug at a time is the optimal approach, especially if the patent's hepatitis was severe.
- Therefore, NTPs using fixed-dose combination tablets should stock limited amounts on single anti-TB drugs.

5.4.2 Management of Cutaneous Reactions

If a patient develops itching without a rash and there is no other obvious cause, try treatment with anti-histamines and avoiding dry skin, and continue TB treatment while observing the patient closely. However, if a severe skin rash develops then all anti- tuberculosis drugs must be stopped.

Once the reaction has resolved, anti-tuberculosis drugs are re-introduced one by one, starting with the drug least likely to be responsible for the reaction (rifampicin or isoniazid) and starting with a small challenge dose such as 25 mg isoniazid (see table 5.5). The dose is gradually increased over five days. The procedure is repeated, adding in one drug at a time. If a reaction occurs after adding a drug, that drug is identified as the offending agent. The alternative regimens listed above can

also be considered when a drug cannot be used because it was implicated as the cause of a cutaneous reaction.

If the reaction is severe give the patients intravenous fluids;

a. Exfoliative dermatitis or toxic epidermal necrolysis

b. Mucus membrane involvement

c. Hypotension

5.4.3 Steroid treatment should be used in moderate to severe skin reactions:

Prednisone 60mg orally can be used for a period until improvement is seen and should then be tapered off gradually.

If the patient is unable to swallow, intravenous hydrocortisone can be used 100—200mg daily, and then on recovery restart anti-TB drugs.

Fatal reactions mean the suspension of TB drugs for about 3-4 weeks. If the patient is severely ill he may die without the drugs and should then be placed on 2 or more unused TB drugs e.g. ethambutol and Levofloxacin.

Isoniazid and rifampicin form the corner stone for TB treatment and have rare hypersensitivity reactions in patients. Desensitization can be done in none HIV patients for these two drugs, (if the skin reaction is not severe).

5.5 Pharmacovigilance of Anti-Tuberculosis Medicines

Monitoring, reporting and management of adverse drug reactions associated with anti-Tuberculosis medicines enhances the safety of the patient infected with Tuberculosis, this practice is called Pharmacovigilance of anti-Tuberculosis medicines.

Pharmacovigilance (PV): the "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem".

Patients on TB treatment are on medication from a few months to at least 2 years, this increases the risk of adverse reactions occurring. These events may damage public confidence in any national treatment programme and affect patient adherence; non-adherent patients are a risk to themselves and to others.

Systematic collection of ADR data is essential for the following reasons:

i. The net benefits of a treatment programme can be accurately determined while factoring in adversities related to the medicines used

ii. It makes it possible to define the contribution of ADRs to treatment failure, default and death.

iii. Widespread recognition by clinicians that anti-TB medicines often cause ADRs is not well reflected in the published information

iv. Allows for understanding of the overall burden of adversity directly attributable to anti-TB medicines

v. With the increasing use of more extensive regimens for drug-resistant TB, the added use of antiretrovirals (ARVs) in patients with HIV-associated TB, and the imminent advent of new classes of medicines to treat TB, the case for improved pharmacovigilance becomes even stronger.

vi. Allows for detections of signals: A signal is the reported information on a possible causal relationship between an adverse event and a medicine, the relationship being unknown or incompletely documented previously.

Pharmacovigilance (PV) is an important arm of patient care that aims to ensure the best outcomes from treatment with medicines. A good pharmacovigilance system will identify the risks within the shortest possible time after the medicine has been marketed and will help to establish or identify risk factors. When communicated effectively, this information allows for intelligent, evidence-based prescribing with the potential for preventing many ADRs.

5.5.1 Aims of Pharmacovigilance Practice:

i. To support the safe, rational and more effective (and more cost-effective) use of medicines

ii. To rapidly identify events that are likely to affect adherence to treatment

iii. To identify signals (**i.e., possible causal relationships between an adverse event and a medicine**) of ADRs of concern following the introduction of a new drug or drug combination

iv. To assess signals to evaluate causality, clinical relevance, frequency and distribution of ADRs in different population groups

v. To calculate rates of adverse events so that:

- risk can be measured
- safety of different medicines can be compared and informed choices made
- risk factors can be clearly identified

- contribution to the assessment of benefit, harm, effectiveness and risk of medicines, leading to the prevention of harm and maximization of benefit
- appropriate response or action in terms of drug registration, drug use and/ or training and education for health professionals and the public
- To measure and evaluate the outcome of the response or of action taken (e.g. reduction in risk, improved medicine use, or improved outcome for patients experiencing a ADR)

vi. To provide timely communication with and recommendations to authorities and the public

vii. To provide feedback to the clinicians who reported adverse events

viii. To continuously monitor quality of medicines used for TB, their storage, use and disposal

5.5.2 Pharmacovigilance Methods

Pharmacovigilance can be practiced through three main approaches which can be adopted by a National Treatment Programme:

i. Spontaneous reporting (SR)
ii. Targeted spontaneous reporting (TSR)
iii. Active Surveillance (e.g. Cohort event monitoring (CEM))

5.5.2.1 Spontaneous (or Voluntary) Reporting

No active measures are taken to look for adverse effects other than the encouragement of health professionals and others to report safety concerns. Reporting is entirely dependent on the initiative and motivation of the potential reporters. This is the most common form of pharmacovigilance, sometimes termed passive reporting.

5.5.2.2 Targeted spontaneous reporting (TSR)

TSR is a variant of spontaneous reporting. It focuses on capturing ADRs in a well-defined group of patients on treatment. Health professionals in charge of the patients are sensitized to report specific safety concerns. TSR is intended to ensure that patients are monitored and that ADRs are reported as a normal component of routine patient monitoring and to achieve the requisite standard of care. This focused approach has the same objectives and flow of information as for spontaneous reporting. The reporting requires no active measures to look for the particular-syndromes.

5.5.2.3 Cohort event monitoring

CEM is a prospective, observational, cohort study of adverse events associated with one or more medicines. A CEM program is essentially an observational study in normal clinical practice of a new medicine in the early post-marketing phase, but it can be used for older medicines.

Objectives of Cohort Event Monitoring include:

i. To characterize known ADRs

ii. To ensure the earliest possible recognition of new ADRs, including interactions with other medicines, complementary and alternative medicines, foods and concomitant diseases

iii. To detect treatment inefficacy, which might be due to

- faulty administration
- poor storage conditions
- poor quality product
- counterfeit product
- interactions

iv. To measure risk (incidence), including comparative risk of different antiTB regimens or individual medicines

v. To identify risk factors for the important reactions so that appropriate risk management can be applied and the risk of harm minimized

vi. To assess safety during pregnancy and lactation

vii. To provide evidence for:

- effective risk prevention and management
- safer use of anti-TB therapy
- the benefits versus harm of different regimens or products
- evidence-based regulatory action.

viii. To provide potential cohorts for further study of safety issues if required in the future. These can include:

- nested case–control studies to determine risk factors (e.g. genetic polymorphism) for ADRs of interest
- follow-up studies for long-term outcomes or more detailed information on events of interest

5.5.3 WHO Recommended Minimum Reporting Requirements for an ADR

a) an identifiable source of information or reporter

b) an identifiable patient

c) name(s) of the suspected product(s)

d) a description of the suspected reaction(s)

5.5.4 Reporting Suspected ADRs to TB Treatment

The Belize National Treatment Programme recommends that health care workers treating TB patients monitor and report suspected adverse reactions due to anti-TB medicines. Any event(s) are recorded on an adverse drug reaction report form (Appendix G1) and submitted to the National TB Program office of the Ministry of Health in Belmopan. **Priority reporting should be given to suspected ADRs that have the following characteristics:**

a)reactions that affect adherence

b) reactions that necessitate hospitalization, cause death

c)reactions of special interest, lack of drug efficacy

d) all suspected reactions in children and pregnant women

5.5.5 Causality Assessments of Suspected Adverse Drug Reactions

Causality assessments are done to ascertain the degree to which a reported reaction is related to the medicines the patient is taking. This means that a complete and accurate reporting form of the case is essential.

Establishing causality is a process which begins by examining the relationship between the medicine and the event. Two basic questions need to be addressed separately:

• Is there a convincing relationship between the drug and the event?

• Did the drug cause the event?

A causality assessment should be provisional and subject to change in the light of further information on the case, or new knowledge coming from other sources.

What to Consider when Assessing Relationship between Drug and Event

i. Did the event begin before the patient started taking the medicine?

ii. Is the duration to onset of the event plausible?

iii. Did the event occur after the commencement of some other medicine?

iv. Did the event occur after the onset of some new illness?

v. Is there any other possible cause for the event?

vi. What is the response to withdrawal of the medicine (dechallenge)?

vii. What is the response to rechallenge?

The Belizean NTP recommends that all health care professionals make it standard practice to monitor, report, and manage adverse drug reactions due to medicines used to manage Tuberculosis. These should be reported to the National TB Program Coordinator.

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6. HIV Infection and Tuberculosis

6.1 : General Information

Among people living with HIV, TB is one of the most frequent life-threatening opportunistic infections and leading cause of death. HIV infection alters the pathogenesis of TB by compromising the cell mediated immune response of the host. HIV increases their risk for developing active TB disease from 10% to 50% over the course of their lifetime. The weakened immune system cannot control the multiplication and spread of tubercle bacilli, leading to TB disease.

TB diseases can develop at any time in an HIV patient, decreasing with effective ARV therapy. In an HIV- infected person, TB disease can develop in two ways.

- A person who has TB infection can become infected with HIV and the develop TB disease as the immune system is weakened
- A person who has HIV infection can become infected with *M. tuberculosis* and then rapidly develop TB disease within weeks

Additionally, in someone with HIV, the presence of other infections, including TB, activates the immune system, resulting in increased HIV replication and subsequent accelerated progression of HIV disease.

6.2 TB/HIV Co-infection

TB occurs in HIV infected persons independently of the CD4 + T cells count levels. Clinical manifestations depend on the level of immunosuppression. Those with more advance immunosuppression (CD4 of <200 cells/mm) are more likely to have extra-pulmonary or disseminated disease. In areas where TB is endemic, many patients have higher CD4+ T cells at the time HIV related TB develops. TB in persons with HIV infection can develop immediately after exposure (primary disease), or because of progression following establishment of latent TB infection (LTBI), sometimes called reactivation disease. Patients with TB have been shown to have higher HIV viral loads and a more rapid progression of their illness when compared to those HIV infected patients without TB.

6.2.1 Clinical Presentations of HIV-related TB

- With CD4+ T cell counts of > 350 cells/mm^3:

  - HIV-related TB presents like TB among HIV-uninfected persons
  - Disease is frequently limited to the lungs
  - Common chest radiographic manifestations include upper lobe fibronodular infiltrates with or without cavitation

- With increasing immunodeficiency, extra-pulmonary TB with or without pulmonary involvement becomes increasingly common. At CD4+ T cell-counts of < 50 cells/mm^3: Extra-pulmonary involvement is common

TB can be a critical systemic disease with high fevers, rapid progression and sepsis syndrome. Evaluation of suspected HIV-related TB should always include a chest radiograph. However, several pulmonary diseases mimic PTB on chest X-ray and in signs and symptoms. The clinician should not diagnose pulmonary TB in every patient with AIDS, with an abnormal chest X-ray, signs and symptoms of chest disease and negative sputum smears.

6.3 Diagnosis of TB /HIV Co-infection

It is strongly recommended that all patients diagnosed with TB be screened for HIV infection and all HIV seropositive patients be examined for TB, (if there is a present cough, fever, weight loss, night sweats). Evaluation of suspected HIV related TB should always include a chest radiograph. However, several pulmonary diseases can mimic pulmonary TB in HIV/AIDS patients and who may have an abnormal chest X-ray and symptoms of chest disease and negative sputum smears. (Table 6.1)

6.4 TB Screening of HIV Patients

Table 6.1: TB screening questions for HIV patients

Questions to ask	Yes	No
Are you presently with a cough? Or have you been coughing for more than two weeks?		
Have you lost weight recently and continue to lose weight?		
Do you have night sweats?		
Do you have a fever?		
Are your lymph nodes enlarged?		
Have you lost your appetite?		
Has he/she had any contact with another person with active TB		

- If "yes" to question 1: the patient is a Presumed TB case, perform sputum collection for AFB smear, Xpert and culture and continue evaluation for TB per the diagnostic algorithm for pulmonary TB (Figure 3)
- If "no" to question 1 but "yes" to any other question: the patient is a Presumed TB case; continue evaluation for TB guided by clinical signs and symptoms. Refer to national reference hospital if necessary
- In "no" to all the questions: the patient is not a Presumed TB case at this time; stop investigations for TB and repeat screening with questionnaire at each health service encounter, whether routine or for treatment.

Source: Adapted from the International Center for AIDS Care and Treatment Program Questionnaire.

Should one or more answers be "Yes", the clinician should be alerted that the patient may have TB disease. A thorough clinical examination should be conducted in which TB features in the differential diagnosis and Initiation of IPT should be withheld until TB disease is ruled out. If the patient is on isoniazid preventive treatments (IPT) consider stopping this medication until TB disease is confidently ruled out.

However, a person with both HIV infection and TB infection has a 5 to 10% annual risk of developing TB disease. HIV affects the progression of TB disease in the following two ways:

- Reactivation of latent TB infection to TB disease, in HIV positive individuals. This is preventable in the individual patient through isoniazid preventive therapy (IPT).
- Rapid progression from recent TB infection to TB disease. If an immunocompromised person is infected with TB bacilli from a patient with infectious TB, TB disease may develop within weeks.

TB is among the leading cause of death in patients dying from advanced HIV infection. Failure to diagnose and treat TB disease promptly in HIV infected patients leads to premature mortality and increased TB transmission in the community. TB disease can spread quickly in congregate settings where persons living with HIV and AIDS (PLWHA) reside. In addition, outbreaks of TB due to HIV/TB have been reported in settings such as hospitals, homeless shelters, jails and prisons.

6.5 Intensified TB case-finding in PLWHA

This involves screening for symptoms and signs of tuberculosis in settings where HIV infected people seek care and are recommended. TB should be suspected in all sick, HIV infected patients who are not doing well clinically. Early identification of signs and symptoms of TB followed by pursuit of a confirmed diagnosis and prompt treatment increase the chances of survival, improve quality of life and reduce transmission of TB in the community.

Figure 5: Algorithm for the TB case finding in ambulatory HIV positive patient (adults and adolescents)

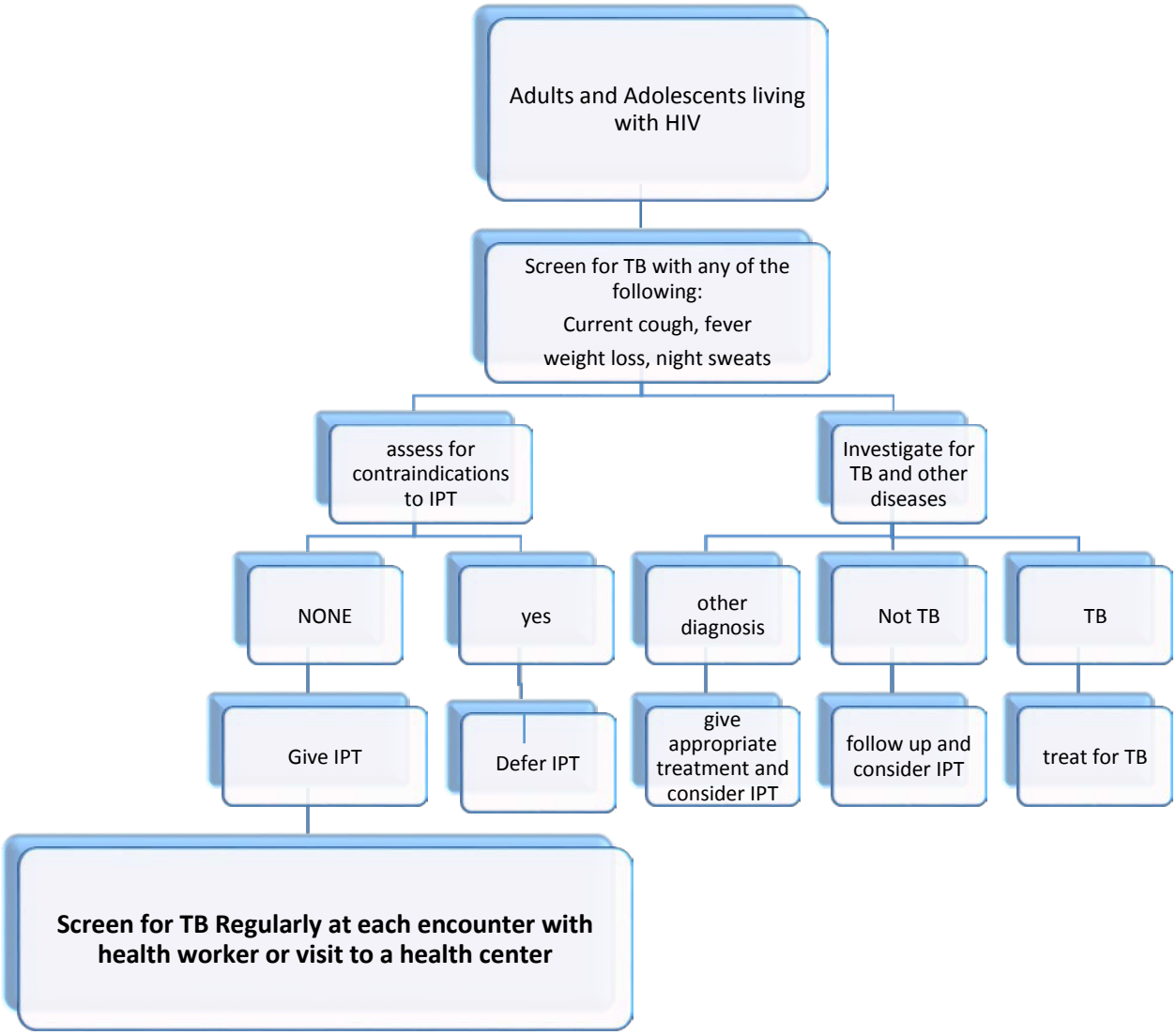
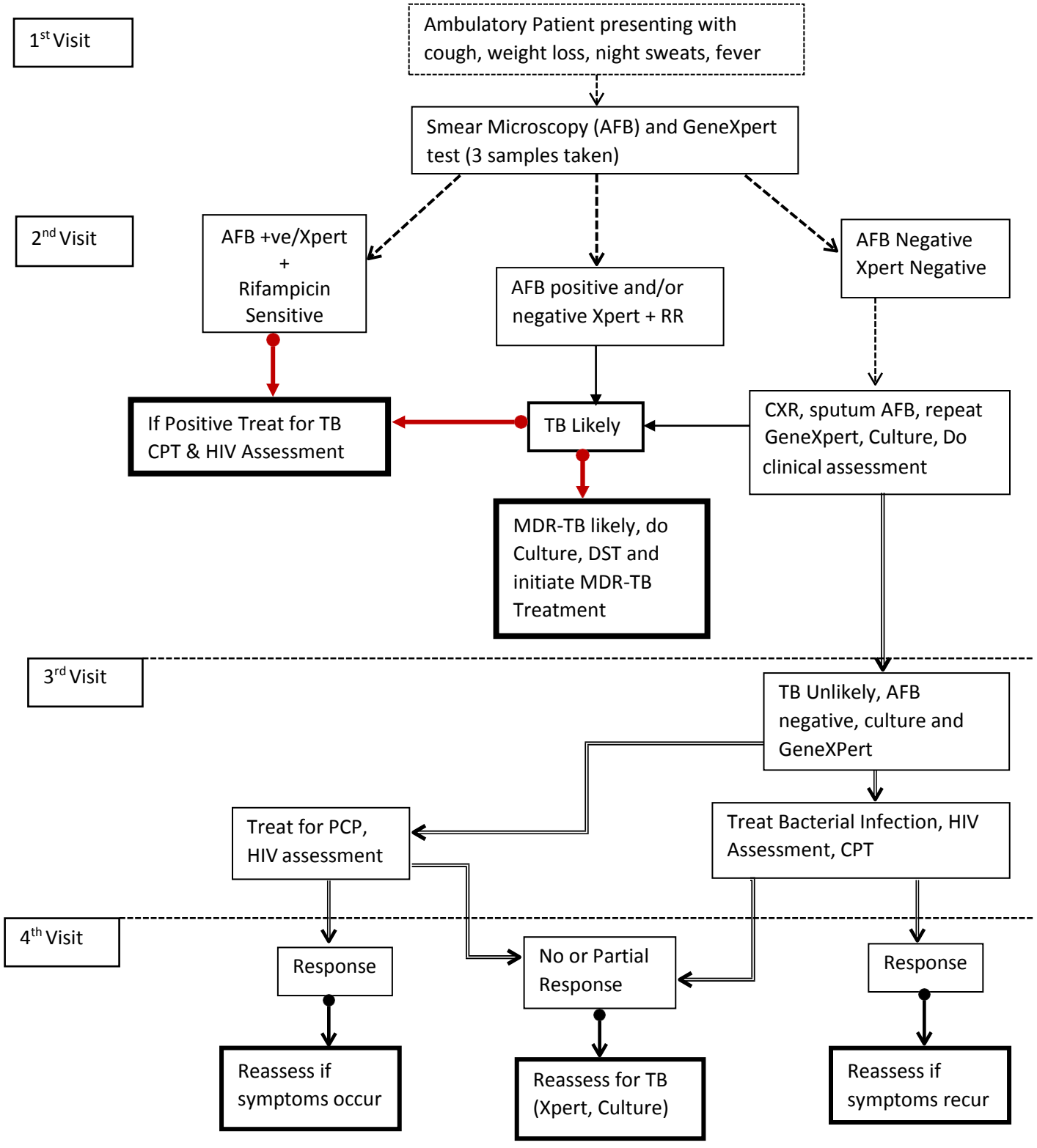


Figure 6: Algorithm for the diagnosis of TB in ambulatory HIV positive patients



Source: Adapted from Improving the Diagnosis and Treatment of Smear-negative Pulmonary and Extra-Pulmonary Tuberculosis among Adults and Adolescents, WHO 2007

From Algorithm 6,

1. AFB = Acid fast bacilli; CPT = Cotrimoxazole preventive therapy, the danger signs include any one of:
   - respiratory rate >30/minute
   - fever >39°C, pulse rate >120/min
   - hypotension >90/60 mmHg and unable to walk unaided.
2. In the absence of HIV testing, classify as HIV status unknown.
3. AFB-positive is defined as at least one positive smear and AFB-negative as two or more negative smears. PCP = *Pneumocystis carinii pneumonia,* also known as *Pneumocystis jirovecii pneumonia.*
4. HIV assessment includes HIV clinical staging, determination of CD4 count if available and referral for HIV care.
5. The investigations within the box should be done at the same time wherever possible to decrease the number of visits and speed up the diagnosis.
6. Antibiotics (except fluoroquinolones) to cover both typical and atypical bacteria should be considered

6.6 Clinical Picture of HIV/TB

Table 6.2: Clinical picture, Sputum Smear Result and Chest X-Ray at different stages of HIV infection.

Features of pulmonary TB	Stages of HIV infection	
	Early	Late
Clinical picture	Often resembles primary pulmonary TB (i.e., intrathoracic adenopathy, effusions, +/- infiltrates)	Often resembles post-primary pulmonary TB
Sputum smear result	May be negative	Often positive
Chest x ray	Often infiltrates (lower lung zones) with no cavitation; miliary pattern; may be normal	Upper lobe infiltrates with cavitation: may be normal

Source: Modified from WHO, TB/HIV. A Clinical Manual. 2004.1

Evaluation of suspected HIV-related TB should always include sputum, Gene Xpert, TB culture and a chest radiograph in addition to smear microscopy and clinical assessment (see figure 5). However, several pulmonary diseases can mimic PTB on chest X-ray and signs and symptoms. The clinician should consider the complete differential diagnosis of the presenting illness and take care not to diagnose pulmonary TB in every patient with AIDS.

6.7 Isoniazid Preventative Therapy (IPT) and Recommendations

WHO strongly recommends that adults and adolescents living with HIV should be screened with the clinical algorithm; those in whom no symptoms such as current cough, fever, weight loss or night sweats have been reported, are unlikely to have active TB and should receive **Isoniazid Prophylactic Therapy (IPT)**.

6.7.1 Duration of IPT:

-All Adults and adolescents living with HIV, with positive or unknown Tuberculin Skin Test (TST) and do not have active TB, should receive at least nine months of IPT, regardless of the CD4+ count (degree of immunosuppression) and including those on ART, those who have been previously treated for TB and pregnant women.

-Children living with HIV who are more than 12 months of age and do not have active TB based on TB-Symptom-screening and have no contact with a TB case, should receive nine months of IPT as part of their routine HIV Care.

-In Children living with HIV who are younger than 12 months of age, only those who have had contact with a TB case but has no active TB disease, should receive nine months of IPT.

-All children living with HIV, who have had active TB disease and have successfully completed treatment for the same, should receive Isoniazid for an additional six months.

Note that a TST is not necessary for initiating IPT in People living with HIV.

*Providing IPT to PLWHA does not increase the risk of developing Isoniazid resistant TB and thus should not pose an obstacle to providing IPT.

Dosage of isoniazid: Adults ---------- isoniazid is 5mg/kg (maximum 300 mg) daily for 9 months
Children ---------- isoniazid dose is 10 mg/kg bodyweight.

Rule out TB before IPT!!!!!! IPT should NEVER be initiated in a patient with HIV infection who has signs and symptoms consistent with active TB, or in whom TB disease cannot be safely excluded. IPT is used most safely in asymptomatic HIV infected patients. Follow the TB screening

Screening should be thorough to ensure none of the following apply:

- Currently ill (new or worsening cough or sputum production, hemoptysis, night sweats, fever, or measured weight loss of >5%)
- Abnormal chest X-ray (even if TB has not been confirmed)
- History of alcoholism (or daily alcohol use)
- Presence of jaundice or active (acute or chronic)
- History of prior allergy or INH intolerance

6.7.2 Monthly monitoring

The person receiving IPT should be evaluated at least once a month to check three important issues:

- **Signs and symptoms of TB:** If symptoms of tuberculosis should develop while taking IPT, isoniazid should be stopped immediately and patient referred for evaluation.
- **Side effects attributable to IPT:** These may include, for example, liver toxicity or peripheral neuropathy.
- **Adherence:** Interruptions in therapy should be followed by counseling and an attempt should be made to understand and remove barriers to adherence.

Xpert MTB/RIF should be used as the initial diagnostic test in patient suspected of having HIV-associated TB or Multidrug-resistant TB.

6.8 Clinical Management of TB/HIV co-infection

In patients with HIV-related TB, the priority is to treat TB, especially in patients with smear-positive PTB. The recommended treatment approach consists of daily DOT during the first two months and daily treatment by DOT during the continuation phase of anti-TB therapy (7 months). See table 6.3 below for clinical features of TB/HIV co-infection.

Table 6.3: Clinical features suggestive of HIV infection in patients with TB

History	- Sexually transmitted infections - Herpes zoster (shingles) - Recent or recurrent pneumonia - Severe bacterial infections - Recent treated tuberculosis
Symptoms	- Weight loss (>.10 kg or >20% of original weight) - Diarrhea (>1 month) - Retrosternal pain on swallowing (suggestive of esophageal candidiasis) - Burning sensation of feet (peripheral sensory neuropathy)
Signs	- Scar of herpes zoster - Itchy papular skin rash - Kaposi sarcoma - Symmetrical generalized lymphadenopathy - Oral candidiasis - Angular cheilitis - Oral hairy leukoplakia - Necrotizing gingivitis - Giant aphthous ulceration - Persistent painful genital ulceration

NOTE: A patient with active TB disease who is HIV positive must receive ARV therapy for life. Anti- retroviral therapy in patients with HIV-associated TB should be individualized, based on patient's initial response to TB therapy, occurrence of side effects, and acceptance of ARVs.

6.9 TB and ART Drug Interactions

Rifamycin's, especially rifampicin, and some of the NNRTIs and protease inhibitors (PIs) cause clinically significant drug interactions. Rifampicin reduces the serum concentration of most PIs by 80% or more, and NNRTIs by 20-60%. Despite these interactions, rifamycin-based regimens remain preferred in HIV-infected patients. Use of PIs with compensatory alterations in dosing or abandonment of the rifamycin should be reserved for settings where the preferred, RIF-compatible NNRTI options (e.g. EFV, +/- nelfinavir) are not possible. As recommendations on combinations of anti-tuberculosis drugs and ARVs are frequently revised, it is advisable to check an authoritative source, e.g. the WHO website (http://www.who.int/hiv/mediacentre/en) periodically for the most up to date information.

The use of HAART among patients being treated for TB may be complicated by overlapping drug toxicity, drug interactions, and the occurrence in some cases of the immune reconstitution inflammatory syndrome (IRIS). The prognosis of HIV-related TB improves with the provision of HAART.

6.10 Co-trimoxazole Prophylactic Treatment

Prophylaxis for Tuberculosis should be given to those HIV + patients who were tested for TB and were not positive. The use of co-trimoxazole (sulfamethoxazole [SMX] and trimethoprim [TMP] 5:1) reduces morbidity and mortality by preventing other opportunistic infections such as pneumocystis pneumonia, other pneumonias, diarrhea, etc.

Adults- 1 double strength tablet (800 mg SMX + 160mg TMP) once daily

Children- SMX 20mg/kg, TMP 4mg/kg once daily.

Co-trimoxazole should be started concurrently with TB treatment as soon as the patient is known to be HIV positive. All HIV-infected children with advanced immunosuppression should be started on co-trimoxazole. Figure 4; flow chart that can be used in patients not responding well to treatment, due to the occurrence of concomitant bacterial infection.

6.11 Management of HV/TB Patients Who Fail to Respond to Antiretroviral Therapy

ART improves survival in HIV-positive patients. Antiretroviral therapy for HIV infection in adults and adolescents' recommendations are as follows:

- Start ART in all HIV-infected individuals with active TB irrespective of CD4 cell count
- Start TB treatment first, followed by ART as soon as possible within the first 8 weeks after starting TB treatment.
- HIV positive TB patients who have severe immunosuppression (e.g. CD 4 counts less than 50 cells/mm^3 or with severe disease) should begin ART within the first 2 weeks of starting TB treatment.
- Use Efavirenz (EFV) as preferred non-nucleoside reverse transcriptase inhibitor (NNRTI) in patients starting ART while on TB treatment.

6.12 ART Regimens for Patients Receiving TB Treatment

Efavirenz-containing regimens are the recommended first line ART regimens for TB patients since interactions with anti-TB drugs are minimal. In several studies of standard-dose EFV and two nucleosides was well tolerated and highly efficacious in achieving complete viral suppression among patients receiving concomitant rifampicin-based TB treatment. (e.g. EFV + ZDV +3TC or EFV + TDF +FTC). However, alternatives to EFV are needed in the following situations:

- Women of childbearing potential without adequate contraception and in pregnant women in the first trimester of pregnancy because of potential teratogenicity.
- Patients who are intolerant to Efavirenz
- Patients infected with a strain of HIV that is resistant to NNRTI's

In selecting alternatives to EFV for the situations noted above. The NTP manager should consult with the country's HIV program and other experts familiar with the most recent results of ongoing studies or change in policies.

HIV treatment must be taken daily without exception to prevent the evolution of drug-resistance. NTP managers should explore the possibility of merging TB medications and ARVs into the DOT program or other methods of adherence support.

6.13 Immune Reconstitution Inflammatory Syndrome (IRIS)

As the patient begins to respond to TB treatment, the patient's immunity is also reconstituted and this may result in an exaggerated immune reaction to the TB bacilli. This reaction, which is called IRIS, and varies in severity from mild to more serious but more commonly presents in a mild to moderate form in patients with TB started on ART. IRIS can occur in non-HIV-infected persons with TB, but it's more common among those with HIV infection, particularly those receiving ART. The syndrome typically manifests itself as a worsening of TB-related signs and symptoms (e.g.)

- Fever
- large lymph nodes and, new lymphadenopathy
- expanding central nervous system lesions
- worsening of pulmonary parenchymal infiltrations and increasing pleura effusions generally occurring within 12 weeks of initiating ART and more common when CD4 count is low (<50 cells/mm^3).

TB-related IRIS can be associated with significant morbidity and even mortality if not appropriately managed. In most cases, TB treatment and ART can and should be continued. Mild symptoms usually resolve over time and can often be managed with the use of non-steroidal anti-inflammatory drugs. Moderate to severe symptoms may require the use of corticosteroids to suppress the immune response.

In the evaluation of patients with suspected IRIS, consider the full differential diagnosis, including:

- Treatment failure due to non-adherence, drug resistance, or malabsorption
- Other opportunistic infections
- Malignancy

6.14 Multidrug-resistant TB and HIV

Multidrug-resistant TB (MDR-TB) is TB that is resistant to at least both isoniazid and rifampicin. Patients who have both MDR-TB and HIV are more difficult to manage clinically and usually have poorer treatment outcomes. PLWHA and in whom MDR-TB is suspected, should be tested using Xpert MTB/RIF where available, since it is more sensitive to detecting the MTB and rapidly detects rifampicin resistance.

WHO recommends that all patients with HIV and Drug-resistant TB, who require second-line Anti- TB drugs, should receive ART as soon as possible (within the first 8 weeks) after initiating anti- tuberculosis medications.

6.15 Treatment Recommendations for HIV/TB Co-infection in Children

* Children living with HIV who have any of the following symptoms: poor weight gain, fever, current cough, or has history of contact with a TB case, may have TB and should be evaluated for Tuberculosis and other conditions. If evaluation shows no TB, they should be given IPT.

In the HIV-infected child with confirmed or presumptive TB, the initiation of TB treatment is the priority. The principles for treatment of TB are the same in the HIV-infected child and in the HIV-uninfected child. Because of the high risk of dissemination of TB in children aged four years or younger, TB treatment should begin as soon as the diagnosis of TB is suspected.

- In the ART-naïve child, ART should be initiated in ANY child with active TB disease as soon as possible within 8 weeks of starting the TB treatment, irrespective of CD 4 count and WHO clinical stage.
- For a child who is already receiving ART, the ART regimen should be reviewed and altered if necessary to ensure optimal treatment for both TB and HIV and to minimize potential toxicities and drug-drug interactions.
- The initial phase of treatment of TB should consist of a four-drug regimen: RIF, INH, PZA, and EMB. Streptomycin should replace EMB in the treatment of TB meningitis.
- In the continuation phase, INH and RIF should then be continued daily to complete 6-9 months' therapy. Note that PAHO/WHO do not recommend the 7 month HR continuation phase but it is considered an option by the CTBG.

Most children with TB, including those with HIV, respond well to a 6-month rifampicin-based regimen.

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7. Multi-Drug Resistance Tuberculosis

Rifampicin is also effective in the management of other infectious diseases (e.g. respiratory infections and sexually transmitted infections). Its use as mono-therapy in tuberculosis leads to resistance quickly even if it is given for short periods, but when in combination with isoniazid there is reduction in the survival of rifampicin-resistant mutants. Because of the importance of Rifampicin in management of Tuberculosis, it is recommended that the drug be reserved only for TB and Leprosy, and no other conditions.

Multidrug-resistant tuberculosis (MDR-TB) refers to resistance to at least the two key first-line anti- tuberculosis drugs, rifampicin and isoniazid. Resistance is seen in erratic drug usage i.e. interrupting treatment frequently that allows for re-growth of bacteria which might favor resistant mutants, and/or treating with a single drug which leads to the same effect. Other situations such as expiry date having been surpassed, being out-of-stock, might lead to some drugs being continued while waiting for new stocks of the others therefore being another potential source of monotherapy.

Drug resistant TB must be addressed urgently and DST is warranted for every patient placed on TB medications. A well administered first-line treatment for susceptible cases and full implementation of DOTS is the best prevention against development of MDR-TB.

7.1 Definitions Anti-Tuberculosis Drug Resistance

i. **Mono-resistance**: isolates of MTB confirmed to be resistant in vitro to one first-line anti-TB drug.

ii. **Rifampicin Resistance (RR)**: as identified by Gene Xpert. An RR strain detected by Xpert can be considered and treated as MDR TB until the DST result proves otherwise. Gene Xpert explores only resistance to Rifampicin.

iii. **Poly-resistance:** isolates are resistant in vitro to more than one first-line anti- TB drug other than both isoniazid and rifampicin.

iv. **Multidrug resistant TB (MDR-TB):** An isolate with in vitro resistance to at least isoniazid and rifampicin. MDR can be seen in new cases but occurs most frequently in retreatment cases, treatment failure,

v. **Pre-Extensive Drug Resistant TB (Pre-XDR TB):** an isolate resistant to at least isoniazid and rifampicin and resistance to any fluoroquinolone OR any one of the second-line anti-TB injectable drugs (kanamycin, amikacin or capreomycin).

vi. **Extensively drug-resistant TB (XDR-TB):** In vitro resistance to at least isoniazid and rifampicin (i.e., MDR-TB) plus resistance to any fluoroquinolone and any one of the second-line anti-TB Injectable drugs (Kanamaycin, Amikacin, or Capreomycin)

7.1.1 Resistance to Anti-TB drugs by the Tuberculosis causing bacilli may develop due to:

a. Clinical errors:

i. Use of suboptimal regimens and treatment interruptions.

ii. Failure to provide effective treatment support and assurance of adherence

iii. Failure to recognize and address patient non-adherence

iv. Inadequate drug regimens

v. Adding a single new drug to a failing regimen

vi. Failure to recognize existing drug resistance.

b. Co-morbid conditions: HIV infection, or use of Antifungal agents may also lead to the acquisition of drug resistance.

c. Inadequate adherence: reduces serum levels of anti-tuberculosis drugs

d. Programmatic causes: Drug shortages and stock-outs, poor-quality drugs, unsuitable drug storage conditions

e. Previous Anti-Tuberculosis Treatment: This is a strong predictor of drug resistance in a patient. The odds of any resistance are at least fourfold higher and that of MDR at least tenfold higher than in new (untreated) patients. Patients who are sputum-positive after retreatment and those who fail treatment (sputum-positive after five months of treatment) are at highest risk of having MDR-TB, especially if rifampicin was used throughout the course of treatment.

f. Contact with a MDR-Patient: Persons who are in close contact with confirmed MDR-TB patients, especially children and HIV-infected individuals, also are at high risk of being infected with MDR strains. In some closed settings, prisoners, persons staying in homeless shelters and certain categories of immigrants and migrants are at increased risk of MDR-TB.

7.2 Identifying Drug Resistance

Drug resistant TB must be diagnosed correctly before it can be treated effectively. In persons with a Xpert test that is positive for MTB and shows RR, DST should be prioritized. Regionally DST must be requested from CARPHA in Trinidad and Tobago via our central medical Laboratory.

7.2.1 Treatment Principles

Although the goals for treatment of chronic TB and MDR-TB cases are like those of all other TB cases, achieving successful treatment outcomes is much more difficult given the need to use less effective and more toxic drugs for a substantially longer time. **The WHO recommends strategic options for treatment of MDR-TB:**

-Standardized regimens preferred

-Individualized treatment regimens (based on DST results and previous treatments) are mainly for Pre-XDR and XDR TB

The basic principles involved in the design of a classical treatment regimen for MDR-TB include:

-Use of at least four drugs with either certain or highly likely effectiveness

-Use any drugs from groups 1-5 based on the potency

-Use any group 1 first line likely to be effective

-Use group 2 an injectable agent

-Use of a fluoroquinolone whenever possible

-Use the remaining group 4 drugs to complete a regimen of at least 4 effective drugs (total number of drugs based on degree of uncertainty of effectiveness/extent of resistance and extent of disease; regimens often contain 5-7 drugs.

-For regimens with fewer than 4 effective drugs, consider adding two group 5 drugs.

-Drug administration at least six days a week;

-The use of an injectable agent (an aminoglycoside or capreomycin) during the initial phase (for at least six months after culture conversion)

-Treatment duration of 12 months beyond culture conversion

-DOT throughout the treatment course.

-Avoid using drugs which there is cross resistance.

NOTE: avoid streptomycin even if DST suggest because of high rates of resistance with drug resistant TB strains, patient is likely to have received this drug in the past, and because of higher incidence of Ototoxicity.

7.3 Standardized Treatment Regimens

Standardized treatment regimens are the choice in settings where susceptibility testing of reserve (second-line) drugs is not available and are based on representative drug-resistance surveillance data or on the history of drug usage in the country. Based on these assessments, regimens can be designed that will have a high likelihood of success.

7.3.1 Classical MDR Treatment Regimen (Resistance to First Line Drugs)

Intensive Phase: 6 months Kanamycin + Levofloxacin + Cycloserine + Ethambutol + Pyrazinamide

Continuation Phase: 12-18 months Levofloxacin + Cycloserine + Ethambutol + Pyrazinamide

*In case of resistance, intolerance or previous use of aminoglycosides or fluoroquinolones, Capreomycin may be used as injectable and PAS and/or Moxifloxacin as replacement drugs. Can be used for pre-XDR and XDR TB

7.4 MDR-TB Empiric Regimen and Monitoring

7.4.1 Individualized Treatment Regimens

Individualized treatment regimens are used for Pre-XDR and XDR TB patients. These patients are to be referred for specialist evaluation and care.

7.4.2 New Recommendations from WHO for a Shortened Treatment Regimen in MDR TB

This WHO recommended regimen is as follows: kanamycin (an injectable agent), moxifloxacin, prothionamide, clofazimine, isoniazid, pyrazinamide and ethambutol, given together in an initial phase of 4 months (with the possibility to extend to six months if they remain sputum smear positive at the end of month 4).

This is followed by 5 months of treatment with four of the medicines (moxifloxacin, clofazimine, pyrazinamide, and ethambutol).

Intensive Phase: 4-6 months Kanamycin-Moxifloxacin-Prothionamide-Clofazimine-Pyrazinamide-High dose Isoniazid

Continuation Phase: Ethambutol / 5 Moxifloxacin-Clofazimine-Pyrazinamide-Ethambutol

Table 7.1: Recommended Drug Doses for MDR-TB

Drug	Weight group		
	Less than 30 kg	30 kg to 50 kg	More than 50 kg
Gatifloxacin	400 mg	600 mg	800 mg
Moxifloxacin	400 mg	600 mg	800 mg
Clofazimine	50 mg	100 mg	100 mg
Ethambutol	800 mg	800 mg	1200 mg
Pyrazinamide	1000 mg	1500 mg	2000 mg
Isoniazid	300 mg	400 mg	600 mg
Prothionamide	250 mg	500 mg	750 mg
Kanamycin	15mg per kilogram body weight (maximum 1 g)		

The shorter MDR-TB regimen is recommended for patients in whom the diagnosis of RR-/MDR-TB has been reliably confirmed by an approved molecular (e.g. Xpert MTB/RIF) or phenotypic DST method. All patients with confirmed rifampicin-resistant disease are treated as MDR-TB, and the shorter MDR-TB regimen could be used in these patients too. Children and people with HIV on antiretroviral therapy could receive the shorter MDR-TB regimen.

7.4.3 Contra-Indications of the New Shortened Regimen

This regimen cannot be applied to Pre-XDR and XDR-TB so it is necessary to carry out DST for second line injectable and fluoroquinolones and ensure that the strain is susceptible to both. It is also contraindicated in Pregnancy.

7.4.4 Monitoring the MDR/XDR-TB Patient

Patients with MDR- or XDR-TB must be monitored closely throughout treatment. Sputum smears and cultures should be performed monthly until both become consistently negative (conversions). **Conversion is defined** as two consecutive negative smears and cultures taken 30 days apart and is a key marker for assessing response to treatment. Once conversion is documented, sputum monitoring at a minimum should continue monthly for smears and quarterly for cultures until completion of treatment.

Patients with MDR or XDR-TB should be seen and evaluated by a clinician at least monthly until sputum conversion then every 2-3 months throughout the treatment. Weight should be documented monthly until stable. This is particularly important for those patients presenting with significant weight loss at the time of TB diagnosis, since weight gain may signify clinical response early during treatment for these patients.

Second line drugs have many more adverse effects than the first-line anti-tuberculosis drugs, but management of these adverse effects is possible. Screening for medication side effects should occur at every DOT and clinician encounter. Patients should be aware of and understand the possible side effects and have access to medications to counteract adverse effects when they occur.

Prompt management of adverse effects caused by the reserve drugs is essential for successful treatment of MDR and XDR-TB.

7.5 Treatment Outcomes for Second-Line Anti-TuberculosisDrugs

Table 7.2: Outcomes for RR-TB/MDR-TB/XDR-TB patients treated using second-line treatment

Outcome	Definition
Cured	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Treatment failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: -lack of conversion (b) by the end of the intensive phase a, or -bacteriological reversion (b) in the continuation phase after conversion (b) to negative, or -evidence of additional acquired resistance to fluoroquinolones or second-line
Died	A patient who dies for any reason during treatment.
Lost to follow-up	A patient whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A patient for whom no treatment outcome is assigned. (This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown)
Treatment	The sum of cured and treatment completed

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

(b) The terms "conversion" and "reversion" of culture as used here are defined asfollows:

Conversion (to negative): culture is considered to have converted to negative when twoconsecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date ofconversion.

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

7.6 **Treatment considerations for contacts of MDR-TB indexcases**.

Since MDRTB is resistant to isoniazid and rifampicin it is unlikely that the use of these two drugs will be effective in the treatment for MDR-TB latent infection and preventing active TBdisease.

Contacts of MDR-TB patients in whom latent infection is newly diagnosed may be infected with isoniazid-susceptible strains, particularly in high-burden areas where many different strains of TB may circulate in the community. Close contacts of MDR-TB patients should receive careful clinical follow-up for a period of at least two years. If active disease develops, prompt initiation of treatment with a regimen designed to treat MDR-TB is recommended, and culture and drug susceptibility testing should be expedited to confirm or rule-outMDR-TB

WHO does not recommend the universal use of second-line drugs for chemoprophylaxis in MDR-TB contacts; however, treatment may be indicated in certain high risk situations. For persons who are likely to be infected with an MDR-TB strain (isoniazid and RR rifampicin-resistant) and who are at high risk for developing TB, pyrazinamide and ethambutol or pyrazinamide and a fluoroquinolone (i.e. levofloxacin, or moxifloxacin) for 6-12 months may be considered. Close monitoring for hepatitis should occur if treating such contacts with a two-drug regimen that includes pyrazinamide. Contacts who are immune-compromised (e.g., HIV-infected persons) should be treated for 12 months. It is advisable in these situations to consult with a clinician familiar with the treatment and management of MDR-TB.

7.7 Second Line Anti-Tuberculosis Drugs

Table 7.3: shows the second-line reserved anti-tuberculosis drugs

Drug (Abbreviation)	Recommended Daily Dosage			Special Considerations and Monitoring
	Average (mg/kg)	Children (mg/kg)	Max (mg/day)	
Group 2 – Injectable agents (bactericidal)				
Kanamycin (Km)	15	15-30	1000	Adjust dose and frequency for renal insufficiency and age >59 Monitor creatinine, electrolytes and vestibular function monthly Obtain baseline and monthly audiology exam
Amikacin (Am)	15	15-30	1000	
Capreomycin (Cm)	15	15-30	1000	
Group 3 – Fluoroquinolones (bactericidal)				
Levofloxacin (Lfx)	750-1000	(15-20)*	1000	Adjust frequency for renal insufficiency *younger children: divide daily dose in two
Moxifloxacin (Mfx)	400b (7.5-10)	(7.5-10)	400	Symptom-based monitoring; may cause QTc prolongation
Group 4 – Oral bacteriostatic				
Cycloserine (Cs)	500-750 (10-15)	(10-20)	1000	Children: divide daily dose in two every 12 hr. Check serum peak concentration 1-2 weeks after initiation (desired peak = 20-30mcG/ml)
Ethionamide (Eto) Protionamide (Pto)	500-750 (10-15)	(15-20)	1000	Divide daily dose into two or three; slowly increase to target dose over several days Monitor TSH and liver function Avoid during pregnancy
p-aminosalycilic acid (PAS)	8-12g (150)	(200-300)	12g	Divide daily dose into two or three; slowly increase to target dose over several days Monitor TSH, electrolytes, liver function, CBC
Group 5 – Agents with unclear efficacy (not recommended by WHO for routine use in MDR-TB patients				
clofazimine (Cfz)	100		100a	Some clinicians begin at 200-300 mg daily and decrease to 100 mg after 4 to 8 weeks. Use with caution in patients with severe hepatic insufficiency
linezolid (Lzd)	600	(10) every 8 hours	600	Give with pyridoxine Monitor for peripheral neuropathy & optic neuritis Monitor CBC weekly initially then monthly
Amoxicillin/Clavulanate (Amx/Clv)	2000/250	(80) divided 2x/d		Dose twice daily Adjust dose and frequency for renal insufficiency
Imipenem (Ipm), Cilastatin (Cln)	Usual adult dose is 500–1000 mg IV every 6 hours.			
High-dose INH	(16-20)	(20-30	1500 3x/wk	Monitor liver function monthly Give with pyridoxine‡ Dosing is twice or thrice weekly (900-1500mg)a
Bedaquiline (Bdq)	400 mg daily for 2 weeks, followed by 200mg 3 times a week for 22 weeks with food	Not yet determined		Special attention to QTc prolongation over .45 ms. (Monitor EKG monthly)
Delamanid	200mg daily	Not yet determined		QT prolongation

[a]Francis J. Curry National Tuberculosis Center. Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 2nd ed., 2008. [b]WHO's Guidelines for the Programmatic Management of Drug-resistant Tuberculosis, Emergency Update 2016 and Companion Handbook WHO/HTM/TB 2011.22.
[c]WHO Guidance for national tuberculosis programs on the management of tuberculosis in children, 2012

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8. Tuberculosis in Children

8.1 General Information

Children can present with TB at any age. Tuberculosis in a child is a result of exposure to an infectious adult or adolescent in their close environment, often within the household. Children frequently develop a primary parenchymal lesion, or a Ghon focus, in the lungs with subsequent spread to the regional lymph node(s). The cell-mediated immune response halts further progression in most situations; however, very young children (< 5 years of age) and those with weakened immune systems are at great risk for disease progression in several weeks.

The risk of infection; depends on two situations;

- extent of exposure to infectious droplet nuclei
- susceptibility to the infection

An infant of a sputum smear positive PTB mother has a high risk of acquiring the infection, since he or she is a close contact and has weaker defenses. An infant with HIV infection has a greater risk of infection with the tubercle bacilli.

8.1.1 Risk of Progression of Infection to Disease

Most TB infected children do not develop the disease since they are healthy, the only evidence of infection is a positive TST. A child may develop TB if these conditions exist;

- Malnutrition (may decrease the immune system and trigger the conversion to TBdisease)
- Physical and emotional stresses
- HIV
- Measles
- Whooping Cough

Note well that children rarely have sputum smear positive TB so they are rarely infectious. Hence the cure of infectious TB in children assures a decrease in morbidity and mortality.

8.1.2 Pathogenesis

TB disease in children is usually primary TB, and may be dormant for years in a child to develop as active TB as an adult. The age of infection determines the pattern of primary disease. In Puberty TB presents as Miliary and extra-pulmonary TB, and after puberty— pulmonary spread.

8.2 Clinical Presentation of Tuberculosis in Children

8.2.1 : Primary TB Disease

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

8.2.2 Acute Disseminated Post-primary TB (often in children under 5 years of age):

a. *Post-primary PTB* (usually in children aged over 10 years): Without cavitation, smear-negative or with cavitation smear-positive.

b. *Post-primary EPTB:* standard regimen

8.3 Clinical Presentation of TB in Children with HIV

- Clinical manifestation of TB disease in the HIV-infected child is like that in the HIV-uninfected child.
- Failure to thrive, splenomegaly, hepatomegaly, and generalized lymphadenopathy as compared with HIV-uninfected children with TB Children with TB/HIV co-infection have longer stay in hospital and greater mortality despite appropriate anti-TB medications.
- Progressive HIV Disease and disseminated TB (Meningitis, Miliary TB, Generalized lymphadenopathy)
- Signs and symptoms may be consistent with acute pneumonia
- Older HIV-infected children may have clinical presentations more like that seen in HIV- infected adults

It is essential to have a high index of suspicion for TB disease in HIV-infected children. As with the non-HIV infected child, a definitive diagnosis of TB disease requires isolation of M. tuberculosis from expectorated sputum, Broncho alveolar lavage fluid (BAL);

- or aspirated gastric fluid (obtained in the early morning after overnight fast);
- Biopsied lung; peripheral lymph node, or other tissue.

8.4 Diagnosing TB in Children

TB may affect any part of a child's body. Children < 5years of age rarely expectorate and they usually swallow it, and specimens may negative for AFB. In very young children, gastric aspirate, laryngeal swabs can be collected, having a positive yield of 20%. TB diagnosis in children is usually presumptive and like smear –negative or extra pulmonary TB. In most case the child may have received treatment with a broad-spectrum antibiotic, with no clinical response, so in certain areas specialized diagnostic tools are necessary X-rays, WRD such as Xpert/RIF, culture, biopsy, and histology.

8.4.1 Recommended Approach for Diagnosis of Tuberculosis in Children

Diagnosis of PTB may be difficult in children < 6-8 years of age, particularly in low resource settings. The approach in TB diagnosis in children includes:

- Symptom and contact history
- Clinical exam (including growth assessment)
- Mantoux tuberculin skin test result
- Bacteriological exam (whenever possible)
- Chest radiograph
- Other specific evaluation indicated by disease site

8.4.1.1 Symptom and Contact History:

A close contact is defined as living in the same household or in frequent contact with a source case (e.g., care giver) with sputum smear-positive TB source cases who are sputum smear-negative but culture-positive are also infectious, but to a much lesser degree. The following points concerning contact are of importance for children:

- Children (especially those < 5 years of age) who have been in close contact with a case of smear-positive TB must be screened for TB (see: TB Contact Investigation).
- After TB is diagnosed in a child or adolescent, an effort should be made to detect the adult source case(s), especially within the household.
- If a child presents with infectious TB, then childhood contacts must be sought and screened as for any smear-positive source case. Children should be regarded as infectious if they are sputum smear-positive or have a cavity visible on CXR.

Symptoms:

Children with symptomatic disease develop chronic symptoms in most cases. The most frequent symptoms are chronic, unremitting cough, fever and weight loss. The specificity of symptoms for the diagnosis of TB depends on how strict the definitions of the symptoms are.

- **Chronic cough:** an unremitting cough that is not improving and has been present for 21 days (3 weeks).
- **Fever:** of 38°C for 14 days after common causes such as malaria or pneumonia have been excluded.
- **Weight loss or failure to thrive:** always ask about weight loss or failure to thrive and look at the child's growth chart.

8.4.1.2 Clinical Examination (including growth assessment)

There are no specific features on clinical examination that can confirm that the presenting illness is due to PTB. Some signs, although uncommon, are highly suggestive of EPTB and the threshold to initiate treatment should be lower. Other signs are common and should initiate investigation as to the possibility of childhood TB.

-Physical signs highly suggestive of EPTB:

- Gibbus, especially of recent onset (vertebral TB)
- Non-painful enlarged cervical lymphadenopathy with fistula formation.

-Physical signs requiring investigation to exclude EPTB*:*

- Meningitis not responding to antibiotic treatment, with a sub-acute onset or raised intracranial pressure
- Pleural effusion
- Pericardial effusion
- Distended abdomen with ascites
- Non-painful enlarged lymph nodes without fistula formation
- Non-painful enlarged joint
- Signs of tuberculin hypersensitivity: phlyctenule conjunctivitis, erythema nodosum.
- Documented weight loss or failure to gain weight, especially after being treated in a nutritional rehabilitation programme, is a good indicator of chronic disease in children, and TB may be the cause.

Table 8.1: An approach to the diagnosis of tuberculosis in children

The risk of tuberculosis is increased when there is an active case (infectious smear-positive tuberculosis) in the same house or when the child is malnourished, is HIV infected or has had measles in the past few months, consider tuberculosis in child with;

A history of;

a. Unexplained weight loss or failure to grow normally

b. Unexplained fever, especially when it continues for more than two weeks

c. Chronic cough

d. Exposure to an adult with probable or definite pulmonary infectious tuberculosis

On examination;

a. Fluid on side of the chest (reduced air entry, stony dullness to percussion).

b. Enlarged non-tender lymph nodes or a lymph node abscess especially in the neck

c. Signs of meningitis, especially when these develop over several days and the spinal fluid contains mostly lymphocytes and elevated protein

d. Abdominal swelling, with or without palpable lumps

e. Progressive swellings or deformity in the bone or a joint, including the spine.

Source; reproduced from WHO/FCH/CAH/00.1

8.4.1.3 Mantoux Tuberculin Skin Test (TST)

The criterion for a positive TST depends on whether the child has had BCG, a weak reaction can occur after several years of the BCG. In these children, the TST is less than 10mm.

Use of the Tuberculin Skin Test

A positive TST occurs when a child is infected with M. Tuberculosis. However, in children, the TST can also be used as an adjunct in diagnosing TB disease, when signs and symptoms of active TB exist.

a. *Using the test:* The TST should be standardized for each country using either 5TU (tuberculin units) of tuberculin purified protein derivative-S (PPD-S) or 2 TU of tuberculin PPD RT23, as these give similar reactions in infected children. Health care workers must be trained in performing and reading a TST (see Appendix A). A TST should be regarded as positive as follows:

- High-risk children: TST > 5mm indurations (high risk includes HIV infected children and severely malnourished children, i.e., those with clinical evidence of marasmus or kwashiorkor)
- All other children: TST > 10mm induration is regarded as positive (whether they have been BCG vaccinated).

b. *Value of the test:* A positive TST indicates that the child has been infected with TB. However, when used in a child with symptoms and other evidence of TB disease (such as an abnormal CXR), it is a useful tool in making the diagnosis of TB in a child. TST can be used to screen children exposed to TB (such as from a household contact with TB), although children can still receive chemoprophylaxis even if TST testing is not available. (see also Appendix B).

The TST is useful in HIV-infected children to identify those with dual TB-HIV infection and as an aid in the diagnosis of TB, although fewer HIV-infected children will have a positive test, as a normal immune response is required to produce a positive TST, and many HIV-infected children have immune suppression. There can be false-positive as well as false-negative TST tests (see Appendix A). It is sometimes useful to repeat the TST in children once their malnutrition has improved or their severe illness (including TB) has resolved, as they may be initially TST negative, but positive after 2– 3 months on treatment.

A negative Mantoux;

TST never rules out a diagnosis of TB in a child. Conditions that may suppress the Tuberculin Skin Test include;

- HIV infection
- Malnutrition
- Severe bacterial infections, including TB itself
- Cancer
- Viral infections (measles, chicken pox, glandular fever
- Immunosuppressive drugs (steroids)

8.4.1.4 Bacteriological Confirmation:

It is important to make a bacteriological diagnosis of TB in a child.

- Samples include sputum
- gastric aspirate
- Other material (e.g., lymph node biopsy or any other material that is biopsied, WRD such as Xpert).

Fine needle aspiration (FNA) of enlarged lymph glands for both histology and staining for AFB has been shown to be a reliable test for diagnosing TB. All, specimens that are obtained should be sent for mycobacterial culture whenever possible. This will improve the yield of the test (i.e., it is more sensitive), but it is also the only way to differentiate M. tuberculosis from other non-tuberculous mycobacteria.

A bacteriological diagnosis is especially important for children who have one or more of the following:

- Suspected drug resistance
- HIV infection
- Complicated or severe cases of disease
- An uncertain diagnosis, which may include (pulmonary lymphoma, bacterial pneumonia, PCP, viral pneumonia (cytomegalovirus), fungal pneumonia (Candida, Cryptococcus)

The more common ways of obtaining sputum for microscopy in children are:

1. Expectoration: smear microscopy is a useful test and should always be obtained in adults and older children (10 years of age) who are pulmonary TB suspects. In children < 5 years of age, sputum is difficult to obtain and most children are 'sputum smear-negative'. However, in children who are able to produce a specimen, it is worth sending for smear microscopy (Xpert and culture if available). Yields are higher in older children (>5 years of age) and adolescents, and in children of all ages with severe disease. As with adult TB suspects, three sputum specimens should be obtained: spot specimen (at first evaluation), early morning, and spot specimen (at the follow-up visit).

2.Gastric aspirates: Gastric aspiration using a nasogastric feeding tube can be performed in young children who are unable or unwilling to expectorate sputum. If performed, gastric aspirates should be sent for smear microscopy and mycobacterial culture.

3.Sputum induction: Several recent studies have found that sputum induction can be performed safely and effectively in children of all ages, and the bacteriological yield is as good as or better than for gastric aspirates. However, training and specialized equipment are required to perform this test properly.

8.5 Investigations Relevant for Presumed PTB and EPTB

1. *Relevant for suspected pulmonary TB, i.e., CXR*: In most cases, children with pulmonary TB have radiological changes suggestive of TB. Images may present as;

- persistent opacification in the lung
- enlarged hilar or subcarinal lymph glands.
- A miliary pattern of opacification in non-HIV-infected children is highly suggestive of TB.

Patients with persistent opacification that does not improve after a course of antibiotics should be investigated for TB.

Adolescent patients with TB have radiological changes similar to adult patients (large pleural effusions, apical infiltrates, cavity formation, hilar adenopathy and collapse lesions visible on CXR.

2. *Relevant for suspected extra-pulmonary TB*: TB will be suspected from the clinical picture and confirmed by histology or other special investigations.

3. *Other tests*: Serological and nucleic acid amplification (e.g., polymerase chain reaction [PCR]) tests are not currently recommended for the routine diagnosis of childhood TB, as they have been inadequately studied in children and they have performed poorly in the few studies that have been done.

4. WHO now recommends the use of gene Xpert in diagnosing TB in children.

NOTE: Other specialized tests, such as computerized chest tomography and bronchoscopy, are not recommended for the routine diagnosis of TB in children.

HIV Testing; Areas with a high HIV prevalence may be associated with increased HIV/TB co-infection. HIV counseling and testing is indicated for all TB and HIV patients as part of their routine management.

8.6 Treatment Regimens for Tuberculosis Infected Children

The recommended standard drug regimen for both children and adults is the same, however drug dosage is not the same for children as for adults. Children dosage is higher. See Chapter 4, Table 4.3. **Note:** Children with TB meningitis should receive streptomycin in place of ethambutol, as ethambutol does not cross the blood-brain barrier. The length of regimen for TB meningitis is 12 months (2HRZS/10HR)

Table 8.2: Selective treatment for TB meningitis in children

Intensive phase	Continuation phase	reference
2HRZS	10HR	American Academy of Pediatrics

TB–tuberculosis; H –isoniazid; R-rifampicin; Z-pyrazinamide; S-streptomycin; Eth –ethambutol

Source: Adapted from WHO Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children. 2014.

8.6.1 Cotrimoxazole Prophylaxis

Daily CPT (20 mg trimethoprim + 100 mg sulfamethoxazole if aged <6 months; 40 mg trimethoprim + 200 mg sulfamethoxazole if aged <5 years; 80 mg trimethoprim + 400 mg sulfamethoxazole if ≥5 years) prolongs survival in HIV-infected children and reduces the incidence of respiratory infections and hospitalization. CPT should be given to all HIV-infected children with advanced immunosuppression.

8.6.2 Antiretroviral Therapy

In the HIV-infected child with confirmed or presumptive TB, initiation of anti-TB treatment is the priority. Treatment of TB in HIV-infected children on ART or who will start on ART needs careful consideration. There are many drug-drug interactions between ARVs and rifampicin as well as the

adverse drug events on anti-TB drugs and ARVs are similar and can cause confusion as to which drug may need to be stopped. The clinical and immunological condition of the HIV-infected child should guide the decision whetherto:

- Start ART treatment soon (2-8 weeks) after the start of anti-TB treatment

Where possible the initiation of ART should be deferred for at least 2-8 weeks in children starting anti-TB treatment who have not yet started ART (e.g. antiretroviral "naïve" patients).

8.6.3 Adjunctive Treatment with Corticosteroids

Corticosteroids may be used in the management of some complicated forms of TB, e.g., tuberculous meningitis, the complications of airway obstruction by TB lymph glands, TB pericarditis. (prednisone,2 mg/kg/ day maximum dosage 60 mg/day for 4 weeks), and taper off over 1–2 weeks before stopping.

8.6.4 Treatment Administration and Adherence

Children, their parents and other family members and other care givers should be educated about TB and the importance of completing treatment. The support of the child's parents and immediate family is vital to ensure a satisfactory outcome of treatment. Preferably someone other than the child's parent or immediate family should observe or administer treatment. All children should receive treatment free of charge, whether the child is smear-positive at diagnosis. Fixed-dose combinations should be used whenever possible to improve simplicity and adherence. Patient treatment cards are recommended for documenting treatment adherence. Children with severe forms of TB should be hospitalized for intensive management where possible.

8.6.5 Conditions that merit hospitalization include:

i. TB meningitis and miliary TB, preferably for the first 2 months;
ii. Any child with respiratory distress;
iii. Spinal TB;
iv. Severe adverse events, such as clinical signs of hepatotoxicity (e.g., jaundice).

8.6.6 Monitoring throughout Treatment:

Each child should be assessed as follows;

- 2 weeks after treatment initiation,
- At the end of the intensive phase, and
- Every 2 months until treatment completion. The assessment should include, at a minimum:

- A symptom assessment
- An assessment of adherence
- Enquiry about any adverse events;
- Weight measurement with medication dosages adjusted to account for weightgain
- Adherence including reviewing the treatment card; and
- Sputum for AFB smear microscopy at 2 months.

- Follow-up chest radiographs are not routinely required in children, particularly as many children will have a slow radiological response to treatment. A child who is not responding to TB treatment should be referred for further assessment and management. These children may have drug- resistant TB, an unusual complication of pulmonary TB, other causes of lung disease, or problems with treatment adherence.

Table 8.3: Monitoring of children with sputum smear positive TB

When to monitor	6-month treatment regime
At time of diagnosis	Sputum smear
At end of initial phase	Sputum smear
In continuation phase	Sputum smear 5 months
On completion of treatment	Sputum smear 6 months

8.7 Immune Reconstitution

A paradoxical reaction, this temporary exacerbation of symptoms, signs or radiographic manifestations sometimes occurs after beginning anti-tuberculosis treatment, presenting with fever, and increased size of lymph nodes or tuberculomas. Immune reconstitution can be brought about by improved nutritional status, TB treatment itself, after initiation of antiretroviral therapy (ART) in HIV-infected children with TB, and is known as the immune reconstitution inflammatory syndrome (IRIS). Anti-tuberculosis treatment should be continued, although in some cases the addition of corticosteroids might be useful. If in doubt, refer the child to the next level ofcare.

8.8 Child Contact and Management Recommendations

New cases of TB infected children are at high risk for miliary TB and possibly meningitis, which can develop within weeks unless the child is given preventive therapy. In HIV positive patients TB infection may progress rapidly to TB disease in as short as 20 days. Close contact screening, clinical evaluation and management is recommended and should be done by the NTP.

This is usually done by the same health care worker (PHN) who registers and/or supervises the treatment of the source case and may provide isoniazid preventive therapy (IPT) or treatment to the children.

If a child is diagnosed with tuberculosis, the child's family must be examined to identify the source case or who may have infected the child. The source case may be a parent or a grandparent or someone else in the child's close social network that may have infectious TB. Additionally, the investigation should attempt to identify others who may have been infected by the source case.

8.8.1 WHO recommendations for management of child contacts to infectious PTB:

8.8.1.1 Mantoux tuberculin skin test positive children

- If clinically well, (child is asymptomatic with normal chest x-ray and growth parameters). Offer IPT for 6 – 9 months;
- If clinically unwell, further evaluate for TB disease, (see section on Diagnosing TB in Children Chapter 8)
- Provide treatment for disease if tuberculosis is evidenced.

8.8.1.2 Mantoux tuberculin skin test negative children

- If clinically well, (child is well with normal chest x-ray and growth parameters) offer IPT for 2 months then repeat the tuberculin skin test;
- If positive at two months, continue IPT for a total of 6 – 9 months;
- If negative at two months, discontinue IPT;
  - If clinically unwell, further evaluate for possible or probable disease, including a detailed history and chest x-ray if possible;
  - Provide treatment for disease if tuberculosis is evidenced.

8.8.1.3 When the Mantoux tuberculin skin test is not possible:

- If clinically well, educate the care giver to return with the child should the child become ill;
- Suggest a routine follow-up in 1 month;
- If clinically unwell, obtain a history and examination for TB and include a chest X-ray if possible (see Fig.5, 6 algorithms)
- Treat for tuberculosis if evidenced Child Contact

Figure 7: Approach to Contact Management when Chest X-ray and Mantoux TST are not Readily Available.

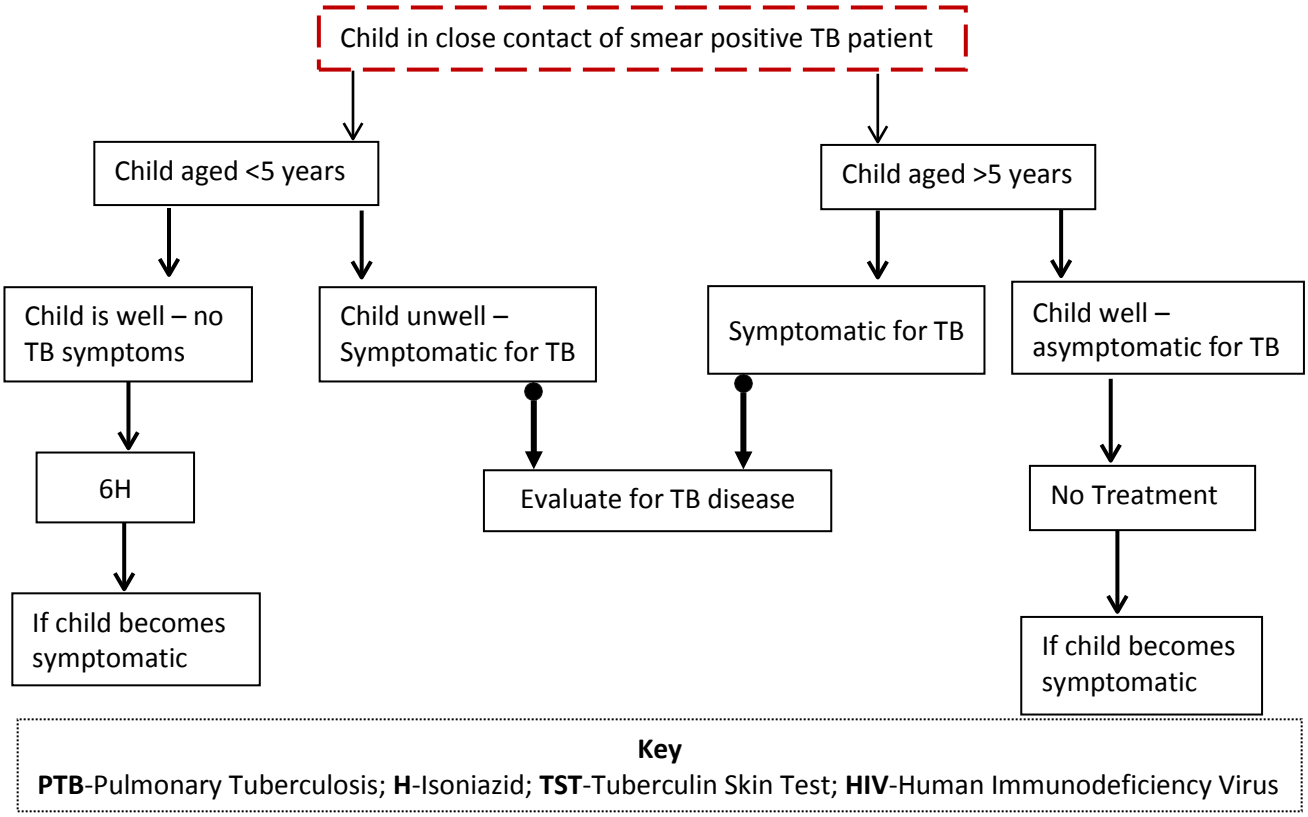
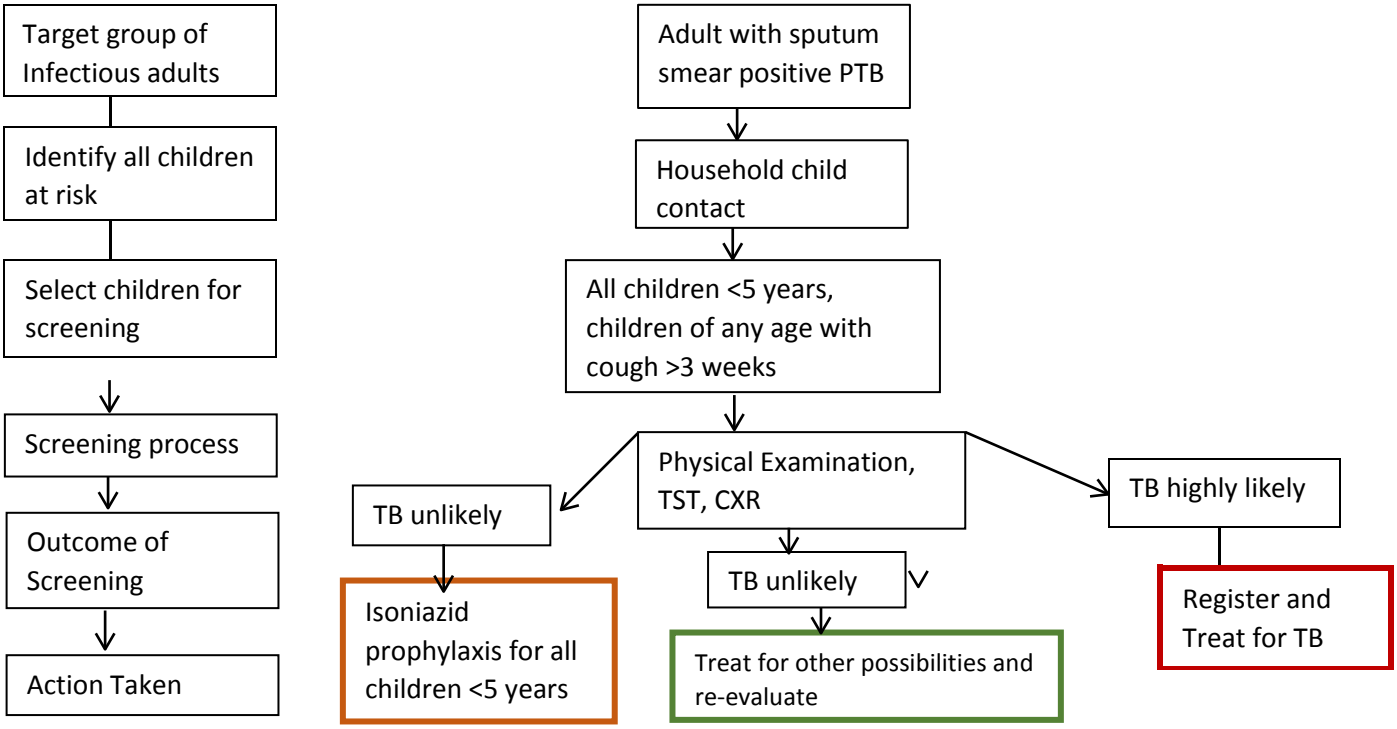


Figure 8: How to Identify and Manage the Child Contact of Infectious Adults



8.8.2 Special Circumstances of Child Contact:

8.8.2.1 Child contact is known to be HIV-infected:

If the child contact is HIV-infected and otherwise well, consider IPT for all ages, including those aged 5 years. As with other contacts, active disease should be ruled out, and only HIV-infected children who are healthy should be offered IPT. HIV-infected children who have symptoms should be carefully evaluated for TB, and if found to have TB disease, treatment can be started. It is important to know that all children < 5 years of age and contact of a sputum smear positive TB case should undergo prophylactic treatment with isoniazid.

8.8.2.2 Suspected HIV infection of source case and contact:

In HIV-endemic countries where HIV prevalence is high among cases with smear-positive PTB, if the source case is a parent, his/her children may be at risk for both TB and HIV infection. It is important to ask whether the HIV status of the source case and child contact is known, and consider HIV counseling and testing.

8.8.2.3 Child contacts of infectious multidrug-resistant tuberculosis (MDR-TB) cases: chemoprophylaxis regimens to have been studied are based on INH and, rifampicin. MDR-TB is resistant to both drugs and using them to treat latent infection caused by an MDR-TB strain will not prevent the development of active TB disease. Close contacts of MDR-TB patients should receive careful clinical follow-up for at least 2 years. If active disease develops, prompt initiation of treatment with a regimen designed to treat MDR-TB is recommended. WHO does not recommend second-line drugs for chemoprophylaxis in MDR-TB contacts.

8.8.2.4 Management of a baby born to mother diagnosed with infectiousPTB:

If a pregnant woman has been on treatment for at least 2–3 weeks, she is generally no longer infectious, but the baby may still have the risk of being infected. The risk is highest if a mother is diagnosed at the time of delivery or shortly thereafter. If a pregnant woman is found to have pulmonary TB shortly before delivery, then the baby, and if possible, the placenta, should be investigated for evidence of congenital TB infection and, if found, the baby should be treated.

A breastfeeding infant has a high risk of infection from a mother with smear-positive PTB, and has a high risk of developing TB.

- The infant should receive 6 months of IPT, followed by BCG immunization. Breastfeeding can be continued safely during this period.
- An alternative policy is to give 3 months of IPT, then perform a TST. If the test is negative, INH should be stopped and BCG vaccination given.
- If the test is positive, INH should be continued for another 3 months, after which it should be stopped and BCG given.

8.8.2.5 Immunizations:

Patients receiving treatment for tuberculosis can be given measles and other live vaccines unless they are very ill or on high dose corticosteroids.

8.9 BCG Vaccination in Children

Bacille Calmette-Guerin (BCG) is a live attenuated vaccine derived from *Mycobacterium bovis*. The WHO Expanded Programme on Immunization (EPI) recommends BCG vaccination as soon as possible after birth in countries with a high TB prevalence.

HIV exposed and HIV- infected children: Although there have been several reports of disseminated BCG infection in HIV-infected individuals, BCG appears to be safe in the clear majority of cases. It is generally accepted that BCG provides protection against the miliary TB and tuberculous meningitis, which are the most common in young children. Therefore, in countries with a high TB prevalence (irrespective of the HIV prevalence), the benefits of BCG vaccination outweigh the risks and the WHO recommends a policy of routine BCG immunization for all neonates unless there is known primary (e.g. congenital) immunodeficiency.

8.9.1: WHO Principles on BCG

WHO does not recommend BCG vaccination for:

- Children with symptomatic HIV infection
- HIV positive children who are at minimal risk for infection with *M.TB*
- Children with known primary (e.g. congenital) immunodeficiency

WHO does recommend BCG vaccination for:

- Asymptomatic children with HIV who are living in a country with a high Prevalence of TB

The recommendations regarding BCG and HIV from the Expanded Programme on Immunization in the Caribbean differs to that from WHO.

The Ministry of Health of Belize has the following recommendations:

- **For the HIV exposed infant –**These children should not receive BCG until their HIV status is known. If the baby tests negative, then the baby can receive BCG vaccine.
- **For the HIV infected infant** – The child should not receive BCG vaccine, regardless of the status of the baby (symptomatic or asymptomatic).

Table 8.4: Score Card for Diagnosing TB in Children (a score of 7 or more indicates a high likelihood of TB)

Score Chart for the Diagnosis of TB in Children						
Score if feature is present						
Feature	0	1	2	3	4	Score
General						
Duration of illness (weeks)	<2	2 - 4		>4		
Nutrition % weight of age	>80	60 – 80		<60		
Family History of TB	none	Yes, reported by family		AFB positive case		
Tuberculin Test				Positive		
Malnutrition				Not improving after 4 weeks		
Unexplained fever and weight loss			No response to malaria treatment			
Local						
				Lymph nodes		
				Joint Bone swelling		
				Abdominal mass or ascites		
				CNS findings and usually abnormal CSF findings		
					Angle of deformity of spine	
Total Score						

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9. TB Contact Investigation

TB Contact Investigation is carried out due to the high likelihood that a person with smear-positive PTB will transmit tuberculosis. Contact investigation is important for TB control and should start with the persons most likely to be infected (family members, other persons who live in the same house, friends and coworkers).

Actively seeking out and evaluating contacts to persons with smear-positive PTB is an important TB control strategy for various reasons:

i. It identifies persons with previously undetected tuberculosis allowing initiation of treatment and halting further transmission

ii. It identifies persons with TB infection who would benefit from IPT to prevent future TB reactivation

iii. It identifies most at risk population (positive HIV clients, children, AFB positive highly infectious patients).

9.1 Steps in a contact investigation

1. Decide whether to initiate a contact investigation
2. Interview the TB patient
3. Determine the infectious period
4. Conduct a field investigation at sites where transmission of TB may have occurred
5. Prioritize contacts
6. Evaluate contacts
7. Follow-up and treatment of contacts
8. Evaluate contact investigation activities

9.1.1 Decide whether to initiate a contact investigation

In general, the decision to identify and evaluate contacts should be based on the likelihood that transmission of TB has occurred. This depends in part on factors associated with the TB patient, the environment of the exposure, contacts immunity level.

A contact investigation should be initiated when any of the following factors are present:

- TB patient is a sputum smear-positive, Xpert or culture positive case
- TB patient is sputum smear-negative but PTB is highly suspect or (vulnerable suspects are exposed (e.g. neonates, HIV infected persons.)
- TB suspect index patient spent time close to vulnerable persons to TB (e.g. neonates, HIV infected persons, etc.)

9.1.2 Interview the TB patient

Information that you may need to establish infectious period

- Establish index case's current understanding of his/her TB diagnosis;(clarify any misinformation and provide patient information about TB, how it is transmitted and the importance of taking treatment as prescribed for the full duration)
- Determine patient's date of onset of symptoms of TB
- Identify the places where the index case spent time during the period he/she was symptomatic
- Identify names and locating information of persons who spent time with during the period the index patient was symptomatic (contacts)

9.1.3 Determine infectious period Table

- Date the TB symptoms began
- Date of first diagnostic test consistent with TB (e.g., sputum or CXR).
- The infectious period is generally considered closed when the TB patient:

i. Has 3 consecutive sputum smears that are negative;

ii. Has been on appropriate TB treatment for > 2 weeks; and

iii. Is showing clinical response to treatment with symptoms diminishing

9.1.4 Conduct a field investigation

This includes visiting each site where the TB patient spent time during the infectious period (e.g., homes, work settings, schools, clinics, jails, etc.). The visit should be made shortly after the patient interview. The site visit allows you to test contacts, refer patients for further evaluation, schedule clinic visits, and provide education. Sometimes additional contacts are identified during these site visits.

9.1.5 Prioritize contacts (high, medium and low with criteria)

This depends on the environment, length of exposure and exposure risk

High priority-- those most likely to have become infected due to the quality of exposure or those most likely to progress to TB disease once infected. These are

- Teachers
- hospital nursery workers
- other health care workers
- HIV infected persons and children < 5 years of age) should be prioritized for testing even though they may not have had close contact.

9.1.6 Evaluate contacts

The Tuberculin skin test (TST) is used to test contacts at risk for TB infection. All high priority contacts should be assessed for evidence of active TB with a symptom evaluation and clinical exam. Contacts with a positive skin test result (> 5mm) or signs or symptoms of TB disease should be evaluated carefully to rule out disease before IPT is started. This requires:

- A CXR and a medical history and examination by a medical officer
- Contacts with abnormal CXR findings suggestive of active TB and those with symptoms of active TB should also have sputum collected for AFB smear microscopy.
- Contacts with an initial negative TST should be told they will require a follow-up Mantoux 8-10 weeks after the date of their last TB exposure and should have a clinic appointment scheduled within that timeframe.

9.1.7 Follow-up and treatment of contacts

If initial TST was negative, repeat TST in 8 – 10 weeks after exposure. If TST is positive during the follow-up testing the patient should be evaluated as described above, and treated for latent TB infection (LTBI). Treating LTBI is an important TB prevention activity.

- Tuberculin positive adults, who have been evaluated for TB disease and found to have TB infection, should be given a course of IPT for 6 – 9 months.
- No further evaluation is required once IPT is completed unless the contact develops TB symptoms or has a subsequent TB exposure.

"Window period" is the time from infection to the body capacity to respond to the TST. Contacts WITH a negative TST should be placed on IPT, during this period until the TST is repeated for a period of 8- 10 weeks after last contact.

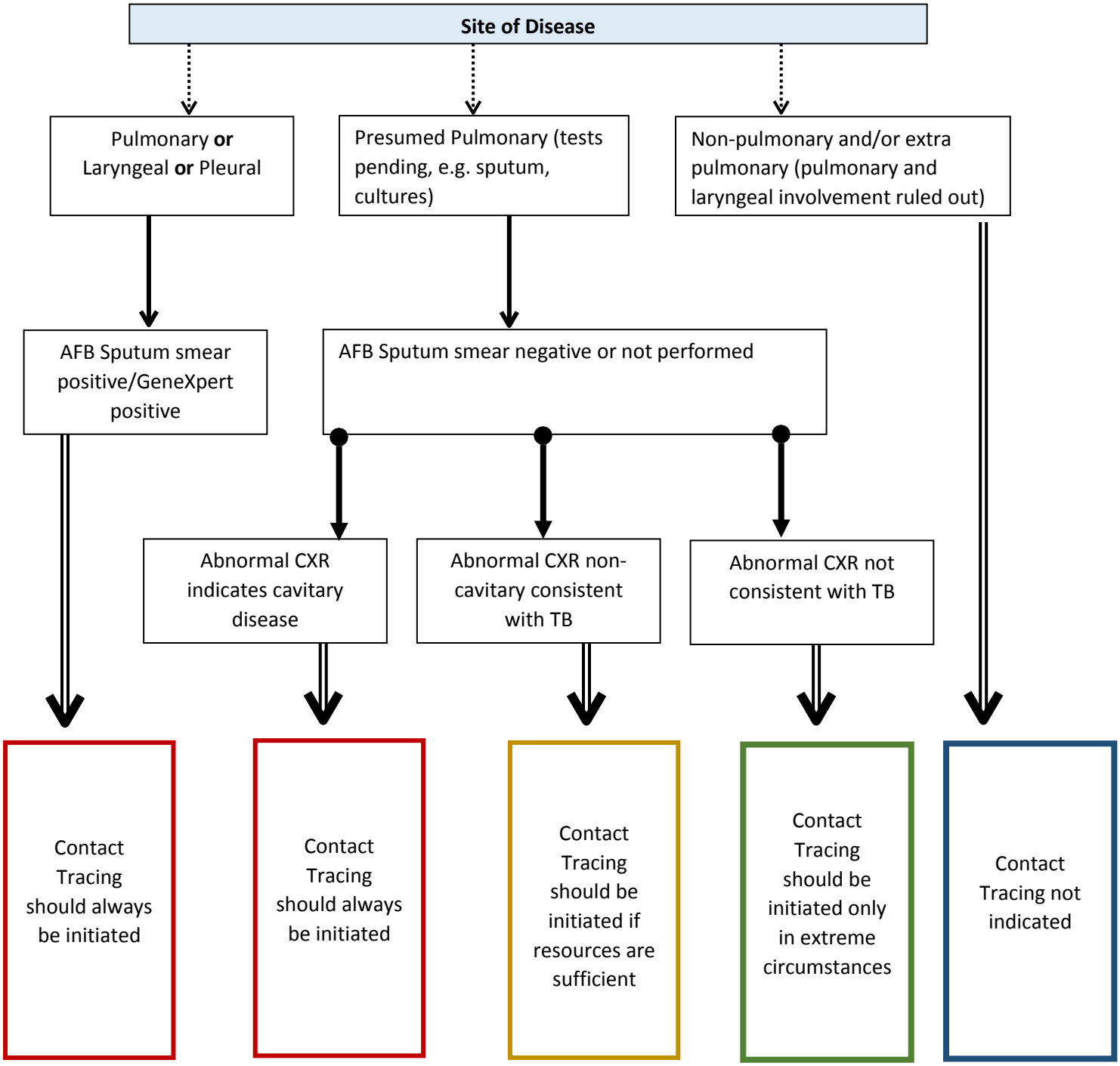
- Once active disease has been ruled out, administer IPT until the follow-up TST is performed (8 – 10 weeks following last TB exposure)
- If the TST remains negative at 8 – 10 weeks following last TB exposure, discontinue IPT
- If follow-up TST at 8 – 10 weeks' post TB exposure is positive, continue IPT for 9 months.

9.1.8 Evaluate contact investigation activities

Monitoring and analyzing is critical and can be used to identify gaps and improve patient management. Information may include:

- Number of contacts evaluated, categorized by age group (e.g., 0-4; 5-14, etc.)
- Number treated for TB disease and outcome
- Number given IPT and outcome, including treatment completion
- Adverse reactions to medications.
- Each contact (on whatever treatment) should have an individual card with important data recorded.

Figure 9: Decision Tree to Initiate Contact Investigation



AFB = Acid-fast bacilli**; CXR** = Chest X-Ray (Chest Radiograph)

Source: Graph modified from: Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis. Recommendations from the National Tuberculosis Controllers Association and CDC. 2005

Table 9.1: Infectious Period

Characteristics			Recommended minimum beginning of likely period of infectiousness
TB symptoms?	**AFB sputum smear positive?**	**Cavitary chest radiograph**	
yes	no	no	3 months before onset of 1st positive findings, consistent with TB disease, whichever is longer
yes	yes	Yes or no	3 months before onset of 1st findings, consistent with TB disease, whichever is longer
No	yes	Yes or no	3 months before onset of 1st positive findings
no	no	Abnormal not cavitary	4 weeks before date of diagnosis as a presumed TB or confirmed case

References

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Appendix A: Screening

Screening is presumptive identification of unrecognized disease by application of a test, examination, or other procedures that can be readily applied. It is not intended to be diagnostic. Screening must always be followed up.

Screening for TB in high risk groups is an active process of case-finding and not a passive activity. These may be:

a) Persons living with HIV and AIDS

b) Health care workers and laboratory staff

c) Prison inmates and staff

d) Elderly in long stay institutions

e) Other immunocompromised persons

f) Household contacts and other close contacts of known cases of TB

g) Persons who will be undergoing immunosuppressive treatment (e.g., organ transplant candidates; some cancer patients;

h) Patient's with autoimmune illnesses who will begin treatment with tumor necrosis factor alpha antagonists. The tuberculin skin test (TST) is used in many TB control programs as part of the procedure for identifying individuals who may be infected with TB.

A1: Mantoux tuberculin skin test (TST)

The Mantoux tuberculin skin test is the recommended method of skin testing to determine whether a person is infected with M. tuberculosis. The Mantoux TST is performed by injecting 0.1 ml of 5 tuberculin units (TU) of purified protein derivative (PPD) intradermally. The preferred injection site is the front (ventral surface) of the forearm. Given the importance of the injection technique in obtaining an accurate result, instruction and training should be provided to those who will be required to place, read and interpret Mantoux tuberculin skin tests (TST).

As vaccination with a live virus vaccine can interfere with the Mantoux TST reaction, test

- Either on the same day as vaccination with the virus vaccines or 4-6 weeks after the administration of the live –virus vaccine.
- At least one month after smallpox vaccination.

Procedure for placing the Mantoux tuberculin skin testing should be done as follows;

- Explain the procedure to the person
- Wash and dry your hands
- Locate and clean the injection site
- Prepare the syringe
- Stretch the skin with the thumb
- Position the syringe at a 10-15 degree angle to the skin
- Insert the needle with the bevel facing upwards
- Push the needle in 2 to 3 mm and inject
- Remove the needle quickly. Discard it in a puncture-proof container
- Do not massage the injection site. Do not apply any dressing
- If properly done, a blanched wheal will appear in which the skin follicles can be clearly seen.

Mark the site and make a record of the date and time of the injection. The next step is to read the result of the Mantoux skin test by examining the patient's arm for induration (palpable swelling). This is done 48 to 72 hours after giving the PPD injection. Using a ruler with millimeter measurements (preferably a transparent ruler), measure the largest transverse (horizontal) diameter of the indurate area at the site of the test on the person's forearm. The area of erythema (redness) around the indurated area is not included in the measurement.

Table A1: Mantoux skin tests and reading

> 5 mm	HIV-infected persons Recent contacts of infectious TB cases Persons with fibrotic changes on chest radiograph consistent with prior TB Organ transplant recipients Persons who are immunosuppressed for other reasons such as: -taking the equivalent of >15 mg/day of prednisone for 1 month or more -taking tumor necrosis factor alpha antagonists Children < 5 years of age, or children or adolescents exposed to adults at high risk
> 10mm	Recent immigrants (within last 5 years) from a high TB prevalence country Injection drug users Residents or employees of high-risk congregate settings Mycobacteriology laboratory personnel Persons with clinical conditions previously mentioned
> 15mm	Persons with no known risk factors for TB

A2: Interpretation of the Tuberculin (Mantoux) Skin Test:

There are many factors that can affect the result of the TST (correct placement, reading), and a thorough history are all important for interpretation.

A positive tuberculin skin test (Mantoux) reaction is defined as follows

- A positive reaction to the tuberculin test is taken to indicate that the person has been infected with TB
- A negative test result, in the absence of immunocompromising conditions (e.g. HIV infection and AIDS, post-measles syndrome, mal-nutrition, corticosteroid treatment and miliary tuberculosis) refers to lack of contact to MTB.

False negative Mantoux TST result; Some persons do not react to the TST even though they are infected. The reasons for these false negative reactions may include:

- Cutaneous anergy (anergy is the inability to react to skin tests because of a weakened immune system).
- Recent TB infection (within 8-10 weeks of exposure)
- Very old TB infection (many years)
- Very young age less than 6months old
- Recent live virus vaccination (e.g. measles, and smallpox).
- Overwhelming TB disease
- Some viral illnesses (e.g. measles and chickenpox)
- Incorrect method of TST administration, incorrect interpretation of the reaction.

False –positive Mantoux TST result; Some persons may react to TST even though they are not infected with M. tuberculosis. The causes of these false –positive reactions may include, but are not limited to, the following.

- Infection with non-tuberculosis mycobacteria
- Previous BCG vaccination
- Incorrect method of TST administration
- Incorrect interpretation of reaction
- Incorrect bottle of antigen used

APPENDIX B: Chemoprophylaxis of Latent TB Infection

In persons infected with Mycobacterium Tuberculosis, the risk of progression to active TB disease varies per the time since infection, age and other host factors. In children and adults, conditions that compromise the immune system will also increase the risk of disease after infection. Treating TB infection, however, can significantly decrease the number of persons who might otherwise go on to develop active TB disease.

There are two types of situations in which treatment should be considered:

a. Primary prophylaxis (window period prophylaxis)

The drug is given to an individual who is exposed to a known source of infection and who is very susceptible to becoming infected and developing tuberculosis.

- This would include children < 5 years of age
- persons known to be significantly Immunosuppressed.
- treatment may be discontinued if, after a period of 8 weeks, the repeated tuberculin skin test (TST) is negative and the child remains asymptomatic and is immunocompetent.
- If the individual is unable to mount a delayed-type hypersensitivity reaction (e.g. infant who is too young or individual with severe immunosuppression), consideration should be given to extending treatment for the full duration (9 months for INH).

b. Treatment of Latent TB Infection

The drug is used to prevent progression to disease in people who have already been infected as demonstrated by a positive Mantoux TST result (see Appendix A for induration size indicating a positive TST result)

B1: Drugs and Regimens for Treating Latent TB Infection

- Isoniazid (INH) for 9 months
- Rifampicin alone daily is the preferred drug in situations of INH resistance for 3-4 months

Dosage of isoniazid

The adult dose of isoniazid is 300mg daily, self-administered or administered under the supervision of a treatment supporter. The current WHO guidelines for treating child contacts to infectious PTB is isoniazid at a dose of 10mg/kg bodyweight (maximum dosage 300 mg) for a total of 9 months.

Use of supplemental Pyridoxine (B6) is recommended. Routine administration of pyridoxine is not recommended for children taking isoniazid, but could be considered in the following circumstances;

i. Children and adolescents with diets likely to be deficient in pyridoxine

ii. Children who experience paresthesia while taking isoniazid

Treatment for latent TB infection should be offered to:

- Mantoux skin test positive contacts of patients with pulmonary smear-positive TB after evaluating and ruling out active TB disease, especially children under five years of age
- Adults and children with Mantoux positive skin test reactions and who have been evaluated for clinical manifestation of the disease and found to be disease free (particularly those with HIV-infection)
- Individuals who have had BCG vaccination but are found to be Mantoux test positive and who are without clinical manifestations of TB disease

B2: Special considerations for treatment of LTBI apply to the following populations:

- When isoniazid is chosen for treatment of LTBI in persons with HIV infection or those with radiographic evidence of prior TB, 9 months rather than 6 months is recommended.
- For pregnant, HIV-negative women, isoniazid given daily or thrice weekly for 9 or 6 months is recommended. For women at risk for progression of LTBI to disease, especially those who are infected with HIV or who have likely been infected recently, initiation of therapy should not be delayed on the basis of pregnancy alone, even during the first trimester. For women, whose risk for active TB is lower, some experts recommend waiting until after delivery to start treatment.

Breastfeeding is not contraindicated when the mother is being treated for LTBI. The Centers for Disease Control and Prevention (CDC) recommends infants whose breastfeeding mothers are taking INH should receive supplemental pyridoxine (see also; CDC. The amount of INH provided by the breast milk is inadequate for treatment of the infant.

For children and adolescents, isoniazid given either daily or thrice weekly for 9 months is the recommended regimen. If using a daily regimen, dosage of INH should be calculated at 5 - 10 mg/kg (maximum 300mg daily). If regimen is twice weekly, dosage of INH is 20 mg/kg (maximum 600mg) and must be given by DOT.

For contacts to an index patient with isoniazid-resistant, rifampin-susceptible TB, rifampin given daily for 4 months is recommended. (6 months for children).

Active hepatitis and end stage liver disease are relative contraindications to the use of Isoniazid and pyrazinamide for treatment of LTBI.

Currently, there are no drug regimens that have been proven effective for treating latent TB infection resulting from exposure to a multidrug-resistant TB (MDRTB) source case; however, treatment may be indicated in certain high risk situations. For persons who are likely to be infected with an MDR-TB strain (isoniazid- and rifampin-resistant) and who are at high risk for developing TB, pyrazinamide and ethambutol or pyrazinamide and a fluoroquinolone (i.e., levofloxacin or moxifloxacin) for 6–12 months are recommended. Contacts who are immunocompromised (e.g., HIV-infected persons) should be treated for 12 months. It is advisable in these situations to consult with a clinician familiar with the treatment and management of MDR-TB (See Chapter 7: Chronic and Multidrug-resistant TB).

Table B1: Revised drug regimens for treatment of latent TB infection in adults

Drug	Interval and duration	Comments†	Rating (Evidence)	
			HIV negative	HIV positive
Isoniazid	Daily for 9 months	In HIV-infected persons, isoniazid may be administered concurrently with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors, or non-nucleoside reverse transcriptase inhibitors (NNRTIs).	A (II)	A (II)
	Thrice-weekly for 9 months	Directly observed therapy (DOT) must be used with thrice-weekly dosing.	B (II)	B (II)
Isoniazid	Daily for 6 months	Not indicated for HIV-infected persons, those with fibrotic lesions on chest radiographs, or children	B (I)	C (I)
	Thrice-weekly for 6 months	DOT must be used with thrice- weekly dosing	B (II)	C (I)
Rifampin§§	Daily for 4 months	Used for persons who are contacts of patients with isoniazid-resistant, rifampin-susceptible TB. In HIV-infected persons, most protease inhibitors should not be administered concurrently with rifampin. Clinicians should consult web-based updates for the latest specific recommendations.	B (II)	B (III)

Strength of the recommendation:	Quality of evidence supporting the recommendation:
A. Both strong evidence of efficacy and substantial clinical benefit support recommendation for use. Should always be offered. **B.** Moderate evidence for efficacy or strong evidence for efficacy, but only limited clinical benefit supports recommendation for use. Should generally be offered. **C.** Evidence for efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy might not outweigh adverse consequences (e.g., drug toxicity, drug interactions) or cost of the treatment or alternative approaches. Optional. **D.** Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered. **E.** Good evidence for lack of efficacy or for adverse outcome	**I.** Evidence from at least one properly randomized controlled trial. **II.**Evidence from at least one well-designed clinical trial without randomization from cohort or case-controlled analytic studies (preferably from more than one center), from multiple time-series studies, or from dramatic results from uncontrolled experiments. **III.**Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees. † Interactions with human immunodeficiency virus (HIV)–related drugs are updated frequently and are available at www.aidsinfo.nih.gov/guidelines. ** Recommended regimen for persons aged <18 years. †† Recommended regimens for pregnant women. §§ The substitution of rifapentin for rifampin is not recommended because rifapentine's safety and effectiveness have not been established for patients with LTBI.

B3: Clinical and laboratory monitoring: Before treatment initiation

Baseline laboratory testing should be routinely indicated for all patients at the start of treatment for LTBI; however, persons at greater risk for hepatitis should have baseline hepatic measurements of (AST/GOT) or alanine aminotransferase (ALT/GPT) and bilirubin.

Baseline Laboratory Should Be Obtained For;

- Individuals whose initial evaluation suggest a liver disorder Individuals with HIV infection
- Pregnant women
- Women in the immediate postpartum period (i.e. within 3 months of delivery)
- Persons with a history of chronic liver disease (e.g. hepatitis or C, alcoholic hepatitis or cirrhosis)
- Persons who use alcohol regularly, and persons at risk for chronic liver disease

Monitoring throughout treatment: All persons taking treatment for LTBI should receive follow-up evaluations at least monthly (if receiving isoniazid alone or rifampicin alone).

Monthly evaluation should include;

- A brief assessment, checking for signs of hepatitis, neurological complaints and hypersensitivity
- Questioning about side effects
- Education about side effects associated with treatment of LTBI and instructions to stop treatment and promptly seek medical evaluation if they occur.

Monthly laboratory monitoring:

- Indicated for persons whose baseline liver function tests are abnormal
- Other persons at risk for hepatic disease

- Laboratory testing may also be indicated for the evaluation of possible adverse effects that occur during treatment (e.g. liver function studies for patients with symptoms compatible with hepatotoxicity, or a uric acid measurement to evaluate complaints of jointpain).

Isoniazid should be withheld if transaminase levels exceed three times the upper limit of normal if associated with symptoms, and five times the upper limit of normal if the patient is asymptomatic.

APPENDIX C: Sputum Collection for Smear Microscopy

Smear microscopy of the sputum is a reliable diagnostic approach and must be done on all individuals where pulmonary and/or extra-pulmonary TB is suspected. Three sputum samples are collected (within 24 – 48 hours where possible – "spot, morning, spot").

- The first specimen is obtained following the initial interview (spot);
- Thereafter, the patient is given a container for collection of an early morning specimen before visiting the clinic the next day (day two). At the second visit the early morning specimen is delivered;
- On day two, after the second interview, another specimen is collected from the patient(spot).
- Use a clean, leak-proof, screw-capped plastic or glass container (do not use wax container).
- "*Requestfor Sputum Examination*" laboratory request form

If the patient does not return for the second interview, and the first specimen is smear positive for AFB, an immediate search must be made to locate and treat the patient.

C1: Recording of Results

The programme coordinator at national/regional level checks the laboratory register at weekly intervals to ensure that all patients diagnosed are properly registered and put on treatment. The registration number (identification) of the patient is written in the laboratory register. The acceptable sputum results to be recorded as follows:

- All positive sputum results must be entered in red ink for ease ofidentification
- Positive denoted as + (per results provided: scanty (1-9 AFB found), +, ++, +++)
- Negative denoted as "No AFB seen"
- Not done denoted as "ND"

REPORT the results of laboratory examinations back to the health unit in the shortest possible time, or telephone the results within 24 hours.

Gene Xpert Reporting are as follows:

i. MTB. Not detected
ii. MTB. Detected without Rifampicin Resistance (RR
iii. MTB. Detected with Rifampicin Resistance
iv. MTB. Detected with Rifampicin Resistance Indeterminate
v. Invalid
vi. Error and NO Results

APPENDIX D: Gastric Aspirates, Patient Preparation and Procedures

Gastric aspiration is a technique used to collect gastric contents that can be used in the diagnosis of tuberculosis and most specifically for children. Children have difficulty in expectorating sputum, when children with pneumonia sleep, their mucociliary mechanism sweep mucus up their airways into their throat. They swallow the mucus and collects in the stomach, unless the stomach empties out this can be a source of the TB organism.

D1: Patient Preparation

i. Early morning and having slept at least six hours

ii. Patient to be NPO after midnight

iii. The family should come to the clinic first thing in the morning. Any family members who could possibly have an active TB should wear mask to prevent transmission to health care workers.

iv. Place the NG tube in the patient. Do not use a lubricant that is bacteriostatic. Use as large bore NG tube as is comfortable (minimum 10 French). Avoid too deep a placement to prevent passage through the pylorus.

D2: Sample collection

i. Aspirate the stomach contents, if less than about 10cc of mucus is aspirated, instill 20-30cc of sterile water into the tube and quickly withdraw (note do not use saline solution or preservatives) infant feeding water is fine. Reposition the tube and /or the patient to maximize the yield of gastric contents

ii. Place the gastric aspirate in a special bicarbonate- containing gastric aspirate tube or regular specimen cup.

iii. Transport the specimen to the microbiology lab. If a special bicarbonate containing tube or cup is not available, the lab must neutralize the stomach acid with bicarbonate within ½ hour

APPENDIX E: Management of HIV/TB Coinfection

Table E1: Management of HIV/TB Co-Infection

Positive HIV status	ARV of Choice	TB First Phase (Intensive)	TB Second Phase (Continuation)	IPT Prophylaxis **After ruling out Active TB Disease	CPT Prophylaxis	Lab Test needed/ full physical examination done. CD4, C X Ray.
First Month Initial Control and then every two months	Start TB medications before if the patient is not on ARVs **AZT or TDF + 3TC or FTC + EFV**;Nevirapine is an option if EFV cannot be used	HRZE Daily		Isoniazid 300mg daily for 6-9 months/ children 10 mg/kg daily* +modify INH if weight gain (Maximum dosage 300mg)	960 mg daily for adults and for children SMX 20 mg TMP 4mg/kg	At diagnosis C-X -RAY, sputum microscopy, CD4, laboratory for LFT & kidney profile and other see guidelines. Weight , BMI
Second Month	AZT or TDF + 3TC or FTC + EFV; Nevirapine is an option if EFV cannot be used	HRZE Daily		Isoniazid 300mg daily for 6-9 months/children 10mg/kg daily * +modify INH if weight gain (Maximum dosage 300mg)	960 mg daily for adults and for children SMX 20 mg TMP 4mg/kg	At diagnosis C-X -RAY, sputum microscopy, laboratory for LFT & kidney profile and other see guidelines. Weight, BMI
Rest of the months	AZT or TDF + 3TC or FTC + EFV; Nevirapine is an option if EFV cannot be used		HR Daily	Isoniazid 300mg daily for 6-9 months/ children 10mg/kg daily* +modify INH if weight gain (Maximum dosage 300mg)	960 mg daily for adults and for children SMX 20 mg TMP 4mg/kg	
Last Month	AZT or TDF + 3TC or FTC + EFV; Nevirapine is an option if EFV cannot be used		HR DAILY	Isoniazid 300mg daily for 6-9 months/ children 10 mg/kg daily * + modify INH if weight gain (Maximum dosage 300mg)	960 mg daily for adults and for children SMX 20 mg TMP 4mg/kg	C-X-RAY, sputum microscopy, CD4, laboratory for LFT & kidney profile and other see guidelines. Weight, BMI

****Active TB diseases (prolonged cough, weight loss, night sweats, fever)* PPD may not be needed to start IPT if there is no signs and symptoms of TB do C-X-RAY, + modify INH if weight gain**
Remember to start TB medications before if the patient is not on ARVs, evaluate progress and then start ARVs in 2-8 weeks. If already on ARVs continue TB medications and evaluate clinical follow up at your discretion

APPENDIX F: Treatment and Bacterial Monitoring of New and Retreatment Cases

Table F1: Treatment and Bacterial Monitoring of New TB Patients and Retreatment Cases

Duration of treatment 6 months	Anti TB drugs	When to do Sputum test	TB culture/Xpert	DST and culture needed	Seen by physician /physical exam/lab
At diagnosis or as suspected cases	HRZE plus	AFB microscopy	Xpert to all AFB PTB		physician follow up
End of First month	HRZE plus				physician follow up
End of Second Month	HRZE plus	AFB microscopy			physician follow up
Third Month	HR plus *vitamin B6		consider if AFB ++ at	if AFB ++ at 2nd month & culture	physician follow up
Fourth Month	HR plus *vitamin B6				physician follow up
Fifth Month	HR plus *vitamin B6	AFB microscopy	consider if AFB ++ at	if AFB ++ at 5th month &	physician follow up
Sixth Month/Completed Treatment/cured	HR plus *vitamin B6	AFB microscopy			physician follow up

*Optional

APPENDIX G1: Reporting Adverse Drug Reactions due to Anti-Tuberculosis Drugs

Report of a Suspected Adverse Drug Reaction due to Anti-TB Medicines				
Patient Details (to allow linkage with other reports)				
Family Name:	**Clinic/Hospital:**			
Forename(s):				
Date of Birth:		**Weight (kg)**	**Gender:**	
Age:			M/F	
Adverse Reaction				
Date of onset:				
Duration:	Less than one hour	Hours	Weeks	
		Days	Months	
Description:				
Outcome:	Recovered	Fatal	Unknown	
	Not yet recovered			
Suspected Medicine(s)				
Medicine:	Generic Name:			
	Brand Name:			
Indication medicine was given for:				
Daily dose/route:				
Date begun:		Date stopped:		
Concomitant (Other) medicines taken & Dates/period taken:	Name of medicine:	Date started:	Date stopped:	
Laboratory test results				
Reported by				
Family Name:				
Forename(s):				
Status:	Doctor	Pharmacist	Nurse	
Address:				
Signature:		Date:		
Send to:	**National Tuberculosis Coordinator, Ministry of Health, East Block Building, Independence Plaza, Belize**			