

A TUBERCULOSIS REFRESHER COURSE FOR PHYSICIANS

THE WORLD MEDICAL ASSOCIATION
WITH SUPPORT FROM
THE LILLY MDR-TB PARTNERSHIP
AND TECHNICAL ASSISTANCE FROM
THE NEW JERSEY MEDICAL SCHOOL
GLOBAL TUBERCULOSIS INSTITUTE



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The World Medical Association,
with support from the Lilly MDR-TB Partnership and technical assistance from New Jersey Medical School Global Tuberculosis Institute

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A TUBERCULOSIS REFRESHER COURSE FOR PHYSICIANS

This course is intended as a refresher course for physicians (both public and private) that may be involved in the management and care of patients with TB. The audience for the course includes internists, family practice physicians and specialists (pulmonary and infectious disease) in public health as well as in the private sector. Though physicians are the primary audience for this course, nurses and other members of the health care team may also find the information useful.

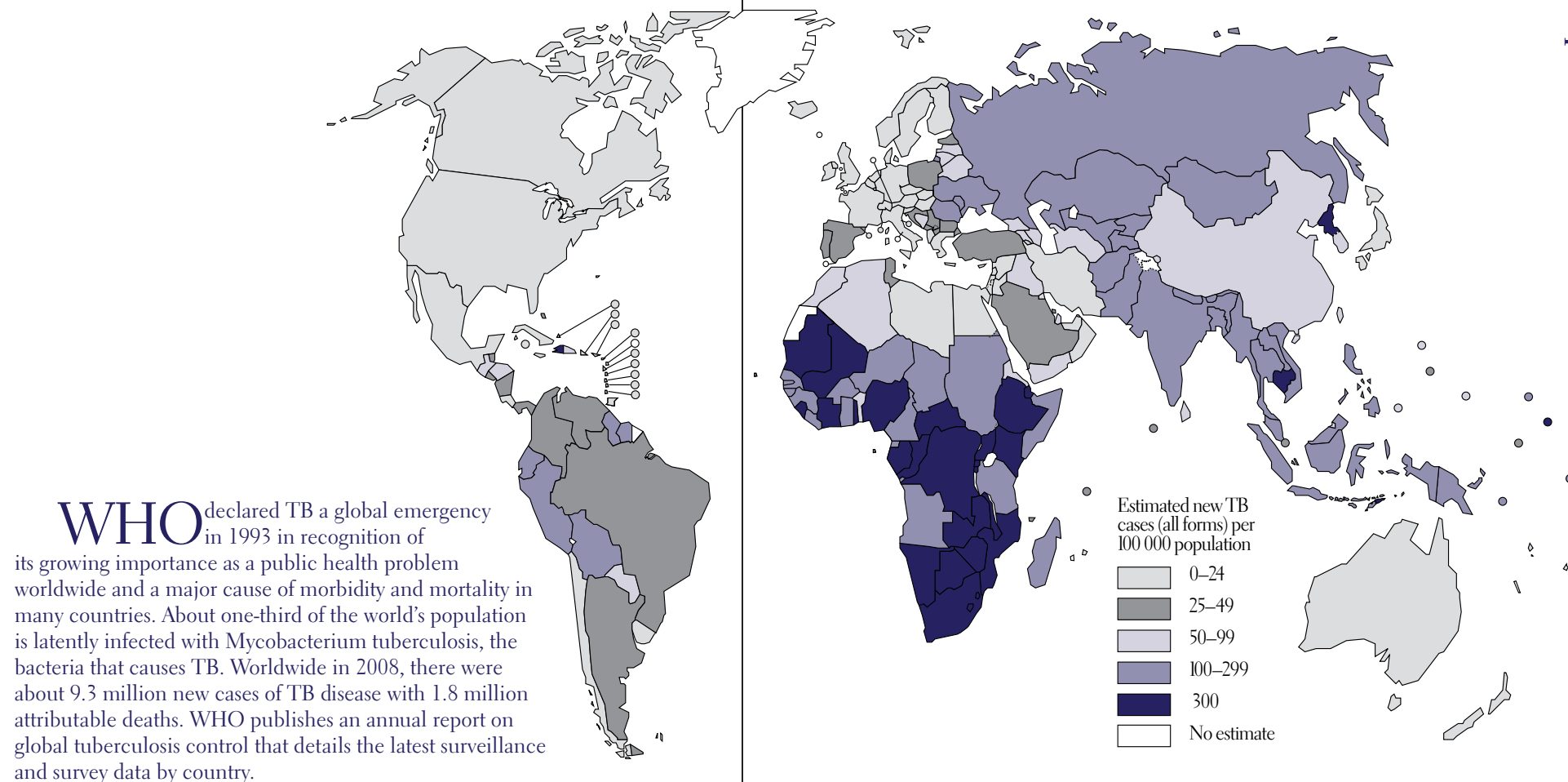
The course is based on the *International Standards for Tuberculosis Care (ISTC)*, which presents a set of widely-accepted, evidence-based standards that all practitioners, public and private, should seek to achieve.

The *ISTC* lays out standards for care and treatment of TB patients that apply to all countries and settings.

The course also refers to and is consistent with the World Health Organization (WHO) Guidelines and recommendations for TB control.

Consistent with the *ISTC*, this course emphasizes general principles and standards and is intended for use in multiple countries and regions. Because this covers a very broad audience geographically and professionally, it would be difficult to create one comprehensive source of information that also provides specific country-level details and guidance for all readers. Therefore, this course is not intended to be a complete source of information on TB, but rather a refresher course, reviewing basic TB management principles and covering a wide array of subjects relevant to physicians, using a didactic approach and incorporating specific learning objectives.

Adequate care for patients with TB is the major determinant of the effectiveness of TB control programs: control cannot be adequate if care is not adequate. For this reason, as well as the concern for the welfare of individual patients, all care providers should be committed to ensuring that TB services in their jurisdictions are of the highest possible quality within the limits of local circumstances. The information compiled in this course is aimed at assisting physicians in delivering high quality, effective care when diagnosing, treating and managing TB patients and thereby reducing the overall burden of TB.



Source: Global tuberculosis control : surveillance, planning, financing: WHO report 2009. World Health Organization, 2009 WHO/HTM/TB/2009.411.

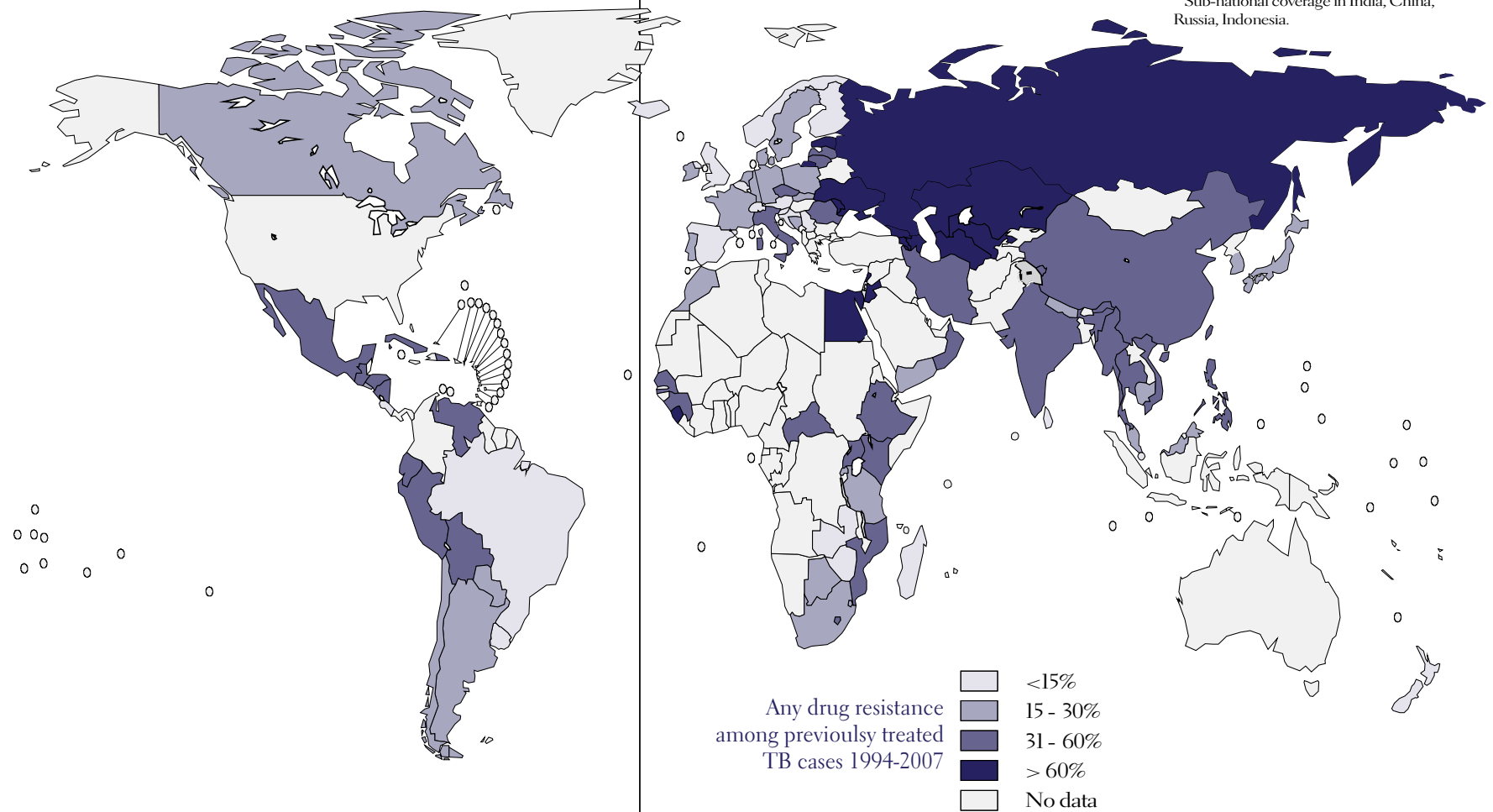
MULTIDRUG-RESISTANT TUBERCULOSIS (MDR-TB)

The emergence of resistance to medications used to treat TB, and particularly MDR-TB has become a significant public health problem in a number of countries and an obstacle to effective global TB control. Multi-drug resistance, defined as resistance to at least rifampicin and isoniazid, the two most effective anti-TB drugs, was found in 77 of 81 countries surveyed in 2002-2007. In many other countries, the extent of drug resistance is unknown. WHO estimates that approximately 500,000 new cases of MDR-TB may emerge every year, with a global prevalence that may be as high as one million cases. Just under 30,000 cases of MDR-TB were notified to WHO in 2007. MDR-TB treatment is less successful than treatment for drug sensitive TB due to the need to use less efficacious, often bacteriostatic, drugs with significant toxicity profiles for long periods of time. The cost of treatment is often prohibitive as well. MDR-TB treatment outcomes have varied greatly depending on the setting and patient characteristics. However, there is evidence to believe that strong, well-managed TB control programs that incorporate the elements of the internationally accepted Stop TB Strategy for TB control can prevent emergence and amplification of drug-resistant TB. For more information on drug resistance epidemiology please consult the report on Anti-Tuberculosis Drug Resistance in the World. More information on MDR-TB is also presented in Section 4 Special Situations.

EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS (XDR-TB)

XDR-TB is defined as resistance to at least rifampicin and isoniazid from among the first-line anti-TB drugs (which is the definition of MDR-TB) as well as resistance to any fluoroquinolone, and to at least one of three injectable second-line anti-TB drugs used in TB treatment (capreomycin, kanamycin, and amikacin). XDR-TB can develop when second-line drugs are misused or mismanaged and therefore also become ineffective. Because XDR-TB is resistant to first- and second-line drugs, treatment options are significantly limited. It is therefore vital that control XDR-TB is managed properly. XDR-TB has emerged worldwide as a threat to public health and TB control, raising concerns of a future epidemic of virtually untreatable TB. New anti-TB drug regimens, better diagnostic tests, and international standards for second-line drug-susceptibility testing are urgently needed for effective detection and treatment of MDR-TB and XDR-TB.

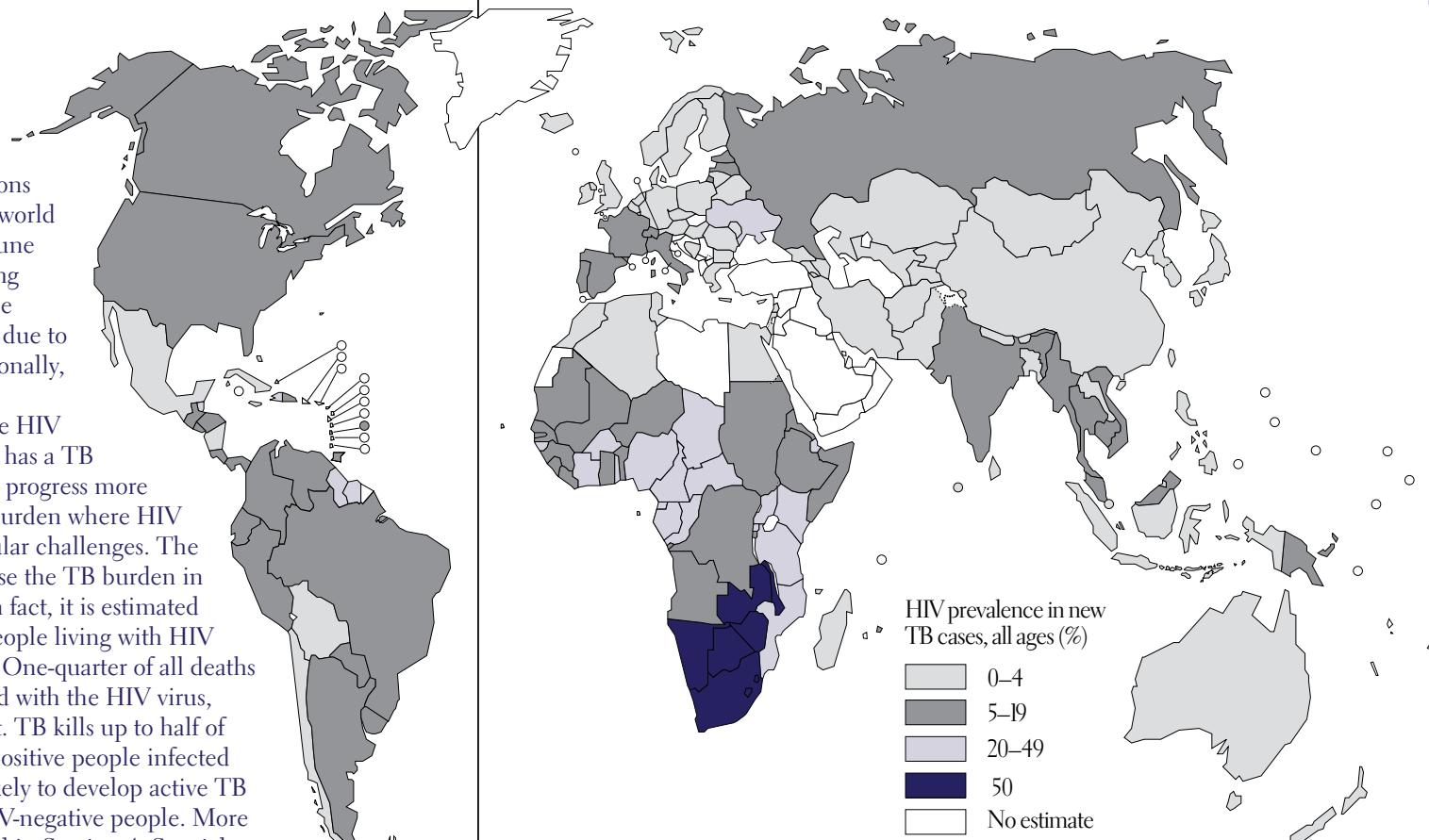
DRUG-RESISTANT



Source: Anti-Tuberculosis Drug Resistance in the World: Fourth Global Report. Geneva, World Health Organization, 2008 WHO/HTM/TB/2008.394

TUBERCULOSIS AND HUMAN IMMUNODEFICIENCY VIRUS (HIV)

TB is the most common cause of death in persons with HIV infection throughout the world and is considered an acquired immune deficiency syndrome (AIDS) defining illness. HIV infection accelerates the development of TB disease ten-fold due to a weakened immune system. Additionally, active TB disease further suppresses the immune system of those who are HIV infected. Therefore, when a patient has a TB and HIV co-infection, both diseases progress more rapidly. Countries with a high TB burden where HIV incidence is increasing have particular challenges. The HIV epidemic is expected to increase the TB burden in many countries across the globe. In fact, it is estimated that one-third of the 33.2 million people living with HIV worldwide are co-infected with TB. One-quarter of all deaths from TB are in patients also infected with the HIV virus, twice as many as previously thought. TB kills up to half of all AIDS patients worldwide. HIV positive people infected with TB are up to 50 times more likely to develop active TB disease in a given year than who HIV-negative people. More information on TB-HIV is presented in Section 4, Special Situations.



Source: Global tuberculosis control: surveillance, planning, financing: WHO report 2009. World Health Organization, 2009 WHO/HTM/TB/2009.411.

THE INTERNATIONAL STANDARDS FOR TUBERCULOSIS CARE, 2ND EDITION (ISTC)*

The ISTC (Annex 1) has been endorsed by more than 40 national and international TB care and control organizations, both public and private. The ISTC are intended to facilitate the effective engagement of all health care providers in delivering high-quality care for all TB patients, including those who are sputum smear-positive, sputum smear-negative, extra pulmonary, drug-resistant, or those with TB/HIV co-infection and other co-morbidities.

Irrespective of the country or setting in which you work, the basic principles of care and management for those with or those suspected of having active TB disease are the same. These include:

- Prompt and accurate diagnosis
- Standardized treatment regimens of proven efficacy with appropriate treatment support and supervision
- Monitored response to treatment
- Implementation of essential public health responsibilities

These actions should be carried out following the national TB guidelines of your country and respecting the recording and reporting requirements. These principles are the key elements in the public health response to TB and are the cornerstone of TB control. The evaluation and treatment of patients with TB involves not only the care of the individual, but the protection of the greater public health needs of the community.

Using the principles of the ISTC, this course provides training material for physicians who would like a brief refresher on a broad set of TB care and management issues. The Patients Charter for Tuberculosis Care, developed in tandem with the ISTC, is also an important document for physicians involved in the management of TB patients. The Charter outlines the rights and responsibilities of people with TB and sets out the ways in which patients, the community, health care providers (both private and public), and governments can work as partners in a positive and open relationship with the goal of improving TB care and enhancing the effectiveness of the healthcare system.

*Tuberculosis Coalition for Technical Assistance. International Standards for Tuberculosis Care (ISTC). The Hague: Tuberculosis Coalition for Technical Assistance, 2nd Edition 2009. (in press)

THE STOP TB STRATEGY

In recognition of the evolving needs and challenges not addressed by the original DOTS strategy, the Stop TB Strategy was developed in 2006 to expand and enhance DOTS and meet existing and new global TB targets. The Stop TB Strategy continues to emphasize the basic components of DOTS while addressing additional constraints and challenges to TB control. Physicians play an integral role in the Stop TB Strategy which has six principal components:

1. Pursue high-quality DOTS expansion and enhancement
2. Address TB/HIV, MDR-TB and the needs of poor and vulnerable people
3. Contribute to health system strengthening based on primary health care
4. Engage all care providers
5. Empower people with TB and communities through partnership
6. Enable and promote research

Physicians continue to be the focal point in the diagnosis and treatment of TB patients with quality-assured bacteriology and standardized treatment at the local level. Diagnosis and treatment of TB/HIV, MDR-TB and XDR-TB are evolving challenges that physicians will face as they are the healthcare professionals who must order and interpret diagnostic tests, make diagnosis and treatment decisions and monitor disease evolution. All physicians are involved in the Stop TB Strategy, regardless of specialty or work in the public or private sector. Physicians provide a vital link to the individuals as well as the communities they serve by participating in TB control activities.

ROLE OF PHYSICIANS IN TUBERCULOSIS CONTROL

Although the role of physicians in TB control may differ from country to country and at different levels of the health care system, there are several common elements, including their connection with the National TB Programme (NTP) and direct contact with patients and communities. Most links between physicians and the TB program exist at the district level. Ideally there should be close collaboration between physicians and the NTP.

Both private and public sector practitioners serve the community and can guarantee their TB patients good care by following national guidelines. Physicians can register TB patients with the NTP and share continued management. While those in the public sector refer patients to the TB program for diagnosis and treatment initiation, private practitioners may undertake diagnosis and treatment but should coordinate care with the NTP and follow national guidelines.

The initial diagnosis of TB frequently relies upon the physician having a high index of suspicion. When a patient presents with signs or symptoms consistent with TB, the physician should examine the patient, take a medical history, and order a chest radiograph and sputum smears if indicated (or refer to a provider who can carry out these steps). The physician may consult or refer to a TB specialist if the diagnosis is unsure. Specific actions depend on the country specific TB guidelines.

Physicians have the unique opportunity to decrease the TB burden through early detection and effective treatment to interrupt further transmission. This is especially important because, according to WHO, a person with active TB, who is undetected and left untreated, will infect an average of 10 to 15 other people per year¹.

HOW TO USE THIS COURSE

This course is designed as a self-study module for physicians. Read through each section and complete the exercises at the end of each section and review any information that you did not understand. You are encouraged to use the references provided in the document to get more detailed information on specific topics. You may also use this course as a quick reference as a printed document.

Since there are variations in policy and guidelines by country, the course cannot reflect country-specific regulations. This course presents general principles of TB control. Just as the *ISTC*, this course is intended to complement, not replace, national, and international guidelines. For specific details about local policies, you should refer to your national TB control guidelines.

ACRONYMS-ABBREVIATIONS

AFB	Acid-Fast Bacilli
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
ART	Antiretroviral Therapy
BCG	Bacille Calmette-Guerin
CDC	US Centers for Disease Control and Prevention
CPT	Co-trimoxazole Preventative Treatment
DOT	Directly Observed Treatment
DOTS	The Basic Package that Underpins the Stop TB Strategy
DRS	Drug Resistance Survey
DST	Drug Susceptibility Test
EPTB	Extrapulmonary TB
EQA	External Quality Assurance
FDC	Fixed-Dose Combination
HEPA	High Efficiency Particulate Air
HIV	Human Immunodeficiency Virus
IPT	Isoniazid Preventive Therapy
IRIS	Immune Reconstitution Inflammatory Syndrome
ISTC	International Standards for Tuberculosis Care
LTBI	Latent TB Infection
MDR-TB	Multidrug-Resistant Tuberculosis
NTP	National TB Program
PCP	Pneumocystis Carinii Pneumonia
PI	Protease Inhibitors
PPD	Protein Purified Derivative
PTB	Pulmonary TB
SLD	Second-Line Drugs
SS	Sputum Smear
TB	Tuberculosis
TST	Tuberculin Skin Test
UNAIDS	Joint United Nations Program on HIV/AIDS
UVGI	Ultraviolet Germicidal Irradiation
WHO	World Health Organization
XDR-TB	Extensively Drug-Resistant TB

ETIOLOGY AND PATHOGENESIS OF TUBERCULOSIS SECTION 1

1

Our understanding of the transmission and pathogenesis of TB has guided us in developing strategies for controlling the spread of TB and for treating TB infection and disease. As a physician detecting and treating TB patients, understanding these concepts is critical so that you can better educate the patients you serve. This section presents a brief overview of the pathogenesis of TB and an overview of the risk factors for developing TB.

SECTION 1

ETIOLOGY AND PATHOGENESIS OF TUBERCULOSIS

LEARNING OBJECTIVES

In this section participants will learn:

- How TB is transmitted
- The differences between primary and post primary TB
- The difference between TB infection and TB disease
- How HIV infection affects the pathogenesis of TB
- Risk factors for the development of TB disease
- How drug resistance develops

1. ETIOLOGY AND TRANSMISSION

TB is an infectious disease caused by bacteria of the *Mycobacterium tuberculosis* complex, of which *M. tuberculosis* is the most common and important agent causing human disease. In 1882, Robert Koch demonstrated that the tubercle bacillus was the true cause of TB, a discovery for which he received the Nobel Prize in 1905. People who are sick with TB in their lungs (pulmonary TB) may be infectious and may transmit TB to others. It only takes a small number of the TB bacilli to infect another person. When a person with untreated infectious pulmonary TB (PTB) coughs, laughs or sneezes, tiny particles containing *M. tuberculosis* are expelled into the air. These particles, about one to five microns in diameter, form droplet nuclei that can remain in the air for several hours, depending on the environment. Transmission of the disease occurs when another person inhales air containing the **droplet nuclei**. This generally occurs indoors, since ventilation removes droplet nuclei from a contaminated space and direct sunlight rapidly kills *M. tuberculosis*.



2. PATHOGENESIS AND CLINICAL MANIFESTATIONS

TB is classified as pulmonary, extrapulmonary or both. Before the advent of HIV infection, approximately 85% of all new cases of TB were limited to the lungs. However, more than half of HIV-infected patients with TB may have both pulmonary and extrapulmonary disease or extrapulmonary disease alone.

2.1. PULMONARY TUBERCULOSIS (PTB)

PTB can be classified as primary or postprimary (secondary).

PRIMARY INFECTION

Primary infection occurs on first exposure to *M. tuberculosis*. Since inhaled droplet nuclei (containing *M. tuberculosis*) are so small, they avoid the mucociliary defenses of the bronchi and lodge in the terminal alveoli of the lungs. Infection begins when the bacilli start replicating in the lungs, forming the pneumonic focus. *M. tuberculosis* replicates slowly but continuously and spreads via the lymphatic system to the hilar lymph nodes. The immune response (delayed hypersensitivity and cellular immunity) develops about 4–6 weeks after the primary infection.

The pneumonic focus and related hilar lymphadenopathy form a primary complex. Bacilli may spread through the blood from the primary complex to other organs in the body of the infected person. The next phase is determined by the strength of the immune response of the infected person. In most people with competent immune systems, the immune response would stop the replication of *M. tuberculosis*, leaving some bacilli dormant. In a few cases, the immune response may not be adequate enough to prevent replication of *M. tuberculosis* and primary TB disease develops within a few months. Although primary TB may be severe and disseminated, it is not generally associated with high-level transmissibility. Reinfection or repeat infection in a person who has already had a primary infection is still considered primary TB.

POST-PRIMARY TB

Post-primary TB may develop several years after the primary infection as a result of reactivation of latent TB infection (LTBI). This may be in response to a trigger, such as weakening of the immune system by HIV infection. The immune response of the patient results in a pathological lesion that is characteristically localized, often with lung tissue destruction and cavitation. TB disease usually affects the lungs (80-85%) but can involve any part of the body. The characteristic features of post-primary PTB are extensive lung destruction with cavitation and positive sputum smears and/or culture. Therefore, this form of TB is often far more infectious than primary TB.

2.2. EXTRAPULMONARY TUBERCULOSIS (EPTB)

In order of frequency, the extrapulmonary sites most commonly involved in TB are the lymph nodes, pleura, genitourinary tract, bones and joints, meninges, peritoneum, and pericardium. However, virtually all organ systems may be affected. As a result of hematogenous dissemination in HIV-infected individuals, EPTB is seen much more commonly today than in the past.

3. BCG VACCINE

BCG (Bacille Calmette-Guerin) is a live attenuated vaccine derived originally from *M. bovis*, a closely related organism to *M. tuberculosis*. The route of injection is intradermal. The usual dose is 0.05 ml in neonates and infants under the age of 3 months, and 0.1 ml in older children. In countries with high TB prevalence, WHO recommends a policy of routine BCG immunization for all neonates except those who are known to be HIV-infected.²

- BCG vaccination should not be given to (i) infants and children with AIDS, (ii) infants and children known to be HIV-infected or (iii) children known to have other immunodeficiencies.
- In situations where infants have been exposed to smear-positive PTB shortly after birth, BCG vaccination should be delayed until completion of six months of Isoniazid preventive therapy (IPT).



The benefit of BCG appears to be that it protects young children against disseminated and severe TB, e.g. TB meningitis and miliary TB. BCG has little or no effect in reducing the number of adult cases of TB. It is important to note that a positive TB skin test in an adult is almost always considered the result of infection and should not be ascribed to residual false positivity effect from the BCG (particularly in countries where TB is endemic), unless the patient has had BCG vaccination as an adult. Therefore, it is important to establish the timing of BCG vaccination in relation to the positive skin test.

4. RISK OF INFECTION

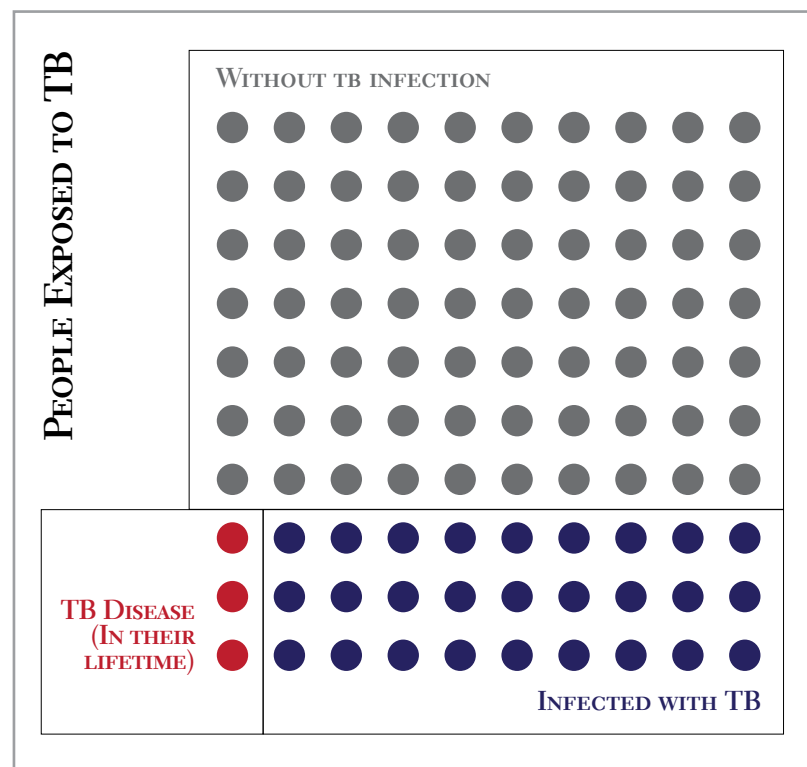
An individual's risk of infection depends on many factors including the concentration of *M. tuberculosis* in the air, the duration of exposure to the air containing droplet nuclei, the bacillary load or infectiousness of the TB patient, the ventilation of the space where exposure occurred and an individual's susceptibility to the infection. Not everyone who is exposed to an infectious TB patient becomes infected with *M. tuberculosis*. Crowding in poorly ventilated rooms is one of the most important factors in transmission of tubercle bacilli, since it increases the intensity of contact with a case within the same household who has untreated sputum smear-positive (SS+) PTB. (See table below) A thorough understanding the risks for infection is essential in contact investigation to detect additional cases of TB.

Factors influencing risk of TB infection	
Exposure	The longer the exposure to infection (longer period of time breathing air shared with someone with infectious TB) the greater the risk.
Air Volume	Exposure in small shared spaces (occupying a small enclosed space with someone with infectious TB) increase the risk of infection.
Ventilation	Lack of or poor ventilation (circulation of air) in the space where exposure occurred increases risk of infection
Bacillary Load of the Infectious Patient	<p>The following factors increase the number of mycobacteria generated by a person with TB</p> <ul style="list-style-type: none"> • Disease of the lungs, upper airways or larynx, • Presence of cough or other forceful expiratory measures (sneezing, singing, etc.), in particular when the patient fails to cover the mouth and nose when coughing or sneezing, • Presence of cavitation and extent of cavitation by chest radiograph, • Absence of or insufficient TB treatment.

Risk of infection is higher in those who are more likely to be exposed to patients with infectious PTB. This includes known contacts of these patients, health care workers, and personnel working in jails or prisons, and people who are members of socially vulnerable groups such as homeless persons or those who use drugs.

5. PROGRESSION OF TUBERCULOSIS INFECTION TO DISEASE

TB infection does not always lead to TB disease. The majority of people infected with *M. tuberculosis* (about 90%) never develop TB disease (provided their immunity is not compromised by HIV infection or other conditions).



TB disease develops when the immune system fails to contain the spread of *M. tuberculosis* and the bacilli begin to multiply rapidly. The risk that TB disease will develop is higher in individuals with a weakened immune system although what triggers reactivation is not well understood.

Although infected persons can develop active TB disease at any time, the risk is highest 1–2 years after a new infection and decreases as time passes. The lifetime risk of developing active TB disease in infected persons with competent immune systems is approximately 10%.

HIV-related decreased immunity is the most significant factor that influences the progression of TB infection to TB disease. A person infected with both HIV and TB has a **5-15% yearly risk** of developing TB disease.

Consider the possible TB risk factors and risk groups as outlined below when examining patients with signs and symptoms suggestive of TB.

RISK GROUPS FOR DEVELOPING TB DISEASE ONCE INFECTED WITH <i>M. TUBERCULOSIS</i>	
	<ul style="list-style-type: none"> • People with HIV infection • People recently infected (within the first 2 years after infection) • People with chest radiograph abnormalities indicating prior TB disease • People who are immunocompromised due to other medical conditions (e.g., persons receiving cytostatics, radiation or corticosteroids, with diabetes mellitus or gastric/duodenal peptic ulcer disease, or other diseases) • People who smoke • People with a decreased body weight (10% or more below ideal body weight) • People with alcohol and/or drug dependency • People belonging to socially vulnerable populations, such as prisoners, unemployed or homeless persons, or those living in extreme poverty

6. DRUG-RESISTANT TUBERCULOSIS

Strains of *M. tuberculosis* resistant to individual drugs arise by spontaneous point mutations in the mycobacterial genome, which occur at low but predictable rates. Because there is no cross-resistance among the commonly used anti-TB drugs, the probability that a strain will be resistant to two drugs is the product of the probabilities of resistance to each drug and thus is low. The development of drug-resistant TB is invariably the result of monotherapy, i.e. the failure of the health care provider to prescribe at least two drugs to which tubercle bacilli are susceptible or the failure of the patient to take properly prescribed therapy. Multiple drugs are always prescribed for TB in order to prevent inadvertent monotherapy and thus protect against development of drug-resistant TB. Drug-resistant TB may be either primary or acquired. Primary resistance occurs when a patient is infected with a drug-resistant strain of *M. tuberculosis*. Acquired resistance develops during treatment with an incomplete or inappropriate regimen.

IN THIS SECTION, YOU HAVE LEARNED THAT...

SECTION 1

- TB is an infectious disease caused by the *Mycobacterium tuberculosis* (*M. tuberculosis*)
- People who are sick with TB in their lungs (PTB) are infectious and can transmit TB to others
- It only takes a small number of the TB bacilli to infect another person. Primary infection occurs on first exposure to *M. tuberculosis*
- Since inhaled droplet nuclei (containing *M. tuberculosis*) are so small, they escape the mucociliary defenses of the bronchi and lodge in the terminal alveoli of the lungs
- Infection begins when the bacilli start replicating in the lungs, forming the pneumonic focus
- Post-primary TB may develop several years after the primary infection as a result of reactivation of a latent TB focus
- An individual's risk of infection depends on many factors including the concentration of *M. tuberculosis* in the air, the duration of exposure to the infected air, the bacillary load or infectiousness of the TB patient, the mechanics of ventilation of the space where exposure occurred and an individual's susceptibility to the infection
- Not everyone who is exposed to an infectious TB patient becomes infected with *M. tuberculosis* and TB infection does not always lead to TB disease
- The majority of people infected with *M. tuberculosis* (about 90%) never develop TB disease (provided their immunity is not compromised by HIV infection or other conditions)
- A person infected with both HIV and TB has a 5-15% yearly risk of developing TB disease

SELF ASSESSMENT QUESTIONS AND EXERCISES: ETIOLOGY AND PATHOGENESIS OF TUBERCULOSIS

1. Which statements describe how TB is transmitted?

Select all that apply.

- a) Close contacts of those with infectious TB are at the highest risk of becoming infected.
- b) *M. tuberculosis* is expelled when a person with latent TB coughs, sneezes, speaks or sings.
- c) TB is spread by droplet nuclei containing tubercle bacilli.
- d) TB is spread by sharing the same eating utensils.

2. Which of the following statements describe primary infection

Select all that apply.

- a) It occurs on first exposure to *M. tuberculosis*
- b) *M. tuberculosis* lodges in the terminal alveoli of the lungs
- c) The immune response develops about 4–6 weeks after the primary infection.
- d) It results in a pathological lesion that is characteristically localized, often with extensive tissue destruction and cavitation

3. In countries with high TB prevalence, BCG Vaccine is recommended for:

- a) all neonates
- b) all neonates except those who are known to be infected with HIV
- c) neonates who are at risk for TB infection
- d) all neonates except those who are at risk for TB infection

4. Complete the following statement.

HIV-related decreased immunity is the _____ factor that influences the progression of TB _____ to TB _____. A person infected with both HIV and TB has a 5-15% _____ risk of developing TB disease..

5. The risk that TB will be transmitted depends on what four factors?

1. _____
2. _____
3. _____
4. _____

6. Which of the following groups are at an increased risk for TB infection progressing to disease?

Select all that apply.

- a) People with HIV infection
- b) People who are immunocompromised due to other medical conditions (e.g., persons receiving cytostatics, radiation or corticosteroids, with diabetes mellitus or gastric/duodenal peptic ulcer disease)
- c) Smokers
- d) People with a decreased body weight (10% or more below ideal body weight)
- e) People with alcohol and/or drug dependency

- 1: a,b,and c
- 2: a,b,c and e
- 3: b
- 4: most important, infection, disease and yearly
- 5: 1. Length of exposure
2. Volume of air
3. Ventilation
4. Bacillary load of the infectious patient
- 6: a,b,c,d and e

ANSWERS



2

Early detection of the most infectious patients (those with SS+ PTB) should be a priority, so that these patients should be treated before spreading the infection to others. Early detection and treatment of these cases also speeds recovery and limits the destruction of the lungs by the TB bacilli. This section will cover the following *ISTC* standards and tasks that all physicians should adhere to:

Identify TB suspects by asking all adults about cough. If an adult has an otherwise unexplained productive cough for 2-3 weeks or more, suspect possible PTB. (Standard 1)

Ensure collection of high quality sputum specimens for microscopy (two samples) as the basic tool for detection of TB and monitoring of treatment. (Standards 2 and 4)

Order (or refer to the appropriate facility for) the necessary diagnostic tests including sputum smears, chest x-rays, M. tuberculosis culture and drug susceptibility testing to correctly diagnose all forms of TB including sputum smear-positive, sputum smear-negative, extrapulmonary, drug-resistant, HIV-associated and pediatric TB. (Standards 3, 5 and 11)

Ensure that in the diagnosis of children with suspected TB, bacteriologic confirmation is sought through examination of sputum for microscopy and culture. In the event of negative bacteriologic results diagnosis should be based on the finding of chest radiographic abnormalities consistent with TB and either a history of exposure to an infectious case or evidence of TB infection (positive tuberculin skin test or interferon gamma release assay). (Standard 6)

Ensure that persons in close contact with patients who have infectious TB are evaluated and managed appropriately and that all close contacts who are children < 5 years of age or persons with HIV infection who have been evaluated for active TB, are treated for presumed LTBI, if active TB is ruled out. (Standards 18 and 19)

Report both new and retreatment TB cases to local public health authorities as dictated by local regulations. (Standard 21)

SECTION 2

DIAGNOSIS OF TUBERCULOSIS

LEARNING OBJECTIVES

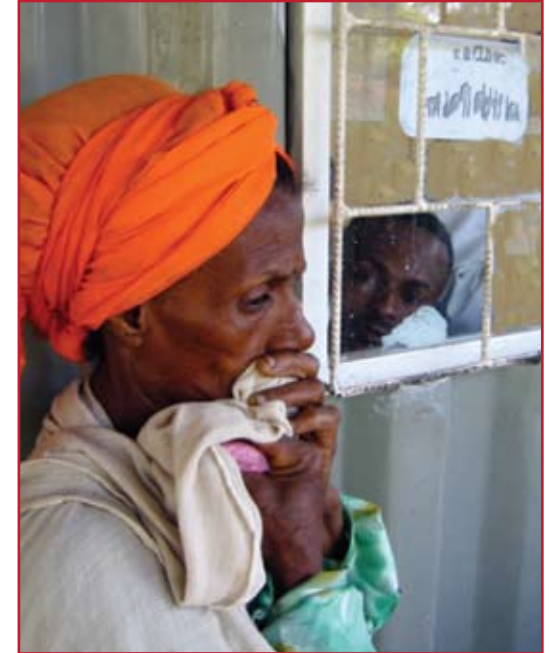
In this section participants will learn:

- How to identify TB and MDR-TB suspects
- How to detect TB in HIV positive patients
- How to detect TB in children
- How to decide which diagnostic exams to order
- About different ways to collect specimens for diagnostic exams
- How to classify a TB case
- How to conduct contact investigations

1. IDENTIFYING TUBERCULOSIS SUSPECTS AMONG SICK PATIENTS COMING FOR CARE

The key to diagnosis of TB is a high index of suspicion. A TB suspect is any person who presents with signs or symptoms suggestive of TB disease, in particular cough of long duration (generally greater than 2 weeks). Other signs or symptoms include hemoptysis (bloody sputum), night sweats, fever, and weight loss. The most appropriate way to detect PTB in a suspect is by sputum smear microscopy.

When a patient (adult or child) comes to you because of prolonged cough, either with or without other signs or symptoms compatible with TB (e.g. hemoptysis), consider the patient a TB suspect. Cough is the most common symptom of PTB and is present in 95% of all sputum smear-positive TB cases. A patient who has a cough should be separated immediately from other patients as a precautionary infection control measure (see section 7 for more details) and have a sputum smear examination to determine whether TB bacilli are present.



1.1. PATIENTS WHO HAVE OTHER SIGNS OR SYMPTOMS OF TB

Other patients may present for diagnosis of illness with signs or symptoms compatible with TB (i.e. night sweats, fever or weight loss) but without cough or sputum production. In this case, the patient is also a TB suspect but sputum examination may not diagnose TB. Chest x-ray examination, culture, biopsy, and clinical assessment will be needed to diagnose these cases as they may be sputum smear-positive or sputum smear-negative and still have active PTB disease and/or have EPTB.

2. CONDUCTING A PRIMARY EVALUATION OF A PATIENT PRESENTING WITH SYMPTOMS SUGGESTIVE OF TB:

1. Obtain an accurate medical history.
2. Complete a physical exam.
3. Ensure (or refer to appropriate services for)
 - Two-three good quality sputum samples for laboratory tests including:
 - * Acid fast bacilli (AFB) microscopy
 - * *M. tuberculosis* culture, if available
 - * Drug susceptibility test (DST), if available
 - Chest X-ray examination
4. Confirm or rule out TB, or refer the patient where a diagnosis can be confirmed or ruled out as required.

3. MEDICAL HISTORY AND PHYSICAL EXAM

Ask TB suspects about their history of TB exposure, infection, or disease. Additionally, contact the TB program or local health department for information about whether a patient has received TB treatment in the past. If the treatment regimen was inadequate or if the patient did not adhere to therapy, TB may recur and may be drug-resistant. Consider other factors or conditions, especially HIV infection, that increase the risk for progression to active TB disease from LTBI or that may increase the patient's risk for developing TB or drug-resistant TB disease. All patients who do not know their current HIV status should be referred for HIV counseling and testing,



especially in areas where HIV is prevalent. A physical examination is an essential part of the evaluation of any patient. It cannot be used to confirm or rule out TB, but it can provide valuable information about the patient's overall condition, including potential sites of EPTB and may contribute information about other factors that may affect TB treatment.

4. DIAGNOSTIC METHODS AND TESTS

4.1. SMEAR MICROSCOPY

M. tuberculosis is classified as an acid-fast bacilli, meaning that once stained, the bacteria cannot be decolorized by acid alcohol. Sputum specimens should be obtained for microscopic examination from all patients suspected of having PTB. Microscopic examination of stained sputum is feasible in nearly all settings. Although microbiological diagnosis is confirmed by culturing *M. tuberculosis* (or, under appropriate circumstances, by identifying specific nucleic acid sequences in a clinical specimen) in many settings neither culture nor rapid amplification methods are currently available or feasible. In such circumstances, the diagnosis of TB may also be confirmed by microscopic examination of the presence of AFB in sputum smear specimens. Repeated sputum smear microscopy may diagnose PTB in up to two-thirds of active cases.



In nearly all clinical circumstances in settings of high TB prevalence, identification of AFB by microscopic examination is highly specific for the *M. tuberculosis* complex. Sputum smear microscopy is the most rapid method for determining whether a person has TB; additionally it identifies people who are the most likely transmitters of infection.

4.2 CULTURE

Positive cultures for *M. tuberculosis* confirm the diagnosis of TB disease. Culture testing is not available in many areas. Although smear microscopy is an effective way to detect TB, bacteriologic culture is the most sensitive method for confirming TB diagnosis. Culture testing is usually performed by specialized bacteriological TB laboratories, often at a regional or national level. Where feasible, cultures should be requested for patients with negative smear results and a strong suspicion of TB, but treatment should not be deferred while waiting for the results.



In nearly all clinical circumstances in settings of high TB prevalence, identification of AFB by microscopic examination is highly specific for the *M. tuberculosis* complex. Sputum smear microscopy is the most rapid method for determining whether a person has TB; additionally it identifies people who are the most likely transmitters of infection.

4.3. DRUG SUSCEPTIBILITY TEST (DST)

To detect if the strain of TB is resistant or not, a culture and a DST must be done. This laboratory procedure determines if the *M. tuberculosis* strain grows in the presence of anti-TB drugs. In general, the initial isolate of *M. tuberculosis* should be tested for susceptibility to isoniazid, rifampicin and ethambutol. If the strain grows, it is said to be resistant to that drug. The sputum must therefore be cultured, and a DST of the isolated *M. tuberculosis* from the culture must be done. To confirm MDR-TB or any

type of drug resistance all patients with suspected MDR-TB must therefore have culture and DST in addition to smear. Conventional DST methods, subsequent to primary culture, can take an additional 4 to 6 weeks. The use of rapid DST methods can substantially reduce this time and should be used when possible.



4.4. NUCLEIC ACID AMPLIFICATION ASSAYS

Several test systems based on amplification of mycobacterial nucleic acid are available. These systems permit the diagnosis of TB in several hours, with high specificity and sensitivity approaching that of culture. These tests are most useful for the rapid confirmation of tuberculosis in persons with AFB-positive specimens but also have a utility for diagnosis of AFB-negative PTB and EPTB.



4.5. LINE PROBE ASSAY

In response to the growing problem of MDR-TB and the threat of an epidemic of virtually incurable XDR-TB, WHO has issued a call for accelerated access to rapid testing for rifampin resistance to improve case detection in all patients with suspected MDR-TB and XDR-TB.

A molecular line probe assay or DNA polymerase-based test can be used directly from sputum in patients with advanced (microscopy-positive) disease and provides results indicating resistance to rifampicin and isoniazid in just one day. This is a tremendous breakthrough, dramatically speeding the detection of drug resistance. Conventional solid culture, which is currently the most common method used to detect drug resistance in developing countries, may take two to three months to produce results.

Rapid diagnosis of MDR-TB has several benefits including earlier treatment of patients which will undoubtedly save more lives by reducing the time spent on inappropriate and ineffective patient treatment. This will reduce the development of further drug resistance and control the spread of MDR-TB.



4.6. CHEST RADIOGRAPHY

Chest radiography is a sensitive but nonspecific test to detect TB. Radiographic examination of the thorax or other suspected sites of involvement may be useful to identify persons for further evaluation, especially among HIV positive suspects. However, a TB diagnosis cannot be established by radiography alone as the chest X-ray will reveal abnormalities of the lungs that may be due to a disease process other than TB. Reliance on the chest radiograph as the only diagnostic test for TB may result in both over-diagnosis and under-diagnosis of TB.³

4.7. TUBERCULIN SKIN TEST

TSTs are mostly used as a diagnostic tool in detecting LTBI in children. Tuberculin is a purified protein derivative (PPD) of tubercle bacilli. A person infected with *M. tuberculosis* develops hypersensitivity to tuberculin, which, when injected into the skin of an infected person, produces a delayed local reaction after 48 hours. This reaction is quantified by measuring the diameter of skin induration (thickening not reddening) at the site of the injection. Various conditions can suppress this reaction (see next page). The reaction only shows that the person has at some time been infected with *M. tuberculosis*. **A TST does not measure immunity and by itself, it does not indicate the presence or extent of TB disease.**



Based on the sensitivity and specificity of the PPD tuberculin skin test and the prevalence of TB in different groups, the Centers for Disease Control and Prevention (CDC) in the United States has established a sliding cut point based on risk of progression to TB disease. People who are more likely to progress to active disease have lower cut point than those less likely to progress to active disease. People more likely to progress include persons with HIV infection, those who are receiving immunosuppressive therapy, who have had recent close contact with persons with infectious TB, children, or those who have abnormal chest radiographs consistent with prior TB)

CONDITIONS THAT MAY SUPPRESS THE TUBERCULIN SKIN TEST

- HIV infection
- Malnutrition
- Severe bacterial infections, including TB itself
- Viral infections, e.g. measles, chickenpox, glandular fever
- Cancer
- Immunosuppressive drugs, e.g. steroids
- Incorrect injection of PPD

4.8. INTERFERON GAMMA RELEASING ASSAYS (IGRAs)

Recently, two in-vitro assays that measure interferon release in response to TB specific antigens have become commercially available. These are QuantiFERON-TB Gold In-Tube® and T-SPOT.TB®. IGRAs are more specific than the TST due to lack of cross-reactivity from BCG vaccination and sensitization by non-tuberculous mycobacteria. IGRAs appear to be at least as sensitive as TST for active TB and have shown better correlation than the TST with exposure to *M. tuberculosis* when used in contact investigations in low incidence settings.

4.9. SEROLOGIC AND OTHER DIAGNOSTIC TESTS FOR ACTIVE TB

A number of serologic tests are based on detection of antibodies to a variety of mycobacterial antigens. Careful independent assessments suggest that they are not useful as diagnostic aids, especially in persons with low probability of TB. Various methods aimed at detection of mycobacterial antigens in diagnostic specimens are being investigated but are limited at present by low sensitivity.

5. COLLECTING SPUTUM FOR SMEAR EXAMINATION

All individuals who are capable of producing sputum and are suspected of having PTB should have two sputum specimens obtained for microscopic examination (two samples identify about 95% of the smear-positive cases). Previously, WHO guidelines recommended that three samples be obtained, but this has been changed to two quality assured samples, one of which should be collected in the early morning to increase AFB load. Collect sputum specimens from each TB suspect as described below and send to the laboratory. If the laboratory is easily accessible, you may send the TB suspect directly to the laboratory to produce the sample.

Some patients may be very ill and need immediate care. The first sputum sample should be collected when the person is identified as a TB suspect. Treatment of a very ill person should not be delayed to obtain a laboratory diagnosis.

5.1. SPUTUM COLLECTION PROCEDURES

Follow your NTP guidelines for sputum collection. General guidelines and a schedule can be found below.

If patients are asked to provide sputum specimens for TB diagnosis on-site, they should always do so in an adequately ventilated booth or outside in the open air and away from other people, avoiding small rooms such as toilets or other enclosed areas.

Patients should be coached and directly supervised when sputum is collected. Unsupervised patients are seldom successful in providing an adequate specimen, especially the first time. See Annex 2 on how to coach a patient to produce a good sputum sample.

General guidelines and schedule for sputum collection:

1. Sample one is collected “on the spot.” Explain why the sputum is needed and show the TB suspect how to cough up sputum. The TB suspect should go outdoors or to a well-ventilated place to collect the sample, to reduce the risk of exposure to others. If possible, observe and guide the TB suspect during sample collection. Give the TB suspect another labeled container to take home and use the next morning.
2. Sample two is collected by the TB suspect upon awaking the next morning. The TB suspect should bring this second sample to the health care facility.
3. Specimens should consist of good quality sputum (not saliva) in order to be useful for sputum smear microscopy. Good quality sputum:
 - Is frequently thick and mucoid
 - May be fluid with chunks of dead tissue
 - May range in color from opaque white to green (bloody specimens will be reddish brown)



6. OTHER SPUTUM COLLECTION METHODS

SPUTUM INDUCTION can be used for patients unable to cough up sputum. Deep coughing may be induced by inhalation of an aerosol of warm, sterile, hypertonic saline (3%-15%). Because induced sputum is very watery and resembles saliva, it should be labeled “induced” to ensure that the laboratory staff workers do not discard it. Patients should have fasted for 3-4 hours prior to the procedure to prevent vomiting and aspiration. Induction should be carried out in a well-ventilated place and all personnel in the room should use an N95 respirator.

GASTRIC ASPIRATION is performed by inserting a tube through the patient’s nose and introducing it into the stomach. The procedure is usually performed in the morning as the patient tends to swallow sputum during the night. Generally, it is performed only when a sample cannot be obtained through expectoration or induction. Most often, it is used to obtain samples from children although children who can produce sputum should go through sputum induction. It is recommended that children should not have had food intake in the past 2-3 hours. For logistic reasons gastric aspiration is usually carried out in a hospital setting or in a procedure room that has the necessary materials.

FIBEROPTIC BRONCHOSCOPY WITH BRONCHO-ALVEOLAR LAVAGE is done for the collection of bronchial secretions by aspiration, through the fiberoptic bronchoscope. These samples are usually diluted or watery and should be labeled as “bronchoscopy specimens” to avoid rejection at the laboratory. Bronchoscopy should be carried out in a procedure room with appropriate infection control measures. It is usually used as a final measure when sputum is very difficult to collect and is not available in all settings. Post-bronchoscopy sputum collection on the next three days is often very productive. Bronchoscopy should not replace sputum collection in a TB suspect.

7. CASE DETECTION OF TUBERCULOSIS AND HIV

In HIV-prevalent populations, cough alone is not sensitive enough to detect TB among HIV-positive persons. HIV increases the rate of recurrence of TB, both reactivation of latent TB and newly acquired infection. HIV is responsible for a large increase in the proportion of patients with smear-negative PTB and EPTB. These patients have inferior treatment outcomes,

including excessive early mortality, compared with HIV-positive, smear-positive PTB patients. Tackling this problem requires rapid diagnosis of SS- PTB and EPTB in settings with high HIV prevalence. For this reason it is particularly important to have a high index of suspicion for TB in an HIV-positive person who has any of the signs or symptoms compatible with TB. Diagnosis of TB in people living with HIV/AIDS also requires adjustment in diagnostic criteria and indications for treatment.

7.1. PULMONARY TUBERCULOSIS SUSPECTS:

When you see adults living with HIV/AIDS and those considered to be at high risk of HIV infection on clinical and epidemiological grounds and TB signs or symptoms, collect sputum. Offer a HIV test to those with unknown HIV status. If the smear examination is negative, the patient should be provided with all available investigations during a second visit including repeated sputum smear, culture, chest x-ray and clinical evaluation. The exam results should be available soon after (except for culture) and a decision should be made based on the exams to determine if the patient should receive treatment for TB, or receive a broad spectrum antibiotic (not a fluoroquinolone alone) for bacterial infection or *Pneumocystis carinii* pneumonia (PCP). Fluoroquinolones, particularly the newer ones, possess good bactericidal activity against *M. tuberculosis*, making them attractive agents for the treatment of PTB but consequently may also result in induction of drug-resistant organisms. Therefore, they should not be used for treatment of non-TB organisms due to the risk of developing resistance. The patient’s response to this treatment should be monitored. PCP may occur in patients with underlying TB and patients should, therefore, be re-evaluated for TB, particularly if respiratory symptoms persist after treatment. See Annex 3 for a description of guidelines for diagnosing PTB in HIV+ patients.



7.2. EXTRAPULMONARY TUBERCULOSIS SUSPECTS:

Since approximately 20% of TB cases are extrapulmonary, and it is the cause of many HIV-related TB deaths, it is important to promptly diagnosis and manage these patients. The most common forms of EPTB disease include lymph node TB (especially in the neck or under the arms), pleural (usually one-sided pleural effusion) and disseminated TB (disease that is not limited to one site in the body). With the exception of lymph node TB, which can usually be confirmed through aspiration of affected lymph nodes, most patients with extrapulmonary TB are often managed without bacteriological or histological confirmation. See Annex 4 for a description of clinical characteristics to assist in diagnosing EPTB suspects.

These clinical algorithms are explained in the TB/HIV recommendations for improving the diagnosis and treatment of smear-negative PTB and EPTB among adults and adolescents.

Furthermore, because unrecognized MDR-TB is associated with such high mortality in these patients with HIV, if possible perform culture and DST on the first sputum collected for all TB-HIV co-infected patients and monitor treatment response closely.

8. MDR-TB SUSPECTS

Drug resistance cannot be diagnosed with smear microscopy alone. This is because a positive smear of drug-resistant TB appears the same as a positive smear of drug-susceptible TB as they are caused by the same organism. To detect if the strain of TB is resistant or not, a culture and DST must be done. This laboratory procedure determines if the *M. tuberculosis* strain grows or does not grow in the presence of specific anti-TB drugs. If the strain grows, despite the presence of an anti-TB drug, it is said to be resistant to that drug.

All patients with suspected MDR-TB must therefore have culture and DST in addition to smear in order to confidently diagnose MDR-TB (or any type of drug resistance) so that an appropriate treatment regimen can be initiated.

Ideally, all TB suspects should receive smear, culture and DST. However, given the limited resources available in most countries, this is not always possible. To more efficiently diagnose those patients who have MDR-TB, WHO has compiled a list of possible high-risk groups for MDR-TB through program reviews, drug resistance surveys and peer-reviewed

articles. This document is available in the Guidelines for the programmatic management of drug-resistant tuberculosis. You should identify patients belonging to the specific groups that have been designated by your country. To detect cases of resistance early, check for MDR-TB risk factors in all TB patients or persons who present with symptoms suggestive of TB. Refer all patients who are found to be in a risk group for MDR-TB to a specialized MDR-TB center for diagnosis and treatment. If a specialized MDR-TB center is not accessible, consult with the local TB control officials regarding patient referral and case management.

8.1 RISK GROUPS FOR MDR-TB

Patients that fall into one or more of these categories should be considered as at risk for MDR-TB and a culture and DST should be performed. They should be referred to a specialized facility immediately for evaluation and possible treatment.

MDR-TB suspects *may* include:

- Failures of retreatment regimens
- Failures of new patient regimens (Category I)
- Failures of TB treatment in the private sector
- Relapses and defaulters who are smear-positive at month 3 of retreatment
- Symptomatic contacts of a known MDR-TB case

They also may include (depending on national guidelines):

- Patients with HIV
- Patients who remain AFB sputum smear-positive at month 3 of new patient treatment
- Patients who have exposure in institutions that have MDR-TB outbreaks or live in a high MDR-TB prevalence setting such as a prison
- Patients who live in areas with high MDR-TB prevalence
- Patients with a history of using TB drugs of poor or unknown quality
- Patients receiving treatment in programs that operate poorly (especially recent and/or frequent drug stock-outs)
- Co-morbid conditions associated with mal-absorption or rapid-transit diarrheas

9. PEDIATRIC DIAGNOSIS

Children can present with TB at any age, but the most common age is between 0–4 years. If any of these signs or symptoms is present, suspect possible TB and follow the recommendations in Section 4 or refer to a specialist. Children with TB commonly have paucibacillary disease (low number of organisms) without evident lung cavitation but with involvement of intrathoracic lymph nodes. Consequently, compared with adults, sputum smears from children are more likely to be negative and children are far less likely to be infectious. Therefore, culture of sputum or other specimens, radiographic examination of the chest, and tests to detect TB infection are of greater importance in diagnosis of pediatric TB. Because many children less than 5 years of age do not cough and produce sputum effectively, culture of gastric washings obtained by naso-gastric tube lavage or induced sputum have a higher yield than spontaneous sputum. Thus, these methods should be utilized to obtain sputum for both smear and culture examination, if sputum is not produced through coughing or expectoration. See the table on the following page for an approach to the diagnosis of TB in children recommended by the Integrated Management of Childhood Illness (IMCI) program of the WHO.



DIAGNOSIS OF TUBERCULOSIS IN CHILDREN

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

Consider TB in any child with:

A history of:

- Unexplained weight loss or failure to grow normally
- Unexplained fever, especially when it continues for more than two weeks
- Chronic cough
- Exposure to an adult with probable or definite pulmonary infectious TB

Abnormal physical findings on examination:

- Fluid in the chest (reduced air entry, dullness to percussion)
- Enlarged non-tender lymph nodes or a lymph node abscess, especially in the neck
- Signs of meningitis, especially when these develop over several days and the spinal fluid contains mostly lymphocytes and elevated protein
- Abdominal swelling, with or without palpable lumps
- Progressive swelling or deformity in the bone or a joint, including the spine

10. CASE REPORTING

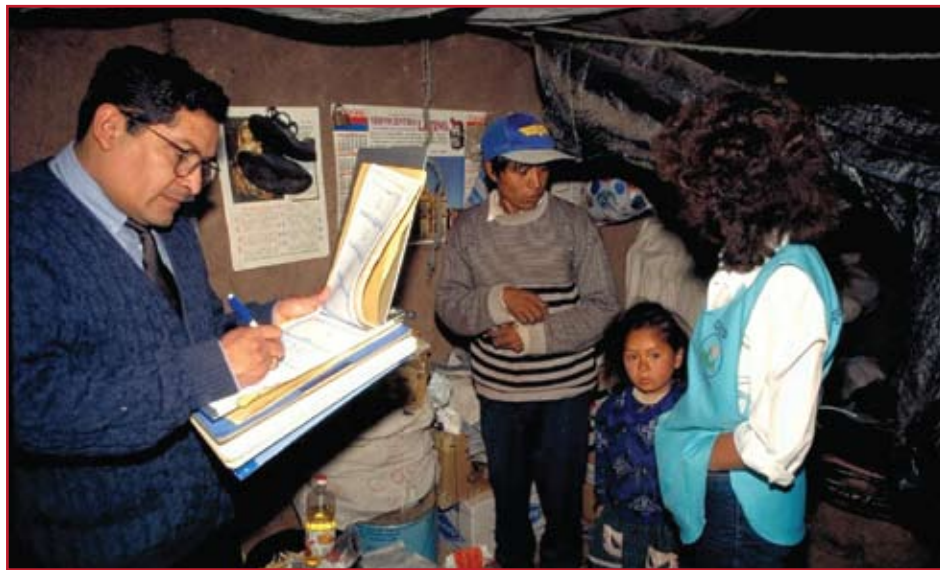
In most countries, TB is a notifiable disease and a physician must report a TB patient under their care to the local TB control program. Case reporting is part of a larger community responsibility and public health function. Case reporting is also part of the proper functioning of an effective TB control program and the case reporting system permits the program to determine resource needs, measure effectiveness of TB control strategy, and properly track the disease within the population as a whole, not just the population served by the national TB program. The physician plays an integral part in this system as part of the Stop TB Strategy by reporting cases and outcomes. Appropriate recording and reporting further permits targeted, individualized



follow-up to help patients who are not progressing as planned, and also helps the evaluation of practitioners' performance. Follow your country's standards and forms for reporting and referring TB cases to improve the overall success of TB control program as well improving the public health of the community in which you work and live.

11. CONTACT INVESTIGATIONS

Once patients are diagnosed with TB, contact investigation should be conducted to find other patients who may have been infected or have active TB disease and need treatment. A household contact is a person who lives in the home of a TB patient and who is therefore at greater risk of becoming infected and developing TB. Every SS+ PTB patient should be interviewed to elicit the names of all contacts in the household. (Some countries ask that smear-negative PTB and EPTB cases to also list household contacts.) The source of infection of most children is an infectious adult in their household. When children present with active TB disease their family members and other close contacts should be investigated for TB to find the source of the disease and treat them as necessary.



The TB patient should be asked to bring in for assessment all contacts age 5 and older with cough, and every child less than 5 years of age living in the household. In some areas health workers are expected to visit the home to assess all children age less than 5 years of age. When household contacts (adults and children aged 5 years or more) come to the health facility, follow the usual procedures to evaluate TB suspects:

- Ask whether the individual has a cough and, if yes, ask about the duration of cough
- Collect 2 sputum samples for sputum examination if the cough has persisted for at least 2 weeks
- Use results of sputum examination, symptom review, and (if applicable) chest x-ray to determine whether the TB suspect has PTB
- Examine all children aged less than 5 years of age identified as household contacts for chronic signs or symptoms suggestive of TB:
- Prolonged cough or other respiratory symptoms
- Fever for more than 14 days (after common causes such as malaria or pneumonia have been excluded)
- Abnormal chest x-ray (nodal enlargement)
- Loss of weight or failure to gain weight (failure to thrive)

Infected persons without disease who are at high risk of developing TB may benefit from treatment of the infection (also known as prophylaxis, preventive therapy, treatment of LTBI, or IPT). These include children who are household contacts of infectious index cases of pan-sensitive TB and HIV infected individuals. WHO and the Joint United Nations Program on HIV/AIDS (UNAIDS) recommend IPT for children under 5 and all HIV-infected individuals who do not have active TB disease. *Note that preventive therapy with isoniazid can be given only to persons who do not have active TB disease, and BCG immunization is not useful for persons already infected or ill with TB*

12. TARGET GROUPS FOR ISONIAZID PREVENTIVE THERAPY

A course of preventive treatment with daily isoniazid (5–10 mg/kg up to 300mg) for at least six and up to nine months is effective in preventing progression of LTBI to active disease. Young children are at special risk, especially if they are HIV-infected. HIV infection, in children and in adults, increases the risk of progression to active TB once latently infected by up to 50 times in a given year.

12.1. INFANTS OF MOTHERS WITH PTB

A breastfeeding infant has a high risk of infection from a mother with PTB, and a high risk of progression to active TB disease once latently infected. The infant should receive six months of isoniazid treatment, followed by BCG immunization.

12.2. CHILDREN UNDER 5 YEARS OF AGE

It is important to screen children who are household contacts of adults with sputum smear-positive PTB. Screening identifies those children less than 5 years of age without symptoms who have been infected. These children should receive 6-9 months of IPT. Children under 5 years of age with symptoms need to be medically evaluated for TB. If the evaluation reveals TB disease, the child should receive anti-TB treatment. If the evaluation does not indicate TB disease, but the child is infected, the child should receive IPT.

12.3. HIV-INFECTED INDIVIDUALS

Controlled clinical studies have shown that IPT reduces the risk of TB disease in HIV-positive individuals also infected with *M. tuberculosis*. The evidence of *M. tuberculosis* infection is a positive TST. In HIV-positive individuals, an additional benefit to IPT of a reduced risk of TB may be a reduced rate of progression of HIV infection.

Prevention and treatment of TB in people living with HIV is an urgent priority for both HIV/AIDS and TB programs. The WHO approach known as the Three I's, IPT, intensified case finding for active TB, and TB Infection Control, incorporates key public health strategies to decrease the impact of TB on people living with HIV.

- TB preventive therapy with isoniazid is safe and effective in people living with HIV, reducing the risk of TB by 33–62%
- Screening and diagnosing TB in people living with HIV can be challenging but TB is curable in people living with HIV
- TB infection control is essential to keep vulnerable patients, health care workers and their community safe from getting TB

Persons with HIV infection who, after careful evaluation, do not have active tuberculosis should be treated for presumed latent tuberculosis infection with isoniazid prevention therapy (IPT).

IN THIS SECTION, YOU HAVE LEARNED THAT...

SECTION 2

- A TB suspect is any person who presents with signs or symptoms suggestive of TB, in particular a cough of long duration
- Other symptoms that are consistent with TB are hemoptysis, night sweats, fever and/or weight loss
- The most appropriate way to detect pulmonary TB is by sputum smear microscopy
- A physical examination is also an essential part of the evaluation of any patient. It cannot be used to confirm or rule out TB, but it can provide valuable information about the patient's overall condition and other factors that may affect how TB is treated
- Smear microscopy provides the basic diagnostic tool for TB
- Culture can confirm *M. tuberculosis* and DST is used for certain groups of TB suspects who are considered high risk for MDR-TB
- New diagnostics such as the line probe assay are being developed that will dramatically reduce the time needed to diagnose MDR-TB
- One or more positive smear exams are sufficient to diagnose a case and patients will be categorized according to the disease site, bacteriology, history of previously treated TB and severity of disease
- Once a patient is confirmed to have TB, the proper case reporting must be done and a contact investigation should be carried out primarily looking for children under 5 and adults with TB symptoms for further testing and possible preventive treatment

SELF ASSESSMENT QUESTIONS AND EXERCISES: DIAGNOSIS OF TUBERCULOSIS

1. Which of the following statements are true about sputum collection?

- a) Patients should be coached and directly supervised when sputum is collected.
- b) Sputum should be collected as soon as possible in an area that guarantees the privacy of the patient such as a bathroom or closet.
- c) Sample one is collected “on the spot” And sample two the following morning
- d) A sputum sample may be induced if the person is unable to produce one by coughing.

2. Which of the following *confirms* a microbiological diagnosis of TB?

- a) Chest radiograph
- b) Detection of acid-fast bacilli in smear examination
- c) Positive tuberculin skin test
- d) Positive culture of *M. tuberculosis*

3. Which diagnostic test is needed to confirm a diagnosis of MDR-TB?

4. For each of the following patients, write down which tests, if any, should be conducted and why.

PATIENT 1

JK a 27 year old street vendor in a country with a high prevalence of TB has presented with cough, fever, weight loss, and fatigue. He says he began coughing 6 weeks ago but needs to work to support his family and could not be troubled to come in until now.

PATIENT 2

RM is a 35 year old woman with no other medical conditions and no risk factors for HIV. She is married to a patient who recently began treatment for MDR-TB. She presents with headaches and is very worried that she may be ill with the same disease. The physical exam is normal and she reports no additional symptoms.

PATIENT 3

A 25 year old mother brings in her one year old child, LM, reporting that the baby has a cough, has not been eating well, and has not seemed to be growing or gaining weight over the last few months. The mother also reports that she herself has had cough and fever for the last several months.

PATIENT 4

HT is a 40 year old male who presents with poor physical condition. He said he was being treated for TB but the drugs didn't seem to do him much good. He said he has been on treatment for 4 or 5 months and said that his doctor told him he still had TB in his lungs and that he must not be taking the drugs. HT tells you he took his drugs most of the time, and that there was no one supervising his treatment.

PATIENT 5

KL is a 52 year old male long distance truck driver who presents with severe

weight loss, cough, fever, chills, and loss of appetite. He works in an area with a high prevalence of HIV and reports that he does not use a condom when he engages in sex with his multiple partners.

PATIENT 6

TM is 23 year old female with a swelling of right side of her neck, which is draining purulent fluid, She reports the swelling began approximately 3 months ago, and the draining began last week.

PATIENT 7

LE a 42 year old male presents to your clinic complaining of weight loss, night sweats and diarrhea; when questioned he says he does not have a cough. He is unable to produce sputum. He reports that his father, who lives with him has recently been diagnosed with TB.

ANSWERS

- 1: a,c and d
- 2: d
- 3: A Drug Susceptibility Test (DST)
- 4:

PATIENT 1

In this case you would take the patients medical history (as the index of suspicion would be higher if he had a history of exposure to person with infectious TB disease) and assess for other risk factors for TB, perform a physical exam, collect sputum for a AFB smear, request a chest x-ray, and request culture and DST if available.

PATIENT 2

Treat headache with analgesics, and try to alleviate her concerns regarding TB. Since TB is unlikely to manifest with headache as the primary symptom you would not order any tests for TB at this point, but ask her to return if symptoms worsen.

PATIENT 3

Perform a complete physical exam of the child including X-ray. Since it is very difficult to collect sputum from a child, and the mother appears sick as well, perform a physical exam, X-ray and collect sputum for AFB smear examination on the mother as well. If the mother has TB, because of the strong epidemiological link, the infant has a high probability to have TB disease as well.

PATIENT 4

In any case of TB disease, obtaining a history of previous treatment for TB is an important component of the initial evaluation. Based on his reported history and self-administered therapy, there is a possibility of drug resistance in this patient. At this point you would collect sputum for AFB smear examination and take a chest x-ray and send his sputum for culture and DST if available.

PATIENT 5

Based on his reported history and symptoms you would order an HIV test and collect sputum for AFB smear examination as well as a chest X-ray if available.

PATIENT 6

Since the differential diagnosis for this patient includes lymphoma in addition to TB you would perform appropriate tests for those conditions as well as AFB smear microscopy of the fluid draining from her lymph node. Biopsy and culture should also be performed if available. Your index of suspicion for TB would depend on any risk factors she may have, including exposure to a person with active pulmonary TB.

PATIENT 7

You would take a medical history, do a physical exam, and take a chest x-ray to assess if there are any abnormalities consistent with TB disease. If available in your setting, sputum induction may also help in the diagnosis.



3

Treatment for TB is not only a matter of individual health; it is also a matter of public health. All providers, public and private, who undertake to treat a patient with TB, must have the knowledge to prescribe an appropriate standard treatment regimen as well as the means to assess adherence to the regimen and to address poor adherence in order to ensure that treatment is completed. This section will cover the following tasks that all physicians should perform and related *ISTC* standards:

Identify the disease site and type of patient (new, default, previously treated, treatment failure) and the treatment course, consistent with internationally accepted treatment regimens, that should be provided to the patient. (Standard 8)

Conduct a thorough assessment for co-morbid conditions that can affect TB treatment response or outcome. (Standard 17)

Monitor progress of TB patient's treatment through follow up care and sputum examinations (Standard 10)

Complete the patient's TB Treatment Card with all medications given, bacteriologic response, and adverse reactions. (Standard 13)

Report both new and previously treated TB cases and their treatment outcomes to local public health authorities, in conformance with applicable legal requirements and policies. (Standard 21)

SECTION 3

TREATMENT OF PATIENTS WITH TUBERCULOSIS

LEARNING OBJECTIVES

In this section participants will learn:

- How to classify a patient and choose the appropriate treatment
- How to prepare a patient's TB Treatment Card, including specifying the treatment regimen and dose
- How to recognize and manage medication side-effects
- How to determine when a patient is due for follow-up sputum examination
- How to determine treatment outcome

1. CLASSIFICATION OF TUBERCULOSIS CASES AND REFERRAL

Once a patient has been diagnosed with TB, the patient is classified based the following determinants:

1. Site of disease
2. Bacteriology
3. History of previously treated TB
4. HIV status

1.1. SITE OF DISEASE

As noted before, there are two main categories of TB, pulmonary and extrapulmonary. Recommended treatment regimens are similar irrespective of site. The importance of identifying disease site is primarily for recording and reporting purposes and assessing the infectiousness of the patient. According to WHO definitions:



- **PTB** refers to disease involving the lung parenchyma. Therefore tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs constitutes a case of EPTB. A patient with both pulmonary and extrapulmonary TB should be classified as a case of pulmonary TB.

- **EPTB** refers to TB of organs other than the lungs, (e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, and meninges). The definition of an EPTB case with several sites affected depends on the site representing the most severe form of the disease.

1.2. BACTERIOLOGY

“Smear-positive” or “smear-negative” is the most useful bacteriological classification of pulmonary cases because it correlates with infectiousness.

PTB, sputum smear-positive (PTB+) is defined as one or more initial sputum smear examinations positive for AFB by microscopy. Note that the definition of a new sputum smear-positive pulmonary TB case is based on the presence of at least one AFB in at least one sputum sample in countries with a well functioning external quality assurance (EQA) system.

PTB, sputum smear-negative (PTB-) is defined as a case of pulmonary TB that does not meet the above definition for smear-positive TB.

Note: In keeping with good clinical and public health practices, diagnostic criteria for PTB- should include all four of the following:

1. At least two sputum specimens negative for AFB,
2. Radiographic abnormalities consistent with active PTB,
3. No response to a course of broad-spectrum antibiotics,
4. Decision by a clinician to treat with a full course of anti-TB chemotherapy.

This group includes patients whose sputum smears are negative but whose culture(s) are positive.

EPTB is defined as a patient with TB affecting organs other than the lungs. Diagnosis should be based on one culture-positive specimen, or histological or strong clinical evidence consistent with active EPTB, followed by a decision by a clinician to treat with a full course of anti-TB chemotherapy.

1.3. HISTORY OF PREVIOUSLY TREATED TB

It is critical to determine whether a patient has previously been treated for TB. Previously treated patients may have acquired drug resistance and need a different treatment regimen from new patients, and may require further testing for drug resistance. See Section 4 on MDR-TB.

DEFINITIONS OF TYPE OF PATIENT	
Type of patient	Definition
New	A patient who has never had treatment for TB or who has taken anti-TB drugs for less than one month
Relapse	A patient previously treated for TB who has been declared cured or treatment completed, and is diagnosed with bacteriologically positive (smear or culture) TB
Treatment after failure	A patient who is started on a re-treatment regimen after having failed previous treatment
Treatment after default	A patient who returns to treatment and has positive bacteriology, following interruption of treatment for two months or more
Transfer in	A patient who has been transferred from another TB register to continue treatment
Other	All cases that do not fit the above definitions. This group includes patients who are SS+ at the end of a re-treatment regimen (previously defined as chronic cases) and who may be resistant to the first-line drugs.

1.4. HIV STATUS

Determining and recording the patient's HIV status is critical for treatment decisions (see the treatment regimen section and Section 4), as well as monitoring. WHO's revised TB Treatment Card (see Annex 6) and TB Register includes dates of HIV testing, starting co-trimoxazole therapy (CPT), and starting anti-retroviral therapy (ART).

2. STANDARDIZED TREATMENT REGIMENS

The World Health Organization's Stop TB Department has recently published the *fourth edition of Treatment of tuberculosis: guidelines for national programmes* using the new WHO process for evidence-based guidelines. The information on recommended treatment regimens provided in the following sections quotes directly from these guidelines but it is advisable that physicians carefully review the new guidelines to gain a complete understanding of the evidence supporting each regimen recommendation.

Most TB patients will receive one of the standardized regimens for anti-TB treatment recommended by WHO. All these regimens are comprised of some combination of five essential medicines designated as “first-line anti-TB drugs”: isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E) and streptomycin (S). For patients with documented drug resistance, second-line drugs (SLD) will be used. See the section on MDR-TB treatment later in this section for information about SLD use and consult Annex 5 for MDR-TB drug information.

These standardized regimens allow for provision of effective treatment and prevent the development of MDR-TB if treatment is taken as prescribed and drugs are of assured quality.

3. FIXED DOSE COMBINATIONS (FDCs)

WHO recommends the use of FDCs for the treatment of TB patients. Several advantages of FDCs over individual medicines (or single-drug formulations) have been identified:

- Prescription errors are likely to be less frequent
- Fewer tablets need to be ingested, which may encourage adherence to treatment
- Patients cannot select only certain medicines to take (when treatment is not observed)

4. DRUG CODE FOR TB TREATMENT REGIMENS

TB treatment regimens are described using a standard code where each anti-TB drug has an abbreviation. Those abbreviations are:

(H) Isoniazid
(R) Rifampicin
(Z) Pyrazinamide
(E) Ethambutol
(S) Streptomycin

The code shows the 2 phases of the regimen, separated by a slash. The letters correspond to the drugs to take during the phase.

This continuation phase is of 4 months' duration.

Example one: A common regimen is written:

2(HRZE)/4(HR)₃

A subscript number after a letter is the number of doses of that drug per week. Frequency of treatment with the combination HR tablet should be 3 times per week.

The number before the letters is the duration of the phase in months. This initial phase is 2 months.

When 2 or more drugs (letters) appear in parentheses, this indicates a FDC for those drugs.

If there is no subscript number after a letter, frequency of treatment with that drug is daily. These initial-phase drugs should be taken daily.

The above regimen uses FDCs. For both phases FDCs are used. This regimen is one of the regimens used to treat pan-sensitive disease.

5. CHOOSE A PROPER TREATMENT REGIMEN

TB patients will be classified based on the site of disease, bacteriology results, history of previous treatment for TB, and the patient's HIV status. **Select the proper treatment regimen for the patient based on the previous treatment history. There are three basic TB regimens to use for TB patients:**

New patient regimen: the 6 month rifampicin-containing regimen* for new patients with **low** likelihood of MDR-TB.

Retreatment regimen: the 8 month retreatment regimen of first-line drugs for patients with **medium** likelihood of MDR-TB, such as patients returning after relapse or default. (Countries with access to rapid DST will not need this regimen.)

MDR-TB regimen: a regimen for patients with **high** likelihood of MDR-TB, such as patients whose prior treatment has failed. (Countries with access to rapid DST will initiate treatment with this regimen once MDR-TB is confirmed, but may later tailor the regimen based on the individual patient's DST to additional drugs beyond isoniazid and rifampicin).

* WHO no longer recommends omission of ethambutol during the intensive phase of treatment for patients with non-cavitary, smear-negative pulmonary TB or extrapulmonary disease who are known to be HIV-negative.

All treatment regimens for tuberculosis consist of two different phases of taking special combinations of drugs. During the first two months, called the **initial or intensive phase**, a patient classified as a **new** case of TB will take 4 drugs: HREZ for pan-sensitive TB. The initial phase is used to rapidly kill *M. tuberculosis* bacilli, prevent selection of resistant *M. tuberculosis* and stop infectiousness. Directly observed therapy (DOT), a health worker watching as the patient swallows anti-TB drugs, is crucial to ensure that the TB patient takes every prescribed dose of medicine. DOT is discussed more fully below.

During the following 4–6 months, called the **continuation phase**, the patient classified as a new case will take two drugs, either daily or intermittently (three times per week, but only by DOT) for pan-sensitive disease. The regimen recommended for each patient depends on the diagnostic category for that patient. This phase serves to kill the remaining *M. tuberculosis* bacilli and sterilizes the lesion. Since the patient may be feeling better and become impatient of a long treatment process, it is more difficult to ensure proper treatment adherence during this phase. This phase should also be directly observed to ensure the patient completes the full regimen.

5.1. NEW TB PATIENT REGIMEN

STANDARD REGIMENS FOR NEW TB PATIENTS	
PRESUMED (OR KNOWN) TO HAVE DRUG SUSCEPTIBLE TB	
Intensive phase treatment	Continuation phase
2 months of HRZE	4 months of HR

Note that new patients should receive a regimen containing 6 months of rifampicin. Ethambutol *should not be excluded* during the intensive phase of treatment for patients with non-cavitary, smear-negative pulmonary TB or extrapulmonary disease who are known to be HIV-negative.

DOSING FREQUENCY FOR NEW TB PATIENTS		
Dosing Frequency		Comment
a) Daily	Daily	Optimal
b) Daily	3 times per week	Acceptable alternative for any new TB patient receiving directly observed therapy
c) 3 times per week	3 times per week	Acceptable alternative as long as the patient is receiving directly observed therapy and is NOT living with HIV or living in an HIV-prevalent setting

Note: Daily (rather than three times weekly) intensive phase dosing may help prevent acquired drug resistance in TB patients starting treatment with isoniazid resistance.

Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy. If this is not feasible, then new patients with pulmonary TB may receive a daily intensive phase followed by three times weekly continuation phase as long as each dose is directly observed. Three times weekly dosing throughout therapy is another alternative, as long as the patient is receiving directly observed therapy of every dose, and is NOT living with HIV or living in an HIV-prevalent setting.

IN SETTINGS WITH HIGH LEVELS OF ISONIAZID RESISTANCE IN NEW PATIENTS

When new patients start out treatment with isoniazid resistant TB, outcomes are worse than for isoniazid-susceptible TB, even with the 6 month rifampicin regimen. In populations with known or suspected high levels of isoniazid resistance, new TB patients may receive HRE as therapy in the continuation phase as an acceptable alternative to HR.*

STANDARD REGIMENS FOR NEW TB PATIENTS	
IN SETTINGS WHERE THE LEVEL OF ISONIAZID RESISTANCE AMONG NEW TB CASES IS HIGH	
AND ISONIAZID SUSCEPTIBILITY TESTING IS NOT DONE (OR RESULTS ARE NOT AVAILABLE) BEFORE THE CONTINUATION PHASE BEGINS	
Intensive phase treatment	Continuation phase
2 months of HRZE	4 months of HRE

* The most effective regimen for the treatment of isoniazid resistant TB is not known. There is inadequate evidence to quantify the ability of ethambutol to “protect rifampicin” in patients with pre-treatment isoniazid resistance. See the WHO Treatment Guidelines for further guidance.

Dosing schedules for new TB patients in settings with high level of isoniazid resistance are the same as for all other new TB patients. See table on preceding page.

5.2. PREVIOUSLY TREATED TB PATIENTS

The *Global Plan to Stop TB 2006-2015* sets a target that by 2015, all previously treated patients should have access to DST at the beginning of treatment. By using DST results, appropriate treatment can be ensured for these patients. For all previously treated TB patients obtain a specimen for culture and drug susceptibility testing (DST) for at least isoniazid and rifampicin before or at the start of treatment.

The approach to the initiation of retreatment depends on available laboratory capacity, specifically when (or if) DST results are routinely available for the individual patient.

- Rapid DST methods will provide results within hours or days, and you can use the results to decide which regimen to start for the individual patient
- Conventional methods will provide results within weeks (if using liquid media) or months (if using solid media). Because of this delay in receiving DST results, if conventional DST is used, the patient will need to start a regimen while awaiting results of DST. This regimen will depend on the patient's risk for MDR-TB as defined by drug resistance surveys and other national data
- If no DST is available, refer the patient to a MDR-TB treatment facility

These three scenarios along with the risk of the patient for MDR-TB will guide your treatment decision. If rapid methods are available treatment should be based on the DST results.

If conventional DST is available then patients will begin a retreatment regimen or a MDR-TB regimen depending on their risk for MDR-TB (based on drug resistance survey (DRS) data and country guidelines).

If there are no DST capabilities available then a retreatment regimen should be used and a standardized MDR-TB regimen should only be used in very high risk individuals. See the table below for more detail.

STANDARD REGIMENS FOR PREVIOUSLY TREATED PATIENTS, DEPENDING ON THE AVAILABILITY OF ROUTINE DRUG SUSCEPTIBILITY TESTING (DST) TO GUIDE THE THERAPY OF INDIVIDUAL RETREATMENT PATIENTS		
	MDR likelihood (Patient Registration group--see first note below)	
DST routinely available for previously treated patients	High (Failure [*])	Medium or low (Relapse, default)
Rapid molecular-based method	DST results confirm or exclude MDR to guide the choice of regimen	
Conventional method	While awaiting DST results:	
	Empiric MDR regimen	2 HRZES / HRZE / 5 HRE
	May modify regimen once DST results are available	
None (interim)	Empiric MDR regimen (only when DST can confirm MDR in patients enrolled in the MDR programme). May modify regimen once DST results are available	2 HRZES / HRZE / 5 HRE for full course of treatment

Although the regimens in the table above are the internationally accepted standards of treatment, different countries may have different treatment guidelines. Follow your national guidelines on TB treatment for both children and adults.

^{*} And other patients in groups with high levels of MDR. One example is patients who develop active TB after known contact with a patient documented to have MDR-TB. Patients who are relapsing or returning after defaulting from their second or subsequent course of treatment probably also have a high likelihood of MDR.



6. DIRECTLY OBSERVED TREATMENT

DOT is a vital element of TB control and, by promoting adherence to TB treatment, reduces the risk of amplified drug resistance, treatment failure, relapse and poor outcomes. During DOT administration of medications, a health care worker watches the patient swallow his or her anti-TB drugs, ensuring that the patient is taking the drugs correctly. DOT:

- **Can be administered** in hospitals, or outpatient settings
- **Can be observed** by physicians, nurses or trained community supporters. Generally DOT by a family member is not recommended due to the complex interpersonal family relationships that may affect acceptance or adherence, however it may be deemed appropriate in certain circumstances
- **May include** incentives and enablers (such as food or transportation) for the adherent patient and/or the health care worker who supervises treatment. This can increase motivation for both the patient and the supervisor



7. ROLE OF PHYSICIANS IN TUBERCULOSIS TREATMENT MONITORING

All physicians treating TB, whether a physician works in the public or private sector should follow the country specific NTP guidelines to ensure the best results. Report **both new and retreatment TB cases and their treatment outcomes to local public health authorities, in conformance with applicable legal requirements and policies**. Patients can be referred directly to the TB program or treated in conjunction with the program if they are having difficulty completing treatment. Coordination with the NTP will lead to better case management services for the patient and improved treatment outcomes.

A physician participating in the supervision of treatment and monitoring of TB patients should:

- **Fill in the Patient Treatment Card** (Annex 6), each time treatment is observed (Patient treatment card originates in the NTP)
- **Stay in regular contact** with the appropriate physician in the NTP to advise of any problems and take action
- **Verify that** drugs from TB services are received on time to ensure that drugs are available to complete the full course of treatment without interruption. (Anti-TB drugs, like most medications, should be stored in a cool dry place, tightly sealed, and kept away from sunlight and heat)
- **Discuss** importance of adherence with the patient. Further information on improving adherence can be found in Section 5, Adherence to Treatment

Good recording practices are necessary for effective patient management. The TB recording and reporting system is part of the health information management system of the country. It consists of detailed patient forms that are filled out at the point of care and summarized in laboratory and medical registers. These data are aggregated to prepare quarterly reports on activities and results as well as annual management reports at the basic management unit for TB usually the district level TB department, and then sent to the central level. The recording (patient registration) and reporting system is used to systematically evaluate patient progress and treatment outcomes, as well as to monitor overall programme performance (through cohort analysis).

8. TREATMENT MONITORING

Regular monitoring is necessary to determine the progress and outcome of all TB treatment, and ensure that the patient completes an effective course of treatment with prompt treatment of any adverse effects. Monitoring treatment is one of the most important elements of an effective TB control programme and vital on an individual level for all patients. Treatment monitoring can help assess:

- **Whether** a patient is becoming more or less infectious
- **How** a patient is progressing clinically
- **Whether** a patient is experiencing adverse effects of anti-TB drugs
- **When** treatment is complete
- **What** is the treatment outcome

8.1. SCHEDULE OF FOLLOW-UP TESTS

For new patient treatment regimens, collect sputum for follow-up examination at the end of the initial phase, just before the patient completes five months of treatment, and in the last week of treatment. This will vary by treatment regimen. Other regimens will have different collection times.

- For a **new** patient, do follow-up sputum examinations at the end of two, five and six months
- For a **retreatment** patient, do follow-up sputum examinations at the end of three, five and eight months
- For MDR-TB patients, the schedule varies according to the test:
 - * **Smear:** Monthly until treatment is completed
 - * **Culture:** Monthly during the intensive phase and every two months during the continuation phase and anytime when the monthly smears are positive
 - * **DST:** Every 4 months while culture-positive (if using individualized treatment regimen)
 - * **Chest x-ray:** Every 6 months
 - * **Blood tests:** As requested by physician during control visits. Test are recommended every 6 months for patients younger than 50 years; every 3 months for patients 50 years and older

For all patients with **negative sputum before treatment**, sputum should be collected as noted but major indicators of response to therapy are the chest radiograph and the clinical evaluation.

8.2. TREATMENT DECISIONS

A presumptive diagnosis can be made if radiographic improvement is noted, generally by the time two months of treatment has been completed. If the radiograph does not improve after the patient has received three months of treatment, the abnormality may be the result of either previous (not current) TB or other lung pathologies that may need further evaluation.

If a patient still has a positive sputum smear at the end of the initial phase, this may indicate one of the following:

- The initial phase of treatment was poorly supervised and drugs were not taken correctly or on schedule
- There is a slow rate of progress with sputum smear conversion, for example, if a patient had widespread destruction of lung tissue and an initial heavy bacillary load, or if there is a problem with drug absorption
- There may be a laboratory error or the patient may have drug-resistant TB that does not respond to first-line treatment

Patients who do not convert their sputum smear from positive to negative at the end of the initial phase of treatment should receive an additional month of initial-phase drugs. Ensure that there have not been problems or gaps with provision of DOT. Where treatment for MDR-TB is available, patients who do not sputum convert should receive DST and clinical evolution should be closely monitored.

A patient whose sputum smear or culture is positive at 5 months or later during treatment, is considered a treatment failure. In this case:

- Stop the current drug regimen. The treatment outcome for this patient is “Treatment Failure” which should be recorded on the patient’s Treatment Card and reported to the TB Program
- If DST has not been requested previously, request a DST now
- Start the patient on a full course of the re-treatment regimen (follow national guidelines)

Treatment failure for non MDR-TB cases should be rare with DOT in countries with low levels of drug resistance.

9. ADVERSE EFFECTS



Typical rash caused by anti-TB drugs

A minority of patients (0.7-14%) on TB treatment using first-line drugs experience adverse effects.⁴ When SLDs are used for treatment of drug-resistant TB, these numbers increase. Evaluate patients monthly to identify possible adverse reactions to medications and to assess adherence. Maintain contact with the DOT provider to ensure that any adverse event is reported and handled in a timely manner. It is not generally necessary to monitor liver or renal function or platelet count for patients being treated with first-line drugs unless there are abnormalities at baseline or there are clinical reasons to obtain them.

Inadequate management of adverse effects is likely to contribute to irregular treatment and default. The table on the following page provides guidance on a symptom-based approach to monitoring anti-TB drugs, and the correct clinical response to side effects. Adverse effects can be classified as minor or major and in most instances should be treated as follows:

Minor adverse effects: Note the problem in the patient's record (preferably on the Treatment Card). Provide encouragement to the patient and treat as needed with ancillary medicines. Generally there is no need to discontinue TB treatment as the effects usually go away and interrupting TB treatment is more harmful.

Major adverse effects: Identify and discontinue use of causal agent and treat adverse reaction. Consult with and refer the patient to specialized hospital services if needed.

SYMPTOM-BASED APPROACH TO MANAGING SIDE-EFFECTS OF ANTI-TB DRUGS		
Side-effects	Drug(s) probably responsible	Management
Major		Stop responsible drug(s) and refer to clinician urgently
Skin rash with or without itching	S, H, R, Z	Stop anti-tuberculosis drugs
Deafness (no wax on otoscopy)	S	Stop streptomycin
Dizziness (vertigo and nystagmus)	S	Stop streptomycin
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)	E	Stop ethambutol
Shock, purpura, acute renal failure	R	Stop rifampicin
Decreased urine output	S	Stop streptomycin
Minor		Continue anti-tuberculosis drugs, check drug doses
Anorexia, nausea, abdominal pain	Z, R, H	Give drugs with small meals or just before bedtime, and advise patient to swallow pills slowly with small sips of water. If symptoms persist or worsen, or there is protracted vomiting or signs of bleeding, consider the side effect to be major and refer to clinician urgently.
Joint pains	Z	Aspirin or non steroidal anti-inflammatory drug, or paracetamol
Burning, numbness or tingling sensation in the hands or feet	H	Pyridoxine 50-75 mg daily
Drowsiness	H	Reassurance. Give drugs before bedtime
Orange/red urine	R	Reassurance. Patients should be told when starting treatment that this may happen and is normal
Flu syndrome (fever, chills, malaise, headache, bone pain)	Intermittent dosing of R	Change from intermittent to daily rifampicin administration

Key for drug abbreviations: H isoniazid, R rifampicin, Z pyrazinamide, E ethambutol, S streptomycin

9.1. HEPATITIS

Three of the first-line anti-TB drugs, H, R and Z can cause drug-induced liver injury (Aspartate Aminotransferase (AST) > 3 times upper limit of normal in the presence of symptoms, or > 5 times upper limit of normal in the absence of symptoms). If the AST and Alanine Aminotransferase (ALT) are < 5 times the upper limit of normal, toxicity can be considered mild. An AST or ALT of 5-10 times normal defines moderate toxicity, and > 10 times normal is severe. When the levels noted above are reached, stop all drugs until biochemical abnormalities are stabilized, then reintroduce drugs one at a time. The drugs should be reintroduced starting with the one that is least likely to be the causative agent, and if there is no change, the next least likely causative agent should be reintroduced (reintroduce R first, then E, and finally I). If the biochemical abnormalities have not recurred then the final drug has been identified as the causative agent and should not be reintroduced.

In addition to elevation of the AST and ALT, occasionally there are disproportionate increases in bilirubin and alkaline phosphatase. This pattern is more consistent with rifampin hepatotoxicity.

9.2. SKIN RASH

If a patient develops itching and there is no other obvious cause (e.g. scabies), the recommended approach is to try symptomatic treatment with antihistamines, reassure the patient and advice to avoid dry skin, continue TB treatment and observe the patient closely. However, if a symptomatic (i.e. itching or painful) skin rash develops, all anti-TB drugs must be stopped. Once the reaction has resolved, anti-TB drugs may be reintroduced. Reintroducing TB treatment can be challenging when the particular TB drug responsible for the reaction is not known. Generally, you should first introduce the most effective drug that is least likely to cause the rash. Generally the order of reintroduction is H, R, Z. You should wait for several days to assess the patient's reaction before re-introducing the next drug.

9.3. SIDE EFFECTS AMONG MDR-TB PATIENTS

Due to the toxicity of the MDR-TB drugs, these patients generally experience more side effects than patients receiving treatment for drug-susceptible TB. Management of these patients should be performed in consultation with a MDR-TB expert. See the section on MDR-TB for more information.

10. OUTCOME DETERMINATION

The treatment regimen is completed when the patient has taken the correct number of doses of the continuation-phase drugs. If the patient has missed some doses along the way, the duration of the treatment is extended until all the doses are taken. Outcome definitions are determined by the NTP but generally adhere to WHO's standard definitions. The table below gives definitions of the six possible treatment outcomes for patients receiving new patient or retreatment regimens.

TREATMENT OUTCOME DEFINITIONS FOR NEW AND RETREATMENT REGIMENS	
Treatment outcome	Definition
Cure	Sputum smear-positive patient who is sputum smear-negative in the last month of treatment and on at least one previous occasion
Treatment completed	Patient who has completed treatment but who does not meet the criteria to be classified as a cure or a failure
Treatment failure	Patient who is sputum smear-positive at 5 months or later during treatment *
Died	Patient who dies for any reason during the course of treatment
Default	Patient whose treatment was interrupted for 2 consecutive months or more
Transfer out	Patient who has been transferred to another recording and reporting unit and for whom the treatment outcome is not known

* Also sputum smear-negative patients who become sputum smear-positive at 2 months.

Record all outcomes on the patient's TB Treatment Card and notify the TB program of the result.

Please note that the treatment outcome definitions above for patients with drug sensitive TB are different than the treatment outcome definitions for MDR-TB regimens. Treatment outcomes for patients with MDR-TB can be found in Annex 7

SECTION 3 IN THIS SECTION, YOU HAVE LEARNED THAT...

- How to identify the disease site and type of patient (new, default, relapse, treatment after failure) and the treatment course that should be provided to the patient according to disease classification
- DOT is a vital element of TB control and the prevention of MDR-TB
- During DOT, a health care worker watches the patient swallow his or her anti-TB drugs, ensuring that the patient is taking the drugs correctly
- Regular monitoring is necessary to determine the progress and outcome of all TB treatment, and ensure that the patient completes the entire course of TB treatment with prompt ancillary treatment of any adverse effects
- In general, sputum is collected for follow-up examination at the end of the initial phase, just before the patient completes 5 months of treatment, and in the last week of treatment. This will vary by treatment regimen
- A minority of TB patients (0.7–14%) treated with regimens using first-line drugs experience adverse effects.⁵ As regimens use second-line drugs for treatment of drug-resistant TB, these numbers increase
- Patients should have clinical evaluations at least monthly to identify possible adverse reactions to medications and to assess adherence
- Record all outcomes on the patient's TB Treatment Card and notify the TB program of the result
- Management of MDR-TB patients should be performed in consultation with a MDR-TB expert

SELF ASSESSMENT QUESTIONS AND EXERCISES: TREATMENT OF PATIENTS WITH TUBERCULOSIS

1. Regimen Selection

The first exercise will be deciding the appropriate treatment regimen based on the type of patient and bacteriology results as follows.

PATIENT 1

JK a 27 year old street vendor
Smear results: First Smear + Second Smear +++
Diagnosis: New case of pulmonary TB

PATIENT 3

LM, a one year old child and 24 year old mother:
Infant X-ray: Reveals miliary TB
Mothers smear results: First Smear ++ Second Smear ++

PATIENT 4

HT is a 40 year old male in poor physical condition had been on self-administered TB treatment for 4-5 months
Smear results: First Smear ++ Second Smear ++
Diagnosis: Pulmonary TB

PATIENT 5

KL is a 52 year old long distance truck driver who presents with complaints of weight loss, cough, fever, chills, and loss of appetite:
Test Results: HIV positive and First Smear ++ Second Smear ++

PATIENT 6

TM is a 23 year old female with swelling of right side of neck, draining purulent fluid.
Test results: Lymphatic node biopsy is AFB smear and culture positive for *M. tuberculosis*.
Diagnosis: New case of lymphatic TB

2. Adverse Effects

In this exercise read the cases below and decide what course of action you will take for each patient with adverse effect.

PATIENT 1

JK a 27 year old street vendor who is smear-positive and classified as a new case of pulmonary TB. He returns after 3 weeks of initiation of treatment with complaints of itchy rash all over his body.

PATIENT 5

KL is a 52 year old HIV positive truck driver with pulmonary TB on TB treatment. During his 2nd month of treat he develops abdominal pain, vomiting, and jaundice.

3. Treatment Monitoring

In this exercise read the cases below and decide what to do with each patient based on their case information and bacteriological results.

PATIENT 1

JK a 27 year old street vendor
After 4 months the patient does not smear convert despite being given DOT. Later he mentions being scared since his wife died of resistant TB. It is found that she was treated with a MDR-TB regimen but died 1 month into treatment. He did not disclose the history of his wife at prior encounters.

PATIENT 4

HT is a 40 year old male in poor physical condition who had been on self-administered TB treatment for five months without smear conversion. Two months after restarting his TB regimen under DOT, the patient is sputum smear-negative, has gained 10 kilos and is no longer coughing.

4. Treatment Outcomes

In this exercise read the cases below and decide what treatment outcome each patient should have based on their case information and bacteriological results.

PATIENT 1

JK a 27 year old street vendor whose smear did not convert after 4 months on new patient treatment.

PATIENT 3

LM is a one year old child with cough and failure to thrive diagnosed with miliary TB. After completing new patient treatment, the X ray appears normal, and the child has begun to grow normally and exhibits no other symptoms.

PATIENT 4

HT is a 40 year old male. He initially presented in poor physical condition, however his smear converted during the intensive phase of treatment and all further AFB sputum smears have been negative. He has completed the continuation phase of treatment for a total treatment length of 6 months. He continues to gain weight and is asymptomatic.

PATIENT 5

KL a 52 year old HIV positive truck driver had been on TB Treatment for two months. He did not return for his last follow-up appointment 2 months ago and his DOT worker has not been able to locate him.

PATIENT 6

TM a 23 year old female with lymphatic TB has completed 9 months of treatment, the lymph node swelling is greatly reduced and the drainage diminishes and eventually heals. You believe that her TB is cured.

ANSWERS

1: Regimen Selection

PATIENT 1

This patient would be treated with a new patient regimen of 2(HRZE)/4(HR)

PATIENT 3

Treat both patients using a new patient regimen of 2(HRZE)/4(HR)

PATIENT 4

HT is a Treatment failure on the new patient regimen. Treat him using the regimen for previously treated patients (2HRZES/5HRE). Request DST if available.

PATIENT 5

Start patient on a new patient regimen. Assess HIV status in preparation for commencing anti-retroviral therapy (if available).

PATIENT 6

This patient would be classified as new. Treat her with 2(HRZE)/4(HR) (In some cases of TB lymphadenitis therapy may need to be extended beyond the standard 6 months due to persistence or recurrence of adenopathy).

2: Adverse Effects

PATIENT 1

Stop JK's medications until the rash goes away – re-introduce the drugs one at time, waiting three days to introduce each new drug, starting with drugs least likely to cause rash, generally R, I, E, and PZA.

PATIENT 5

Consider possible hepatotoxicity from INH, PZA or RIF. Evaluate liver function. Hold all medications and rule out viral hepatitis. Once liver function improves re-challenge (waiting 3 days for before adding an additional drug) starting with Rifampin and Ethambutol combined. Then add INH and lastly PZA. If symptoms recur after adding a specific drug, this points to this particular drug as the offending agent and the drug would need to be discontinued. Consultation with a TB specialist would be advisable.

3: Treatment Monitoring

PATIENT 1

Do DST on JK. If wife was on MDR-TB treatment, her DST results should be available from the TB Programme. In consultation with an MDR-TB expert, treat JK empirically using a regimen for MDR-TB based on her resistance patterns until his DST results come back. DOT must be provided.

PATIENT 4

The patient should be started on the continuation phase of treatment of 4HR, but maintained on DOT based on his history of inconsistent treatment.

4: Treatment Outcomes

PATIENT 1

JK would be classified as a treatment failure and would begin treatment, under the care of an MDR-TB specialist.

PATIENT 3

LM would be classified as treatment complete since sputum was never available and no AFB results were ever obtained.

PATIENT 4

This patient's treatment outcome is cure.

PATIENT 5

KL would be classified as a treatment default.

PATIENT 6

The patient's outcome in this case would be treatment complete, based on the physician's decision.



4

Although the majority of TB cases diagnosed can be treated using a standardized regimen that is effective, there are a number of special situations that must be handled with great care. This section will outline the management of patients with TB and HIV, pediatric TB, TB in pregnant and breastfeeding women and MDR-TB. As described in the *ISTC*, all physicians should:

Provide HIV counseling and testing to all patients with, or suspected of having tuberculosis. This is of special importance in areas with a high prevalence of HIV infection, for patients with symptoms of HIV related conditions and patients with a history of risk for HIV exposure. (Standard 14)

Evaluate HIV positive patients with TB for indications for antiretroviral therapy (ART) and provide cotrimoxazole as prophylaxis for other infections (Standard 15)

Evaluate persons with HIV infection for active TB and if active TB is ruled out, treat for presumed latent tuberculosis infection. (Standard 16)

Identify patients who are at risk for MDR-TB and Treat confirmed MDR-TB as soon as possible for with appropriate regimens. (Standards 11 and 12)

SECTION 4

SPECIAL SITUATIONS

LEARNING OBJECTIVES

In this section participants will learn:

- How to treat TB patients who need specialized care such as TB-HIV co-infected, MDR-TB patients, pregnant and breastfeeding women and pediatric cases.



1. TUBERCULOSIS AND HIV

Since TB kills more HIV infected persons than any other infectious disease, it is very important to screen all persons with HIV disease for TB infection and disease and to screen TB patients for HIV infection. Although the principles of the WHO strategy for TB control are the same in HIV-positive and HIV-negative patients, HIV is the most significant factor known to increase the risk of TB infection, progression to active TB, and poor TB outcomes. A high index of suspicion is needed for TB infection in HIV-positive patients, as HIV is a significant cause of progression from TB infection to TB disease and increased mortality. Management of TB-HIV patients should be performed in consultation with a TB-HIV expert. As mentioned in Section 2, in keeping with the WHO Three I's strategy to decrease the burden of TB in people living with HIV, persons with HIV infection who, after careful evaluation, do not have active tuberculosis should be treated for presumed latent tuberculosis infection with isoniazid prevention therapy (IPT).

1.1. WHEN TO START ANTIRETROVIRAL THERAPY (ART)

For patients with active TB in whom HIV infection is diagnosed and ART is indicated, the first priority is to initiate TB treatment in accordance with NTP guidelines as there is continuing debate and discussion regarding the optimal time for initiation of ART. Case-fatality rates in patients with

TB during the first two months of TB treatment are high HIV prevalence settings. This suggests that ART should begin early.⁶ Alternatively, the potential issues of high pill burden, drug-drug interactions, toxicity and immune reconstitution inflammatory syndrome (IRIS) suggest that later initiation of ART may be helpful. Below is a table taken from ART for HIV infection in adults and adolescents: recommendations for a public health approach where more information on this topic can be found.

INITIATING FIRST-LINE ART IN RELATIONSHIP TO STARTING ANTI-TB THERAPY		
CD4 cell count	ART recommendations	Timing of ART in relation to start of TB treatment
CD4 <200 cells/mm ³	Recommend ART ^a	Between two and eight weeks ^b
C CD4 between 200 and 350 cells/mm ³	Recommend ART	After eight weeks
D4 >350 cells/mm ³	Defer ART ^c	Re-evaluate patient at eight weeks and at the end of TB treatment
Not available	Recommend ART ^d	Between two and eight weeks

^a An Efavirenz (EFV)-containing regimen is the preferred first-line regimen.

^b ART should start as soon as TB treatment is tolerated, particularly in patients with severe immunosuppression.

^c ART should be started if other non-TB stage 3 or 4 events are present.

^d For some TB diagnoses that generally respond well to anti-TB therapy (i.e. lymph node TB, uncomplicated pleural effusion), deferral of ART should be considered.

1.2. RIFAMPIN AND ANTIRETROVIRAL THERAPY

The most important drug-drug interactions in the treatment of HIV-related TB are those between rifampin and the non-nucleoside reverse transcriptase inhibitors (NNRTIs), efavirenz (EFV) and nevirapine (NVP). Rifampin is the only rifamycin available in most of the world, and initial antiretroviral regimens in areas with high rates of TB consist of EFV or NVP (in combination with nucleoside analogues). Furthermore, because of its potency and durability on randomized clinical trials, EFV-based therapy is a preferred option for initial ART in developed countries.⁷ There are a certain considerations based on drug-drug interactions between rifampin and NNRTIs, EFV and NVP.

• RIFAMPIN AND EFAVIRENZ

Rifampin causes a measurable, though modest, decrease in EFV concentrations. Increasing the dose of EFV from 600 mg daily to 800 mg daily compensates for the effect of rifampin, but it does not appear that this dose increase is necessary to achieve excellent virological outcomes of therapy. Trough concentrations of EFV, the best predictor of its virological activity, remain well above the concentration necessary to suppress HIV in-vitro among patients on concomitant rifampin. Therefore, this combination—EFV-based ART and rifampin-based TB treatment, at their standard doses—is the preferred treatment for HIV-related TB (see Table 1 in the original guideline document). Some experts recommend an 800 mg dose of EFV for patients weighing >60 kg.

• ALTERNATIVES TO EFAVIRENZ-BASED ANTIRETROVIRAL THERAPY

Alternatives to EFV-based antiretroviral therapy are needed for certain patients with HIV-related TB: EFV cannot be used during pregnancy (at least during the first trimester), some patients are intolerant to EFV, and some are infected with NNRTI-resistant strains of HIV. Alternative first-line treatment regimens include Nevirapine (NVP) and triple Nucleoside Retro-Transcriptase Inhibitors (NRTIs) - based on Tenofovir DF (TDF) or Abacavir (ABC) regimens. For NVP-containing regimens, ALT should be checked at 4, 8 and 12 weeks; treatment should be decided on the basis of symptoms thereafter. Standard protease inhibitor regimens, whether Ritonavir boosted or not, cannot be given with Rifampin.



1.3. IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

Occasionally, patients with HIV-related TB may experience a temporary exacerbation of symptoms, signs or radiographic manifestations of TB after beginning anti-TB treatment. This paradoxical reaction in HIV infected patients with TB is thought to be a result of immune reconstitution. This can occur as a result of TB treatment alone or the initiation of ART with concomitant TB treatment. Symptoms and signs may include high fever, lymphadenopathy, expanding central nervous system lesions and worsening of chest x-ray findings. A thorough evaluation is necessary to exclude other causes, particularly TB treatment failure, before diagnosing a paradoxical reaction.

1.4. PROVISION OF CO-TRIMOXAZOLE PREVENTIVE THERAPY (CPT)

Administering prophylactic co-trimoxazole may prevent *Pneumocystis Carinii* and bacterial infections in HIV-positive TB patients. CPT substantially reduces mortality in HIV-positive TB patients (by up to 48% in the WHO African Region).⁸ For TB patients, CPT should be initiated as soon as possible, irrespective of the CD4 cell count, and given throughout anti-TB treatment; continuation of CPT after TB treatment is completed should be considered in accordance with national guidelines.

1.5. ENSURE DOT FOR ANTIRETROVIRAL THERAPY AS WELL AS TUBERCULOSIS TREATMENT

DOT should be employed for all TB patients infected with HIV as the adverse reactions and mortality associated with treatment interruption are much greater than with TB patients without HIV infection. DOT strategies can be adopted for ART as well, at least during TB treatment. This approach is resource-intensive and difficult to introduce on a large scale and for the lifelong duration of ART. However, it may be helpful for early patient training. Coordination between TB and HIV services to provide joint DOT for both medications would be ideal. More information on the clinical management of HIV infection in TB patients is available in the WHO publication, TB/HIV: A Clinical Manual. More information on collaborative TB/HIV Activities, including the Three I's can be found in the WHO publication, Interim Policy on Collaborative TB/HIV Activities.

2. TUBERCULOSIS TREATMENT IN CHILDREN

Anti-TB chemotherapy is well tolerated by children and teenagers. Categories of TB treatment regimens are the same as for adults. Once TB has been diagnosed, the TB specialist will determine the appropriate regimen and dose based on weight.

- Since children usually develop TB disease as an immediate consequence of primary infection, they typically have fewer mycobacteria than adults. Therefore, anti-TB drug resistance that develops during treatment is usually uncommon in children. Most drug resistance found in children is usually a result of primary infection with a drug-resistant strain
- While every effort should be made to establish a bacteriological diagnosis (and obtain DST) in a child with suspected MDR-TB, in practice paediatric cases are often not confirmed bacteriologically. Because children with TB may never become sputum smear-positive, it is reasonable to initiate MDR-TB therapy based on the DST pattern of the index case
- Children are more likely than adults to develop extrapulmonary forms of TB, particularly disseminated disease and TB meningitis
- The pharmacokinetics of anti-TB drugs differs between children and adults. Children tend to tolerate larger doses per kilogram of body weight and have fewer adverse reactions than adults
- Children may have problems absorbing the available dosage forms of anti-TB drugs since most are formulated for adults. When possible, pediatric formulations should be used

3. TUBERCULOSIS IN PREGNANT AND BREASTFEEDING WOMEN

All female patients of childbearing age should be tested for pregnancy upon initial evaluation for TB. In principle, most first-line anti-TB drugs (rifampicin, isoniazid, pyrazinamide and ethambutol) can be used safely during pregnancy and while breastfeeding. Whenever possible the six-month regimen based on isoniazid, rifampicin and pyrazinamide should be used during pregnancy. When using pyrazinamide, vitamin K should be administered to the infant at birth due to the risk of postnatal hemorrhage; treatment should be monitored in conjunction with a pediatrician. During the intensive phase for a pregnant woman, ethambutol should be used rather than streptomycin which crosses the placenta and can cause auditory nerve impairment and nephrotoxicity to the fetus.

Streptomycin should not be used during pregnancy as it can cause permanent deafness in the baby; however it may be used safely during breastfeeding. Active TB in pregnancy must be treated because untreated disease has a greater risk for the health of the mother and unborn child than the use of first-line drugs.

Rifampicin decreases the effectiveness of birth control pills in preventing ovulation. All non-pregnant women should be advised to use an alternative form of birth control while on TB treatment such as a condom or intrauterine device if they do not wish to become pregnant.

Pregnancy is not a contraindication for treatment of active drug-resistant TB, which poses great risks to the lives of both mother and fetus. However, birth control is strongly recommended for all non-pregnant women receiving therapy for drug-resistant TB because of the potential consequences for both mother and fetus resulting from frequent and severe adverse drug reactions. Pregnant patients should be carefully evaluated, taking into consideration gestational age and severity of the drug-resistant TB. The risks and benefits of treatment should be carefully considered, with the primary goal of smear conversion to protect the health of the mother and child, both before and after birth. The following are some general guidelines:

- Start treatment of drug-resistant TB in second trimester or sooner if patient's condition is severe
- Avoid injectable agents
- Avoid ethionamide

4. DRUG RESISTANT TUBERCULOSIS

Although MDR-TB may be the most well known type of drug-resistant TB, four different categories of drug resistance have been established:

- **Mono-resistance:** resistance to one anti-TB drug
- **Poly-resistance:** resistance to more than one anti-TB drug, but not both isoniazid and rifampicin
- **Multidrug-resistance:** resistance to at least isoniazid and rifampicin
- **Extensive drug-resistance:** in addition to multidrug-resistance, resistance also to any fluoroquinolone, and at least one of three injectable second-line drugs (capreomycin, kanamycin and amikacin)

Treatment of drug-resistant TB can be very challenging due to the limited number of drugs available, the toxicity of these drugs, and the severity of adverse reactions. Consult with an MDR-TB specialist from the NTP when treating these patients.

There are two alternatives for drug-resistant TB treatment regimens: standardized and individualized. Standardized regimens are based on the prevalent pattern of drug resistance in the community, identified in special DST studies by reference laboratories with controlled quality control. These regimens are decided upon at national level by the TB control program. Individualized regimens are normally based on the susceptibility pattern of the *M. tuberculosis* isolate of the case patient; except in severely ill patients when treatment may be based on the history of previous treatment. Care should be taken to avoid amplification of drug resistance by never adding a single drug to a failing regimen.

Drugs used to treat patients with drug-resistant strains are grouped according to hierarchy, starting with the group that is most important to include in a drug regimen for MDR-TB. The drugs used to treat drug-resistant TB are grouped into five categories.

GROUP 1 First-line oral TB agents

GROUP 2 Injectable TB agents

GROUP 3 Fluoroquinolones

GROUP 4 Oral bacteriostatic second-line TB drugs

GROUP 5 Anti-TB agents with unclear efficacy (not recommended by WHO for routine use in MDR-TB patients)

In general, regimens should consist of all drugs in group 1 to which the strain of MDR-TB can be expected to be susceptible, an injectable agent from group 2, a fluoroquinolone if the strain is thought to be susceptible, and drugs from group 4 to complete a regimen based on efficacy and cost. Group 5 drugs are not generally used unless the drugs from the other four groups cannot be used to constitute a regimen with at least 4 effective drugs. The table on the following page provides a summary of the different TB drugs. Note that national guidelines generally limit the prescription of MDR-TB regimens to a special approval committee comprised of MDR-TB experts.

Because XDR-TB is resistant to first- and second-line drugs, treatment options are limited. However, XDR-TB can be treated through the use of

a well-organized management scheme including systematic drug-susceptibility testing, strict treatment supervision, adverse-event management, psychological support, nutritional support, and bacteriologic and clinical monitoring, in addition to individualized drug regimens and, if needed, surgery. XDR- TB should only be treated by experienced TB clinicians.

Drug grouping and basic principles the selection of drug-resistant TB regimens ⁹		
GROUPING	DRUGS (ABBREVIATION)	PRINCIPLES
GROUP 1 First-line oral TB agents	Isoniazid* (H); Rifampicin* (R); Ethambutol (E); Pyrazinamide (Z)	These drugs are the most potent and best tolerated TB drugs. They should be used in patients only where there is laboratory evidence or clinical history to suggest their efficacy. The newer rifamycins should be considered ineffective if results of DST show resistance to rifampicin.
GROUP 2 Injectable TB agents	Streptomycin (S); Kanamycin (Km); Amikacin (Am); Capreomycin (Cm); Viomycin (Vi)	One injectable agent should be given to every patient. There is a hierarchical order for injectables based on efficacy, adverse effects and cost. If the strain is susceptible, streptomycin (S) is the injectable agent of choice. Otherwise, kanamycin (Km) is the logical second choice given its lower cost and good experience of use. Km and amikacin (Am) are considered to be very similar and have close to 100% cross-resistance. If an isolate is resistant to S, Km and Am, then capreomycin (Cm) should be used.
GROUP 3 Fluoroquinolones	Ofloxacin (Ofx); Levofloxacin (Lfx); Moxifloxacin (Mfx); Gatifloxacin (Gfx)	One fluoroquinolone should be used if the strain is susceptible. Currently, the most potent available quinolones in descending order based on in vitro activity and animal studies are: moxifloxacin (Mfx) = gatifloxacin (Gfx) > levofloxacin (Lfx) > ofloxacin (Ofx). However, the long-term safety of the newer generation fluoroquinolones (Mfx, Gfx and Lfx) has not yet been fully evaluated. The choice of fluoroquinolones is based on efficacy and cost

Drug grouping and basic principles the selection of drug-resistant TB regimens ⁹		
GROUPING	DRUGS (ABBREVIATION)	PRINCIPLES
GROUP 4 Oral bacteriostatic second-line TB drugs	Ethionamide (Eto); Prothionamide (Pto); Cycloserine** (Cs); Para-aminosalicylic acid (PAS); Terizidone (Trd)	<p>These are added based on estimated susceptibility, drug history, efficacy, adverse effects, profile and cost.</p> <ul style="list-style-type: none"> • If only one of these agents is needed, ethionamide/prothionamide is often added because of its proven efficacy and low cost. • If two agents are needed, cycloserine is commonly used in conjunction with ethionamide/prothionamide. • Since the combination of ethionamide/prothionamide and PAS has a high incidence of potentiated gastrointestinal adverse effects, these two agents are commonly used together only when all three Group 4 agents are needed. • Ethionamide/prothionamide should be started at a low dose (250 mg) for a few days and then gradually increased until the full dose is reached. • If necessary to add a third agent, PAS should be used. It is costly, has significant gastrointestinal adverse effects and the microgranules requires cold chain for storage which make it less convenient to use.
GROUP 5 Anti-TB agents with unclear efficacy (not recommended by WHO for routine use in MDR-TB patients)	Clofazimine (Cfz); Amoxicillin/Clavulanate (Amx/Clv); Clarithromycin (Clr); Linezolid (Lzd) Thioacetazone (Th)	These are not recommended by WHO for routine use in MDR-TB treatment because their contribution to the efficacy of multidrug regimens is unclear. However, they can be used in cases where adequate regimens are impossible to form with the drugs from Groups 1–4.

*Used in patients who are susceptible to H and/or R

**Vitamin B6 (pyridoxine) should be given to all patients receiving cycloserine to prevent adverse neurological side effects, 50 mg for every 250 mg of cycloserine. It is also useful in patients with alcoholism that receive isoniazid.

4.1. MDR-TB TREATMENT IN CHILDREN

There is only limited reported experience with the use of SLDs for extended periods in children. The risks and benefits of each drug should be carefully considered in designing a regimen. Frank discussion with family members is critical, especially at the outset of therapy. In general, anti-TB drugs should be dosed according to body weight. Monthly monitoring of body weight is therefore especially important in pediatric cases, with adjustment of doses as children gain weight. Treatment of MDR-TB in children should be managed in consultation with an MDR-TB specialist.

4.2. TREATMENT DURATION

The recommended duration of treatment for MDR-TB regimens is guided by culture conversion. Currently, WHO recommends continuing therapy for a minimum of 18 months after culture conversion. Extension of therapy to 24 months may be indicated in chronic cases with extensive pulmonary damage. However it is important to keep in mind that management of MDR-TB can be difficult, as these cases can be very complex, and should only be undertaken in consultation with an expert. As mentioned earlier, a table of MDR-TB outcomes can be found in Annex 7.

4.3. DOT FOR MDR-TB

Given that many patients develop resistance while receiving anti-TB drugs due to poor supervision or inadequate regimen design it is imperative that all MDR-TB treatment be given by full DOT with incentives and enablers. DOT should be given by health care workers trained specifically for MDR-TB case management. Many patients are hospitalized until they smear convert or in some cases until the end of the intensive phase. You should consult with a MDR-TB specialist from NTP when involved in provision of DOT for these patients.

Consult the WHO Guidelines for the programmatic management of drug-resistant tuberculosis for more information on MDR-TB management. The MDR-TB online course is a continuation training course from the WMA and is available free of charge by internet on the web page: <http://www.wma.net>

IN THIS SECTION, YOU HAVE LEARNED THAT...

SECTION 4

- For patients with active TB, in whom HIV infection is diagnosed and ART is required, the first priority is to initiate TB treatment in accordance with NTP guidelines
- Efavirenz-based antiretroviral therapy and rifampin-based TB treatment, at their standard doses—is the preferred treatment for HIV-related tuberculosis
- For TB patients, CPT should be initiated as soon as possible, irrespective of the CD4 cell count, and given throughout anti-TB treatment; continuation after treatment is completed should be considered in accordance with NTP guidelines
- Anti-TB chemotherapy is well tolerated by children and teenagers and categories of TB treatment are similar to those for adults
- Once TB has been diagnosed in a child, the TB specialist will determine the appropriate regimen and dose based on weight
- In principle, most first-line anti-TB drugs (rifampicin, isoniazid, pyrazinamide and ethambutol) can be used safely during pregnancy and while breastfeeding
- Although the safety of pyrazinamide in pregnancy has not been established, whenever possible the six-month regimen based on isoniazid, rifampicin and pyrazinamide should be used during pregnancy
- The recommended duration of treatment for MDR-TB treatment regimens is guided by culture conversion and other factors such as extent of disease
- WHO recommends continuing therapy for a minimum of 18 months after culture conversion

SELF ASSESSMENT QUESTIONS AND EXERCISES: SPECIAL SITUATIONS

1. The most important drug-drug interactions in the treatment of HIV-related TB are those between _____ and the non-nucleoside reverse transcriptase inhibitors (NNRTIs), efavirenz (EFV) and nevirapine (NVP)

2. Multidrug-resistance is defined as resistance to:

3. Initially, the regimen for a patient with confirmed MDR-TB should include: (check all that apply)

- a. At least four drugs with either certain, or almost certain, effectiveness
- b. First-line anti-TB drugs whenever there is no proof of resistance
- c. All drugs to which the patient's strain showed susceptibility by DST
- d. An injectable agent
- e. Isoniazid and Rifampicin, the two most powerful anti-TB drugs

4. Under which circumstances may a MDR-TB patient receive drugs for self-administration?

- a. When the patient has to travel
 - b. When the patient has a family emergency
 - c. When the patient cannot come to the DOTS center because s/he feels sick
 - d. When the patient has completed the intensive phase
 - e. When a patient has never missed a dose
 - f. None of the above
- _____

5. At a minimum, how long must treatment for MDR-TB last?

6. Which first-line anti-TB drug(s) should not be used in pregnant women?

- a. Rifampicin
- b. Isoniazid
- c. Pyrazinamide
- d. Streptomycin
- e. Ethambutol

7. In this exercise, read the cases below and answer the related questions.

CASE 1 (TB/HIV)

A 23 year old female is diagnosed with pulmonary TB and tests positive for HIV. You order a CD4 count and find that the patient has a CD4 count between 200 and 350 cells/mm³.

1. *When should you initiate ARVs based on above information?*
2. *What other treatments have been shown to be beneficial in this situation?*

CASE 2 (PREGNANCY/TB)

A 19 year old female who is 21 weeks into pregnancy is diagnosed with pulmonary TB after presenting with cough, fever, and weight loss.

What is the next appropriate step?

- a. terminate pregnancy
- b. start anti-TB treatment with 4 oral first-line drugs
- c. start TB treatment after delivery
- d. await culture results and drug susceptibility testing before starting treatment

CASE 3 (PEDIATRIC TB)

A 4 year old boy presents with fever, cough, and weakness. The chest x-ray shows right mid-lung pneumonia. TST is 8mm. The mother was started on standard anti-TB therapy 5 weeks ago. Her DST reveals pan-sensitive MTb.

Choose the best answer:

- a. start broadspectrum antibiotics for pneumonia
- b. no treatment pending sputum cultures
- c. start on TB treatment with first-line TB medications
- d. admit to hospital for observation

CASE 4 (MDR)

A 28 year old male presents with cough, fever, and weight loss. The chest x-ray shows right upper lung opacity with cavitation and fibrosis. Sputum smear microscopy and TST is positive. He was treated for TB 4 years prior for 2 months, self administered therapy and was lost to follow-up.

1. *What factors point to potential drug-resistant TB?*
2. *Which test should you order?*
3. *Which combination of drugs should be considered?*

ANSWERS

1:
Rifampicin

2:
at least isoniazid and rifampicin, the two most powerful anti-TB drugs

3:
a,b and d

4:
f

5:
WHO recommends continuing therapy for a minimum of 18 months after culture conversion.

6:
d

7:
CASE 1
1. After 8 weeks
2. Co-trimoxazole preventive therapy (CPT)

CASE 2:
b

CASE 3:
c

CASE 4:
1. prior treatment, self-administered therapy, non-adherence
2. DST
3. Use any available first-line agents + one injectable + one fluoroquinolone + 2 or more group 4 drugs and consult an expert



5

Patient-physician communication is an integral part of clinical practice. How a physician communicates information to a TB patient is as important as the information being communicated. This section focus on the skills needed to ensure the *ISTC* standard 9 is met. All physicians who care for TB patients should be able to provide the full range of recommended interventions and available support services, including patient counseling and education. How to provide that education intervention as well as how to communicate more effectively with patients during medical visits will be discussed below.

SECTION 5

PATIENT-PHYSICIAN COMMUNICATION

LEARNING OBJECTIVES

In this section participants will learn:

- Skills useful for communicating with TB patients
- How to gauge patient understanding about TB during the first visit
- How to use simple language to convey information
- How to ask questions about patient comprehension

1. THE IMPORTANCE OF GOOD PATIENT-PHYSICIAN COMMUNICATION

A TB patient who understands the information their physician is giving them is more likely to acknowledge health problems, understand their treatment, modify their behavior accordingly, and follow their medication schedules. One of the main reasons for TB patient default is the perceived attitude of the health worker. Even if this was not the case, patients' perceptions play an important role in the patient-provider relationship. Patients who default often report that the health worker was rude, impatient, or seemed too busy to care.

In many places, there is still much stigma associated with TB, and in addition to potentially being very ill, patients may be fearful of:

- Reaction of their family and community
- Dying as a result of their disease
- Potential loss of income or employment

In order to try to address some of these fears and concerns, physicians should communicate with patients and their families clearly and in a supportive way from the time of diagnosis, throughout the long treatment process, until the patient is cured.

Below, a number of steps are outlined that will help a physician communicate more effectively with a TB patient about their disease and the options they have.

1.1. ASSESSMENT OF PATIENT KNOWLEDGE (ASK QUESTIONS AND LISTEN)

Before providing information, find out what a patient already knows about TB. Many times, other health care providers have already communicated information to the patient, which can affect the patient's perceptions and cause confusion when you provide new and possibly different information. For example, a DOT worker might inform a patient that a certain number of doses is needed to successfully complete treatment while a nurse might tell the patient that sputum exams are the best measures for cure. Other times, patients will come to you with preconceived ideas (possibly from unreliable sources) about TB, such as how TB is transmitted or how long treatment is. It is important, therefore, to determine what a patient already understands (or misunderstands) about TB from the beginning.

Ask questions about what the patient knows and allow the patient to answer. As much as possible, ask questions that are open-ended. These are questions that cannot simply be answered “yes” or “no.” You will usually obtain more information if you ask questions that begin with such words as “What..., Why..., How...and When...” These types of questions require the patient to think about the answer and elaborate. However, sometimes it may be necessary to ask a direct “yes” or “no” question. Listen carefully to each answer. If the patient is slow to respond, do not be tempted to “fill the silence” by suggesting an answer yourself. Give the patient time to think.

1.2. "USE OF SIMPLE LANGUAGE

Provide information in a slow and deliberate fashion, with simple language, allowing time for patients to comprehend the new information. Speaking slowly with appropriate pauses also gives the patient time to formulate questions, which you can then use to provide further pieces of targeted information. A dialogue punctuated with pauses can lead to deeper comprehension on both sides.



Speak clearly, using words that the patient can understand. For example, many patients would not understand the following statement:

“You are pulmonary sputum-positive for TB. TB is not hereditary but is acquired by airborne transmission.”

It would be better to use simple words such as the following:

“The tests of the phlegm you coughed up show that you have tuberculosis, or TB, in your lungs. TB is not a disease that you are born with. It is spread from person to person by germs. When an infected person coughs or sneezes, the germs go into the air. Another person can then become infected by breathing these germs.”

1.3. NONVERBAL COMMUNICATION

Your body language and facial expression are important for patient understanding and can both improve or detract from the experience. The physician who hurriedly enters the examination room several minutes late, takes notes quickly, and turns away while the patient is talking, almost certainly conveys impatience and minimal interest in the patient. Over several such encounters, patients may understand this nonverbal behavior to mean their visit is unimportant, even if you told the patient otherwise. Be aware of the implicit messages that are conveyed through nonverbal actions as well as recognizing these cues from the patient.

1.4. ENCOURAGE QUESTIONS

Make sure that the patient feels comfortable enough to ask questions. After giving instructions or an explanation, pause and ask, “Do you have any questions? I know this is a lot of information at once.”

Patients may be timid and concerned about appearing uneducated. They may be nervous and simply want to leave the health facility in a hurry. It may take courage for them to ask questions. Praise patients for asking questions and answer them thoughtfully and carefully. For example, say:

*“I’m glad you asked that question....”
“Good question....”*

1.5. ASK CHECKING QUESTIONS

Checking questions are questions intended to find out what a person has learned, so that you can provide more information or clarify your instructions as needed. **After providing information**, ask checking questions to ensure that the patient understands. **At the end of a visit**, ask checking questions to ensure that the patient understands what to do next. Do not ask “Do you understand?” This will generally just get you a “Yes” reply and you will not really know anything more.

For example, after explaining how to prevent TB from spreading (covering the mouth etc), to check if the patient understands, you might ask:



*“What will you do to
avoid spreading TB
germs?”*

IN THIS SECTION, YOU HAVE LEARNED THAT... SECTION 5

- Simple decisions to ask questions, word choice, information depth, speech patterns, body language, and facial expression can greatly affect the quality of one-to-one communication between the patient and physician
- To a large degree, these are conscious choices that can be learned and customized to fit the TB patient or suspect during clinic visits
- Improving the basic communication skills described above can help strengthen the patient-physician relationship
- Strengthening your communication skills takes time and practice but is important for optimal patient experience and outcome

SELF ASSESSMENT QUESTIONS AND EXERCISES: PATIENT PHYSICIAN COMMUNICATION

1. Identify strategies that could be used in the following situations. Briefly describe what you would say or do.

- A) After being on MDR-TB treatment for 4 months, a family member says that JK cannot stay at home because the children will catch MDR-TB just as he did. The family member is scared since JK's wife died of MDR-TB.
- B) A patient has missed 1 day of treatment and reports the following day.

2. Rewrite the following statement so that it would be easier for a patient to understand.

"Your drug susceptibility pattern shows resistance to first-line agents H and R. The treatment for MDR-TB requires daily combination therapy including a fluoroquinolone and SLDs."

3. A TB patient who has just been shifted to the continuation phase began to interrupt treatment. You stress the following information:

"Even now that you feel well, it is important that you must continue coming for treatment. You have successfully finished 2 months of treatment. You must continue to take all of these tablets 3 days a week. Taking only some of the drugs, or taking them irregularly, is dangerous and can make the disease difficult or impossible to cure and you may get sick again."

List two checking questions that you might ask at the end of the visit to ensure that the patient understand the information you provided:

ANSWERS

1: Identify strategies

- A: Explain that while it is important to take precautions to prevent the spread of TB, JK has done the best thing and taken treatment for 4 months. The drugs that he has taken have killed the bacilli that can come out when people sneeze or cough. JK does not pose a danger to the children any more because he has been taking the medicines.
He still needs your support for the treatment is long and it is important to have family support for such a long treatment.
Encourage the family member to help JK continue treatment so he stays well and can be cured.
- B: Ask the patient if there is something wrong. If there was something that prevented the patient for coming to treatment. Remind the patient that missing days gives the TB germs a chance to recover and grow and that it is very important to take all the drugs every day. Tell the patient they are doing the right thing by coming back and refer them to possible support options when available if needed.

2: Rewrite the statements

There are many responses - here is one example:

The laboratory tests showed that the germs in your lungs cannot be killed by the normal TB drugs we use. We have to use special drugs to treat this stronger, drug resistant disease. You will have to take a number of different drugs every day, including an injection to be able to be cured.

3: Two checking questions

1. How many times a week will you take the drugs from now on?
2. Why is it important to continue treatment without interruption?



6

This section will discuss adherence to treatment. A physician for TB patients must monitor, promote and ensure adherence to treatment. Successful treatment of a TB patient benefits both the patient and the community, and the responsibility for successful treatment lies with the health care provider, not only for prescribing an appropriate treatment regimen but also to ensure completion of therapy. Any physician treating a patient for tuberculosis is assuming an important public health responsibility.

To fulfill this responsibility, a physician must not only **prescribe** an appropriate regimen but also **assess** the adherence of the patient to the regimen and **address** poor adherence when it occurs. By doing so, you will be able to ensure adherence to the regimen until treatment is completed. Studies have shown that health care providers cannot reliably identify which patients will adhere to treatment and which will not before it occurs. One of the best indicators of patient adherence is if patients have been irregular or defaulted in the past as these patients are likely to do so again. These patients may need special attention. To accomplish this:

Develop and employ a patient-centered approach to administration of TB treatment, based on the patient's needs and mutual respect between the patient and the provider. (Standards 7 and 9)

Familiarize yourself with the Patients' Charter for Tuberculosis Care, which delineates the rights and responsibilities of patients and has been developed together with the *ISTC*.

SECTION 6

ADHERENCE TO TREATMENT

LEARNING OBJECTIVES

In this section participants will learn:

- How to support TB patients as they come for observed treatment
- How to monitor the adherence of TB patients
- How to identify patients who may interrupt treatment
- How to help solve the problems patients may have to ensure continuation of TB treatment
- What types of incentives and enablers you can offer to promote treatment adherence

1. IMPORTANCE OF ADHERENCE

For anti-TB therapy to be effective, appropriate drugs should be used in appropriate doses and ingested correctly for the appropriate length of time. Therefore, adherence to treatment is crucial to completing treatment and achieving cure. Services providing TB care should offer full support to patients to ensure that treatment will be completed.

Many TB patients come from socially vulnerable populations, including the very poor, homeless, substance abusers, or persons with HIV. For many patients in these groups, their TB diagnosis is not the most important problem they are facing. These patients need close supervision. This section provides a number of techniques you can use to improve and support patient adherence to treatment and will be useful in working with these populations. Informing and supporting patients as well as addressing other concerns may help motivate patients to care more about their health and adhere to treatment. From a clinical perspective, informing patients and providing support may seem less significant than TB treatment, but they present one of the most important elements in the larger TB control effort.

You should identify and address factors that may make patients interrupt or stop treatment. Although impossible to tell which patients will adhere to treatment, some of the predictors of lack of adherence include substance abuse, poor adherence to treatment in the past, and homelessness. Monitoring the patient's adherence to treatment assists patients to take their drugs regularly and in to complete their treatment, thus helping to achieve cure, prevent further transmission and the development of drug resistance. It protects the patient and the general public from TB.

2. PATIENT-CENTERED APPROACH

A patient-centered approach to TB care and management is based on the patient's needs and mutual respect between the patient and the provider. A central element of the patient-centered strategy is the use of measures that are tailored to the individual patient's circumstances and are mutually acceptable to the patient and the provider. Promoting adherence through a patient-centered approach includes choosing with the patient the most convenient time and place for DOT and, when possible, providing other social and medical services. Adherence monitoring during treatment is much more effective than spending resources later on defaulter tracing.



This relationship of trust and confidence between the TB patient and physician helps promote adherence to treatment. The patient must understand basic information about TB, including what is necessary for treatment and cure to properly adhere to treatment and is part of the Patients Charter for TB Care. Although patient counseling and education are integral parts of the treatment process, ensuring adherence involves more than just providing information.

3. DIRECTLY OBSERVED TREATMENT

DOT is meant to ensure adherence on the part of both the providers (in giving proper care and detecting treatment interruption) and the patients (in taking regular treatment). It should be carried out in patient-

friendly manner and be directed to the patient's situation. DOT that is convenient for the patient is a key element to ensure adherence to treatment and part of a patient centered approach. A TB patient who must travel far for treatment is less likely to be adherent. Because of this, the TB services often try to coordinate DOT as close to the patient's home (or sometimes the workplace) as possible. Depending on the local conditions, treatment observation may be undertaken at a health facility, in the workplace, in the community or at home by a nurse or trained community treatment supporter. The treatment supporter should be a person acceptable to and chosen with the patient, and trained and supervised by the health services. Patient and peer support groups may also help to promote adherence to treatment. DOT is not a choice but a requirement for all patients, however choice exists in providing it in the most easily accessible manner.



4. ADHERENCE: BARRIERS AND STRATEGIES

Although the relationship with the provider is important, many times curing TB disease will not be the highest priority for a patient:

- More pressing needs such as food, work, housing, alcohol or drug addition may take precedence over TB treatment
- Attempt to link these patients with the appropriate social services or patient support groups available in your area and use the local TB program for assistance when possible
- Patient incentives or enablers for treatment completion might include transportation reimbursement or a food basket
- Look for creative ways to help the patient complete treatment

4.1. STIGMA

In many countries and cultures there is a significant stigma around TB. Family and community members may be fearful of getting TB, which may result in the patient being socially isolated. Additionally, in some countries, a current or past diagnosis of TB may affect the ability to get certain jobs. In countries with a high burden of HIV, a treatment for TB may be seen as an admission of a HIV diagnosis. Because of the additional stigma associated with HIV, some TB patients may be concerned and fearful of others learning about their TB diagnosis. This could affect adherence to treatment. Physicians and other care providers should be aware of this, and sensitive to a patient's fears and needs. Whenever possible, treatment including DOT should be provided in a way that makes the patient comfortable and is most likely to ensure privacy and therefore, promote adherence.

The table below presents a variety of patient education techniques that can be used to address some of the common underlying reasons why patients could be having difficulty completing treatment.

Do everything possible to give every TB patient the best chance of completing treatment. By showing genuine concern and gentle persistence, you can almost always often persuade a reluctant patient to successfully complete anti-TB treatment.

REASON FOR POOR ADHERENCE	POSSIBLE SOLUTIONS
Patient has poor relationship with the health worker	<ul style="list-style-type: none"> • Try to identify the cause of the problem and speak with the health worker as well as the patient about possible solutions • Ensure the patient is being treated with respect and consider changing the worker if possible, and all else fails
No longer feels sick	<ul style="list-style-type: none"> • Reiterate importance of completing regimen and consequences of incomplete treatment such as development of resistance and more severe disease later on
Stigma (fear or unwillingness to be seen as TB patient)	<ul style="list-style-type: none"> • Emphasize that anyone can get TB • Emphasize TB is curable and that once treatment is initiated, most patients quickly become non-infectious • Reassure patient that you will maintain confidentiality • Inform patient about regulations that protect TB patients from discrimination or job loss (If such regulations exist nationally)
Alcohol or drug abuse	<ul style="list-style-type: none"> • Refer patient to appropriate services, if available • Involve patient's family in trying to encourage adherence to treatment • Provide encouragement and reassurance and emphasize importance of treatment • Offer incentives (food, not money) if available
Personal or cultural beliefs or is using alternative regimens	<ul style="list-style-type: none"> • Be sensitive • Do not discourage other actions, unless they are harmful
Unhappy with adverse effects	<ul style="list-style-type: none"> • Discuss possible adverse effects with patient in advance. • Teach the patient how to recognize and report adverse effects • Assure patient that you are monitoring for adverse effects as well • Treat adverse effects promptly and consult a specialist for major adverse reactions
Lack of hope for recovery into the community	<ul style="list-style-type: none"> • Emphasize that since TB is curable with proper treatment, patient can resume previous activities soon after starting treatment • Keep patient informed on progress of treatment

REASON FOR POOR ADHERENCE	POSSIBLE SOLUTIONS
Lack of skills for adherence (e.g. do not understand, patients with limited dexterity, or patients with mental illness)	<ul style="list-style-type: none"> • Explain again, involve family or set up a system to assist the patient with the regimen and schedule • Come up with solutions, such as arranging someone to accompany patient to the clinic
Competing medical problems	<ul style="list-style-type: none"> • Discuss existing medical conditions with the patient • Determine the most important actions necessary for treatment of the patient's multiple conditions • Explain the importance of TB treatment • Work with other care providers to identify solutions
Lack of access to care	<ul style="list-style-type: none"> • Refer to social services, where available, for assistance with transportation, etc • Provide incentives and/or enablers for care
Language barrier	<ul style="list-style-type: none"> • Try to find an interpreter or family member who you can speak with to ensure that your message is being understood
Other problems (e.g., fear of job Loss, financial burden)	<ul style="list-style-type: none"> • Reiterate importance of completing regimen • Emphasize ability to resume previous activities when treatment is complete • Offer patient assistance in providing employer with proof of treatment completion and cure

4.2. REFERRAL FOR CARE AND HOSPITALIZATION

Hospitalization may be necessary for patients in poor clinical condition, with complications or associations requiring closer clinical monitoring. It might also be an alternative, especially during the initial phase of treatment, for a small number of patients for whom other options of ensuring treatment adherence and support are not available. However, hospitalization does not ensure regular drug intake or completion of the treatment. DOT should still be provided in hospital settings. Some countries have passed legal regulations that can compel patients to take treatment, if no other methods have worked.

IN ADDITION:

Use the local TB control program for help (when it is possible or necessary) to assist you

Refer patients to specialized programs, if available, such as assistance or counseling, to address specific problems including mental health and alcohol or substance abuse.

Make appointments when it is convenient for the patient but without missing a dose; this may improve adherence.

Use incentives, such as food or transportation assistance where available to encourage adherence. These may be especially effective for patients from socially vulnerable populations.

Enlist the support of the patient's family, if possible.

Cooperate with social workers or nurses where available to try to locate patients who are non-adherent.



4.3. PROVIDING INCENTIVES AND ENABLERS

Incentives are small rewards given to patients to encourage them to keep their clinic DOT appointments. Enablers are those things that make it possible or easier for the patients to receive treatment by overcoming barriers such as transportation difficulties. Incentives and enablers can be used in facilities providing TB services; they have been shown to effectively help patients stay with and complete treatment.

Incentives and enablers should be chosen according to the patients' special needs and interests, or the patients may not care if they receive them. For example, if the health care worker knows that transportation is a problem, he or she could offer bus tokens, bus fare, or taxi fare as an enabler. If transportation is not a problem, then he or she should offer something that is needed. Learning as much as possible about patients will help to identify their needs and interests and better motivate them to complete treatment. The best time to begin using incentives is after a good relationship has been established with a patient. Enablers, however, may be vital to the initiation of treatment and should be provided as soon as treatment starts.

Examples of incentives and enablers include:

- Food and beverages either at the clinic or as a food voucher to be used
- Clothing such as socks or gloves
- Services such as social service referrals, help in obtaining housing, social security or drug treatment, help in obtaining other medicines
- Household items such as fuel oil for heat or cooking utensils
- Transportation such as bus or taxi fare, bicycle or arranging transport with a local vendor
- Personal care such as razor blades, shaving cream or make-up
- For children: toys, games, books and school supplies

5. PATIENTS WHO MISS DOSES

If a TB patient misses doses of anti-TB drugs (considered at risk for defaulting), you should take the following actions as soon as possible:

Inform the local TB control program or nurse (if such nurses are available) and enlist their help to locate the patient.

Contact the patient by phone or/and visit at home or in the workplace to check the reason for non-adherence, discuss the situation and encourage the patient to continue his/her treatment without interruptions.

Take the daily dosage of the patient's anti-TB drugs with you, to provide directly observed treatment during your visit.

Determine if other circumstances (such as other illness or family situations) are preventing the patient from reporting for treatment and work to resolve these circumstances.

Talk to the patient's family and request that they provide assistance and encouragement to the patient.

Reiterate importance of completing treatment to both the patient and family members.

Report the defaulter immediately to the TB Control Program. If a patient is also on CPT, ART, or other treatments related to HIV or another illness, you may want to ask if this treatment was also missed. If so, encourage the patient to resume treatment and/or inform someone familiar with the patient's other care.

SECTION 6 IN THIS SECTION YOU LEARNED THAT...

- Successful treatment of a TB patient benefits both the patient and the community, and the responsibility for successful treatment lies with the health care provider, not only for prescribing an appropriate treatment regimen but also to ensure completion of therapy
- Promoting adherence through a patient-centered approach includes choosing with the patient the most convenient time and place for DOT and, when possible, providing other social and medical services
- Although there are many reasons that a patient does not adhere to treatment, one of the most important is a poor relationship with the health care provider
- Providers should do everything possible to give every TB patient the best chance of treatment
- By showing genuine concern and gentle persistence, you can often persuade a patient to continue anti-TB treatment
- In some cases, despite your best efforts, patients will default
- If a TB patient misses doses of anti-TB drugs or is at risk for defaulting, you should take action as soon as possible. This may include introduction of incentives and enablers to help with treatment completion

SELF ASSESSMENT QUESTIONS AND EXERCISES: ADHERENCE TO TREATMENT

1. HT, a 40 year old male patient has been on treatment for 2 months now and feels much better. He has gained 10kg since beginning treatment and although he had a few side effects initially, they have gone away. He comes to you today and mentions that he thinks the medicines have worked fine and that he doesn't need to take them any more. He definitely does not want to continue to have to meet his DOT worker every day and mentions that he has other things to do now that he feels better.

What are some of the things that you should discuss with HT to convince him to continue his treatment and DOT?

ANSWERS

Reiterate importance of completing regimen and consequences of incomplete treatment. Explain that someone must watch the patient swallow all the drugs to ensure that the correct drugs are taken regularly for the required time. By seeing the patient regularly, a health worker can also notice whether the patient has side-effects or other problems.

Explain that if a patient does not take all of the drugs he can continue to spread TB to others in the family or community and the disease TB will not be cured. It is dangerous to stop or interrupt treatment, because then the disease may become incurable or the patient may even die.



7

There is an urgent need to refocus attention on TB infection control, particularly in high-risk settings. Infection control is one of the components of WHO's The Three I's strategy to combat TB, especially in HIV prevalent areas. The increasing importance of drug-resistant TB, as well as the impact of HIV infection, has led to a reappraisal of the importance of infection control in health-care and other congregate settings. The presence of many HIV-infected and immunocompromised patients, health-care workers and visitors coupled with the lack of appropriate infection control policy and practice has created a favorable environment for transmission and spread of TB within health care facilities. The three types of infection control strategies used to diminish the transmission of TB within a health facility are administrative (managerial); environmental; and personal respiratory protection which address infection control at different points in potential transmission. Consistent with the *ISTC*, physicians should:

Ensure that appropriate infection control practices in keeping with facility infection control plans are utilized when caring for patients who have, or are suspected of having, infectious TB. (Standard 20)

SECTION 7

TUBERCULOSIS INFECTION CONTROL

LEARNING OBJECTIVES

In this section participants will learn:

- The three different types of TB infection control strategies and their priority
- The important components of an infection control plan
- When a TB patient should be considered infectious
- How to ensure good ventilation in a health facility
- How and when to choose to use a personal respirator
- The differences between a respirator and face mask

1. TUBERCULOSIS INFECTION CONTROL STRATEGIES

There are three types of infection control strategies used to diminish the transmission of TB within a health facility: administrative (managerial); environmental; and personal respiratory protection. Each of these strategies addresses infection control at a different point in the mycobacterial transmission process.

In general, work practice and administrative strategies have the greatest impact on preventing TB transmission within institutional settings or facilities, and they are the first priority in any facility setting regardless of available resources. These measures prevent aerosolized droplet nuclei containing *M. tuberculosis* from being generated in the facility, and thus reduce exposure of patients and staff to TB. Ideally, if aerosol droplet nuclei are not generated (aerosolized) then exposure is eliminated; and no further controls are needed. However, since it is not possible to eliminate all exposure, environmental strategies such as improved ventilation must be added to reduce the concentration of mycobacterial droplet nuclei in the air. Personal respiratory protection equipment such as respirators and masks block the droplet nuclei from being inhaled but are not effective without establishing the other two strategies and should be used in situations that pose a relatively high risk for exposure to TB.

DIFFERENT STRATEGIES		
Strategy	Priority	Effect
Administrative Strategies	First Priority	Minimizes generation of droplet nuclei in the air
Environmental Control Strategies	Second Priority	Reduces concentration of bacilli in the air
Personal Respiratory Protection	Third Priority	Blocks TB bacilli from being inhaled

2. PATIENT INFECTIOUSNESS

TB patients and TB suspects are to be considered infectious if they:

- Have PTB disease (lungs, airway or larynx)
- Are coughing or are undergoing cough inducing procedures
- Have sputum smears positive for AFB

These patients may be considered infectious if they are not on anti-TB treatment or have just started anti-TB treatment, or if they have a poor clinical or bacteriologic response to anti-TB treatment.

Patients with extrapulmonary TB are not usually infectious. They may be infectious if they have:

- Concomitant pulmonary disease
- Non-pulmonary disease in the oral cavity or larynx
- TB disease that includes an open abscess or lesion, especially if the drainage fluid from the abscess or lesion is extensive or there is aerosolization of the drainage fluid

Patients with confirmed TB disease should remain in isolation if possible or be separated while hospitalized until they:

- Have had two negative sputum smears collected on different days
- Demonstrate clinical improvement
- Are on adequate, supervised anti-TB treatment (> two weeks)



Isolation throughout hospitalization may be considered for patients with MDR-TB or XDR-TB since these patients are more likely to experience treatment failure or relapse and prolonged infectious periods. Extreme care should be used to separate HIV infected individuals, children and other immunocompromised patients from smear-positive TB patients. TB is the most common opportunistic infection and a leading cause of death in persons living with HIV/AIDS.

3. ADMINISTRATIVE CONTROL STRATEGIES

The most effective measures against transmission of TB within a facility are the prompt detection, education and separation of TB suspects and diagnosis and proper treatment of TB patients. Additionally, all health facilities should have a TB infection control plan in place, and all physicians and other health care providers should follow the plans and procedures for their facility.

Screen	Early recognition of patients with suspected or confirmed TB disease is the first step to control the spread of TB. It can be achieved by screening patients for prolonged duration of cough when first seen. Patients with cough of more than two weeks duration, or who report being under investigation or treatment for TB* should be managed as outlined below.
Educate	Instruct patients who are identified through screening to have a prolonged cough in cough hygiene . This includes instructing them to cover their noses and mouths when coughing or sneezing, and when possible providing face masks or tissues to assist them in covering their mouths. In the absence of a facemask or tissue, using the forearm shirtsleeve or inner side of the elbow have been promoted to cover a cough or sneeze.
Separate	Patients who are identified as TB suspects or cases by the screening questions should be separated from other patients and requested to wait in a separate well-ventilated waiting area, and provided with a surgical mask or tissues to cover their mouths and noses while waiting.
Investigate for TB or Refer	TB diagnostic tests should be done onsite or, if not available onsite, the physician should have an established link with a TB diagnostic center to which symptomatic patients can be referred for diagnosis and treatment.

*Although TB patients on adequate treatment are no longer infectious, it may be difficult for you to determine if anyone reporting being on treatment for TB has indeed received adequate treatment. The most cautious procedure is to manage those who are on treatment in the manner described.

In general, there are five components to administrative strategies for the prevention and control of TB in health care facilities:

1. Infection control plan
2. Administrative support for procedures in the plan, including quality assurance

3. Training of staff
4. Education of patients and increasing community awareness
5. Coordination and communication with the local TB program

Each facility should have a written TB infection control plan that outlines a protocol for:

- Prompt recognition and separation of TB suspects
- Provision of services
- Investigation for TB
- Referral of patients with suspected or confirmed TB disease

This plan should identify an infection control team of health professionals and hospital management and designate a staff member who is responsible for enforcing the plan or protocol. However, it is everyone's responsibility (especially the physician and clinical staff) to ensure that measures are followed. Physicians should take the following administrative steps at all times as a basic component of any TB infection control plan.

4. ENVIRONMENTAL CONTROL STRATEGIES

Environmental controls are the second-line of defense for preventing the spread of TB in HIV care settings. It is important to recognize that if administrative strategies and work practices are inadequate, environmental strategies **will not eliminate the transmission risk**. They are based on mechanical or natural ventilation, and may be supplemented with filters (high efficiency), and UltraViolet Germicidal Irradiation (UVGI).

Although many environmental strategies are technologically complex and expensive, controlled natural ventilation can reduce the risk of spreading *M. tuberculosis*.

Ventilation is the movement of air. Ventilation can be used to attain dilution and exchange of air in a specific area and to control the direction of airflow in a room or facility. These processes decrease the concentration of aerosolized droplet nuclei and the possibility of infection in health personnel and patients. There are many ways to implement appropriate ventilation including maximizing natural ventilation, using fans, local exhaust ventilation (sputum collection booths, external hoods for laboratory equipment) and general ventilation systems to create negative pressure for isolation and special procedure rooms such as airborne isolation rooms.

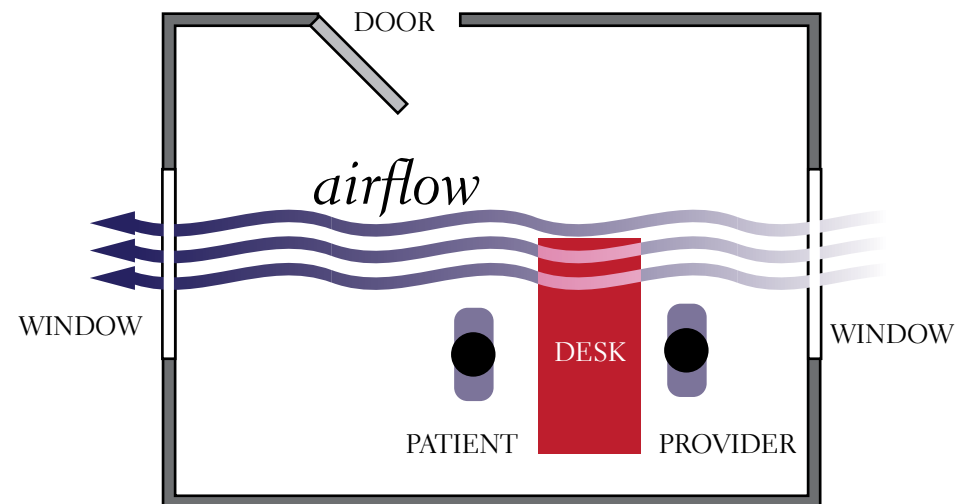
4.1. NATURAL VENTILATION

The simplest way to attain better ventilation is to maximize natural ventilation patterns for the hospital, medical offices, wards or rooms. Waiting areas, sputum collection rooms, examination rooms and wards should be “opened” to the outside (for example, they should be set up in open, covered areas or in areas with open windows). If possible, the sputum collection area should be located outdoors not in small rooms such as toilets or other enclosed areas.



4.2. LOCATION OF FURNITURE AND PEOPLE

In offices and other units it is necessary to observe airflow direction and to place furniture in such a way that health workers, other patients and visitors do not breathe infected air. When possible, providers should position themselves so that the air flows from the provider to the patient and then to the outside. Simple fans can assist in this process as well.



4.3. FILTERS

High efficiency filtration units can be an alternative to mechanical ventilation measures that may require structural changes. There are different types of filters. One of the most well known is the High Efficiency Particulate Air (HEPA), which filters 99.97% of particles $\geq 0.3 \mu\text{m}$ or microns in diameter. Other high efficiency filters can also be used if HEPA filters are too costly. Filters can be used in small and closed rooms with a limited number of TB patients. It is important to ensure that the position of the filter allows it to filter contaminated air according to its source and the positioning of people in the area. It is not enough to simply place a filter inside a room. Each system has a specific power to filter air and an expert should be consulted to ensure that it provides the exchanges required and that it mixes and cleans the air in the selected room adequately. All HEPA and other high-efficiency filters should be carefully installed, following the manufacturer's instructions, and meticulously maintained in order to guarantee their proper functioning.

4.4. ULTRAVIOLET GERMICIDAL IRRADIATION

UVGI can kill or inactivate *M. tuberculosis* and other bacteria and viruses contained in droplet nuclei. Various studies have shown that the use of UVGI is effective at disinfecting air containing *M. tuberculosis*.^{11,12} It can be used as a complement to other control measures in situations where clearing *M. tuberculosis* from the air is important. Ideally, the UVGI should be shone for as long as possible in order to deactivate the *M. tuberculosis* as there is a dose required to kill the bacilli. Generally, UVGI is used to disinfect the air in the upper part of the room. Shielding devices are used to direct the light upwards away from eyes and skin (See photo below). The use of these protection devices to deflect UVGI enables health personnel, patients and their visitors to remain in these areas for extended periods as the major concerns about UVGI have been adverse reactions, such as acute and chronic skin and eye changes from overexposure if the UVGI is not installed and maintained properly. Note that alone, UVGI does not provide outside air or circulate interior air, both of which are essential in achieving acceptable air quality in occupied spaces. When needed, UV lamps should always be cleaned with alcohol, not water. Protocols for maintenance should be followed.



5. PERSONAL RESPIRATORY PROTECTION

Personal respiratory protection (i.e., the selection and training in the use of respirators) is generally not a priority intervention, and should be only used in areas where concentrations of infectious droplet nuclei of *M. tuberculosis* cannot be adequately reduced by environmental and administrative control measures. Respirators are expensive, require specialized equipment to determine proper fit, and will protect staff from inhaling *M. tuberculosis* only if administrative and environmental controls are functioning. Their use should be restricted to specific high-risk areas in hospitals and referral centers, such as rooms where spirometry or bronchoscopy are performed or specialized treatment centers for persons with MDR-TB.

For a respirator to protect against airborne *M. tuberculosis* droplet nuclei it must be capable of filtering a particle 0.3 μm in diameter. Respirators are special types of masks that usually have a minimum filter efficiency of at least 95% for particles of 0.3 μm in diameter. There are different kinds of respirators and two classification systems for them, the US system and the European system (see the table below). Both provide adequate levels of filtration and choosing one over the other will depend on availability, the structure of the user's face and their cost. The US system is divided into nine types that differ according to the protection level. There are three efficiency levels (95%, 99% and 99.97%) and three categories of degradation resistance for filters (N, R and P). The European system has three different efficiency levels (FFP1-80%, FFP2 – 94% y FFP3 – 99%). Each filter or box should show the designation of the filter. In the majority of health care settings, using N95 or FFP2 (or higher) respirators provides adequate protection.



US CLASSIFICATION SYSTEM				EU CLASSIFICATION SYSTEM	
Category	95	99	100	Filter Category	Filter Efficiency
N	95%	99%	99.97%	FFP1	80%
R	95%	99%	99.97%	FFP2	94%
P	95%	99%	99.97%	FFP3	99%
N = Not resistant to oils R = Resistant to oils P = Oil proof	Filter Efficiency				

5.1. RESPIRATOR CARE

Respirators are disposable, but can be used many times if they are properly cared for, avoiding humidity, dirt and being crushed. They should be stored in a clean, dry place, not wrapped in a plastic bag, to avoid humidity and mold. Often times the elastic band of a respirator will be the weakest point. In order for respirators to be effective, they must adjust snugly to the face to avoid leaks. Consequently, storing respirators by hanging them by their elastic band is not recommended because it will stretch the elastic.



5.2. FIT AND FIT TESTING

It is important to note that respirators should adjust snugly to the face of the user, thus avoiding leaks at the borders. If there are leaks at the borders then it will be easier to inhale infectious particles. The presence of facial hair prevents the proper use of respirators and permits the potential entry of infectious particles. Additionally, since different people have different face shapes, there is no single respirator that will fit all people. For this reason, it is important to perform a fit test to know the proper size and model to use and to be sure that users can recognize a good fit. A fit test should be performed by a trained staff member. The health care facility should have several types and sizes of respirators to assure respiratory protection for health care workers at risk.

Using respirators without performing a fitting test offered only 67% protection, much less than the expected level. Using the fitting test, the level of protection increases to 96%, which is considered adequate protection. Without using the fit test health care workers may be exposed to a higher risk of infection.





5.3. FACE MASKS

Face masks, such as surgical masks made of cloth or paper may look similar to fit-tested respirators, but use of a surgical or face mask does not protect health care workers, other staff, patients, or visitors against TB. Therefore, it is NOT recommended that health care workers and other staff or visitors in TB care settings wear these face masks for protection. Some face masks can be used by infectious patients to diminish the number of TB bacilli propagated into the air.

However, the use of face masks should not take the place of educating TB patients on effective cough hygiene. The use of personal respiratory protection should be part of a program that includes training of health care workers on personal protection, the selection of appropriate well-fitting respirators, and training of patients on respiratory hygiene and cough etiquette.

For more information on infection control policies and guidelines Please consult the WHO publication: *Guidelines for the Prevention of Tuberculosis in Health Care Facilities in Resource-Limited Settings* and its addendum: *Tuberculosis Infection Control In The Era of Expanding HIV Care And Treatment* or consult the recommended reading at the end of this section.

IN THIS SECTION YOU LEARNED THAT...

SECTION 7

- There are three types of infection control strategies used to diminish the transmission of TB within a health facility: administrative (managerial); environmental; and personal respiratory protection
- TB patients and suspects are to be considered infectious if they have pulmonary TB disease (lungs, airway or larynx), are coughing or are undergoing cough inducing procedures and are AFB sputum smears positive
- The most effective measures against transmission of TB within a facility are the prompt detection, education and separation of TB suspects and diagnosis and proper treatment of TB patients
- Environmental strategies are the second line of defense for preventing the spread of TB in HIV care settings
- It is important to recognize that if administrative strategies and work practices are inadequate, environmental strategies will not eliminate the transmission risk
- Environmental strategies are based on mechanical or natural ventilation, and may be supplemented with filters
- Personal respiratory protection (i.e., the selection and training in the use of respirators) is generally not a priority intervention, and should be only used in areas where concentrations of infectious droplet nuclei of *M. tuberculosis* cannot be adequately reduced by environmental and administrative strategies
- Respirators are different from face masks, such as surgical masks made of cloth or paper
- Use of a face mask does not protect health care workers, other staff, patients, or visitors against TB

SELF ASSESSMENT QUESTIONS AND EXERCISES: TUBERCULOSIS INFECTION CONTROL

1. Rate each case below according to likelihood of transmitting TB as either

“P” for Possible transmission of TB, or

“U” for Unlikely to transmit TB.

- a) ___ 31 year old female who brings her 1 month old daughter for immunization. She reports a cough since her daughter's birth.
- b) ___ 24 male patient on new patient treatment for two months under DOT
- c) ___ A 45 year old male asking for an exam due to cough. He mentions his wife is being treated for TB.
- d) ___ A 18 year old female with pulmonary TB who has been on retreatment for 1 week
- e) ___ A 58 year old patient with lymphatic TB (no other disease site)
- f) ___ A pediatric patient with sputum smear-negative pulmonary TB

2. List the order of priority and at least two examples of each type of TB infection control strategies

Priority	
	Respiratory Protection 1. _____ 2. _____
	Environmental Strategies 1. _____ 2. _____
	Administrative Strategies 1. _____ 2. _____

3. Write “T” for true or “F” for false beside each of the following statements:

- ___ A face mask (surgical type) worn by a coughing patient with TB can help prevent TB transmission.
- ___ A surgical mask worn by a health worker is a good way to prevent TB transmission.
- ___ Coughing patients should be sent outdoors to produce sputum samples.
- ___ A person who enters a closed examination room (no ventilation) 30 minutes after a newly-diagnosed pulmonary TB patient was there is at no risk of infection with TB.
- ___ Health staff should be checked for TB whenever they develop a cough for more than 2 weeks.

4. The following picture depicts a patient waiting area at a health facility.



- a. What are two things about this situation that are good infection control measures.
- b. What are two things that should be done if a patient is found to be coughing.

5. The following picture depicts a waiting area in at a TB program. What are some potential problems with this situation, what questions would you have about this situation?



ANSWERS

1: a) P b) U c) P d) P e) U f) U

2:

First priority: Administrative Strategies

(There are multiple responses possible) Fit Testing and Use of N 95 Respirator in high risk situations

Second priority: Environmental Strategies

(There are multiple responses possible) Natural ventilation (opening windows and doors) and UV light

Third priority: Respiratory Protection

(There are multiple responses possible) An infection control plan for your facility, Screen all patients for cough and

3: T, F, T, F, T

4: a: Open air, natural ventilation, not crowded

b: Quickly separate patient, inquire about length of cough, collect sputum

5:

Answers: Are infectious patients being separated from others? Is there a less crowded space for TB patients to wait? Are TB patients waiting a long time to take medicines? Are there non TB patients waiting with the TB patients?

Congratulations on finishing the course!

This refresher TB course was designed to build your capacity to detect, diagnose and treat TB among their patients. It also provides useful TB information for other health care providers who may be involved with the care of TB patients. In many countries, TB constitutes a significant health burden and depletes important health and human resources. TB control is an important and necessary part of any health service offering. It must be implemented in coordination with the NTP and based in the WHO guidelines and recommendations noted in this course. It is important to note that NTPs are key partners as they tailor TB control priorities to meet the specific epidemiological and resource needs of their countries. Therefore, this course supplements and does not replace any NTP guidelines for TB control.

In all sections, there are links to more documents in case you choose to research a specific area further. The bibliography at the end of this course also provides further reading and many technical guidelines are available on the WHO website in several languages. Physicians are encouraged to research areas that they find particularly relevant to TB epidemiology in their setting, such as drug resistance or high rates of HIV infection.

Standards for Diagnosis

Standard 1. All persons with otherwise unexplained productive cough lasting two-three weeks or more should be evaluated for tuberculosis.

Standard 2. All patients (adults, adolescents, and children who are capable of producing sputum) suspected of having pulmonary tuberculosis should have at least two sputum specimens submitted for microscopic examination in a quality-assured laboratory. When possible at least one early morning specimen should be obtained.

Standard 3. For all patients (adults, adolescents, and children) suspected of having extra-pulmonary tuberculosis, appropriate specimens from the suspected sites of involvement should be obtained for microscopy, culture, and histopathological examination.

Standard 4. All persons with chest radiographic findings suggestive of tuberculosis should have sputum specimens submitted for microbiological examination.

Standard 5. The diagnosis of sputum smear-negative pulmonary tuberculosis should be based on the following criteria: at least two negative sputum smears (including at least one early morning specimen); chest radiographic findings consistent with tuberculosis; and lack of response to a trial of broad-spectrum antimicrobial agents. (NOTE: Because the fluoroquinolones are active against *M. tuberculosis* complex and, thus, may cause transient improvement in persons with tuberculosis, they should be avoided). For such patients, sputum cultures should be obtained. In persons who are seriously ill or have known or suspected HIV infection, the diagnostic evaluation should be expedited and if clinical evidence strongly suggests tuberculosis, a course of antituberculosis treatment should be initiated..

Standard 6. In all children suspected of having intrathoracic (i.e., pulmonary, pleural, and mediastinal or hilar lymph node) tuberculosis, bacteriological confirmation should be sought through examination of sputum (by expectoration, gastric washings, or induced sputum) for smear microscopy and culture. In the event of negative bacteriological results, a diagnosis of tuberculosis should be based on the presence of abnormalities consistent with tuberculosis on chest radiography, a history of exposure to an infectious case, evidence of tuberculosis infection (positive tuberculin skin test or interferon gamma release assay) and clinical findings suggestive of tuberculosis. For children suspected of having extrapulmonary tuberculosis, appropriate specimens from the suspected sites of involvement should be obtained for microscopy and for culture and histopathological examination.

Standards for Treatment

Standard 7. Any practitioner treating a patient for tuberculosis is assuming an important public health responsibility to prevent ongoing transmission of the infection and the development of drug resistance. To fulfill this responsibility the practitioner must not only prescribe an appropriate regimen, but also utilize local public health services and other agencies, when necessary, to assess the adherence of the patient and to address poor adherence when it occurs.

Standard 8. All patients (including those with HIV infection) who have not been treated previously should receive an internationally accepted first line treatment regimen using drugs of known bioavailability. The initial phase should consist of two months of isoniazid, rifampicin, pyrazinamide and ethambutol. The continuation phase should consist of isoniazid and rifampicin given for 4 months. The doses of antituberculosis drugs used should conform to international recommendations. Fixed dose combinations (FDCs) of two (isoniazid and rifampicin), three (isoniazid, rifampicin, and pyrazinamide) and four (isoniazid, rifampicin, pyrazinamide, and ethambutol) drugs are highly recommended.

Standard 9. To assess and foster adherence, a patient-centered approach to administration of drug treatment, based on the patient's needs and mutual respect between the patient and the provider, should be developed for all patients. Supervision and support should be individualized and should draw on the full range of recommended interventions and available support services, including patient counseling and education. A central element of the patient-centered strategy is the use of measures to assess and promote adherence to the treatment regimen and to address poor adherence when it occurs. These measures should be tailored to the individual patient's circumstances and be mutually acceptable to the patient and the provider. Such measures may include direct observation of medication ingestion (directly observed therapy-DOT) and identification and training of a treatment supporter (for tuberculosis and, if appropriate, for HIV) who is acceptable and accountable to the patient and to the health system. Appropriate incentives and enablers, including financial support may also serve to enhance treatment adherence.

Standard 10. Response to therapy in patients with pulmonary tuberculosis should be monitored by follow-up sputum microscopy (two specimens) at the time of completion of the initial phase of treatment (two months). If the sputum smear is positive at completion of the initial phase, sputum smears should be examined again at 3 months and, if positive, culture and testing for resistance to isoniazid and rifampicin should be performed. In patients with extra-pulmonary tuberculosis and in children, the response to treatment is best assessed clinically.

Standard 11. An assessment of the likelihood of drug resistance, based on history of prior treatment, exposure to a possible source case having drug resistant organisms, and the community prevalence of drug resistance, should be obtained for all patients. Drug susceptibility testing should be performed at the start of therapy for all previously treated patients. Patients who remain sputum smear positive at completion of 3 months of treatment and patients who have failed, defaulted from or relapsed following one or

more courses of treatment should always be assessed for drug resistance. For patients in whom drug resistance is considered to be likely, culture and testing for susceptibility/resistance to at least isoniazid and rifampicin should be performed promptly. Patient counseling and education should begin immediately to minimize the potential for transmission. Infection control measures appropriate to the setting should be applied.

Standard 12. Patients with or highly likely to have tuberculosis caused by drug-resistant (especially MDR/XDR) organisms should be treated with specialized regimens containing second-line anti-tuberculosis drugs. The regimen chosen may be standardized or based on suspected or confirmed drug susceptibility patterns. At least four drugs to which the organisms are known or presumed to be susceptible, including an injectable agent, should be used and treatment should be given for at least 18 months beyond culture conversion. Patient centered measures are required to ensure adherence. Consultation with a provider experienced in treatment of patients with MDR/XDR tuberculosis should be obtained.

Standard 13. A written record of all medications given, bacteriologic response, and adverse reactions should be maintained for all patients.

Standards for Addressing HIV Infection and other Co-morbid Conditions

Standard 14. HIV testing and counseling should be recommended to all patients with, or suspected of having tuberculosis. Testing is of special importance as part of routine management of all patients in areas with a high prevalence of HIV infection in the general population, in patients with symptoms and/or signs of HIV-related conditions, and in patients having a history suggestive of high risk of HIV exposure. Because of the close relationship of tuberculosis and HIV infection, in areas of high HIV prevalence integrated approaches to prevention and treatment of both infections are recommended.

Standard 15. All patients with tuberculosis and HIV infection should be evaluated to determine if antiretroviral therapy is indicated during the course of treatment for tuberculosis. Appropriate arrangements for access to antiretroviral drugs should be made for patients who meet indications for treatment. However, initiation of treatment for tuberculosis should not be delayed. Patients with tuberculosis and HIV infection should also receive co-trimoxazole as prophylaxis for other infections.

Standard 16. Persons with HIV infection who, after careful evaluation, do not have active tuberculosis should be treated for presumed latent tuberculosis infection with isoniazid for 6-9 months.

Standard 17. All providers should conduct a thorough assessment for co-morbid conditions that could affect tuberculosis treatment response or outcome. At the time the treatment plan is developed, the provider should identify additional services that would support an optimal outcome for each patient and incorporate these services into an individualized plan of care. This plan should include assessment of and referrals for treatment of other illnesses with particular attention to those known to affect treatment outcome, for instance care for diabetes mellitus, drug and alcohol treatment programs, tobacco smoking cessation programs, and other psychosocial support services, or to such services as antenatal or well baby care.

Standards for Public Health

Standard 18. All providers of care for patients with tuberculosis should ensure that persons who are in close contact with patients who have infectious tuberculosis are evaluated and managed in line with international recommendations. The determination of priorities for contact investigation is based on the likelihood that a contact: 1) has undiagnosed tuberculosis; 2) is at high risk of developing tuberculosis if infected; 3) is at risk of having severe tuberculosis if the disease develops; and 4) is at high risk of having been infected by the index case. The highest priority contacts for evaluation are:

- Persons with symptoms suggestive of tuberculosis
- Children aged <5 years
- Contacts with known or suspected immunocompromise, particularly HIV infection
- Contacts of patients with MDR/XDR tuberculosis

Other close contacts are a lower priority group.

Standard 19. Children <5 years of age and persons of any age with HIV infection who are close contacts of an infectious index patient and who, after careful evaluation, do not have active tuberculosis, should be treated for presumed latent tuberculosis infection with isoniazid.

Standard 20. Each health care facility caring for patients who have or are suspected of having infectious tuberculosis should develop and implement an appropriate tuberculosis infection control plan.

Standard 21. All providers must report both new and retreatment tuberculosis cases and their treatment outcomes to local public health authorities, in conformance with applicable legal requirements and policies.

Tuberculosis Coalition for Technical Assistance. International Standards for Tuberculosis Care (ISTC). The Hague: Tuberculosis Coalition for Technical Assistance, 2nd Edition 2009. (in press)

SPUTUM COLLECTION INSTRUCTIONS FOR A PATIENT

ANNEX 2

COLLECT SPUTUM FOR EXAMINATION

- **Explain** that the TB suspect needs a sputum examination to determine whether there are TB bacilli in the lungs.
- **Label** the sides of the sputum containers (not the lids).
 - 3 samples are needed for diagnosis of TB.
 - 2 samples are needed for follow-up examination.
- **Fill out Request for Sputum Examination form.**
- **Explain and demonstrate, fully and slowly, the steps to collect sputum.**
 - * Show the TB suspect how to open and close the container.
 - * Breathe deeply and demonstrate a deep cough. The TB suspect must produce sputum, not only saliva.
 - * Explain that the TB suspect should cough deeply to produce sputum and spit it carefully into the container.
 - *
- **Collect**
 - * Give the TB suspect the container and lid.
 - * Send the TB suspect outside to collect the sample in the open air if possible, or to a well-ventilated place, away from other people and with sufficient privacy.
 - * When the TB suspect returns with the sputum sample, look at it. Is there a sufficient quantity of sputum (not just saliva)? If not, ask the TB suspect to add some more.
 - * Explain when the TB suspect should collect the next sample, if needed. (See schedule below.)
 - *

TB SPECIMEN

Name: _____
Health facility: _____
Date: _____
Specimen no. _____

SCHEDULE FOR COLLECTING THREE SPUTUM SAMPLES

Day 1:

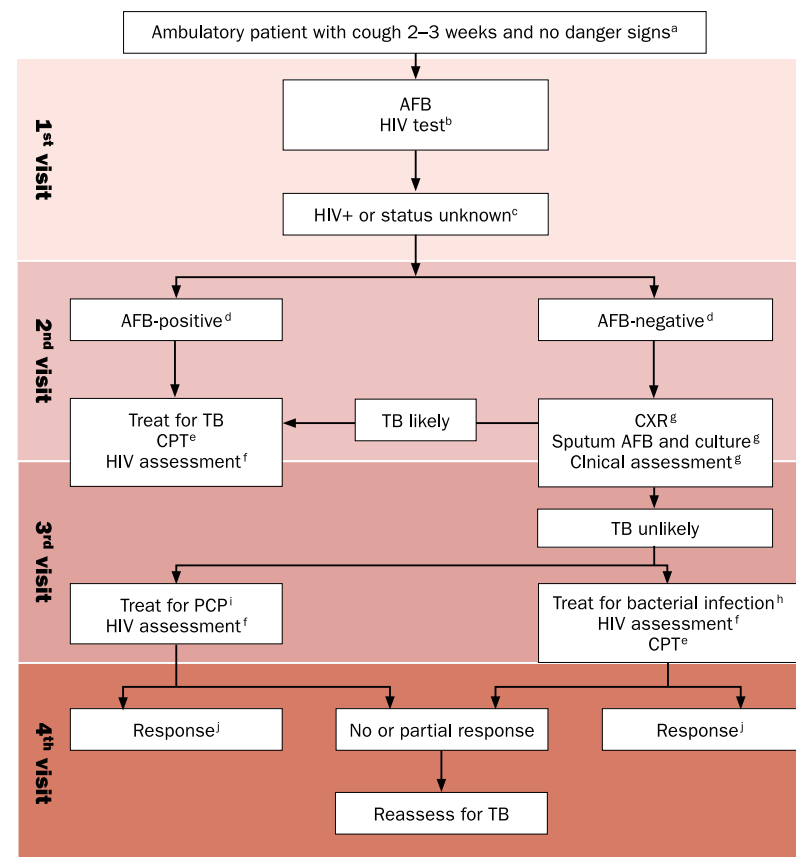
- * Collect “on-the-spot” sample as instructed above (**Sample 1**).
- * Instruct the TB suspect how to collect an early morning sample tomorrow (first sputum after waking). Give the TB suspect a labeled container to take home. Ask the TB suspect to bring the sample to the health facility tomorrow.

Day 2:

- * Receive early morning sample from the TB suspect (**Sample 2**).

- When you collect the third sample, tell the TB suspect when to return for the results.
- Store
 - * Check that the lid is tight. Wipe off the outside of the container, if needed.
 - * Isolate each sputum container in its own plastic bag, if possible, or wrap in newspaper.
 - * Store in a cool place.
 - * Wash your hands.
- Send
 - * Send the samples from health facility to the laboratory.
 - * Total time from collection until reaching laboratory should be no more than 5 days.

Algorithm for the diagnosis of tuberculosis in ambulatory patient in HIV-prevalent settings



^a The danger signs include any one of: respiratory rate >30/minute, fever >39 °C, pulse rate >120/min and unable to walk unaided.

^b For countries with adult HIV prevalence rate ≥1% or prevalence rate of HIV among tuberculosis patients ≥5%.

^c In the absence of HIV testing, classifying HIV status unknown as HIV-positive depends on clinical assessment or national and/or local policy.

^d AFB-positive is defined as at least one positive and AFB-negative as two or more negative smears.

^e CPT = Co-trimoxazole preventive therapy.

^f HIV assessment includes HIV clinical staging, determination of CD₄ count if available and referral for HIV care.

^g The investigations within the box should be done at the same time wherever possible in order to decrease the number of visits and speed up the diagnosis.

^h Antibiotics (except fluoroquinolones) to cover both typical and atypical bacteria should be considered.

ⁱ PCP: *Pneumocystis carinii* pneumonia, also known as *Pneumocystis jirovecii* pneumonia.

^j Advise to return for reassessment if symptoms recur.

Suspect ETB in patients with

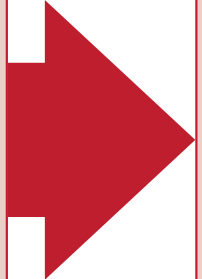
Cough for two weeks or more *or*

- Unintentional weight loss with
 - Night sweats *and*
 - Temperature >37.5 °C or feels feverish
- Breathlessness (effusion/pericarditis) *or*
- Enlarged glands in neck/armpit *or*
- Chest X-ray
 - Miliary or diffuse shadowing
 - Large heart (especially if symmetrical and rounded)
 - Pleural effusion
 - Enlarged lymph nodes inside the chest
- Chronic headache or altered mental state

Suspect disseminated tuberculosis in all people living with HIV who experience rapid or marked weight loss, fever and night sweats

Establish HIV status if ETB is suspected

- Advise and arrange for rapid HIV testing if status is unknown or last test was negative
 - Explain that this will affect the way that this illness is investigated and treated
 - Discuss the need for antiretroviral treatment if HIV-related tuberculosis is diagnosed
 - If consent is given, try to arrange testing on the same day



Look and listen for

- Lymph nodes swelling in the neck or armpits (if present with other types of ETB it may provide the only way to confirm the diagnosis)

Possible tuberculosis lymphadenitis

- Signs of fluid in the chest
 - Absent breath sounds
 - Reduced chest wall movement
 - Dull to percussion

Possible tuberculosis pleural effusion

- Signs of fluid around the heart
 - Heart sounds distant
 - Swollen legs and/or abdomen
 - Neck and hand veins distended with arm held above the shoulder

Possible tuberculosis pericarditis

- Signs of meningitis
 - neck stiffness
 - confusion
 - abnormal eye movements

Possible tuberculosis meningitis

Recommended dosages of anti-TB drugs

Drug (with abbreviation)	Recommended dosage		Presentations
	Daily	3 times per week	
Rifampicin (R)	8 – 12 mg/kg	8 – 12 mg/kg	150 mg or 300 mg tablets
Isoniazid (H)	4 – 6 mg/kg	8 – 12 mg/kg	100 mg or 300 mg tablets
Pyrazinamide (Z)	20 – 30 mg/kg	30 – 40 mg/kg	400 mg tablets
Ethambutol (E)	15 – 20 mg/kg	25 – 35 mg/kg	100 mg or 400 mg tablets
Streptomycin (S)	12 – 18 mg/kg	12 – 18 mg/kg	Vial 1g (IM)

Available presentations of fixed-dose combinations

Fixed-dose combinations	Presentations (combination tablets)	
	For daily administration	For administration 3 times per week
Rifampicin + Isoniazid (RH)	(R 300 mg + H 150 mg), or (R 150 mg + H 75 mg), or (R 60 mg + H 30 mg)*	(R 150 mg + H 150 mg), or (R 60 mg + H 60 mg)*
Isoniazid + Ethambutol (HE)	(H 150 mg + E 400 mg)	NA
Isoniazid + Thioacetazone (HT)	(H 300 mg + T 150 mg), or (H 100 mg + T 50 mg)*	NA
Rifampicin + Isoniazid + Pyrazinamide (RHZ)	(R 150 mg + H 75 mg + Z 400 mg), or (R 60 mg + H 30 mg + Z 150 mg)*	(R 150 mg + H 150 mg + Z 500 mg)
Rifampicin + Isoniazid + Pyrazinamide + Ethambutol (RHZE)	(R 150 mg + H 75 mg + Z 400 mg + E 275 mg)	NA

Weight-based dosing of antituberculosis drugs TB for treatment drug resistant TB				
Medication (drug abbreviation), (common presentation)	<33 kg	Weight class		>70 kg (also maximum dose)
		33–50 kg	51–70 kg	
Group 1: First -line oral antituberculosis drugs				
Isoniazid (H) (100, 300 mg)	4–6 mg/kg daily or 8–12 mg 3 x wk	200–300 mg daily or 450–600 mg 3 x wk	300 mg daily or 600 mg 3 x wk	300 mg daily or 600 mg 3 x wk
Rifampicin (R) (150, 300 mg)	10–20 mg/kg daily	450–600 mg	600 mg	600 mg
Ethambutol (E) (100, 400 mg)	25 mg/kg daily	800–1200 mg	1200–1600 mg	1200–1600 mg
Pyrazinamide (Z) (500mg)	30-40 mg/kg daily	1000–1750 mg	1750–2000 mg	2000mg - 2500mg
Group 2: Injectable antituberculosis drugs				
Streptomycin (S) (1 g vial)	15–20 mg/kg	500–750 mg	1000 mg	1000 mg
Kanamycin (Km) (1 g vial)	15–20 mg/kg	500–750 mg	1000 mg	1000 mg
Amikacin (Am) (1 g vial)	15–20 mg/kg	500–750 mg	1000 mg	1000 mg
Capreomycin (Cm) (1 g vial)	15–20 mg/kg	500–750 mg	1000 mg	1000 mg
Group 3: Fluoroquinolones				
Ofloxacin (Ofx) (200, 300, 400 mg)	15–20 mg/kg daily	800 mg	800 mg	800–1000 mg
Levofloxacin (Lfx) (200, 500 mg)	7.5–10 mg/kg daily	750 mg	750 mg	750–1000 mg
Moxifloxacin (Mfx) (400 mg)	7.5–10 mg/kg daily	400 mg	400 mg	400 mg

Weight-based dosing of antituberculosis drugs TB for treatment drug resistant TB				
Medication (drug abbreviation), (common presentation)	<33 kg	Weight class		>70 kg (also maximum dose)
		33–50 kg	51–70 kg	
Group 4: Oral bacteriostatic second-line antituberculosis drugs				
Ethionamide (Eto) (250 mg)	15–20 mg/kg daily	500 mg	750 mg	750–1000 mg
Protonamide (Pto) (250 mg)	15–20 mg/kg daily	600 mg	750 mg	750–1000 mg
Cycloserine (Cs) (250 mg)	15–20 mg/kg daily	500 mg	750 mg	750–1000 mg
Terizidone (Trd) (250 mg)	15–20 mg/kg daily	600 mg	600 mg	900 mg
P-aminosalicylic acid (PAS) (4 g sachets)	150 mg/kg daily	8 g	8 g	8-12 g
Sodium PAS	Dosing can vary with manufacture and preparation: check dose recommended by the manufacturer.			
Thioacetazone (Thz)	Usual dose is 150 mg for adults			

Weight-based dosing of antituberculosis drugs TB for treatment drug resistant TB	
GROUP 5: Agents with unclear role in dr-tb treatment (not recommended by who for routine use in mdr-TB patients). optimal doses for DR-TB are not established	
Clofazimine (Cfz)	Usual adult dose is 100 mg to 300 mg daily. Some clinicians begin at 300 mg daily and decrease to 100 mg after 4 to 6 weeks.
Linezolid (Lzd)	Usual adult dose is 600 mg twice daily. Most reduce the dose to 600 mg once a day after 4 to 6 weeks to decrease adverse effects.
Clavulanate (Amx/Clv)	Dosages for DR-TB not well defined. Normal adult dose 875/125 mg twice a day or 500/125 mg three times a day. Dosages of 1000/250 have been used but adverse side effects may limit this dosing.
Thioacetazone (Thz)	Usual adult dose is 150 mg
Imipenem/cilastatin (Ipm/Cln)	Usual adult dose is 500–1000 mg IV every 6 hours.
Clarithromycin (Clr)	Usual adult dose is 500 mg twice daily
High-dose isoniazid (High-dose H)	16–20 mg/kg daily

[illegible]

Name: _____

Sex: ☐ M ☐ F Date of registration in District TB Register: _____

Age: _____ Health facility: _____

Address: _____

Name / address of treatment supporter (if applicable)
_____**I. INITIAL PHASE** - prescribed regimen and dosagesRegimen: ☐ New ☐ Retreatment

Number of tablets per dose, doses per week, dosage of S:

(RHZE)

S

Cotrimoxazole

ARV

Other

Referral by:

- ☐ Self-referral
☐ Community member
☐ Public facility
☐ Private facility/provider: _____

☐ Other, specify: _____**Disease site** (check one)☐ Pulmonary ☐ Extrapulmonary, specify _____**Type of patient** (check one)

- ☐ New ☐ Treatment after default
☐ Relapse ☐ Treatment after failure
☐ Transfer in ☐ Other

Sputum smear microscopy				Weight (kg)
Month	Date	Lab No.	Result	
0				

TB/HIV		
	Date	Result*
HIV test		
HIV test		
CPT start		
ART start		

* (Pos) Positive; (Neg) Negative; (I) Discordant/inconclusive; (ND) Not Done/unknown

Tick appropriate box after the drugs have been administered

Daily intake observed: enter ✓. Periodic supply: enter X on day when drugs are collected and draw a horizontal line (——●——) through number of days supplied. Ø = drugs not taken

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	Number doses this month	Total number doses given	Drugs given to supporter	
Month																																		Date	Doses

Number of tablets per dose

(RH)

(RHE)

Other

Daily supply: enter ✓. Periodic supply, enter X on day when drugs are collected and draw a horizontal line (———●) through the number of days supplied. Ø = drugs not taken

Day Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

X-ray (at start)

Date: _____

Results (-), (+), *ND***HIV care**

Pre ART Register No. _____

CD4 result _____

ART eligibility (*Y/N/Unknown*) _____

Date eligibility assessed _____

ART Register No. _____

Comments: _____

Treatment outcome

Date of decision _____

☐ Cure☐ Treatment completed☐ Died☐ Treatment failure☐ Default☐ Transfer out

Name and address of contact person: _____

Treatment outcome	Definition
Cured	A culture-positive patient who has completed treatment with at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment. If only one positive culture is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart
Treatment completed	A patient who has completed treatment approved by the Approval Committee, but does not meet the definition for cure because of lack of bacteriological results (i.e. fewer than five cultures were performed in the final 12 months of treatment). These include patients who are extrapulmonary or have negative cultures at the start of treatment.
Failed	Treatment will be considered to have failed if two or more of the five cultures recorded in the final 12 months of therapy are positive, or if any one of the final three cultures is positive. (Treatment will also be considered to have failed if a clinical decision has been made to terminate treatment early because of poor response or adverse events. These latter failures can be indicated separately to do sub-analysis.)
Died	A patient who died for any reason during the course of treatment
Defaulted	A patient whose treatment was interrupted for 2 consecutive months or more for any reason
Transferred out	A patient who has been transferred to another recording and reporting unit with proper referral form and for whom the treatment outcome is not known.

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PHOTOGRAPHS

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