Caribbean Guidelines for the Prevention, Treatment, Care, and Control of Tuberculosis and TB/HIV

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I-TECH
International Training & Education Center for Health

CHART
Caribbean HIV/AIDS Regional Training Network

Institut Pasteur de la Guadeloupe

Francis J. Curry National Tuberculosis Center

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List of Abbreviations

ACH	Air changes per hour
AFB	Acid fast bacilli
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
BCG	Bacille Calmette Guerin
BSL	Biosafety Level
CAREC	Caribbean Epidemiology Centre
CDC	Centers for Disease Control and Prevention
CMCs	CAREC member countries
CTWG	Caribbean Technical Working Group
CXR	Chest X-ray
DNA	Deoxyribonucleic acid
DOT	Directly observed treatment
DOTS	Directly observed treatment, short-course (global strategy for TB control)
DST	Drug susceptibility testing
EMB/E	Ethambutol
EPTB	Extrapulmonary tuberculosis
EQA	External Quality Assessment (or Assurance)
FEFO	First expiry, first out
HIV	Human immunodeficiency virus
IGRA	Interferon-gamma release assay
IMAAI	Integrated management of adolescent and adult illness
INH/H	Isoniazid
IPT	Isoniazid preventive therapy
IQA	Internal quality assurance
IRIS	Immune reconstitution inflammatory syndrome
ISTC	International Standards for Tuberculosis Care
IUATLD	International Union Against Tuberculosis and Lung Disease
LTBI	Latent tuberculosis infection
MAC	*Mycobacterium avium* complex
MAI	*Mycobacterium avium-intracellulare*
MDR	Multidrug-resistant
M. tb	*Mycobacterium tuberculosis*

MOH	Ministry of Health
MOTT	Mycobacteria other than tuberculosis
NAP	National AIDS Program
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside/nucleotide reverse transcriptase inhibitor
NTM	Nontuberculous mycobacteria
NTP	National Tuberculosis Program
PAHO	Pan American Health Organization
PCR	Polymerase chain reaction
PCTC	Patients' Charter for Tuberculosis Care
PHCO	PAHO HIV Caribbean Office
PI	Protease inhibitor
PITC	Provider-initiated approach to HIV testing and counseling
PMTCT	Prevention of mother-to-child transmission
PPD	Purified protein derivative
PPE	Personal protective equipment
PTB	Pulmonary tuberculosis
PZA/Z	Pyrazinamide
QA	Quality assurance
QC	Quality control
RIF/R	Rifampicin
RNA	Ribonucleic acid
S	Streptomycin
SOP	Standard operating procedure
STI	Sexually transmitted infection
TB	Tuberculosis
TST	Tuberculin skin test (Mantoux)
UNAIDS	Joint United Nations Program on HIV/AIDS
USAID	United States Agency for International Development
VCT	Voluntary counseling and testing
WHO	World Health Organization
XDR	Extensively drug-resistant
ZN	Ziehl Neelsen

Preface

The need to improve systems for the management and control of tuberculosis (TB) in the Caribbean is evident from the growing number of cases of TB in Caribbean Epidemiology Centre (CAREC) member countries. These revised guidelines for TB and TB/HIV prevention, treatment, care, and control are intended for use by National TB and HIV Programs in the Caribbean. Their purpose is to:

- Reemphasize and underscore the importance of full implementation of the Stop TB Strategy to TB prevention and control efforts in the Caribbean
- Serve as a reference document for Caribbean Nations in order to demonstrate where the *International Standards for Tuberculosis Care* (*ISTC*) can support National TB Program (NTP) guidelines
- Highlight areas where NTPs and National AIDS Programs (NAP) can collaborate to improve diagnosis, treatment and management of patients with TB, HIV and TB/HIV co-infection
- Provide practical recommendations and useful tools that can be adapted to meet the diversity of Caribbean NTPs

The content of this document incorporates the revised guidelines of the World Health Organization (WHO) "Treatment of Tuberculosis, Fourth Edition, 2009" and the revised *ISTC*, 2009. Technical Working Groups (TWGs) were convened to review the revised WHO recommendations and other relevant literature to determine application to the Caribbean Region settings. Technical input regarding HIV treatment and care was taken from the *Caribbean Guidelines for the Care and Treatment of Persons with HIV Infection: Recommendations for Antiretroviral Therapy for Adults and Adolescents with HIV Infection*, 2007. Relevant references are noted after each chapter.

The primary aims of the document are to promote the use of internationally recognized standards of care and operational procedures, and to emphasize a programmatic approach to prevention, treatment, care, and control of TB and TB/HIV in the Caribbean Region. The primary target audience is NTP personnel with a secondary audience being National AIDS Programs and other integrated care service providers. The objectives of improving efficiency, equity, and quality of services as highlighted, are in concert with the principles of effective TB control, as articulated in the Stop TB Strategy.

This document is not intended to serve as a comprehensive clinical text. However, general recommendations related to diagnosis, treatment and care have been included to promote adherence to current standards and best practices. Policy makers, program managers and coordinators in member countries may wish to use these guidelines, noting that some customization may be needed to describe country-specific processes and procedures. We recommend the use of an in-service training program to familiarize national care providers with these guidelines and to sensitize them on best practices for TB and TB/HIV prevention, care, treatment and control. Educators in health institutions may also find the guidelines useful in developing teaching materials for pre-service education and training of students.

Quality-assured Directly Observed Treatment, Short-course (DOTS) is the cornerstone of TB control and National authorities would do well to have this important strategy implemented without further delay. Without this essential strategic approach, it is doubtful that NTP targets and goals will be realized.

Introduction

1

Tuberculosis continues to be an important global public health problem, intensified by the human immunodeficiency virus (HIV) epidemic. The World Health Organization (WHO) reported an estimated 9.27 million new TB cases (139/100,000 population) and over 1.7 million deaths resulting from TB in 2007.[1] Nearly two billion people worldwide are infected with *Mycobacterium tuberculosis* (*M. tb*); 40 million are HIV infected and approximately one-third of these (13 million) are dually infected with *M. tb* and HIV.[2] HIV is the most powerful risk factor known to increase the likelihood of progression of TB to overt disease or to influence the reactivation of latent TB; for a person dually infected with HIV and *M. tb*, the lifetime risk of developing TB is about 50%. It is noteworthy from a public health point of view that, among the more serious opportunistic infections associated with HIV, TB is one of the few that is transmissible, treatable, and preventable. In addition, transmission of TB can occur from a person who is dually infected to an otherwise healthy host, and this has implications for the spread of the disease to HIV-negative members of households and healthcare personnel.

Methods for diagnosis, treatment, and prevention of TB are well established and can be effectively delivered through National Tuberculosis Programs (NTPs). These guidelines present best practices related to preventing, diagnosing, and treating patients affected with TB and address the fundamental challenges that NTPs face in preventing and controlling tuberculosis today. The growing problems of drug-resistant tuberculosis and concurrent HIV and TB global epidemics are our most pressing threats to TB control. NTPs must forge partnerships with National AIDS Programs (NAPs) and others in order to effectively tackle both of these special problems. These partnerships should include opportunities for joint planning to define activities where collaboration can occur. It is recommended that the framework for an effective NTP should be based on the Stop TB Strategy, which includes a well-coordinated referral system, well-managed diagnostics, and delivery of treatment utilizing directly observed therapy (DOT) and patient-centered care approaches. Other key areas to success are the involvement of the general community and the private sector.

Progress toward TB control in the Caribbean has been slow despite recognition that emergence and/or increasing trends for the disease pose a threat to public health. The challenge ahead for Caribbean Nations is to deal with tremendous barriers to ensuring consistent access to directly observed treatment, short-course (DOTS) services and achieving TB control targets. There is urgent need to ensure high quality TB services through implementing the components of the Stop TB Strategy, which are summarized as follows:

1. Pursue high-quality DOTS expansion and enhancement
2. Address TB/HIV, multidrug-resistant TB (MDR-TB) and other challenges
3. Contribute to health system strengthening
4. Engage all care providers
5. Empower people with TB and communities
6. Enable and promote research

The Stop TB Strategy sets out the steps that the NTP and their stakeholders and partners

must embark upon, assisted by the national, regional, and global TB community. NTPs should use this framework when developing or updating a national TB control and prevention procedure manual. In this way, all facets of disease control will be incorporated. The organizational and management structure of the NTP should be described and linkages to the NAP outlined, including areas where clinical management and operational aspects are co-coordinated. In addition, monitoring and reporting requirements, roles and responsibilities of the different healthcare providers, as well as human resource needs must be defined.

Included in this manual are guidelines for establishing DOTS and coordination of activities between the NTP and NAP. These requirements can be tailored to the specific needs of the local situation.

When countries are yet to develop some of the strategies or when they are on the verge of implementation, revision to the NTP manual provides an opportunity for including operations and procedures that incorporate coordination and collaboration between TB and HIV programs and their activities.

Tuberculosis in the Caribbean

The CAREC region has experienced a resurgence of TB. During the first half of the 1980s, there was a progressive decline in the number of TB cases in CAREC member countries, followed by a leveling off in 1988 to 1989. Since that time, there has been a gradual but distinctly notable increase in TB in some member countries. The upward trend in HIV and the acquired immunodeficiency syndrome (AIDS) and the recent socioeconomic decline with its attendant problems are factors which favor the increase of active TB.

Recent health sector reform in CMCs has resulted in a number of major changes in health policy within the Ministries of Health (MOH). In this environment of change, it is opportune to accept the idea of changing the managerial approach to prevention and control of HIV and tuberculosis. Cooperation in planning and implementation of programs related to TB and HIV would undoubtedly help to conserve scarce resources and help both programs to achieve their stated goals. Historically these programs have evolved separately, although the biological link has been evident for some time. Now, in countries where teams have been functioning separately, it would be advantageous for them to work together in response to increasing demands for health services for persons with or at risk for tuberculosis, and persons with or at risk for HIV and AIDS. A proposed model is that collaborative activities can be coordinated and governed vertically by each program while interventions can be delivered in an integrated fashion. Maintenance of excellent documentation, adherence to the principles of the Stop TB program, supervised administration of antiretroviral drugs and other medication to persons with HIV and AIDS as required, and attention to the holistic needs of persons with both diseases should be promoted and practiced.

As with HIV, TB control must be mainstreamed into the health agenda. It must be included in the broader strategic planning approaches and financial framework aimed at poverty reduction.

Political commitment as well as cooperation and collaboration with healthcare workers at all levels of the health sector and the population at large are essential for the achievement of program goals.

HIV in the Caribbean

Surveillance efforts in the Caribbean must be improved to enable better characterization of the HIV epidemic in the region and to inform strategic planning. The UNAIDS 2007 annual Caribbean summary epidemiological update states that "…inadequate surveillance systems in several [Caribbean] countries are making it difficult to gauge recent trends in their epidemics."[3] A considerable share (17%) of AIDS cases reported in the Caribbean have no assigned risk category. As many cases are only officially reported long after the diagnosed individual has died, it is often too difficult or impossible to carry out epidemiological investigations.[4] Earlier in this decade sharp declines in HIV incidence were reported in some countries of the Caribbean; however, the most recent statistics indicate the stabilization of the regional HIV incidence. Given the scarcity of behavioral data in the region, it is challenging to determine if the earlier reduction in new HIV infections were due to the natural course of the epidemic or related to the impact of HIV prevention efforts.

UNAIDS estimated that in 2008, a total of 240,000 (220,000–260,000) persons were living with HIV in the Caribbean.[4] Additionally, it is estimated that the HIV epidemic has left approximately 250,000 Caribbean children orphaned.[5] Haiti and the Dominican Republic comprise the epicenter of the HIV epidemic in the Americas, accounting for nearly three-quarters of the people living with HIV in the Caribbean.[4] In 2008, the region's estimated adult HIV prevalence was 1.0% (0.9–1.1%),[4] (ranging from 0.1% in Cuba to 3.0 in the Bahamas).[4] Overall, roughly 20,000 (16,000-24,000) new infections and 12,000 (9,300–14,000) deaths due to AIDS occurred in 2008, with AIDS remaining one of the leading causes of death among persons aged 25–44 years.[4] Reports from the 21 CMCs for the period 1982-2005, have documented approximately 31,000 cases of AIDS.[6]

In the Caribbean, approximately half of those who need ART do not have access. The Universal Access report, 2009 indicated that at the end of 2008, 51% of those in need of ART in low and middle income countries in the Caribbean region had access to treatment, compared to 43% at the end of 2007.[7]

Throughout the Caribbean, the primary mode of transmission of HIV is through unprotected sexual intercourse, with unprotected intercourse between sex workers and their clients being a significant factor.[4] In the early years of the epidemic, surveillance data revealed that "transmission of HIV was primarily homosexual; [whereas] current data reveal a mosaic of homo/bi and heterosexual transmission, with a current male-to-female ratio of almost one-to-one."[6]

Persons selling and buying sex and persons engaging in other patterns of transactional sex are among the key drivers of the Caribbean HIV epidemic. A 2005 study among sex workers in Jamaica found a seroprevalence of 9%,[8] and PAHO/CAREC-supported studies documented sex worker prevalence as high as 31% in Guyana (2000)[9] and 21% in Suriname (2004).[10] Although women are believed to account for the vast majority of sex workers in the Caribbean, emerging evidence suggests that male sex workers who sell their services to tourists in the region may also face considerable risks of acquiring HIV.[4]

Approximately 11% of reported HIV cases are estimated to be due to unsafe sex between men, with HIV prevalence in populations of men who have sex with men as high as 33% in Kingston, Jamaica (2000), 11% in the Dominican Republic (1998), 6.7% in Suriname (2005), and 20% in Trinidad and Tobago (2005).[11] Data from selected studies in 2004 and 2005 suggest that 12% of reported HIV infections in men are likely to have resulted from unprotected sex with other men.[12,13] Underreporting of cases among this sub-population

is a challenge for researchers as well as for national health information systems. Under-reporting is attributed largely to the illegality, stigma and discrimination surrounding sex work and homosexuality.

The HIV epidemic is also shifting to younger populations, with certain Caribbean countries having patterns of markedly higher prevalence in either one sex or the other. For example, in 2007, prevalence in young males 15–24 years of age in the Bahamas, Barbados, and Jamaica was twice as high as prevalence in the corresponding female cohort. In contrast, the reverse was true in 2007 in the Dominican Republic, Haiti, and Trinidad and Tobago, where HIV prevalence in young females 15–24 years of age was twice as high as their male cohort.[14] Country specific surveillance and behavioral surveys will be very important to identify key factors that differentially place young men and women at risk of HIV infection in these countries.

Earlier UNAIDS annual epidemiological updates (2006 and 2007) emphasized the particular risk of HIV infection faced by young Caribbean females. The 2006 UNAIDS annual Caribbean summary epidemiological update noted: "New HIV infections among women are surpassing those among men. Young women in particular face considerably higher odds of becoming infected than do young men." In Trinidad and Tobago, for example, HIV infection levels were six times higher among 15–19 year-old females than among males of the same age.[13] Earlier studies indicated that women younger than 24 years in the Dominican Republic were almost twice as likely, and teenage girls in Jamaica were two-and-a-half times more likely, to be HIV-infected, compared with their male counterparts.[15] Norms that tolerate males having multiple concurrent sexual partners are among the factors underlying these findings. The 2007 UNAIDS annual Caribbean summary epidemiological update reiterated: "Young girls are at high risk of exposure to HIV."[3] The same report mentioned that: "An important contributing factor to their susceptibility is the common practice of young girls maintaining relationships with older men, who, by virtue of their age, are more likely to have acquired HIV."

HIV can be transmitted from country to country as infected persons move around and interact in ways that facilitate spread of the virus. Among the characteristic features of life in the Caribbean are high levels of intraregional mobility and interdependence. Short- and long-term migration is often linked to economic factors and is a major determinant that drives the epidemic in the Caribbean. Migration is often motivated by poverty and a desire for socioeconomic improvement. Prospects for legal migration have been recently enhanced with the advent of the Caribbean Single Market and Economy. Some migration is illegal and illegal migrants tend to live in relative isolation, with limited access to health services and increased vulnerability to exploitation. The phenomenon of mobility is one of a number of factors that indicate the need for regional coordination of services in addressing the HIV epidemic.

Stigma and discrimination continue to exist in Caribbean countries, not only against those who are HIV-positive, but often against behaviours that make individuals and populations most vulnerable. This prevents some people from accessing services, including HIV testing and counseling, and from seeking care and treatment when HIV-positive. Healthcare providers and other health workers, who operate in very close-knit societies on small islands, continue to need training to support provision of confidential services without stigma and prejudice.

References

1. World Health Organization Report 2009. Global Tuberculosis Control: Surveillance, Planning, Financing. Geneva: World Health Organization, 2009 (WHO/HTM/TB/2009.411).
2. World Health Organization Frequently asked questions about TB and HIV, 2009 (www.who.int/tb/hiv/faq/en/).
3. UNAIDS Fact Sheet: 2007 AIDS Epidemic Update, Caribbean Regional Summary. March 2008 (http://data.unaids.org/pub/Report/2008/jc1528_epibriefs_caribbean_en.pdf).
4. UNAIDS. AIDS epidemic update: November 2009 (UNAIDS/09.36E/JC1700E) (http://data.unaids.org/pub/Report/2009/JC1700_Epi_Update_2009_en.pdf).
5. USAID Caribbean HIV/AIDS Health Profile, September 2008 (www.usaid.gov/our_work/global_health/aids/Countries/lac/caribbean_profile.pdf).
6. CAREC. The Caribbean HIV/AIDS Epidemic and the Situation in Member Countries of the Caribbean Epidemiology Centre. February 2007 (www.carec.org/documents/Caribbean_HIV_Epidemic.pdf).
7. WHO/UNAIDS/UNICEF, Towards Universal Access, Scaling Up priority HIV/AIDS Interventions in the health sector, progress Report, September 2009.
8. HIV/AIDS Surveillance Data Base, US Census Bureau International Programs Center, Health Studies Branch. September 2005 Release (www.census.gov/ipc/www/hivaidsn.html).
9. Allen C, et al. Sexually Transmitted Infections, service use and risk factors for HIV infection among female sex workers in Georgetown, Guyana. J Acquir Immune Defic Syndr, 2006;43:96Y101.
10. Ministry of Public Health. Suriname HIV/AIDS Quick Reference Sheet, 2004.
11. Lee RK et al.. Risk behaviours for HIV among men who have sex with men in Trinidad and Tobago. Abstract CDD0366.XVI International AIDS Conference. 13–18 August. Toronto. 2006.
12. Caribbean Technical Expert Group. Strengthening the Caribbean regional response to the HIV epidemic: report of the Caribbean Technical Expert Group meeting on HIV prevention and gender. Draft working document. 28–29 October. Kingston. 2004.
13. Inciardi JA, Syvertsen JL, Surratt HL. HIV/AIDS in the Caribbean Basin. AIDS Care, 17(Suppl. 1):S9–S25. 2005.
14. UNAIDS. 2008 Report on the Global AIDS Epidemic. Geneva: Joint United Nations Programme on HIV/AIDS, 2008 (http://data.unaids.org/pub/GlobalReport/2008/JC1510_2008GlobalReport_en.zip).
15. Monitoring the AIDS Pandemic Network (MAP). HIV infection and AIDS in the America. Havana, MAP. 2003.

2 Tuberculosis Transmission and Pathogenesis

Etiology

M. tb is the organism responsible for most of the tuberculosis infection and disease seen in the Caribbean. *M. tb* organisms are rod-shaped bacilli of approximately 0.3–0.6 microns in diameter and 1–4 microns in length.[1] There are several other species and subspecies that are included in the *M. tb* complex because of their close genetic relationship to tuberculosis. These include *M. bovis*, *M. africanum*, *M. microti*, *M. canettii*,[2] *M. caprae*,[3] and *M. pinnipedii*.[4] With the exception of *M. pinnipedii*, all of the species in the *M. tb* complex have been shown to cause disease in humans; however, *M. tb* is by far the most prevalent.

The mycobacteria that cause tuberculosis are aerobic, non-spore forming, non-motile, and multiply very slowly (once every 18–24 hours). *M. tuberculosis* organisms have a thick lipid cell wall which retains dye and resists decolorization when washed with acid or alcohol, and thereby are referred to as "acid fast bacilli" or AFB.

Mycobacteria commonly found in the environment rarely cause disease in humans and are not able to be spread from person to person. These mycobacteria other than tuberculosis (MOTT) most often cause disease in individuals with weakened immune systems. *M. avium* and *M. intracellulare* are the more common of the MOTT sometimes seen in patients co-infected with HIV. Because of their close association with each other, *M. avium* and *M. intracellulare* is sometimes referred to as *Mycobacterium avium* complex (MAC) or *Mycobacterium avium/intracellulare* (MAI).[5]

Transmission

Transmission is the spread of organisms, such as *M. tuberculosis*, from one person to another. The primary mode of transmission for tuberculosis is through inhalation of infectious particles. When a person with TB disease of the lungs or larynx coughs, sneezes or sings, droplet nuclei containing the TB bacilli are expelled into the air. These droplets or particles, called droplet nuclei, are about 1 to 5 microns in diameter—less than 1/5000 of an inch. Droplet nuclei can remain suspended in the air for several hours, depending on the environment. Transmission occurs when droplet nuclei are breathed in through the airway and reach the terminal air spaces of the lungs (alveoli).[2]

Tuberculosis Infection

Tuberculosis infection means that tubercle bacilli are in the body but the intact immune system is keeping them under control. The pulmonary macrophages act as scavengers and engulf the bacilli. Some are walled off within the macrophage and live there for many years. If the immune system is compromised, then the bacilli multiply and spread to other sites in the body. People who have latent TB infection (LTBI) but not TB disease do not have symptoms of their infection, and they cannot spread the infection to other people. It is very important to remember that latent TB infection is not considered a case of TB.

Risk Factors for Tuberculosis Infection

The WHO estimates that approximately one-third of the population worldwide has TB infection.[6] Certain populations, however, have a greater risk for exposure to TB and are therefore more likely to have been infected.[7]

Conditions that increase the risk for TB infection include:

- Known exposure to a person with TB disease
- Persons who live or spend time in certain congregate or institutionalized settings such as:
  - Prisons, jails, and correctional facilities
  - Group homes or facilities for the elderly
  - Shelters for homeless and displaced persons post-disaster
  - Acute inpatient and outpatient care facilities
- Overcrowded habitation
- Living or working in a high TB-prevalent country
- Endogenous factors (low natural resistance to infection)

Tuberculosis Disease

TB disease develops when the immune system cannot keep the tubercle bacilli under control and the bacilli begin to multiply unchecked. Tuberculosis disease can develop very soon after infection (primary TB) or many years after infection (reactivation or post-primary TB). In individuals without HIV co-infection, about 5% of people who have been recently infected with *M. tuberculosis* will develop TB disease in the first year or two after infection.[2] Another 5% will develop disease later in their lives. The remaining 90% will stay infected but free of disease for the rest of their lives (see Chapter 5 for symptoms of pulmonary and extrapulmonary TB).

Risk Factors for the Development of Tuberculosis Disease

Some conditions appear to increase the relative risk that latent TB infection will progress to TB disease. The risk may be 1.7 times higher (as with diabetes) to more than 10 times higher (as with HIV infection) for people who have these conditions than for those who do not.

Conditions that increase the risk for TB infection progressing to disease include:

- Co-infection with HIV[7,8]
- History of prior active TB or chest X-ray finding suggestive of prior untreated or inadequately treated TB[7]
- Recent TB infection (within the past 2 years)[7]
- Substance abuse (e.g., injection drugs,[7] alcohol)
- Extremes of age (particularly children <5 years of age)[7]
- Tobacco smoking[9]

- Certain medical conditions, such as:[7]
  - Silicosis
  - Diabetes mellitus
  - Chronic renal failure or on hemodialysis
  - Solid organ transplantation
  - Gastrectomy or jejunoileal bypass
  - Certain types of cancer (e.g., leukemia, Hodgkin's disease, or cancer of the head and neck)
  - Underweight or malnourished (i.e., body mass index 10% or more below ideal)
- Use of immunosuppressive agents,[2,7] such as:
  - Prolonged corticosteroid therapy (>15mg daily for over 4 weeks)
  - Certain cancer chemotherapy agents
  - Anti-rejection drugs for organ transplant
  - Tumour necrosis factor alpha antagonists[10]

Common Sites for Tuberculosis Disease

Following infection, tubercle bacilli can travel from the original site of infection to other sites of the body through the lymphatic and circulatory systems. Although TB most commonly affects the lungs, any organ or tissue can be involved.

- **Pulmonary tuberculosis (PTB)** occurs in the lungs and accounts for the majority of TB cases
- **Extrapulmonary tuberculosis (EPTB)** occurs in places other than the lungs
- **Common forms of Extrapulmonary Tuberculosis:**
  - TB of the central nervous system, includes TB meningitis and brain tuberculoma
  - Tuberculosis of the spine (Pott's disease)
  - Tuberculosis of the cervical lymph nodes (scrofula)
  - Tuberculous pleural effusion
  - Tuberculous pericarditis
  - Disseminated tuberculosis, including miliary TB
  - Genitourinary tuberculosis

Co-pathogenesis of TB and HIV

HIV infection alters the pathogenesis of TB by compromising the cell-mediated immune response of the host and therefore the host's ability to contain the TB bacilli. For persons with *M. tuberculosis* infection, the presence of HIV increases their risk for developing TB disease from 10% to 50% over the course of their lifetime.[2] Recent data from WHO suggests that this risk may be even higher than was previously estimated, particularly in countries with high HIV prevalence in the general population (incidence rate ratio of 20.6 compared with previous estimate of 6).[7] When the immune system is weakened, the body becomes less able to control the multiplication and spread of tubercle bacilli. For

this reason, people who are infected with both *M. tuberculosis* and HIV are much more likely to develop TB disease than people who are infected only with *M. tuberculosis*.

TB disease can develop at any stage in the course of HIV disease progression although the risk increases with advancing immunosuppression and decreases in patients receiving effective antiretroviral therapy.[11] In an HIV-infected person, TB disease can develop in either of two ways:

- A person who has TB infection can become infected with HIV and then develop TB disease as the immune system is weakened
- A person who has HIV infection can become infected with *M. tuberculosis* (includes exogenous reinfection) and then rapidly develop TB disease

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

References

1. Canadian Lung Association. Canadian tuberculosis standards, 5th edition. 2000. Canadian Lung Association/Canadian Thoracic Society and Tuberculosis Prevention and Control, Centre for Infectious Disease Prevention and Control, Health Canada.
2. American Thoracic Society. Diagnostic Standards and Classification of Tuberculosis in Adults and Children. Am J Respir Crit Care Med. 2000; 161:1376–1395.
3. Aranaz A, Cousins D, Mateos A, Dominguez L. Elevation of Mycobacterium tuberculosis subsp. caprae Aranaz et al. 1999 to species rank as Mycobacterium caprae comb. nov., sp. nov. Int J Syst Evol Microbiol. 2003; 53:1785–1789.
4. Cousins DV, Bastida R, Cataldi A, et al. Tuberculosis in seals caused by a novel member of the Mycobacterium tuberculosis complex: Mycobacterium pinnipedii sp. nov. Int J Syst Evol Microbiol. 2003; 53(Pt 5):1305–1314.
5. Jacobson MA, Aberg JA. Mycobacterium avium complex and atypical mycobacterial infections in the setting of HIV infection. University of California, San Francisco. HIV InSite Knowledge Base Chapter. January 2006 (http://hivinsite.ucsf.edu/InSite?page=kb-05-01-05).
6. American Thoracic Society; Centers for Disease Control and Prevention (CDC). Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. Am J Respir Crit Care Med. 2000; 161:S221-S247.
7. World Health Organization Report 2009. Global Tuberculosis Control: Surveillance, Planning, Financing. Geneva: World Health Organization, 2009 (WHO/HTM/TB/2009.411).
8. Sonnenberg P, Glynn JR, Fielding K, et al. How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort study in South African gold miners. J Infect Dis 2005; 191: 150–158.
9. World Health Organization. A WHO/The Union monograph on TB and tobacco control: Joining efforts to control two related global epidemics. World Health Organization and International Union Against Tuberculosis and Lung Disease. 2007 (WHO/HTM/TB/2007.390).
10. Centers for Disease Control and Prevention. Tuberculosis Associated with Blocking Agents Against Tumor Necrosis Factor-Alpha—California, 2002–2003. MMWR August 5, 2004 / 53(30);683-686.
11. Golub JE, et al. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. AIDS, 2007; 21:1441–48.

3 Framework and Standards for Effective TB Control

In 1993, the World Health Organization declared TB a global emergency given its increasing importance as a public health problem. It is well recognized that poverty, population growth, migration and the concurrent HIV epidemic in some countries has contributed greatly to the global TB situation. In addition to these factors, the persistence of TB is also due to:[1]

- Failure to ensure accessible diagnosis and treatment services, including directly observed treatment
- Inadequate treatment regimens and failure to use standardized treatment regimens
- Lack of program supervision and use of an information management system to ensure rigorous evaluation of treatment outcomes of TB patients
- Misguided policies for health sector reform, with cuts in healthcare budgets and resultant reduction in financial support to peripheral health services

In response to WHO's global emergency declaration, a new framework for effective TB control was developed and a global strategy called Directly Observed Treatment, Short-course was introduced.

The 5 components of the DOTS Strategy correspond to the first component of the Stop TB Strategy and are as follows:[1]

1. Sustained political commitment
2. Access to quality-assured sputum microscopy
3. Standardized short-course chemotherapy for all cases of TB under proper case management conditions, including directly observed treatment
4. Uninterrupted supply of quality-assured drugs
5. Recording and reporting system enabling outcome assessment of all patients, and assessment of overall program performance

The organizing principles which create the foundation for successful implementation of the DOTS Strategy include:

- Availability of a decentralized diagnostic and treatment network based on existing health facilities and integrated with primary healthcare
- Good program management based on accountability and supervision of healthcare workers
- An evaluation system of case-finding and cohort analysis of treatment outcomes

The Stop TB Strategy[3]

In 2001, the first Global Plan to Stop TB (the Stop TB Strategy) was launched through the Stop TB Partnership. This strategic plan serves as a roadmap for reaching the goals of ensuring access to treatment and cure, protection of vulnerable populations from TB, and a reduction in the social and economic tolls of TB on families, communities, and nations.[2]

Effecting tuberculosis control requires a coordinated response and innovative approaches. In this regard, the role of the Stop TB Partnership emphasizes the need for more extensive and effective engagement of broad-based health systems partners and others working in related areas such as HIV. This strategy must be aligned with other strategies and partnerships to face all major public health challenges. The Stop TB Strategy builds on and enhances DOTS to meet the TB-related Millennium Development Goals.

Goal:

To reduce dramatically the global burden of TB by 2015 in line with the Millennium Development Goals and the Stop TB Partnership targets and to achieve major progress in the research and development needed for TB elimination.

Objectives:

- To achieve universal access to high-quality diagnosis and patient-centered treatment
- To reduce the human suffering and socioeconomic burden associated with TB
- To protect poor and vulnerable populations from TB, TB/HIV and MDR-TB
- To support development of new tools and enable their timely and effective use

Targets:

- Millennium Development Goal 6, Target 8: halt and begin to reverse the incidence of TB by 2015
- Epidemiological targets linked to the Millennium Development Goals and endorsed by Stop TB Partnership:
  - By 2005, detect at least 70% of new sputum smear-positive TB cases and cure at least 85% of these cases
  - By 2015, reduce prevalence of and deaths due to TB by 50% relative to 1990
  - By 2050, eliminate TB as a public health problem (<1case/million population)

Components of the Stop TB Strategy

1. **Pursue high-quality DOTS expansion and enhancement**
   - Secure political commitment, with adequate and sustained financing
   - Ensure early case detection and diagnosis through quality-assured bacteriology
   - Provide standardized treatment with supervision, and patient support
   - Ensure effective drug supply system and management
   - Monitor and evaluate performance and impact
2. **Address TB-HIV, MDR-TB, and the needs of poor and vulnerable populations**
   - Scale-up collaborative TB/HIV activities
   - Scale-up prevention and management of multidrug-resistant TB
   - Address the needs of TB contacts, and poor and vulnerable populations

3. **Contribute to health system strengthening based on primary health care**
   - Help improve health policies, human resource development, financing, supplies, service delivery and information
   - Strengthen infection control in health services, other congregate settings and households
   - Upgrade laboratory networks, and implement the Practical Approach to Lung Health
   - Adapt successful approaches from other fields and sectors, and foster action on the social determinants of health
4. **Engage all care providers**
   - Involve all public, voluntary, corporate and private providers through Public- Private Mix approaches
   - Promote use of the *International Standards for Tuberculosis Care* (*ISTC*)
5. **Empower people with TB, and communities through partnership**
   - Pursue advocacy, communication and social mobilization
   - Foster community participation in TB care, prevention and health promotion
   - Promote us of the Patients' Charter for Tuberculosis Care (PCTC)
6. **Enable and promote research**
   - Conduct program-based operational research, and introduce new tools into practice
   - Advocate for and participate in research to develop new diagnostics, drugs, and vaccines

The International Standards for Tuberculosis Care

The *ISTC* pull together research findings and expertise to provide guidance that is current, based on evidence and experience over time. The *ISTC* was designed to be complementary to local and national TB control policies that are consistent with WHO recommendations. These standards augment existing guidelines in that they describe **what** should be done, whereas guidelines describe **how**. Several documents related to the *ISTC* have been produced to enhance TB control program efforts worldwide (available at www.istcweb.org). These include:

- *International Standards for Tuberculosis Care*
- *Patients' Charter for Tuberculosis Care*
- *Handbook for using the International Standards for Tuberculosis Care (The Handbook)*
- ISTC *Training Modules and Facilitator's Guide*

The *ISTC* presents a set of widely-accepted, evidenced-based standards describing a level of care that all practitioners, public and private, should seek to achieve in managing patients with, or suspected of having, tuberculosis.[4]

The *ISTC* has recently been revised (2009) to ensure consistency with existing international recommendations. In total, there are 21 standards related to TB diagnosis, treatment, addressing HIV and other co-morbid conditions, and public health responsibility.

As the *ISTC* is intended to unify approaches to diagnosis and treatment of TB in the private and public sectors, it has been included throughout this document to reinforce the guidelines relevant to each of the *ISTC* content areas.

The *PCTC* was developed by the World Care Council in tandem with the *ISTC* to promote a "patient-centered" approach to tuberculosis care. Initiated and developed by patients from around the world, the *PCTC* makes the relationship with healthcare providers a mutually beneficial one. The *PCTC* outlines the rights and responsibilities of people with tuberculosis and serves as a resource for addressing the fifth element of the "Stop TB Strategy."

The Handbook presents suggestions and guidance for using the *ISTC* as a tool to foster and guide the delivery of high-quality care by all practitioners providing TB services. *The Handbook* should be viewed as a companion to the WHO publication, "*Engaging All Health Care Providers in TB Control: Guidance on Implementing Public–Private Mix Approaches*" that presents a comprehensive approach to developing public-private partnerships for delivery of tuberculosis care. Both of these documents are the major implementation resources to accomplish the fourth element of the "Stop TB Strategy."

The National Tuberculosis Program

The aim of the NTP is to reduce morbidity, mortality, and disease transmission, while preventing the development of drug resistance. In settings with high HIV prevalence, these strategies should be coordinated with those of the National AIDS Program.

The short-term program objectives are:

- To achieve a cure rate of 85% among new sputum smear-positive TB cases
- To detect 70% of existing cases of sputum smear-positive tuberculosis
- To prevent the emergence of acquired drug-resistant *M. tuberculosis*

The Policy Package for the NTP[1]

- General public health services to be enhanced to expand and sustain DOTS implementation without compromising quality case detection and treatment
- Community involvement in TB care and a patient-centered approach emphasizing improved access to and use of health services
- Collaboration and synergy among public, private, and voluntary sectors, as well as the NTP, NAP, and all other stakeholders so as to ensure early case detection, diagnosis and treatment under the guidance of national health authorities
- Develop new partnerships and approaches to address the impact of HIV on TB
- Effective implementation of the DOTS Strategy and measures to cure existing multidrug-resistant TB

Key NTP Features

While the NTP structure varies among the Caribbean Nations with both centralized and decentralized systems, there are key features that should exist in every NTP to ensure effectiveness and accountability:

- A central unit
- NTP manual available at the periphery level

- A tuberculosis management information system using standardized registers
- A training program covering all aspects of the policy package
- A nationwide network of quality-assured microscopy services in close contact with primary healthcare services and subject to regular quality control
- Access to laboratory services for TB culture, identification, and drug sensitivity testing for the diagnosis and management of previously treated patients and others with risk factors for multidrug-resistant (MDR) TB and extensively drug-resistant (XDR) TB
- Treatment services within the primary healthcare system, with priority for directly observed short-course chemotherapy
- Uninterrupted supply of quality-assured drugs and diagnostic materials with reliable procurement and distribution systems
- Plan of supervision of key operations at all levels of program delivery
- Mechanisms for stakeholder and health service collaboration, with special attention to TB and HIV operations
- A project development strategic plan, with budget details, funding sources and responsibilities
- Information, education, communication, and social mobilization to empower patients and communities

Activities of the NTP

- Early and intensified case-finding, supported by voluntary counseling and testing, or provider-initiated testing for HIV and TB detection
- Administering adequate treatment to achieve cure under DOT supervision

Supporting Activities

- Training of healthcare workers in National TB Prevention and Control guidelines
- Health education for patients, members of the public, and the general health staff
- Sputum smear microscopy and other supportive laboratory examinations
- Culture and drug susceptibility testing (DST)
- Contact investigation
- Defaulter retrieving
- Recording and reporting for monitoring and evaluation (including cohort analysis)
- Coordinating collaborative activities between NTP and NAP
- Supervision
- Epidemiological surveillance of tuberculosis and co-infection of TB/HIV
- Tuberculin skin test surveys; TB drug-resistant surveys
- Operational and other research
- HIV-antibody testing and counseling
- Provision of isoniazid preventive therapy (IPT)

Structure of the NTP

Activities of the NTP should be integrated into the existing health services so that all health units are involved in the achievement of the objectives of the NTP. Since case-finding and treatment can be carried out at any health unit, healthcare workers of the general services must also be aware of the mechanisms which are in place to facilitate this process, and share the responsibility for the implementation of the control measures. It is mandatory that managerial and supervisory staff be responsible for the TB-specific technical competence of all healthcare workers involved in the program.

The structure of the NTP must also reflect:

- The multi-disciplinary approach to surveillance and case management
- The mechanisms for implementing TB and HIV collaboration

Ministry of Health (Central Level)

The tuberculosis program is headed by a TB Program Manager (a senior medical officer, preferably with specialization in infectious diseases, epidemiology or public health) who is responsible to the Chief Medical Officer of Health. The TB Program Manager is responsible for planning the work and collaborating with healthcare staff on the periphery level. The manager must work closely with the national coordinator and other key individuals in the program, such as the pharmacist, senior microbiologist, and the lead person in the National AIDS Program.

Regional/District/Parish Level

A TB coordinator can assist in the supervision of TB control activities at the regional/district/parish levels. The coordinator is one of the key workers in the TB Control Program. Critical functions of the coordinator include:

- Liaise with the healthcare workers in the field and the national TB Program Manager
- Facilitate close cooperation between the NTP and laboratory services to ensure access to critical diagnostic and monitoring examinations
- Coordinate the implementation of activities and feedback related to TB and TB/HIV to increase the efficacy and efficiency of the NTP
- Supervise general health staff in TB case-finding and treatment
- Provide education for the healthcare workers and the general public
- Oversee/supervise the collection, processing, reading, recording and reporting of sputum at centers with AFB microscopy

The purpose of supervision is to enable continuing improvement in the performance of staff. It plays a major role in staff management (see Appendix D: Supervision).

Health Promotion, Communication, and Education

Health promotion, communication, and education are an integral part of the Stop TB Strategy and a key function of a successful NTP. The basic principle is that primary health-care must incorporate a commitment to communities' participation, inter-sectoral action, and maintaining the skills and knowledge of staff. NTPs should actively work toward achieving the following:

Formulate public health policy:

- Promote health as a strategic input and priority outcome of a country's development

Re-orient health services through:

- Ensuring health services' respond to needs of individuals and communities
- Educating health professionals to recognize communities and individuals as partners
- Promoting curative and preventive patient-centered care

Empower communities to achieve well-being through:

- Collaboration with communities to determine priorities
- Facilitation and support of community action
- Provision of information and skills for action

Build alliances with special emphasis on the media through:

- Accessing and pooling resources from all sectors for the promotion of health
- Forming alliances with other government sectors: education, social and community development, culture and gender affairs, youth and sport
- Forming alliances with nongovernmental organizations(NGO), faith-based organizations, service clubs, and NAPs

The healthcare worker has an important role in direct patient education. Healthcare workers must be diligent in instructing and educating the patient about the curability of the disease and that treatment must be regular, adequate, and for a sufficient period of time. Patient and communities must understand the following:

- What is tuberculosis?
- What is TB/HIV co-infection?
- How is the disease spread?
- What can be done to limit the spread of the disease?
- When, where and how can care be accessed?
- How is the disease cured?
- What medications are used and for how long?
- How is the treatment to be followed?
- What side effects are to be expected?

Adequate training and continuing education opportunities for all TB program staff are needed to ensure that accurate and appropriate information is delivered to the patients, community members, and media.

Collaboration Between TB and HIV/AIDS Programs

Tuberculosis is a global public health problem and continues to be a significant health threat in some Caribbean countries. Untreated HIV infection leads to progressive immunodeficiency and increased susceptibility to opportunistic infections, including TB. For many years, the efforts to tackle TB and HIV have been largely separate, despite the overlapping epidemiology. However, it is now increasingly recognized that only through combined and coordinated efforts for both TB and HIV can this dual epidemic be halted.

Guiding principles for collaboration:

- Prevention of HIV should be a priority for TB control, given the impact HIV has on TB morbidity and mortality
- TB care and prevention should be a priority for HIV programs, given the high morbidity and mortality from TB among people with HIV
- Joint TB/HIV program planning, implementation, and coordination of activities is critical to the successful control of both diseases

Joint activities should focus on areas of mutual interest. The following lists some of these areas of mutual interest which should be considered when developing a policy document for collaborative TB/HIV activities:

- Advocacy
- Policy consensus
- Information, education, and communication strategies
- Training activities
- Procurement and distribution of drugs, consumables, and laboratory reagents
- Monitoring and evaluation (M & E)
- Information systems
- Surveillance and referral
- Counseling and testing services and provision of preventive therapy
- Provision and supervision of antiretroviral therapy (ART) and TB treatment

TB/HIV Collaborative Activities

Good coordination and management of joint activities between the two programs are critical to ensure a continuum of quality care for people with, or at risk of, tuberculosis and HIV. The policy goal is to decrease the burden of tuberculosis and HIV in populations affected by both diseases (see Chapter 9, HIV Infection and Tuberculosis, for further detail on joint activities).

TABLE 1:

Recommended TB/HIV objectives and activities[5]

Establish the mechanisms for collaboration

- Set up a coordinating body for TB/HIV activities
- Conduct surveillance of HIV prevalence among TB patients
- Carry out joint TB/HIV planning
- Conduct monitoring and evaluation

Decrease the burden of TB in people with HIV

- Establish intensified tuberculosis case-finding
- Introduce isoniazid preventive therapy
- Ensure TB infection control in healthcare and congregate settings

Decrease the burden of HIV in tuberculosis patients

- Provide HIV testing and counseling
- Introduce HIV prevention methods
- Introduce cotrimoxazole preventive therapy
- Ensure HIV care and support
- Introduce antiretroviral drugs

References

1. World Health Organization. Treatment of Tuberculosis: Guidelines for National Programmes. Third Edition. Geneva: World Health Organization, 2003 (WHO/CDS/TB/2003.313).
2. World Health Organization. The Global Plan to Stop TB. Stop TB Partnership. Geneva: World Health Organization, 2002 (WHO/CDS/STB/2001.16).
3. World Health Organization. The Stop TB Strategy Fact Sheet. Stop TB Partnership, 2009. Available at: www.stoptb.org/resource_center/assets/factsheets/stoptb_strategy_en_3_10_noon.pdf.
4. Tuberculosis Coalition for Technical Assistance. International Standards for Tuberculosis Care (ISTC), second edition. Tuberculosis Coalition for Technical Assistance, The Hague, 2009.
5. World Health Organization. Interim Policy on Collaborative TB/HIV Activities. Geneva: World Health Organization, 2004 (WHO/HTM/TB/2004.330, WHO/HTM/HIV/2004.1).

4 World Health Organization Case Definitions

Case Definitions[1]

It is essential that patients be categorized correctly for the following reasons:

- For proper patient registration and case notification
- To select appropriate standard treatment regimens (See Chapter 7)
- To standardize the process of data collection for TB control
- To evaluate the proportion of cases according to site, bacteriology and treatment history
- For cohort analysis of treatment outcomes
- To accurately monitor trends and evaluate the effectiveness of TB programs within and across districts, countries and global regions

The WHO TB case definitions below are based on the level of certainty of the diagnosis and whether or not laboratory confirmation is available.

Tuberculosis suspect: Any person who presents with symptoms or signs suggestive of TB. The most common symptom of PTB is a productive cough for over two weeks,[a] which may be accompanied by other respiratory symptoms (shortness of breath, chest pains, haemoptysis) and/or constitutional symptoms (loss of appetite, weight loss, fever, night sweats, and fatigue).[b]

Case of tuberculosis: A definite case of TB (defined below) or one in which a health worker (clinician or other medical practitioner) has diagnosed TB and has decided to treat the patient with a full course of anti-TB treatment.
Note: Any person given treatment for tuberculosis should be recorded as a case. Incomplete "trial" TB treatment should not be given as a method for diagnosis.

Definite case of tuberculosis: A patient with *M. tuberculosis* complex identified from a clinical specimen by culture or newer method (e.g., nucleic acid amplification). In countries where laboratories cannot yet routinely identify *M. tuberculosis* complex, a pulmonary case with one or more initial sputum smear examinations positive for acid-fast bacilli (AFB) is also considered to be a "definite" case, as long as there is a functional external quality assurance (EQA) system with blind rechecking.[c]

a Standard 1 of the International Standards for TB Care states that all persons with otherwise unexplained productive cough lasing two-three weeks or more should be evaluated for TB

b The definition of a "TB suspect" depends on other local factors (e.g., patient's age and HIV status,HIV prevalence in the population, prevalence of TB in the population, etc.)

c www.who.int/tb/dots/laboratory/policy/en/index1.html

Cases of TB are also defined by:

- Anatomical site of TB disease
- Bacteriologic results (including drug resistance)
- History of previous TB treatment
- HIV status of the patient

Site of TB Disease[1]

With a few exceptions, defining the site of TB disease is primarily for epidemiologic purposes and for identifying the more infectious patients rather than for determining treatment regimen or approach to management. While tuberculosis can occur in almost any part of the body, the site of TB disease is generally classified as either pulmonary or extrapulmonary.

Pulmonary Tuberculosis

PTB refers to TB disease involving the lung parenchyma.

- A patient with both pulmonary and extrapulmonary TB involvement should be classified as a case of *pulmonary* TB
- Miliary TB is classified as pulmonary TB because there are lesions in the lungs

Extrapulmonary Tuberculosis

EPTB refers to TB disease of organs other than the lungs.

- Tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar), or tuberculous pleural effusion (without radiographic abnormalities in the lungs) constitutes a case of EPTB
- The site representing the most severe form of disease will be used to define the case of EPTB with multiple sites affected
- Of note, EPTB is considered WHO Clinical Stage 4 for HIV infection and related disease (see also Chapter 9)

Diagnosis of EPTB should be based on one or more of the following:

- At least one specimen with confirmed *M. tuberculosis*
- Histological specimen (i.e., granulomatous inflammation and/or AFB)
- Strong clinical evidence consistent with active EPTB and a decision to treat with a full course of anti-TB treatment

Unless the extrapulmonary case is confirmed to contain *M. tuberculosis* by culture or newer method, it cannot meet the "definite case" definition.

Bacteriologic Results[1]

Bacteriology refers to the smear status of pulmonary cases, and the identification of *M. tuberculosis* for any case by culture or newer methods. Culture and drug susceptibility testing are discussed in Chapters 5 and 6.

Defining the AFB smear result in pulmonary cases is important to:

- Identify sputum smear-positive cases, as they are the most infectious and most likely to transmit disease, therefore, they are the focus for infection control measures[2] and contact investigations[3]

- Identify sputum smear-negative cases, especially in persons living with HIV for whom mortality is higher than in smear-positive PTB cases[4,5]
- Record, report, and evaluate program performance (smear-positive cases are the most practical cases for monitoring bacteriologic response to treatment)

Pulmonary TB: Sputum Smear-positive

A case of PTB is considered smear-positive if:

- There is a functional EQA system and one or more sputum smear examinations at the start of treatment is positive for AFB[a]
- There is not yet a functional EQA system, then one of the following apply at the start of treatment:
  - Two or more sputum specimens are AFB smear-positive
  - At least one sputum specimen is AFB smear-positive and radiographic abnormalities consistent with active PTB are present as determined by a clinician
  - At least one sputum specimen is AFB smear-positive plus culture-positive for *M. tuberculosis*

Under program conditions, when microscopy laboratory services are available and diagnostic criteria are properly applied, PTB sputum smear-positive cases represent at least 65% of the total PTB cases in adults and 50% or more of all TB cases. These proportions may be lower, however, in high HIV-incidence populations.[6]

Pulmonary TB: Sputum Smear-negative

Determining whether a patient has PTB when sputum smear is negative requires more careful diagnostic evaluation (see Chapter 5 for diagnosing PTB in the sputum smear-negative patient).

Revised definitions for what constitutes a smear-negative PTB case are provided in the WHO guidelines, Treatment of Tuberculosis, Fourth edition, and are as follows:

Smear-negative PTB cases should either:

- Have sputum that is smear-negative but culture-positive for *M. tuberculosis:*
  - In countries with a functional EQA system, where the workload is very high, and human resources are limited, a case of PTB is considered smear-negative if at least two sputum specimens at the start of treatment are negative for AFB and **no specimens are smear-positive**
  - In all settings with an HIV prevalence >1% in pregnant women or an HIV-prevalence ≥5% in TB patients, sputum culture for *M. tuberculosis* should be performed in patients who are sputum smear-negative to confirm the diagnosis of TB[4]

or

- Meet the following diagnostic criteria:[7,8]
  - Decision by a clinician to treat with a full course of anti-TB therapy

    and
  - Radiographic abnormalities consistent with active PTB

a Note that the definition of a new sputum smear-positive pulmonary TB case is based on the presence of at least one acid fast bacilli (AFB+) in at least one sputum sample in countries with a well functioning EQA system (www.who.int/tb/dots/laboratory/policy/en/index1.html)

and either:

- laboratory or strong clinical evidence of HIV infection

or

- if HIV-negative (or unknown HIV status living in an area of low HIV prevalence), no improvement in response to a course of broad-spectrum antibiotics (excluding anti-TB drugs, fluoroquinolones and aminoglycosides)

NOTE: For PTB cases in which smear results are not obtained, these **should no longer be classified as smear-negative**[4] rather they should be labelled **"smear not done"** on the TB Register and on the annual country surveillance report to WHO.[9]

History of Previous TB Treatment[1]

A case should be defined according to whether or not the patient has previously received TB treatment, and if so, what the outcome was (if known) in order to:

- Identify patients at increased risk of acquired drug resistance, determine need for drug sensitivity testing (DST), and to ensure selection of appropriate treatment
- Monitor the TB epidemic and program performance at regional and national levels

Case Registration Groups[1]

New Case

A patient who has never had treatment for TB or who has taken anti-tuberculosis drugs for less than 1 month (regardless of whether or not their smear or culture results are positive). New patients may have positive or negative bacteriology and may have disease at any anatomical site.

Previously Treated

A patient who has received a month or more of anti-TB drugs in the past and may have positive or negative bacteriology from any anatomical site. These cases are further classified by outcome of their most recent course of treatment as defined below.

Relapse: A patient previously treated for TB who has been declared cured or treatment completed, and is diagnosed with bacteriologically positive (smear, culture or other newer means of identifying *M. tuberculosis*) tuberculosis.

Failure: A patient who is started on a re-treatment regimen after having failed previous treatment (see Chapter 12, Table 28 for definition of treatment failure).

Default: A patient who returns to treatment and is bacteriologically positive following interruption of treatment for one month or more. It's important to note that while WHO defines default as an interruption in treatment for ≥2 months, the Pan American Health Organization considers an interruption of ≥1 month to represent default for practical reasons.

Transfer In

A patient who has been transferred from another TB register to continue treatment in a different register area.

Other

This includes all cases that do not fit the above definitions, such as:

- Patients for whom previous treatment history is unknown
- Previously treated patients but the outcome of previous treatment is unknown[3,10]
- Patients who have returned to treatment with smear-negative PTB or bacteriologically negative EPTB[3]

Patients whose sputum is smear-positive at the end of (or returning from) a second or subsequent course of treatment are no longer defined "chronic." They should now be classified by the outcome of their most recent re-treatment course (e.g., relapsed, defaulted or failed).

HIV Status[1]

Determining and recording the patient's HIV status is critical for treatment decisions (see Chapter 7), as well as monitoring trends and assessing program performance. The 2006 revised WHO TB Treatment Card and TB Register include dates of HIV testing, starting cotrimoxazole, and starting ART.[9] These important interventions are discussed more fully in Chapter 9. The register/records can be downloaded from the WHO website at: www.who.int/tb/dots/r_and_r_forms/en/index.html.

References

1. World Health Organization. Treatment of Tuberculosis: Guidelines. Fourth Edition. Geneva: World Health Organization, 2009 (WHO/HTM/TB/2009.420).
2. World Health Organization. WHO policy on TB infection control in health-care facilities congregate settings, and households. Geneva: World Health Organization, 2009.
3. World Health Organization. Implementing the WHO Stop TB Strategy: A Handbook for National Tuberculosis Control Programmes. Geneva, World Health Organization, 2008 (WHO/HTM/TB/2008.401).
4. World Health Organization. Improving the Diagnosis and Treatment of Smear-negative Pulmonary and Extrapulmonary Tuberculosis Among Adults and Adolescents: Recommendations for HIV-prevalent and Resource-constrained Settings. 2007 (WHO/HTM/TB /2007.379, WHO /HIV/2007.01).
5. Maher D, Harries A, Getahun H. Tuberculosis and HIV interaction in sub-Saharan Africa: impact on patients and programmes; implications for policies. Torp Med Int Health 2005; 10(8):734-42.
6. World Health Organization. Treatment of Tuberculosis: Guidelines for National Programs, Third Edition. Chapter 3, page 24. Geneva: World Health Organization, 2003 (WHO/CDS/TB/2003.313).
7. Tuberculosis Coalition for Technical Assistance. International Standards for Tuberculosis Care (ISTC), second edition. Tuberculosis Coalition for Technical Assistance, The Hague, 2009.
8. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency update 2008. Geneva: World Health Organization, 2008 (WHO/HTM/TB/2008.402).
9. World Health Organization. Revised TB recording and reporting forms and registers: version 2006. Geneva: Word Health Organization, 2006 (WHO/HTM/TB/2006.373).
10. World Health Organization Report 2009. Global Tuberculosis Control: Surveillance, Planning, Financing. Geneva: World Health Organization, 2009 (WHO/HTM/TB/2009.411).

Case-finding and Diagnosis 5

Clinicians must think of the possibility of TB when they see a patient with symptoms of the disease or abnormal chest X-ray findings consistent with tuberculosis. Delay in diagnosing tuberculosis may result in ongoing transmission and potentially severe consequences for the individual, including disability and death.

Care providers must know the signs and symptoms of tuberculosis and the procedures for TB evaluation and/or referral.

Case-finding

Active case-finding can be designed and implemented in several ways. For example, unreported cases of TB disease can be identified through active laboratory and pharmacy audits, through follow-up of close contacts of smear-positive patients, and through follow-up with certain high risk groups, e.g., HIV-positive individuals.

Passive case-finding is based on the referral of symptomatic individuals who seek treatment at a care facility. To this end, a bi-directional referral system must be established between HIV testing and counseling sites and TB diagnostic and treatment centers.

Sites where opportunities for case-finding exist:

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

At the sites which do not provide services for TB investigations, a system for referral must be in place and should be made known to all care providers.

ISTC STANDARD 1

All persons with otherwise unexplained productive cough lasting 2–3 weeks or more should be evaluated for tuberculosis.[1]

Suspect Case

Anyone with symptoms of TB must be suspected of having TB and evaluated for the disease.[1] Traditionally, the presence of a chronic cough lasting two–three weeks or more has served as the criterion for defining suspected TB and is used in most national and international guidelines, particularly in areas of moderate- to high-prevalence TB.[2]

Given the impact HIV has on the approach to treatment for TB, anyone being evaluated for tuberculosis should also be evaluated for HIV infection. Those with HIV infection should also be counselled and evaluated for tuberculosis.

The Steps in Diagnosing TB Disease

Medical History

The medical history plays an essential role in the diagnosis and classification of TB, as well as providing important information relative to establishing the infectious period that will guide the contact investigation. It includes social, family, medical, and occupational information on the patient. For TB evaluation, the patient history should include the following information:

- Known exposure to a person who has infectious TB
- Symptoms of TB disease and onset
- Previous treatment for TB infection or TB disease
- Risk factors for developing the disease (see pages 7–8)
- Other medical conditions that might impact treatment (e.g., HIV, renal disease, etc.)

Signs and symptoms of PTB disease include:

- Persistent (productive or non-productive) cough for two–three weeks or more
- Chest pain when coughing or breathing
- Shortness of breath
- Bloodstained sputum or haemoptysis

The systemic symptoms of tuberculosis disease (pulmonary or extrapulmonary) include:

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

Symptoms of EPTB disease depend on the part of the body that is affected by the disease.

Bacteriologic Examination

ISTC 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.[1]

A confirmative diagnosis of tuberculosis can only be achieved by culturing *M. tuberculosis* complex from a clinical specimen or through use of molecular-based test methods (e.g., nucleic acid amplification). However, culture is not currently feasible at the national level for many CMCs. Fortunately, microscopic examination of stained sputum is available in all CMCs and plays an essential role in the diagnosis of tuberculosis.[3]

Identification of AFB by sputum smear microscopy is particularly important for three reasons:

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

Two sputum samples should be collected from patients suspected of having PTB (within 24 hours where possible: "spot, early morning, spot") and sent for AFB smear microscopy.

ISTC STANDARD **3**

For all patients (adults, adolescents, and children) suspected of having extrapulmonary tuberculosis, appropriate specimens from the suspected sites of involvement should be obtained for microscopy, culture, and histopathological examination.[1]

In low-HIV prevalence populations, EPTB alone (without pulmonary involvement) accounts for approximately 15–20% of all tuberculosis cases.[1] This proportion can be even higher in areas with a high prevalence of HIV infection (over 30% in some countries of Africa and S.E. Asia).[4] While obtaining specimens for bacteriological examination from EPTB sites may be more difficult, the basic principle that bacteriological confirmation should be sought still holds.

Specimens that may be sent for AFB smear microscopy, culture, and other histopathological examination might include any of the following:

- Bronchoalveolar lavage
- Aspirated fluid from pleura, stomach, or other site
- Biopsied tissue from lung, lymph node, or other site where TB is suspected
- Blood, urine or cerebral spinal fluid (due to the rarity of visualizing AFB on smear of these specimens, they often are only submitted for TB culture)

Culture, Identification, and Drug Susceptibility Testing (DST)

Culture and identification for *M. tuberculosis* should be performed as part of the initial diagnostic investigation. This is particularly important in high HIV prevalent areas as EPTB and smear-negative PTB is more common in persons with HIV, especially as immunosuppression progresses. Recognizing that essential laboratory infrastructure for CMCs to achieve culture and identification on all initial diagnostic specimens for TB is not yet in place, arrangements should be made for culture and identification of specimens in priority circumstances, which include:

- Patients meeting the criteria for sputum smear-negative PTB or EPTB
- Childhood tuberculosis
- HIV-positive TB suspect
- Currently in or history of having lived in a prison, jail or correctional facility
- Patients at risk for MDR-TB:
  - History of previous treatment for TB
  - History of exposure to MDR-TB
  - History of residence in areas with high MDR-TB prevalence (>3% in new patients)
  - Patients failing treatment and defaulters prior to a change in regimen

Drug Susceptibility Testing

Given the growing problem of TB drug resistance globally, ensuring access to quality drug susceptibility testing (DST) is becoming recognized as an important diagnostic tool. The procedure for obtaining DST will vary depending on country laboratory capacity and must be described in NTP policies and procedures. Ideally, first-line DST would be performed on all initial positive TB cultures to identify the presence of drug resistance early in the course of treatment. At least two sputum specimens for TB culture should be obtained and DST performed on the specimen that produces the best culture. In interpreting the results of *in vitro* drug susceptibility testing, it is also important to always consider the clinical situation, as laboratory errors or discrepant results may occur.[5]

Not all laboratories can conduct DST for *M. tuberculosis*, as it requires specialized equipment and procedures in addition to an ongoing and rigorous quality-assurance program. Of the CMCs, only the Curacao Level II Laboratory currently conducts DST for isolates in-country (see Chapter 6 for additional information on DST).

The Program Manager must liaise with the Laboratory Manager/Director to ensure procedures are outlined for facilitating access to DST for the following:

- All initial positive TB cultures
- Positive cultures from patients who are failing treatment, are defaulters or relapse cases

Radiographic Examination

While the chest X-ray (CXR) can support a diagnosis of tuberculosis when combined with the clinical presentation, it has substantial limitations. It's important to remember that many conditions can show CXR abnormalities that resemble TB.

During case-finding and diagnosis, a CXR may be most useful for the purposes of:

- Increasing the predictive value of a TB diagnosis in a person who has only one of three sputum smears that are positive in settings without EQC laboratory or who has persistent TB symptoms with negative sputum smears
- Checking for lung abnormalities in people who have symptoms of TB disease, especially in the HIV-infected
- Evaluating persons with a newly identified positive reaction to the tuberculin skin test or interferon-gamma release assay (IGRA)
- Evaluating localization and extent of lesions

The chest X-ray results alone cannot confirm that a person has TB disease

ISTC STANDARD **4**

All persons with chest radiographic findings suggestive of TB should have sputum specimens submitted for microbiological examination.[1]

When radiographic abnormalities suggestive of active tuberculosis are identified during non-TB related medical evaluations, sputum specimens should be obtained and sent for AFB smear and culture examination.

Radiographic presentations suggestive of active PTB include:

- Acute upper lobe pneumonia
- Unresolving pneumonia
- Cavitation, cavitary lesion
- Pleurisy, pleural effusion
- Lung infiltrate, especially in the upper lung zones
- Intrathoracic adenopathy

Radiographic presentations suggestive of previous or presumed inactive PTB include:

- Apical fibrosis
- Upper lobe fibronodular abnormality
- Pleural (fibro) calcification
- Upper lung zone bronchiectasis
- Thoracoplasty or partial pneumonectomy
- Healed primary lesion (Ghon focus/complex)

ISTC STANDARD **5**

The diagnosis of sputum smear-negative pulmonary TB 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 TB; 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 TB, 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 anti-tuberculosis treatment should be initiated.[1]

Diagnosing TB in the Sputum Smear-negative Patient

The diagnosis of TB in a patient whose sputum smear is negative is more complex given the nonspecific nature of TB symptoms and the number of other diseases that could be causing the patient's illness. Sputum smear microscopy is only about 50–60% sensitive when compared with culture[1] and many factors can affect the sensitivity of smear microscopy (e.g., whether there is laboratory capacity to concentrate sputum specimen; access to fluorescence microscopy). Therefore, it is important that a rigorous approach be taken in diagnosing TB in a patient in whom at least two sputum smears are negative and no smears are positive for AFB at the start of treatment.

For TB suspect patients with HIV co-infection, it is crucial to be systematic in the approach to evaluating for TB for the following reasons:

- Patients with HIV infection and tuberculosis frequently have negative sputum smears
- Extrapulmonary sites of tuberculosis are more common
- Broad differential diagnoses (including *Pneumocystis jiroveci* pneumonia and bacterial and fungal lower respiratory infections) are a concern in this group

It is important, however, to balance the need for a systematic approach in order to avoid both over- and under-diagnosis of TB, with the need for prompt initiation of treatment in a patient with an illness that is progressing rapidly.[1]

When evaluating a TB suspect whose initial sputum smear is negative, many if not all of the following investigations will be required (see Chapter 4, pages 22–23 for sputum smear-negative PTB case definition):

- **At least** two sputum specimens for AFB smear microscopy
- Sputum specimens must also be sent for TB culture[6]
- HIV test should be expedited
- Chest X-ray obtained (See page 29, Radiographic presentations suggestive of active PTB)
- Thorough physical exam
- When indicated, a course of broad spectrum non-anti-TB antibiotic (See #2 under **points of caution** page 31)

A number of algorithms have been developed as a means to systematize the diagnosis of smear-negative PTB, although none has been adequately validated under field conditions. In particular, there is little information or experience on which to base approaches to the diagnosis of smear-negative tuberculosis in persons with HIV infection when culture is not routinely available.[1]

Figure 1 is a composite algorithm modified from algorithms developed by WHO and is included as an example of a systematic approach to diagnosis that incorporates the main components of, and a framework for, the diagnostic evaluation of the sputum smear-negative TB suspect. It should be recognized that, commonly, the steps in the algorithm are not followed in a sequential fashion, but rather, may occur concurrently.

There are several points of caution regarding the algorithm (Figure 1):[1]

1. Completion of all of the steps requires a substantial amount of time; thus, it should not be used for patients with an illness that is worsening rapidly. This is especially true in patients with HIV infection in whom tuberculosis and other infections may be rapidly progressive.
2. Several studies have shown that patients with tuberculosis may respond, at least transiently, to broad-spectrum antimicrobial treatment, which could lead to delay in diagnosis of tuberculosis.[7,8,9] Fluoroquinolones, in particular, are bactericidal for *M. tuberculosis* complex. Empiric fluoroquinolone monotherapy for respiratory tract infections has been associated with delays in initiation of appropriate anti-tuberculosis therapy and acquired resistance to the fluoroquinolones.[10] Consequently, use of these agents is discouraged for treatment of infections in which there is a reasonable possibility of TB being in the differential diagnosis.
3. The approach outlined in the algorithm may be costly to the patient and deter her/him from continuing with the diagnostic evaluation.

Given all these concerns, application of such an algorithm in patients with at least two negative sputum smear examinations must be done in a flexible manner. Ideally, the evaluation of smear-negative tuberculosis should be guided by locally-validated approaches, suited to local conditions, and the needs (financial or otherwise) of the patient.[1]

All EPTB cases should be investigated also for the presence of PTB

Cases with Clinical Diagnosis of Extrapulmonary TB (EPTB)

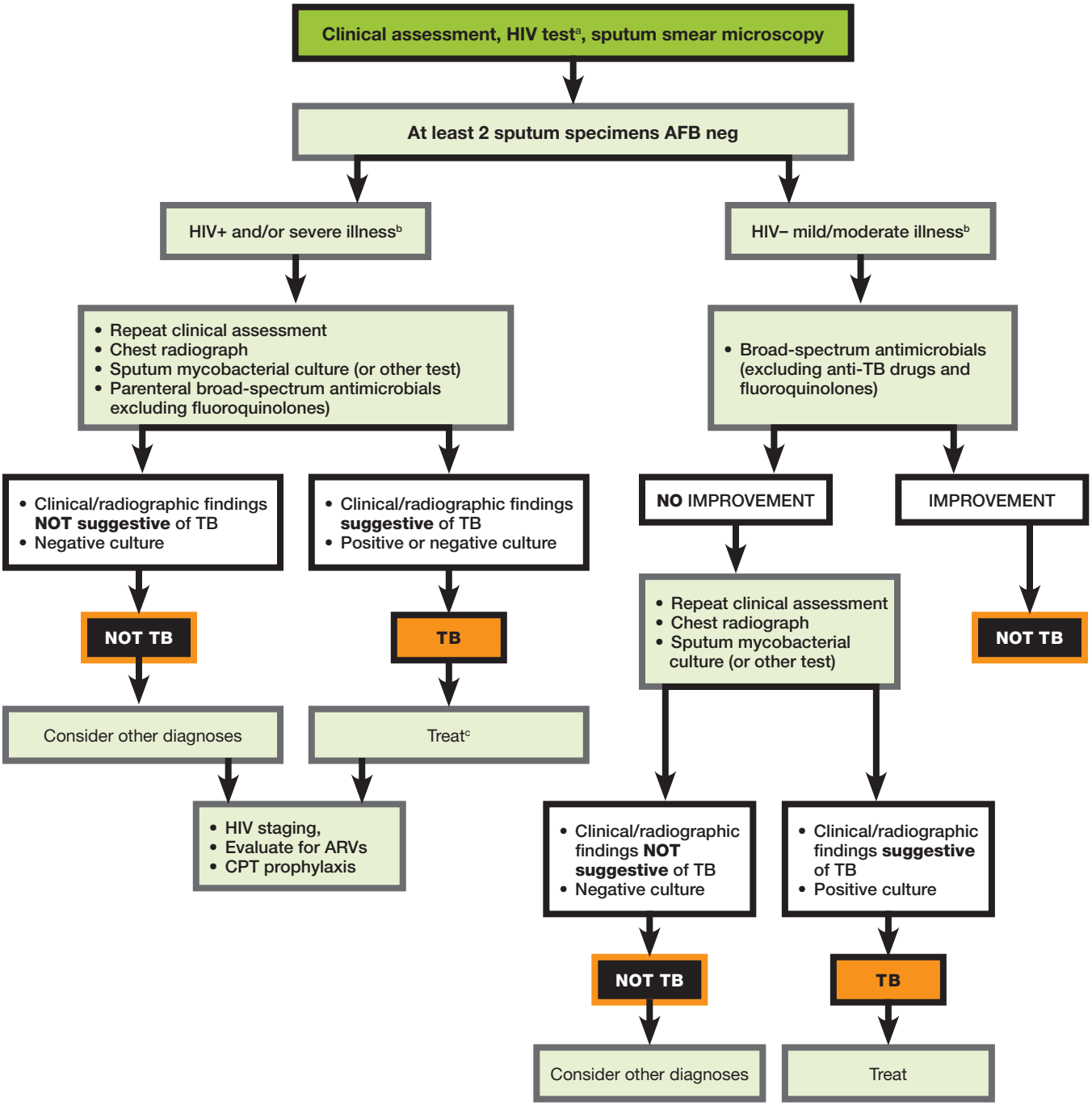
Any smear-negative specimens obtained from cases with a clinical diagnosis of EPTB should be sent for culture and identification of *M. tb* and MOTT. Although HIV testing is recommended for all TB suspect and confirmed cases, it is especially important for those suspect or confirmed EPTB patients because of the increased frequency of extrapulmonary involvement in persons with immunosuppression.

Presentations and specific investigations for various forms of EPTB

- **Pleural tuberculosis** encompasses a wide array of manifestations. **Tuberculosis pleural effusion** is a common condition, and it can be formed by an allergic phenomenon due to sensitisation of the tissue to *Mycobacterium tuberculosis* protein or due to direct infection of the pleura by *M. tb* organisms. Tuberculous pleural effusions tend to be free flowing in the early stage of development, but with time, adhesions develop that can trap or loculate the fluid. The most common related symptoms include cough (often non-productive), fever, and pleuritic chest pain. Dyspnea, chills, sweats, weight loss,

FIGURE 1:

An illustrative approach to the diagnosis of sputum smear-negative PTB in patients presenting with an illness suggestive of PTB



AFB = acid-fast bacilli; **TB** = tuberculosis; **ARVs** = antiretroviral drugs; **CPT** = Cotrimoxazole prophylaxsis;

HIV = Human immunodeficiency virus

‡ If HIV +, refer to Figure 3 on page 85 Algorithm for the diagnosis of TB in ambulatory HIV-positive patient

* See points of caution on page 31

a Recommended in countries or areas with adult HIV prevalence >1% or prevalence among TB cases >5%

b Severe illness= respiratory rate >30 breaths/min, temperature >39ºC, pulse >120 beats/min, unable to walk unaided, symptoms/signs progressing rapidly

c In patients with severe illness empiric treatment for TB may be initiated prior to confirmation of diagnosis

Source: Tuberculosis Coalition for Technical Assistance. International Standards for Tuberculosis Care (ISTC), second edition. Tuberculosis Coalition for Technical Assistance, The Hague, 2009.

and malaise occur more frequently with advancing disease and may reflect underlying parenchymal involvement.[11] Tuberculous pleural effusions are typically lymphocytic exudates with low yield on AFB smear (10%) and culture (30%); however, diagnosis ideally is made through culture of the tubercle bacilli from pleural fluid obtained from the site. Classic radiographic findings include unilateral effusion of modest scale (although massive fluid collections have been reported, particularly in patients with AIDS)[11]

- **Lymphatic tuberculosis** is one of the more common forms of EPTB, historically known as "scrofula." Tuberculous lymphadenitis is particularly common in the posterior cervical and supraclavicular group of lymph nodes. In immunocompromized individuals and children, mediastinal, peribronchial, and paratracheal lymph node involvement are more commonly seen as part of primary disease. The disease is indolent with gradual, painless enlargement of the node(s) over several weeks to months. Patients typically present with a unilateral and painless, non-tender neck mass. Over time, the overlying skin may become shiny, pink to red, and warm to the touch, and nodes may become fluctuant and drain spontaneously with sinus tract formation. Intrathoracic lymph node TB in adults often presents with chest pain and dyspnea, along with typical systemic symptoms of TB. Constitutional symptoms are rare except in patients with HIV. Investigations include excisional lymph node biopsy for AFB; histology or fine needle aspiration biopsy for AFB smear and culture; or other routine investigation (e.g., history, tuberculin skin test [TST], CXR, HIV test, etc.)

- **Genitourinary tuberculosis.** Patients with **renal tuberculosis** may present with asymptomatic sterile pyuria, hematuria, dysuria, and flank pain resembling acute pyelonephritis. Many patients remain asymptomatic early in the course of the disease, resulting in diagnostic delay. Diagnostic investigations should include urine for TB culture (3 to 5 first-void morning urine samples); fine needle aspiration biopsy for histology as well as AFB smear and culture may be indicated; radiologic procedures such as intravenous pyelography, ultrasonography or computed tomography may be useful[12] when available; and routine TB workup should be included (e.g., history, TST, CXR, HIV test, etc.)

  Genital tuberculosis may present with mass lesions of the testes or epididymis in men, frequently without fever or other systemic complaint. The most common presentations of genital tuberculosis in women include infertility, pelvic pain, and menstrual disturbances (excessive menstrual loss, amenorrhoea, and postmenopausal bleeding). Diagnosis entails culture of the tubercle bacilli from the affected tissue. Mass lesions should be biopsied for both histological and cultural studies. More formal procedures such as uterine curettage, cervical biopsy, or laparoscopic biopsy may be required to obtain a diagnosis in women with suspected genital TB[11]

- **Disseminated tuberculosis** is the involvement of two or more non-contiguous organs with TB or the presence of tuberculosis bactereamia. This form is more commonly seen in children and immunosuppressed individuals. Clinical presentations of disseminated TB are diverse. Constitutional symptoms in patients with disseminated TB include fever, weakness, anorexia, and weight loss.[11] Chest radiography is a critical element in the diagnosis of disseminated TB, often demonstrating a typical miliary pattern. In addition to sputum collection, efforts should be made to collect tissue or fluid samples from affected sites and submit them for pathologic and mycobacteriologic examination when feasible

- **Tuberculosis of the spine (Pott's disease)** can result in long-term physical disability, and thus is of major concern. Patients may experience pain over a localized area, usually over the lower thoracic, lumbar, and lumbar sacral vertebrae. In children and adolescents, the thoracic vertebrae are most often affected, and in adults, the lumbar vertebrae are more commonly involved.[11] After disease progression, abscesses may be evidenced over the affected area. When feasible, send aspirate of vertebral lesion and/or paraspinous abscess for pathologic and mycobacteriologic examination

- **TB of the central nervous system** includes both TB meningitis and brain tuberculoma. Unless recognized and treated early, this form of tuberculosis can be fatal or lead to permanent disability. The clinical onset of TB meningitis is usually gradual. Early symptoms may include malaise, headache, irritability, anorexia, nausea, and vomiting. Fever and neck stiffness may be seen as the TB progresses. More advanced central nervous system TB usually presents with a constellation of signs that may include altered mental status, focal or mutifocal sensory and motor deficits, and seizure activity leading eventually to coma, hemiplegia, and death. At presentation, the cerebrospinal fluid is often clear and the pressure normal. Cerebrospinal fluid glucose levels are lower than serum glucose levels, with an increase in cells and protein

- **Tuberculosis pericarditis** often presents with hemodynamically significant pericardial effusion and is frequently accompanied by pleural effusions and intrathoracic lymphadenopathy. It can result in constrictive pericarditis. Baseline investigations might include: echocardiogram, chest ultrasound to measure and identify pericardial effusion, pericardio-centesis and pericardial biopsy with fluid and/or tissue sent for AFB smear and culture, in addition to the routine TB workup (e.g., history, TST, CXR, HIV test, etc.)

ISTC STANDARD **18**

All providers of care for patients with TB should ensure that persons who are in close contact with patients who have infectious TB 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 TB; 2) is at high risk of developing TB if infected; 3) is at risk of having severe TB if the disease develops; 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.[1]

TB Contact Investigation

There is a high likelihood that a person with smear-positive PTB will transmit tuberculosis. Therefore, prompt and thorough contact investigation is essential for the control of TB. Contact investigations should start with the persons most likely to be infected (those who most frequently come in contact with the person who has infectious TB). These close contacts are usually family members or other persons who live in the same household, but may also include friends and co-workers.

The case-finding potential resulting from contact investigation in high- and low-incidence settings has been reviewed and suggests that in low TB-incidence settings (e.g., United States), about 20–30% of contacts evaluated have latent tuberculosis infection (LTBI), and another 1% have active TB.[13] Much higher rates of both LTBI and active disease have been reported in high TB-prevalence countries, where about 50% of household contacts have LTBI and on average 4.5% have active TB at the time of initial investigation.[14]

Actively seeking out and evaluating contacts to persons with smear-positive PTB is an important TB control strategy for two reasons:[1]

1. It identifies persons with previously undetected tuberculosis, allowing initiation of treatment and halting further transmission
2. It identifies persons with TB infection who would benefit from isoniazid preventive therapy (IPT) to prevent future TB reactivation

When contact investigations are not conducted, opportunities to prevent additional cases of TB are missed, particularly among children. At a minimum, NTPs should strive to implement a process for **evaluation of high-risk contacts** (children <5 years of age and persons with HIV infection and other immunocompromising illnesses) **to the most infectious TB patients** (sputum smear-positive).[15,16]

See Appendix C: Implementing TB Contact Investigation, for further information on the steps involved and priorities for this case-finding strategy.

References

1. Tuberculosis Coalition for Technical Assistance. International Standards for Tuberculosis Care (ISTC), second edition. Tuberculosis Coalition for Technical Assistance, The Hague, 2009.
2. World Health Organization. Treatment of Tuberculosis: Guidelines. Fourth Edition. Geneva: World Health Organization, 2009 (WHO/HTM/TB/2009.420).
3. CAREC/PAHO. Smear Microscopy Quality Assurance Consensus Meeting, Regional Guidelines for CAREC Member Countries. CAREC/PAHO, April 2007.
4. World Health Organization. Report 2009. Global Tuberculosis Control: Surveillance, Planning, Financing. Geneva: World Health Organization, 2009 (WHO/HTM/TB/2009.411).
5. Francis J. Curry National Tuberculosis Center. *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians*, Second Edition. Francis J. Curry National Tuberculosis Center and California Department of Public Health, 2008.
6. World Health Organization. Implementing the Stop TB strategy: A handbook for national tuberculosis control programs. World Health Organization. Geneva, 2008 (WHO/HTM/TB/2008.401).
7. Bah B, Massari V, Sow O, et al. Useful clues to the presence of smear-negative pulmonary tuberculosis in a West African city. Int J Tuberc Lung Dis 2002; 6(7):592-8.
8. Somi GR, O'Brien RJ, Mfinanga GS, Ipuge YA. Evaluation of the MycoDot test in patients with suspected tuberculosis in a field setting in Tanzania. Int J Tuberc Lung Dis 1999;3(3):231-8.
9. Wilkinson D, De Cock KM, Sturm AW. Diagnosing tuberculosis in a resource-poor setting: the value of a trial of antibiotics. Trans R Soc Trop Med Hyg 1997;91(4):422-4.
10. Sterling TR. The WHO/IUATLD diagnostic algorithm for tuberculosis and empiric fluoroquinolone use: potential pitfalls. Int J Tuberc Lung Dis 2004;8(12):1396-400.
11. Iseman, Michael D. A 'Clinician's Guide to Tuberculosis, Chap. 7, Extrapulmonary Tuberculosis in Adults. Lippincott Williams & Wilkins. Philadelphia, 2000.
12. Public Health Agency of Canada and Canadian Lung Association. Canadian Tuberculosis Standards, 6th Edition, 2007. Chap. 5, Non-respiratory tuberculosis. Minister of Health, Canada.
13. Jereb J, Etkind SC, Joglar OT, Moore M, Taylor Z. Tuberculosis contact investigations: outcomes in selected areas of the United States, 1999. Int J Tuberc Lung Dis 2003;7:S384–90.
14. Morrison JL, Pai M, Hopewell P. Yield of tuberculosis contact investigations within households in high incidence countries: a systematic review [Abstract 239]. Infectious Diseases Society of America (IDSA) 43rd Annual Meeting 2005, San Francisco, October 6-9, 2005.
15. World Health Organization. Guidance for National Tuberculosis Programs on the management of tuberculosis in children, Childhood contact screening and management (Chapter 4), Int J Tuberc Lung Dis 11(1):12–15. The Union, Stop TB Partnership Childhood TB Subgroup, World Health Organization. Geneva, 2007.
16. World Health Organization. Dept. of HIV/AIDS. Essential prevention and care interventions for adults and adolescents living with HIV in resource-limited settings. Geneva: World Health Organization; 2008.

Essential Laboratory Services for Tuberculosis

6

Tuberculosis in the Caribbean still remains a priority, especially in countries with relatively high TB burden and/or with high HIV prevalence. Globally, the growing drug resistant TB crisis resulted in the World Health Assembly (WHA60.19) to call for enhanced laboratory capacity to provide drug susceptibility testing for all cases of culture-positive TB. Rapid diagnostic laboratory services are therefore essential to National and Regional TB programs and must be coordinated with other fundamental components of the program such as management, epidemiological and clinical aspects. This chapter addresses the infrastructure and guidelines necessary to ensure essential quality TB diagnostics including DST are accessible to countries in the Caribbean.

During the mid-1990s, many of the Caribbean laboratories were upgraded to facilitate acid-fast bacilli smear microscopy as this is the cornerstone for early diagnosis of TB[1] and remains the highest priority for detection of infectious cases and monitoring of treatment progress. A few laboratories proceeded to culturing of *M. tuberculosis*; however, this is still a major challenge for many as the infrastructure required for this activity is still lacking. Access to DST, which is required for patient care and monitoring of treatment, is also a major challenge in the Caribbean.

A definitive diagnosis of TB can only be made by culturing *M. tb* organisms in the laboratory from specimens taken from the patient. It is therefore very important and necessary for National Tuberculosis Programs to have access to a well functioning laboratory or laboratory network.

The diagnostic laboratory services must follow general principles as outlined below:

- Use of international, national, and regional standards relating to laboratory methods, procedures and techniques
- Creation of and participation in a laboratory network for diagnostic and reference activities
- Development of and participation in a quality assurance program to ensure valid and reliable service
- Conduct of operational research as necessary
- Enhanced program-laboratory partnerships and dissemination of information

In addition, laboratory scientists must have access to appropriate training and continuing education to assure they maintain expertise and competence in testing methods. All training activities should be evaluated to confirm that intended outcomes are practiced and integrated into laboratory procedures.

Laboratory Services for Mycobacteriology

Laboratory services for tuberculosis should form part of an integrated TB control program. In the CAREC Member Countries, laboratories vary in their capacity to diagnose tuberculosis. While most laboratories are capable of performing smear microscopy using the acid fast stain, a few laboratories are able to perform culture using solid media. However, there remains a need for a Regional Laboratory in the Caribbean which could support national and academic laboratories to ensure access to and sustained high quality TB laboratory diagnostic tests.

The officially designated "Caribbean Regional Laboratory" could provide training, support, and reference services to these laboratories for microscopy, culture, identification, and DST, in particular for countries not having the capacity and resources to perform this task. Depending on the needs of the participating laboratories, the Caribbean Regional Laboratory could support External Quality Assessment for smear microscopy.

A Supranational Reference Laboratory will work in close collaboration with the Caribbean Regional Laboratory for any guidance needed. Additionally, the Supranational Reference Laboratory will work directly with countries having the capacity to do culture, identification and DST (for support on drug resistance surveys, culture and DST proficiency testing, and training).

The activities performed at each laboratory are based on the level of technical complexity for conducting these tests as well as the level of biosafety facilities available in the laboratories.

Laboratories performing smear microscopy only (Level I)

This service is provided by the peripheral or district laboratory and their functions include:

- Receipt of specimens and dispatch of AFB smear results to healthcare providers within 1 day. New positives should be telephoned to the healthcare provider
- Prompt processing of sputum and other clinical material for AFB smear microscopy utilizing proper biosafety measures
- Preparation and staining of AFB smears
- Use of Ziehl Neelsen (ZN) and fluorescence microscopy (based on number of smears) and reporting of results within 1 day
- Participation in Internal Quality Assurance (IQA) and External Quality Assurance programs
- Referral of AFB smears to a reference laboratory for smear validation
- Prompt referral of specimens for culture, identification, and DST
- Documented maintenance of equipment
- Inventory control procedures that document management of reagents and laboratory supplies
- Maintenance of a laboratory register documenting patient identification labeling requirements

Laboratories performing culture and identification (Level II)

This service is usually provided by the intermediate or hospital laboratory once the biosafety conditions are suitable. These laboratories should also be capable of providing

supervision, monitoring, training, and quality assurance to laboratories performing smear microscopy. In addition to providing culture, these laboratories having a Biosafety Level-III (BSL-III) facility may also perform the identification of *M. tb*.

The functions of this laboratory include:

- All functions of the laboratory performing smear microscopy
- Digestion and decontamination of specimens for culturing of *M. tb*
- Culture results should be provided as soon as *M. tb* complex is detected/identified. A negative culture should be reported latest within 8 weeks of receipt of the specimen if using solid agar or 6 weeks if using broth-based media
- Identification of *M. tb* complex (labs with a BSL-III facility)
- Preparation and distribution of quality controlled reagents for microscopy in peripheral laboratories
- Training of microscopists in peripheral laboratories
- Support to and supervision of peripheral staff with respect to microscopy
- Quality improvement and proficiency testing of microscopy at peripheral laboratories
- Management of data and preparation of reports

Laboratories performing culture and drug susceptibility testing (Level III)

This service can be provided by the Central or National Laboratory. Central laboratories should be the apex of the health laboratory structure and should be capable of performing microscopy, culture, identification and DST of *M. tb*.

The functions of a Central laboratory include:

- All functions of laboratories performing culture and identification
- Specimen processing and culture of *M. tb* performed promptly with culture result reported no later than 8 weeks after receipt of the specimen if using solid agar or 6 weeks if using liquid media
- Clear-cut discrimination between *M. tb* complex and nontuberculous mycobacteria (NTM)
- Species-level identification of major NTM should be performed if an opportunistic pathogenic species is suspected, and if this expertise exists. If not, help may be requested to a higher level reference laboratory
- DST for *M. tb* complex to first-line drugs (streptomycin, isoniazid, rifampin, ethambutol; using solid or liquid media)
- DST for *M. tb* complex to second-line drugs (ofloxacin, capreomycin, kanamycin, amikacin: provided proficiency testing has been achieved in 1st-line drugs, and the personnel was duly trained by the Caribbean Regional Laboratory or Supranational Reference Laboratory)
- Selected laboratories may perform rapid molecular tests for species-level identification and/or drug resistance determination provided personnel were duly trained by the Caribbean Regional Laboratory or Supranational Reference Laboratory. Where provided, the test should be performed within one week of a culture being shown to be positive
- Preparation and distribution of quality controlled reagents for microscopy to intermediate and peripheral laboratories
- Organization of EQA of smear microscopy programs for intermediate and peripheral levels

- Conducting national training programs on smear microscopy, culture, identification and DST
- Supervision of intermediate and peripheral laboratories that includes on-site supervision and documented audits
- Co-ordination and/or conducting operational research
- Technical control of and repair services for laboratory equipment
- Collaboration with the NTP in defining technical specifications for equipment, reagents and other materials used in bacteriological investigations and in estimating laboratory materials and equipment requirements for the program budget
- Updating and dissemination of manuals and Standard Operating Procedures (SOPs) on bacteriological methods for diagnosing TB
- Drug resistance surveys for the National TB Program

Caribbean Regional Laboratory

A regional laboratory has, at minimum, an established expertise of a Level III laboratory, with additional human and financial resources to support other Level III laboratories within the region. In a regional context, the Caribbean Regional Laboratory provides support in laboratory issues on culture, identification, DST, quality assurance, and training.

However, keeping in mind a highly heterogeneous structure of the Caribbean, a Caribbean Regional Laboratory may also support certain smaller nations with routine culture and DST if such a facility is not available onsite.

Lastly, a Caribbean Regional Laboratory should collaborate actively with the Supranational Reference Laboratory for guidance and support on DST surveys, quality assurance through proficiency testing, and training.

Supranational Reference Laboratory

The World Health Organization (WHO)/Union Global Project on Antituberculosis Drug Resistance Surveillance[2] requires that data on drug resistance is gathered using standard methodology in order to determine the magnitude of resistance to first- and second-line antituberculosis drugs. The standard methodology includes representative sampling of patients with adequate sample sizes, standardized data collection distinguishing between new and previously treated patients, and quality-assured laboratory DST supported by a network of Supranational Reference Laboratories.[2]

In this context, quality-assured culture and DST are indispensable. Internal quality control and external quality assurance should therefore be in place, including a link for proficiency testing with a recognized reference laboratory such as one of the WHO-recognized Supranational Reference Laboratories. This service will be provided for the Caribbean network of laboratories by an officially designated Supranational Reference Laboratory. Additionally, this laboratory will also provide support for research, molecular typing, and validation of new technology.

Essential Laboratory Tests for TB Control

Diagnosis of tuberculosis and monitoring of treatment progress rely heavily on bacteriological examination of clinical specimens. The usefulness, priority, and scope of the various techniques used in the laboratory depend on the epidemiological situation prevailing in individual countries and on the resources available. Table 2 shows a list of essential laboratory tests for tuberculosis control.

Direct Sputum Smear Microscopy

- Smears are usually prepared directly from the sputum sample using either the ZN AFB method for light microscopy or the Auramine O stain method for fluorescence microscopy[3]
- Early laboratory diagnosis of TB relies on the prompt microscopic examination and reporting (within 1 day of receipt) of respiratory specimens for AFB. Direct smear microscopy using acid fast stains is generally considered to be relatively insensitive (25–65%) when compared to culture; however, it is relatively simple and inexpensive, and is currently indispensable in the detection of the most infectious cases of pulmonary TB

TABLE 2:

Essential laboratory tests for tuberculosis control

Test	Method & turnaround times (to results)
Microscopy for acid fast bacilli	• Fluorescence, 24 h • Ziehl Neelsen, 24 h
Mycobacterial growth detection by culture	• Lownstein Jensen slants, 3-8 wk • MGIT manual, 7-42 d • MGIT 960, 7-42 d
Identification of cultured mycobacteria	• Biochemicals, 2 wk • Immunochromatographic assays commercialized under following names: Capilia test, SD Bioline TB AgMPT64 Rapid, BD MGIT TBc Identification Test, 24 h • Molecular tests (AccuProbe, GenoType® Mycobacterium CM/AS tests, PCR Restriction Analysis [PRA], etc.), 24 h (minimum once weekly)
Drug susceptibility testing – first-line drugs	• LJ slants, 4 wk • Agar proportion, 3-4 wk • MGIT Manual, 1-2 wk • MGIT 960, 1-2 wk
Drug susceptibility testing – second-line drugs	• Same as first-line drugs
Nucleic Acid Amplification tests for tuberculosis diagnosis; molecular tests (to be done minimum once weekly)	• Various commercialized methods such as : Mycobacterium tuberculosis Direct Test (MTD Gen-Probe), Hain GenoType Mycobacteria Direct Assay, etc., 24h

- Fluorescence microscopy is more sensitive than standard light microscopy for TB diagnosis. Modern improved fluorescent microscopes equipped with a light-emitting diode (LED) offer a promising alternative to standard fluorescence lamps, avoiding the need for dark rooms. Their use is recommended, where possible, in laboratories examining 30 or more smears per laboratory scientist per day. This allows more rapid examination and improved efficiency of AFB

Culture

- Mycobacterial culture is more sensitive than smear microscopy and provides a definitive diagnosis of TB. It is therefore seen as the gold standard for bacteriological confirmation
- Culturing of mycobacteria requires a suitable infrastructure including biosafety measures, sound technical skills, and motivation of laboratory personnel
- Culture on solid media, such as Lowenstein-Jensen, is the most widely used technique. The disadvantages of using this media is the length of time (4 to 8 weeks) for growth of mycobacteria and the resulting delays in starting treatment especially in AFB smear-negative patients
- Culture in liquid media is the standard rapid method for TB diagnosis and patient management. This method can provide results within 10–42 days
- When using liquid culture methods, special precautions are needed to avoid bacterial contamination. Strengthening the capacity to perform culture on liquid media at country level is necessary to adequately address multidrug-resistant *M. tb* (MDR-TB) and extensively drug-resistant *M. tb* (XDR-TB)

Drug Susceptibility Testing

- DST of *M. tb* requires a suitable infrastructure including biosafety measures, sound technical skills and motivation of laboratory personnel
- Recommendations for DST differ for new cases according to the country's epidemiological situation. At a minimum, DST should be performed on the target groups defined recently (Table 5.1, Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008, WHO) including the following categories of patients:
    - All new cases in high MDR-TB burden countries; or in countries where the HIV prevalence in the general population is at least 1.0%; or where the HIV prevalence among TB patients is at least 5%
    - Patients belonging to high-risk groups (previously treated patients, particularly those who have failed treatment, defaulters, and those who have relapsed; immigrants from high prevalence areas and from areas with high MDR-TB)
    - When primary drug resistance is suspected
    - TB in HIV positive patients
- DST can be performed using either solid or liquid media and provides bacteriological confirmation of drug-resistant TB; DST should be available within 30 days of the initial receipt of an isolate in the source laboratory if using solid media, and less than 30 days if using broth-based assays. Results of testing should be reported within one working day of obtaining the final result. If a new isolate is found to be resistant, this should be telephoned to the appropriate healthcare provider

- WHO recommends carrying out DST for first-line (isoniazid, rifampicin, ethambutol) and second-line anti-TB drugs (particularly the fluoroquinolones and injectable drugs) to detect MDR-TB and XDR-TB respectively[2]
- Laboratory services for culture and DST should be introduced in a phased manner at appropriate referral levels of the health system
- Culture and DST should be based on a well-performing laboratory network that maintains a high quality of service by regular training, supervision, and support demonstrated by documented performance in an appropriate EQA program
- Rapid molecular methods are commercially available for detecting drug resistance mutations against commonly used first- and second-line drugs. This technology can be implemented in a high-performing Level III national laboratory

WHO Recommendation on Use of Line Probe Assays for Rapid MDR-TB Detection

- A WHO Expert Panel (June 2008) concluded "that there was sufficient generalisable evidence to justify a recommendation on the use of line probe assays for rapid detection of MDR-TB, at country level, and with further operational research to address country-specific implementation needs. Line probe assays are not a complete replacement for conventional culture and DST, as mycobacteriological culture is still required for smear-negative specimens, while conventional DST is still necessary to confirm XDR-TB. Nevertheless, the implementation of line probe assays in MDR-TB screening algorithms may significantly reduce the demand on conventional culture and DST laboratory capacity"[4]

Nucleic Acid Amplification (NAA) Tests and Line Probe Assays

- Traditional methods for laboratory diagnosis of TB may require weeks and delay can impede treatment and control efforts. Nucleic acid amplification tests, such as Polymerase Chain Reaction (PCR) and other methods for amplifying DNA and RNA, are not broadly used in the Caribbean but is an optional methodology that may facilitate rapid detection of *M. tb* in a high-functioning Level II/III laboratory
- In January 2009, the Centers for Disease Control and Prevention (CDC) recommended that NAA testing should be done on at least one respiratory specimen from each patient who has signs and symptoms of pulmonary TB and for whom a diagnosis of TB is being considered[5]

Collection and Transport of Specimens for Mycobacteriology

Proper specimen collection, storage, and transport are critical in order to produce laboratory results that clinicians can rely on for definitive diagnosis and treatment decisions. Therefore, specimens must be obtained following the instructions outlined in Tables 3A and 3B.

TABLE 3A:

Specimen collection techniques for smear microscopy and culture

Specimen Type	Specimen Requirements	Special Instructions	Unacceptable Specimens
Sputum	Collect 2 to 3 specimens from each patient according to NTP policy. Submit 5 to 10 ml in a sterile screw-cap container. Smaller quantities (3 to 5 ml) are acceptable if the quality is satisfactory. Refrigerate or transport rapidly to prevent overgrowth of normal flora.	Instruct patients on how to produce sputum specimen as distinct from saliva. Have patient rinse his or her mouth with water before collecting sputum to minimize contamination of the specimen. (Aerosol [saline] induced sputum should be performed only in an enclosed area with appropriate airflow and taking all appropriate measures to avoid exposure. The patient inhales slowly and deeply through the mouth, and then coughs at will, vigorously and deeply, which is collected in a sterile container.)	Pooled specimen. Food particles, residues and other extraneous matter. Specimens in waxed containers may produce false positive results. Unrefrigerated specimens more than 24 hrs old may yield contaminated results if culture being performed. Frozen specimen.
Tracheal aspiration, bronchoscopy and laryngeal swabbing	Collect 2 to 3 specimens from each patient according to NTP policy. Submit 5 to 10 ml in a sterile screw-cap container. Smaller quantities are acceptable. Refrigerate or transport rapidly to prevent overgrowth of normal flora.	These specimens are collected by trained personnel according to Institutional Guidelines.	Pooled specimen. Food particles, residues and other extraneous matter. Specimens in waxed containers may produce false positive results. Unrefrigerated specimens >24 hrs old may yield contaminated results if culture being performed.
Gastric lavage	Submit as much as possible (ideally 10 ml or more; though smaller quantities are acceptable) in a sterile screw-cap container. Without any preservative; neutralized if >4 hours before specimen will be processed.	On 3 consecutive days, collect the specimen soon after the patient awakens and while he/she is fasting in order to obtain sputum during sleep. Use sterile saline for lavage. Neutralize the specimen with 100 mg sodium carbonate, if the time between collection and processing exceeds 4 hours (see Appendix E).	Specimen that has not been neutralized and is over 4 hours old.

Specimens must be collected in sterile, leak-proof, disposable plastic containers, kept refrigerated, and processed quickly to inhibit contamination by normal flora. Sputum is the specimen of choice for patients with suspect pulmonary tuberculosis. When extrapulmonary TB is suspected, other specimens (e.g., urine, other body fluids, or tissue) may be more appropriate for testing.

Containers should be labeled in legible handwriting, clearly stating patient name, laboratory identification number, and type of specimen, as well as date and time of specimen collection. Specimen container(s) should be sent in a sealed, biohazard-labeled plastic

TABLE 3B:

Specimen collection techniques for smear microscopy and culture

Specimen Type	Specimen Requirements	Special Instructions	Unacceptable Specimens
Body fluids (spinal, pleural, pericardial, synovial, ascetic, blood, pus, marrow and aspirates)	Submit as much as possible (at least 10-15 ml) in a sterile screw-cap container. Without any preservative.	Disinfect the site with alcohol if collection is made using a needle and syringe. Blood collected with heparin or sodium polyanethol sulfonate (SPS) may be inoculated into any appropriate blood culture media for detection of mycobacteria.	Coagulated blood and blood collected in EDTA, which greatly inhibits mycobacterial growth, even in trace amounts.
Tissue	Submit 1 g tissue without fixative or preservative. A sterile container with a small amount of sterile water or sterile saline (to keep the specimen moist) is acceptable.	Collect the specimen aseptically. Do not immerse the specimen in saline (or other fluids) or wrap in gauze. Do not freeze as freezing decreases yield.	Specimens in formalin.
Urine	Submit clean-catch urine in a sterile screw-cap container. Collect either a single early morning voided midstream specimen or the total first morning specimen. Multiple single specimens may be required to obtain positive results.	Wash external genitalia before collection to minimize contamination. Specimen should be immediately refrigerated.	Specimen contaminated with fecal matter. Catheter urine.
Wound, skin lesions and aspirate	No specific volume requirements.	The skin should be cleaned with alcohol before aspirating material into syringe. Swab or pus exude may be used if volume is insufficient.	Dried swabs are unsuitable. Aimes or Stuarts transport medium, or a few drops of normal sterile saline solution may be used.

bag to the laboratory as soon as possible after collection. Each specimen should be accompanied by a request form with relevant patient and clinical information. The request form should be attached to the outside of the plastic bag, not stapled through the sealed portion of the bag.

In situations where an unacceptable specimen has been received, the receiving laboratory should immediately notify the sender of the reason specimen is unacceptable (e.g., insufficient amount, improper packaging, delayed transport, etc).

Shipment of specimens to referral laboratories out of the country should be done in accordance with International Air Transport Association (IATA) regulations by certified shippers.[6] Preferably, the national laboratory would be responsible for sending specimen(s) to the referral laboratory.

Safety Guidelines for the Mycobacteriology Laboratory

To obtain reliable results, all laboratory techniques including microscopy, culture and DST should be performed by appropriately trained staff working in properly equipped safe laboratories. Occupational health requirements (medical surveillance) should be applied and training in safety measures should be part of the basic training curricula for laboratory personnel. Training should include information on control of exposure to TB bacilli, control of laboratory hazards, and safe laboratory procedures and practices.[1]

TABLE 4A:

Biosafety components and guidelines related to TB laboratory diagnostic[7,8]

Task: Direct AFB microscopy from clinical specimens				
Activities	**Facility**	**Equipment**	**Practices**	**Risks/Comments**
• Collection of clinical specimens • Preparation, staining and examination of smears for AFB • Transportation of specimens to a higher level laboratory • Participation in EQA for smear microscopy	Adequately ventilated laboratory • Unidirectional airflow of 6–12 air changes per hour (ACH) • The bench for smear preparation should be separate from other laboratory benches. • A hand washing sink	• Personal protective equipment (PPE) including gloves/lab coat • If a Biosafety Cabinet (BSC) is available, smears should be prepared and dried inside this cabinet	Standard Microbiological Practices including: • Limited access to laboratory • A Medical surveillance of TB laboratory workers should be performed in accordance with national laws and practices, e.g., tuberculin skin test, chest X-ray	• Sputa are viscous and not prone to generate aerosols • Infectious materials generated from the laboratory should be autoclaved or incinerated depending on what is available at the facility

TABLE 4B:

Biosafety components and guidelines related to TB laboratory diagnostic[7,8]

Task: Processing of specimens for concentrated AFB microscopy and/or culture and/or line probe assays				
Activities	**Facility**	**Equipment**	**Practices**	**Risks/Comments**
• Processing specimens for microscopy and culture on solid (LJ) and liquid medium • Extraction of DNA for line probe assays • Referral of solid or liquid culture to reference laboratory for identification and DST	• Restricted access to laboratory (with administrative and physical separation) • Floors, walls, ceilings, benches and furniture should have impervious surfaces • A controlled ventilation system to maintain a unidirectional airflow in lab from clean to dirty areas with 6 to 12 ACH • Extraction of BSC exhaust air to outside may be used to create negative pressure (nonetheless, one must ensure proper BSC functioning and room design for required 6-12 ACH) • Windows must be hermetically closed. The BSC exhaust outlet should be placed away from people and air inlets • Air conditioners (split level type) should be placed without air recirculation to other areas within the building • An autoclave must be available onsite	• Biosafety Cabinet (BSC) Class I (EN12469/NSF49) or ClassIIA2 (NSF49) or ClassII (EN12469) equipped with HEPA filters H14. • BSC must be properly installed, regularly maintained and recertified on site. In case of irregular power supply, BSCs must be connected to a suitable UPS system and a backup generator. • BSC vented to the outside are preferred • PPE required includes gloves and lab coat. Respiratory protection is not mandatory, but should be available in lab in case of accidental biohazard (e.g., spillage), or may be used based on specific risk assessment • Centrifuge with aerosol tight safety cups must be used	Strict adherence to Standard Microbiological Practices including: • Controlled access to the laboratory • Risk assessment should be carried out, regularly reviewed and revised when necessary to define the safest possible conditions for work • Safety cups used for centrifuging specimens must be loaded and opened inside the BSC • Microcentrifuge for concentrating sediment for DNA extraction should be operated using an aerosol-tight rotor, which should be opened inside a BSC • Heating block for killing mycobacteria should also be operated inside the BSC; time and temperature strictly monitored • Decontamination of laboratory waste before removal from the TB laboratory using an autoclave • Decontamination of laboratory clothing before laundering or disposal • Proper hand-washing with liquid soap and adequate care in the handling of contaminated materials are critical elements of safe laboratory practice • A Medical surveillance of TB laboratory workers should be performed in accordance with national laws and practices, e.g., tuberculin skin test, chest X-ray	• A high risk is the creation of aerosols from manipulation of the clinical specimen during centrifugation and after processing when concentrated mycobacteria is handled • These manipulations should be carried out inside a certified BSC preferably vented to the outside • In case of accidental spill, the written laboratory procedure on spill response should be strictly followed

TABLE 4C:

Biosafety components and guidelines related to TB laboratory diagnostic[7,8]

Task: Manipulation of cultures for identification, DST and/or line probe assays				
Activities	**Facility**	**Equipment**	**Practices**	**Risks/Comments**
• Identifying *Mycobacterium* species from clinical specimens • Performing required DST studies against *M. tuberculosis* • Conducting research and providing training to other laboratories	• Same as above. **In addition** the laboratory should have a double door entry	• See Table 4B	• See Table 4B	• Due to the high load of viable TB bacilli in grown cultures, various manipulations required for bacterial identification and drug-susceptibility testing should be done in a certified BSC, preferably vented to the outside • In case of accidental spill, the written laboratory procedure on spill response should be strictly followed

Exposure to biohazards differs accordingly to the type of services performed and includes the following:

- In laboratories where sputum samples are handled for microscopy only, exposure to infectious particles generated from specimens is low due to the high viscosity of sputum. In these laboratories, adequate protection of laboratory staff is provided by appropriately directed airflow ensuring sufficient air changes in the room
- Specimen processing for concentrated AFB microscopy, culture or DST purposes should be performed in biological safety cabinets (BSCs), at least in Biosafety Level II (BSLII) facilities. However, because culture manipulation represents a high biohazard risk with exposure to high concentrations of TB bacilli, identification and DST activities should be performed in BSLIII facilities by appropriately qualified staff in accordance with BSLIII practices (see Tables 4A, 4B, and 4C). Upgrading to BSLIII should be planned and implemented with identification of adequate resources. Any proposal to create a BSLIII laboratory should take into account all the structural, logistic and staffing requirements as well as maintenance associated costs over time
- Laboratories that send cultures of *M. tb* to other laboratories should comply with national and international regulations on the transportation of dangerous goods (IATA regulations)[6]
- All specimens submitted to a Level II or Level III laboratory should be suspected of containing viable tubercle bacilli and treated in a manner to minimize the risk of infection to laboratory personnel. Clinical specimens that may contain tubercle bacilli include sputum, fluids, gastric or bronchial lavage, cerebrospinal fluid, urine, other body fluids and caseous lesions in tissues. Much of the risk to laboratory personnel can be attributed to inhalation of infectious aerosols. Therefore, our primary control measures in the laboratory are to eliminate if possible those practices that lead to the generation of aerosols and to confine the aerosol if it is generated within the BSC

- The three elements of containment include facility design, safety equipment, and practices and procedures. Tables 4A, 4B, and 4C highlights the various levels of laboratories and the elements of safety that are applicable

Quality Assurance

Quality Assurance (QA) in a tuberculosis laboratory is a system designed to continuously improve the reliability, efficiency and use of tuberculosis laboratory services. The purpose of a QA program is to improve the efficiency and reliability of laboratory services. In order to achieve the required technical quality in laboratory diagnosis, a continuous system of quality assurance needs to be established. Intermediate laboratories should supervise the peripheral network, while the central or reference laboratory should supervise the intermediate network.

The components of a quality assurance program are:

- Quality Control (QC)
- Quality Improvement
- External Quality Assessment (EQA)

Quality Control

QC is a systematic internal monitoring of working practices, technical procedures (SOPs) equipment, and materials including quality of stains.

Quality Improvement

Quality improvement is a process by which the components of smear microscopy diagnostic services are analyzed with the aim of looking for ways to permanently remove obstacles to success. Data collection, data analysis, and creative problem solving are the key components of this process. It involves continued monitoring, and identifying defects, followed by remedial action, including retraining when needed, to prevent recurrence of problems. Quality improvement often relies on effective on-site evaluation visits.

External Quality Assessment

EQA is a process to assess laboratory performance. EQA includes on-site evaluation of the laboratory to review QC and should include on-site rereading of smears.[9] EQA also allows participant laboratories to assess their capabilities by comparing their results with those obtained in other laboratories in the network through panel testing and rechecking, often referred to as Proficiency Testing.

References

1. International Union Against Tuberculosis and Lung Disease. Management of Tuberculosis: A Guide for Low Income Countries, Fifth Edition. IUATLD, 2000.
2. Aziz, M.A., Wright, A., Laszlo, A., De Muynck, A., Portaels, F., Van Deun, A., Wells, C., Nunn,P., Blanc, L., Raviglione, M. Epidemiology of antituberculosis drug resistance (the Global Project on Anti-tuberculosis Drug Resistance Surveillance): an updated analysis. Lancet 2006; 368: 2142-54.
3. Rieder HL, Van Deun A, Kam KM, Kim SJ, Chonde TM. Trébucq A, Urbanczik R. Priorities for tuberculosis bacteriology services in low-income countries, 2nd ed. International Union Against. Tuberculosis and Lung Disease 2007, Paris, France.
4. World Health Organization Molecular Line Probe Assays for Rapid Screening of Patients at Risk of Multidrug-Resistant Tuberculosis (MDR-TB). WHO Policy Statement. June 2008.
5. Centers for Disease Control and Prevention. Updated Guidelines for the Use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis. MMWR 2009; 58 (1): 7-10.
6. International Air Transport Association (IATA). Dangerous Goods Regulations: International Air Transport Association, 50th Edition. IATA 2009.
7. Vincent V, et al. WHO recommendations: summary report of expert meeting for Guidance on Biosafety Related to TB Laboratory Diagnostic Procedures. 2009. Geneva: World Health Organization. Available at: www.stoptb.org/wg/gli/assets/documents/Summary%20April%2009.pdf.
8. Centers for Disease Control and Prevention and National Institutes of Health. Biosafety in Microbiological and Biomedical Laboratories, 5th edition. Department of Health and Human Services, Public Health Service 2007 (www.cdc.gov/OD/ohs/biosfty/bmbl5/bmbl5toc.htm).
9. Association of Public Health Laboratories and Centers for Disease Control and Prevention. External Quality Assessment for AFB Smear Microscopy. September 2002.

Standard Treatment Regimens

7

"The main interventions to prevent the spread of tuberculosis in the community are the detection of patients with infectious TB and providing them with effective treatment to ensure a rapid and lasting cure. Consequently, treatment for TB is not only a matter of individual health, as is the case with, for example, treatment of hypertension or diabetes mellitus, it is also a matter of public health."[1]

An early start of TB treatment is critical

ISTC STANDARD 7

Any practitioner treating a patient for TB 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.[1]

The aims of treatment of TB are the following:

- To cure the patient of TB
- To prevent death from active TB or its late effects
- To prevent relapse of TB
- To decrease transmission of TB to others
- To prevent the development of acquired drug resistance

The Essential Anti-tuberculosis Drugs

Of note, WHO updated pediatric dose recommendations for first-line agents following a meeting of experts held in Geneva in July 2008[2] (www.who.int/selection_medicines/committees/subcommittee/2/TB.pdf). Table 5 lists the standard first-line anti-tuberculosis drugs and dosing recommendations for adults as well as the revised dosing recommendations for children. The WHO Model List of Essential Medicines provides the WHO-recommended formulations of anti-tuberculosis drugs and fixed-dose combinations of drugs (www.who.int/medicines/publications/essentialmedicines/en/). Countries should ensure that the formulations and combinations of anti-tuberculosis drugs available within the country conform to this list.[3]

Fixed-dose Combination Tablets

The WHO continues to recommend the use of fixed-dose combination tablets for treatment of TB (see also *ISTC* Standard 8), citing the following advantages:

- Reduces prescription errors because dosage recommendations are more straightforward and adjustment of dosage according to weight is easier

- The number of tablets to ingest is smaller and may positively impact patient adherence
- Decreases chance of acquired drug resistance due to patient self-selection of drugs when DOT is not used

Fixed-dose combination tablets may not fit the needs of all NTPs and will not suit all treatment situations. Of note, the WHO Expert Committee on Essential Drugs recently recommended that "low dose" pediatric fixed-dose combinations be removed from the WHO Model Essential Drug List and that new formulations should be made available on the grounds of concerns about inefficacy.[4] For NTPs using fixed-dose combination tablets, it will be necessary to have some stock supply of individual drugs for case situations where the patient may experience drug toxicity, drug intolerance or when drug resistance is identified as well as for treatment of childhood TB until new formulations based on the recommended higher daily dosages become available.

TABLE 5:

Doses of first-line anti-tuberculosis drugs in adults and children

Drug	Recommended dose in mg/kg body weight (range)	
	Daily	Three times weekly
isoniazid (INH, H)	**children:** 10 (10-15)[a], max. 300mg/day **adults:** 5 (4-6), max. 300mg/day	**children:** —— **adults:** 10 (8-12), max. 900 mg/dose
rifampicin (RIF, R)	**children:** 15 (10-20)[a, b], max. 600mg/day **adults:** 10 (8-12), max. 600mg/day	**children:** —— **adults:** 10 (8-12), max. 600 mg/dose
pyrazinamide (PZA, Z)	**children:** 35 (30-40)[a], max. 2000mg/day **adults:** 25 (20-30), max. 2000mg/day	**children:** —— **adults:** 35 (30-40), max. 3000mg/dose
ethambutol (EMB, E)	**children:** 20 (15-25)[c], max. 1000mg/day **adults:** 15 (15-20), max. 1600mg/day	**children:** 30 (25-35) **adults:** 30 (25-35), max. 2400mg/dose
streptomycin[d] (SM, S)	**children & adults:** 15 (12-18), max. 1000mg/day	**children & adults:** 15 (12-18)

a Daily dose recommendations for children as determined following review of existing pharmacokinetic studies and in consultation with pediatric pharmacology and TB experts[2] www.who.int/selection_medicines/committees/subcommittee/2/TB.pdf

b RIF dosages at the higher ranges may be preferable for children under 10 kilograms, and children with HIV infection or malnutrition[2]

c The recommended daily dose of E is higher in children than in adults, because the pharmacokinetics are different (peak serum E concentrations are lower in children than in adults receiving the same mg/kg dose)[5]

d Streptomycin should be avoided when possible in children because the injections are painful and irreversible auditory nerve damage may occur. The use of streptomycin in children is mainly reserved for the first 2 months of treatment of TB meningitis. Streptomycin should also be avoided in patients with renal failure because of increased risk of nephrotoxicity and ototoxicity. If streptomycin must be used, decrease frequency to two or three times per week, and monitor serum levels of the drug. Some sources recommend reduction of streptomycin dose to 10mg/kg/day (max. 750 mg/day) in patients >59 years of age. Patients weighing less than 50 kg may not tolerate doses above 500–750 mg daily (WHO Model Formulary 2008. www.who.int/selection_medicines/list/en/)

Source: Adapted from Tuberculosis Coalition for Technical Assistance. International Standards for Tuberculosis Care (ISTC), 2nd edition. Tuberculosis Coalition for Technical Assistance, The Hague, 2009.

Standard Code for TB Treatment Regimens

Treatment regimens for TB have a standard code using drug abbreviations (see Table 5 for first-line anti-tuberculosis drug abbreviations) and numbers to indicate frequency (daily or thrice-weekly) and duration of treatment.

All TB treatment regimens consist of two phases: an initial phase and a continuation phase. The number that appears before the drug abbreviations indicates the duration of that phase in months. A number in subscript (e.g., $_3$) after a letter or letters in parentheses indicates the number of doses of that drug per week. If there is no subscript number, treatment is daily (or six times weekly, excluding for instance Sunday).

Standard Regimens for Defined Patient Groups

The use of standardized regimens for treating patients within a defined group has a number of benefits:

- Reduces errors in prescriptions
- Facilitates estimates of drug needs, purchasing, distribution and monitoring
- Facilitates staff training
- Reduces costs
- Facilitates regular drug supply
- Makes outcome evaluation convenient and comparable

The WHO Treatment of Tuberculosis Guidelines, Fourth Edition incorporates findings from systematic reviews conducted to evaluate the available evidence on seven key questions related to treatment and monitoring. Recommendations made by the WHO Guidelines Group reflect the quality of evidence, patient values and costs, as well as judgements about tradeoffs between benefits and harms. The recommendations were then rated as "strong" for those where desirable effects of adherence to the recommendation clearly outweigh the undesirable effects, and "conditional" for those where there is probably a benefit with adherence to the recommendation but the trade-offs are not that clear.[3] These WHO recommendations are reflected in chapters 7, and 8.

Diagnostic Categories I – IV are no longer used to guide standard treatment regimen selection. In line with this significant change in the WHO Treatment of Tuberculosis Guidelines, Fourth Edition, standard "optimal" and "acceptable" regimens are described under the recording and reporting registration groups. These registration groups differentiate new patients from those with prior treatment and specify reason for retreatment. WHO recommendations 4.3 was removed and 7.1 was modified in this guideline document to reflect the recommendations of the Caribbean TB guideline Technical Working Group (CTWG) following a review of the proposed WHO standard treatment regimen recommendations in March 2009. The recommendations of the CTWG establish a higher standard for treatment of HIV-related tuberculosis (daily treatment throughout) and for ensuring that drug susceptibility testing is obtained for all previously treated tuberculosis patients.

New Patients

New patients are presumed to have drug susceptible TB with two exceptions:

- Where there is a high prevalence of isoniazid resistance in new patients, or
- If they have developed active TB after known contact with a patient documented to have drug-resistant TB. Although they are new patients, they are likely to have a similar drug resistance pattern as their source case,[6] and should have DST obtained at the start of treatment. While awaiting DST results, they should begin a regimen based on the DST of the presumed source case

Table 6 summarizes the recommended standard treatment regimens by defined new patient group.

Presumed or Known Drug Susceptible TB

The 8 month treatment regimen with 2 months of rifampicin (2HRZE/6HE) is associated with more relapses and deaths than the 6 month treatment regimen that includes rifampicin throughout (2HRZE/4HR).[7] Therefore, WHO recommends the following for new patients presumed or known to have drug susceptible TB[3] (see also *ISTC* Standard 8).

> WHO Recommendation 1.1. New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR.[a,b,c] (Strong/High grade of evidence)
>
> WHO Recommendation 1.2. The 2HRZE/6HE treatment regimen should be phased out. (Strong/High grade of evidence)
>
> **Note:** WHO no longer recommends omission of ethambutol during the intensive phase of treatment for patients with non-cavitary, smear-negative PTB or extrapulmonary disease who are known to be HIV-negative.

ISTC 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 four months. The doses of anti-tuberculosis drugs used should conform to international recommendations. Fixed-dose combinations of two (isoniazid and rifampicin), three (isoniazid, rifampicin, and pyrazinamide), and four (isoniazid, rifampicin, pyrazinamide and ethambutol) drugs are highly recommended.[1]

a Recommendation 1.1 also applies to extrapulmonary TB, except TB of the central nervous system, bone or joint for which some expert groups suggest longer therapy (see Extrapulmonary TB section, page 61)

b WHO recommends that NTPs ensure that supervision and support are provided for all TB patients in order to achieve completion of the full course of therapy

c WHO recommends drug resistance surveys (or surveillance) for monitoring the impact of the treatment program as well as for designing standard regimens

Intermittent Use

The systematic review which looked at dosing frequency for HIV-negative patients, found little evidence of difference in failure or relapse with daily or three times weekly regimens.[7] However, patients receiving three times weekly dosing throughout therapy had higher rates of acquired drug resistance than patients who received daily drug administration throughout treatment. Additionally, in patients with pre-treatment isoniazid resistance, treatment failure and acquired drug resistance was significantly higher in patients on thrice weekly dosing during the intensive phase compared to those receiving daily dosing in the intensive phase.

> WHO Recommendation 2.1. **Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy.** (Strong/High grade of evidence)

There are two alternatives to WHO Recommendation 2.1:

> WHO Recommendation 2.1A. **New patients with PTB may receive a daily intensive phase followed by three times weekly continuation phase [2HRZE/4(HR)$_3$], provided that each dose is directly observed.** (Conditional/High and moderate grade of evidence)

> WHO Recommendation 2.1B. **Three times weekly dosing throughout therapy [2(HRZE)$_3$/4(HR)$_3$] may be used as another alternative to Recommendation 2.1, provided that every dose is directly observed and the patient is NOT living with HIV or living in an HIV-prevalent setting.** (Conditional/High and moderate grade of evidence)

There is insufficient evidence to support the efficacy of two times per week dosing administered throughout therapy.[7] Daily intensive phase dosing followed by a continuation phase administered 2 times per week is not recommended because missing one dose means the patient receives only half the treatment.[3]

> WHO Recommendation 2.2. **New patients with TB should not receive twice weekly dosing for the full course of treatment unless this is done in the context of formal research.**[a] (Strong/High grade of evidence)

New TB Patients with HIV

The revised WHO guidelines, Treatment of Tuberculosis, Fourth edition no longer recommend a three times weekly intensive phase as an optional regimen for the treatment of TB in new patients with HIV. This new recommendation is based on a systematic review showing that HIV-positive TB patients who were treated with intermittent TB therapy throughout treatment had a 2 to 3 times higher incidence of relapse and failure, compared to those who received a daily intensive phase.[8] While the revised WHO guidelines included a conditional allowance for thrice weekly dosing during the continuation phase for new patients with HIV (recommendation 4.3),[3] the CTWG opposed this option and voted to recommend daily dosing only as the treatment frequency (see Table 6).

> WHO Recommendation 4.1. **TB patients with known positive HIV status and all TB patients living in HIV prevalent settings**[b] **should receive daily TB treatment at least during the intensive phase.** (Strong/High grade of evidence)

a The available evidence showed equivalent efficacy of daily intensive-phase dosing followed by two times weekly continuation phase. However, twice weekly dosing is not recommended on operational grounds, since missing one dose means the patient receives only half the regimen

b Countries, subnational administrative units, or selected facilities where the HIV prevalence among adult pregnant women is ≥1%, or HIV prevalence among TB patients is ≥5%

> WHO Recommendation 4.2. **For the continuation phase, the optimal dosing frequency is also daily for these patients.** (Strong/High grade of evidence)

Lower relapse rates were found on systematic review in TB patients living with HIV treated with ≥8 months of rifampicin-containing regimens compared to those treated for 6 months.[9] However, given the low quality of data and operational challenges of separate durations of TB treatment for HIV-positive and negative, WHO recommendation for duration of treatment in patients with HIV remains unchanged.

> WHO Recommendation 4.4. **It is recommended that TB patients who are living with HIV should receive at least the same duration of TB treatment as HIV-negative TB patients.** (Strong/High grade of evidence)

Despite the operational challenges that may present with separate durations for HIV-positive and HIV-negative TB patients, the CTWG felt strongly that the 7 month HR continuation phase should be reflected as an alternative acceptable regimen. In situations where the patient with HIV-related TB is slow to respond to treatment, (e.g., patient re-

TABLE 6:

Recommended treatment regimens by defined new patient group

New patient groups	TB treatment regimens	
	Initial phase	Continuation phase
New patient - presumed or known drug-susceptible	**Optimal** 2 HRZE[a]	**Optimal** 4 HR
	Acceptable 2 HRZE[a] **or** 2 $(HRZE)_3$ [a,b]	**Acceptable** 4 $(HR)_3$
New patient - presumed or known drug-susceptible and **living with HIV or in a high HIV prevalence setting**	Optimal 2 HRZE[a]	Optimal 4 HR
	Acceptable 2 HRZE[a]	Acceptable 7 HR[c]
New patient - in setting with high levels of isoniazid resistance where DST at start of treatment is not universal	**Acceptable** 2 HRZE[a]	**Acceptable** 4 HRE
New patient - in settings where >3% of new patients have MDR	Obtain DST at the start of therapy[3]	

E = ethambutol; **H** = isoniazid; **R** = rifampicin; **S** = streptomycin; **Z** = pyrazinamide;
DRS = drug resistance survey; **DST** = drug susceptibility testing

a Note that WHO no longer recommends omission of ethambutol during the intensive phase of treatment for patients with non-cavitary, smear-negative PTB or EPTB who are known to be HIV-negative

b Acceptable alternative EXCEPT for TB patients who are living with HIV or live in HIV prevalent settings

c Some experts recommend prolonging the continuation phase to 7 months when there is slow or suboptimal response to treatment.[8] This alternative regimen is not endorsed by PAHO/WHO but is considered an option by the CTWG

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

mains culture positive after 2 month initial phase of treatment), extending the continuation phase to 7 months (total 9 months treatment) should be considered.[8] Previously treated TB patients who are living with HIV should receive the same retreatment regimens as HIV-negative patients.[3]

The clinical management of HIV-related TB is discussed in detail in Chapter 9.

Settings with High Levels of INH Resistance in New Patients

At present, the threshold for what constitutes a high level of INH resistance in new patients in a given setting has not yet been defined. However, given the significant proportion of non-MDR-TB cases worldwide showing any INH resistance (global weighted mean of 7.4%),[10] the WHO has added a recommendation based on expert opinion for the addition of ethambutol to the continuation phase in countries where DST at the start of treatment is not universal for all new patients (see Table 6). The intent of this recommendation is that it may help prevent the development of MDR-TB in patients with unrecognized INH resistance in settings where DST is not readily available.

> **WHO Recommendation 3. 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.** (Weak/Insufficient evidence, expert opinion)

Given the potential benefit and low risk of toxicity from ethambutol, the pressing need to prevent MDR warrants this recommendation; however, this is a conditional recommendation with the following arguments noted:[3]

- 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
- The evidence for ocular toxicity from ethambutol was not systematically reviewed for the WHO guidelines, Treatment of Tuberculosis, Fourth edition but the risk of permanent blindness exists
- Further research is needed to define the level of INH resistance that would warrant the addition of ethambutol to the continuation phase of the standard new patient regimen (in countries without universal DST at start of treatment for all new cases)

Previously Treated Patients and Multidrug Resistance (MDR)

Previous treatment for TB is a strong determinant of drug resistance and of MDR. A review of the WHO drug resistance surveillance data from 1994-2007 revealed that 15% of previously treated cases were MDR compared to 3% of new cases.[3] MDR is critical to detect as regimens with first-line drugs are much less effective[11] and resistance can be further amplified.[12] Prompt identification of MDR and initiation of MDR treatment with second-line drugs gives a better chance of cure, and prevents the development and spread of further resistance. Because of its clinical significance, MDR (rather than any drug resistance) is used to describe the retreatment patient groups.

The level of MDR in previously treated patients can be influenced by many factors, and levels are likely to vary widely by setting. Therefore, assignment of the retreatment patient groups to medium versus high likelihood of MDR may need to be modified by country-specific data of similar groups of patients.

WHO Recommendation 7.5. National TB Programs (NTPs) should obtain and use their country-specific drug resistance data on failure, relapse and default patient groups to determine the levels of MDR.[a]

Determining Approach to Retreatment[1]

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.[13] The purpose is to identify MDR as early as possible so appropriate treatment can be given (See *ISTC* Standard 11).

CTWG modified WHO Recommendation 7.1. Specimens for culture and drug susceptibility testing **must** be obtained from all previously treated TB patients at or before the start of treatment. DST should be performed for at least isoniazid and rifampicin.[b,c]

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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 (see Chapter 11), culture and testing for susceptibility 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.[1]

The approach to the initiation of retreatment in large part depends on the country's laboratory capacity, specifically **when** (or if) DST results are routinely available for the individual patient. All DST requires Level III Laboratory Service (see Chapter 6) which is supported by a well performing EQA program. **Rapid DST methods** can produce results within hours or days, however, additional delays may occur when testing is performed out of country due to specimen transportation time. **Conventional DST methods** will have results available within weeks (if using liquid media) or months (if using solid media); therefore, countries using conventional DST methods will need to start an empiric regimen while awaiting results.

Table 7 summarizes the approach to retreatment (use of standard or empiric regimen) based on type of DST available and estimated turnaround time of DST results. DST methods and suggestions on approach to selecting the appropriate standard regimen for

a Country-specific drug resistance data should include data stratified by type of regimen given for the patient's first course of TB treatment (i.e., 2 vs. 6 months of rifampicin)

b DST may be carried out by rapid molecular-based methods or by conventional methods. Sputum should be obtained, as well as appropriate specimens for extrapulmonary TB, depending on the site of disease

c Obtaining specimens for culture and DST should not delay the start of treatment. Empirical therapy should be started promptly, especially if the patient is seriously ill or the disease is progressing rapidly

defined patient groups is discussed in more detail in Section 3.8. of the WHO Treatment of Tuberculosis Guidelines, Fourth Edition) (http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf).

TABLE 7:

Framework for approaching retreatment, depending on the routine availability of DST results for individual previously treated patients

Type of DST	Results available	Approach to retreatment
Rapid	Hours to days	Use DST results to select which regimen to start and use throughout treatment
Conventional	Weeks to months	Start **empiric** regimen (see note below) while awaiting DST results. (Once DST results are available, may need to modify the regimen.)
None (interim)	Not available	Use **empiric** regimen (see note below) for the full course of treatment. (This is an interim approach while the country is developing lab capacity.)

Source: WHO Treatment of Tuberculosis Guidelines, Fourth edition, 2009.

Approach to retreatment in settings with access to rapid DST

With line probe assays, MDR can be essentially confirmed[a] or excluded within hours to days, which allows the results to guide the regimen at the start of therapy.

> WHO Recommendation 7.2. In settings where rapid molecular-based DST is available, the results should guide the choice of regimen.

Approach to retreatment in settings where conventional DST results are routinely available for individual patients

Obtaining specimens for conventional culture and DST should not delay the start of therapy. Empiric regimens are used while awaiting the results of conventional DST (liquid or solid media), and should be started promptly.[b] This is especially important if the patient is seriously ill or the disease is progressing rapidly. Placing a patient on an empiric regimen pending DST is done to avoid clinical deterioration as well as to attempt to render the patient non-infectious and thereby, halt further transmission. Empiric regimens are often based on drug-resistance surveillance data, (see Table 23 in Chapter 11 for suggested empiric regimens by drug resistance profile).

a Line probe assays detect resistance to rifampicin alone or in combination with isoniazid resistance. Overall high accuracy for detection of MDR is retained when rifampicin resistance alone was used as a marker for MDR[14]

b In some individual patients who have been treated multiple times, waiting to start treatment until DST results are available may be prudent, as long as the patient is clinically stable and transmission to contacts is prevented. However, in most countries adequate infection control measures are not yet in place

While awaiting the results of conventional DST, WHO recommends:

- To administer the empiric MDR regimen[a] for patient groups with high levels of MDR, and
- The retreatment regimen with first-line drug regimen for patient groups with medium or low levels of MDR (Table 8)

For many countries, drug resistance surveys will show that patients whose prior course of therapy has failed have a high likelihood of MDR so this group should receive an empirical MDR regimen. Often drug resistance surveys show that those relapsing or returning after default will have a medium or low likelihood of MDR, so these patients could receive the retreatment regimen of first-line drugs, as described below and on Table 8. However, levels of MDR in these patient registration groups vary by setting.[b] Furthermore, several other considerations (including the number of MDR-TB cases the program has the capacity to treat) will impact what level of MDR the NTP designates as "high" in a given country (see also *ISTC* Standard 12).

WHO Recommendation 7.3. In settings where rapid molecular-based DST results are not routinely available to guide the management of individual patients, empirical[c] treatment should be started as follows:

WHO Recommendation 7.3.1. TB patients whose treatment has **failed**[d] or other patient groups with high likelihood of multidrug-resistant (MDR) TB should be started on an empirical MDR regimen.

Note: In the absence of culture and DST results, the patient should be clinically evaluated before the MDR regimen is administered.

WHO Recommendation 7.3.2. TB patients returning after **defaulting** or **relapsing** from their first treatment course may receive the retreatment regimen containing first-line drugs 2HRZES / 1HRZE / 5HRE if country-specific data show low or medium levels of MDR in these patients, or such data are not available.

Note: When DST results become available, regimens should be adjusted appropriately.

Approach to retreatment in settings where DST is not routinely available for individual patients

In many countries, there is not yet laboratory capacity to routinely conduct DST for each previously treated patient (or the results arrive too late to guide therapy). In these countries, it is urgent to strengthen laboratory capacity. For countries without sufficient domestic funding, financial assistance is available from the Global Fund to Fight AIDS, Tuberculosis and Malaria, as well as from UNITAID or other international financing mechanisms. Technical assistance in laboratory strengthening is available from WHO, Global Laboratory Initiative and other partners.

a Guidance on designing a country's standard MDR regimen is provided in Chapter 11 of this document, and in Chapter 7 of the 2008 WHO Guidelines for the programmatic management of drug resistant TB

b If drug resistance surveys show that patients relapsing or returning after default have high levels of MDR, they will need an MDR regimen instead

c In these guidelines, empirical means providing treatment before (or without) knowing whether the patient's TB organisms are MDR or not

d Failures in a well-run NTP should be infrequent in the absence of MDR-TB. If they do occur, they are due either to MDR-TB or to program factors such as poor DOT or poor drug quality. If drug resistance data from failure patients are available and show low or medium levels of MDR, patients should receive the retreatment regimen outlined in WHO Recommendation 7.3.2., and every effort should be made to address the underlying programmatic issues

In countries without access to DST for individual patient management, the NTP may be able to collect or access some information on levels of MDR-TB in previously treated patients, by using data from a drug resistance survey, a regional, national or supranational reference laboratory, or from a referral or research center. These data are critical for ascertaining the level of MDR in retreatment patients.[a] For example, the results of representative drug resistance surveys may identify a group of patients in whom a very high percentage have MDR, which could justify the use of MDR regimens in all patients in the group (even if individual DST is not available).[6] The NTP manager is encouraged to obtain technical assistance from the Green Light Committee (see Chapter 11, page 126).

If a very high level of MDR is documented in a specific group (such as patients who have failed a retreatment regimen) the NTP manager should urgently seek means to routinely obtain DST on all such patients at the start of treatment, in order to confirm or exclude MDR. If this cannot yet be achieved with any in-country laboratory, most NTPs can make arrangements to send these patients' specimens to a supranational reference or other international laboratory for DST while the country rapidly builds domestic laboratory capacity.

A country may face a short gap in time before a domestic or an international laboratory can perform DST on specimens from patients who are members of a group shown to have very high levels of MDR-TB. Under this exceptional circumstance, an NTP may consider a short-term policy of directly starting patients from such a group on an empirical MDR-TB regimen while awaiting confirmation of isoniazid and rifampicin resistance (last row of Table 8).[6] This is a temporary measure that can only be implemented if culture and DST can be arranged in the first few months of MDR treatment in each enrolled patient. It is essential to confirm the presence of MDR, and to monitor the response to treatment. (Groups of patients whose likelihood of MDR is medium or low will receive the 8 month retreatment regimen with first-line drugs.)

> WHO Recommendation 7.4. In settings where DST results are not yet routinely available to guide the management of individual patients, the empirical regimens will continue throughout the course of treatment.

Treatment of Extrapulmonary TB (EPTB) and Special Situations

Extrapulmonary TB (EPTB)

With perhaps a few exceptions, most experts now agree that virtually all forms of EPTB can be treated with the same regimens used to treat PTB (see Tables 6 and 8). Of note, WHO no longer recommends omitting EMB during the intensive phase of treatment for patients with EPTB disease who are known to be HIV-negative.[3]

- In TB meningitis, a 6–month regimen with rifampicin throughout was shown to be as effective as the traditional 9–12 month regimens, with streptomycin used instead of ethambutol in the initial phase.[15] However, some experts still recommend a 9–12 month

a This information is also needed to determine the patterns of MDR, so a standard MDR regimen can be chosen for empiric treatment of patients with high likelihood of having MDR

TABLE 8:

Standard regimens for previously treated patients by patient registration group and availability of DST

DST routinely available for previously treated patients	MDR likelihood (Patient Registration group—see first note below)	
	High (Failure[a])	**Medium or low** (Relapse, default)
Rapid method	DST results confirm or exclude MDR to guide the choice of regimen	
Conventional method	*While awaiting DST results:*	
	Empiric MDR regimen	2 HRZES / 1 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 program. *May modify regimen once DST results are available.*	2 HRZES / 1 HRZE / 5 HRE *for full course of treatment.*

Notes:

- The assumption that failure patients have a high likelihood of MDR (and relapse or defaulting patients have a medium likelihood of MDR) may need to be modified based on the level of MDR found in these patient registration groups
- A country's standard MDR regimen is based on country-specific DST data from similar groups of patients (see Chapter 11)
- In the country's standard regimens, the 8 month retreatment regimen should not be "augmented" by a fluoroquinolone or an injectable drug; this practice jeopardizes second-line drugs that are critical treatment options for MDR patients. The use of second-line drugs should be restricted to MDR regimens, and these should only be used if quality-assured drugs can be provided by DOT for the whole course of therapy. In addition, laboratory capacity for cultures to monitor treatment response, as well as a system for detecting and treating adverse reactions must be in place (see Section on the Green Light Committee- Chapter 11)

Source: WHO Treatment of Tuberculosis, Guidelines, Fourth edition, 2009.

regimen for the treatment of TB meningitis given the serious risk of disability and mortality.[8] (See Chapter 10, Table 19 for recommended regimen options for TB meningitis in children)

- Treatment response in TB of the bone or joint is difficult to assess and therefore, some experts recommend extension of treatment to 9 months in these cases
- Finally, adjunctive steroids are recommended in pericardial and meningeal TB.[8,16,17,18] If drug resistance is suspected, do culture and rapid DST and use second-line drugs with steroids

Surgery plays little role in the treatment of EPTB, being reserved for management of late complications of disease such as hydrocephalus, obstructive uropathy, constrictive pericarditis, and neurological involvement or severe kyphosis from Pott's disease (spinal TB)

a 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

and perhaps in some cases of highly drug-resistant EPTB (e.g., MDR/XDR). For large, fluctuant lymph nodes that appear to be about to drain spontaneously, aspiration or incision and drainage may be beneficial.[8]

Managing the Smear-Negative Suspect Case

The following description assumes that the initial set of sputum specimens for smear microscopy were negative x 2 (see page 32, Figure 1: An illustrative approach to the diagnosis of sputum smear-negative PTB in patients presenting with an illness suggestive of PTB).

For any **HIV-positive and/or severely ill** patient with chest symptoms typical of tuberculosis, but whose sputum smear is negative x 2:

- Repeat clinical assessment
- Get a chest X-ray (CXR)
- Obtain sputum mycobacterial culture (or other test if extra-pulmonary site involved)
- Start antibiotic treatment for pneumonia (excluding fluoroquinolones)
  - If clinical/radiographic findings are **not suggestive of TB** and culture is negative then patient does not have TB and other diagnoses should be considered. Patient should be evaluated for ART and begin CPT if not already initiated
  - If clinical/radiographic findings **are suggestive of TB** (positive or negative culture), register as a case of TB and initiate treatment. Patient should also be evaluated for ART and begin CPT if not already initiated

For patients that are **HIV-negative and/or** present with **mild/moderate illness**, but whose sputum smear is negative x 2:

- Provide trial broad-spectrum antimicrobials (excluding anti-TB drugs and fluoroquinolones)
  - If improvement noted upon completion of antimicrobials, patient does not have TB and requires no further follow-up unless symptoms recur
  - If no improvement noted upon completion of course of antimicrobials:
    - Repeat clinical assessment
    - Obtain CXR
    - Obtain sputum mycobacterial culture (or other test if extra-pulmonary site involved)
      - If clinical/radiographic findings **are suggestive of TB** and/or culture is positive, register as a case of TB and initiate treatment
      - If clinical/radiographic findings are **not suggestive of TB** and culture is negative, patient does not have TB and other diagnoses should be considered

Treatment of TB in Other Special Situations

Pregnancy and Breastfeeding

The risk to a pregnant woman and her fetus is far greater from untreated tuberculosis than from the drugs used in its treatment. Isoniazid, rifampicin, and ethambutol have been well studied and are known to be safe for administration during pregnancy. Although detailed teratogenicity data are not available, pyrazinamide can probably be used safely during pregnancy.[3] Use of streptomycin, however, is contraindicated during pregnancy because it is ototoxic to the fetus.[19] It is important to explain to a pregnant woman that successful treatment of TB with the recommended standardized regimen is important for a successful outcome of pregnancy.

A woman who is breastfeeding and has TB should receive a full course of anti-tuberculosis treatment. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to her baby. All the anti-tuberculosis drugs are compatible with breastfeeding, and a woman taking them can safely continue to breastfeed.[3] The mother and baby should stay together, the baby should continue to breastfeed in the normal way, and the baby should also be given 6 months of isoniazid followed by BCG once active disease has been ruled out.[20] (See Chapter 10: Tuberculosis in Children for additional guidance on BCG vaccination for children at risk for HIV.)

Pyridoxine supplementation is recommended for all pregnant or breastfeeding women taking isoniazid.

Considerations in Women Taking Oral Contraceptive

Rifampicin interacts with the oral contraceptive pill, with a risk of decreased protective efficacy against pregnancy. A woman who usually takes the oral contraceptive pill may choose between the following two options while receiving treatment with rifampicin:

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

Treatment for Patients with Liver Disorders

INH, RIF and PZA are all associated with hepatitis. Rifampicin is the least likely of the three to cause hepatocellular damage, although it is associated with cholestatic jaundice.[15] Pyrazinamide is the most hepatotoxic.[15]

Patients with the following conditions can receive the usual short-course chemotherapy regimens provided that there is no clinical evidence of chronic liver disease; however, hepatotoxic reactions to anti-tuberculosis drugs may be more common among these patients and should therefore be anticipated (see Chapter 8 for management of drug-induced hepatitis):[3]

- Hepatitis virus carriage
- A past history of acute hepatitis
- Current excessive alcohol consumption

Rarely a patient may have TB and at the same time acute hepatitis (i.e. viral) unrelated to TB or anti-tuberculosis treatment. In such cases if possible, consider deferring TB treatment until the acute hepatitis has resolved.

In patients with unstable or advanced liver disease, liver function tests should be obtained at the start of treatment if possible.[3] If the serum alanine aminotransferase (ALT) is more than 3 times normal before the initiation of treatment and TB is not thought to be the cause, the regimen options include the following with the caveat to use fewer hepatotoxic drugs in the regimen the more unstable or severe the liver disease[3] and provided isolate shows sensitivity by DST:

- Two hepatotoxic drugs
  - Nine months of isoniazid and rifampicin, plus ethambutol (until or unless isoniazid susceptibility is documented)
  - Two months of isoniazid, rifampicin, streptomycin and ethambutol, followed by 6 months of isoniazid and rifampicin
  - Six to nine months of rifampicin, pyrazinamide and ethambutol
- One hepatotoxic drug
  - Two months of isoniazid, ethambutol and streptomycin, followed by ten months of isoniazid and ethambutol
- No hepatotoxic drugs
  - 18–24 months of streptomycin, ethambutol and a fluoroquinolone

All patients should be educated to promptly report symptoms suggestive of hepatitis immediately; they should not wait until their next scheduled clinical evaluation to do so.

Clinical monitoring (and liver function tests, if possible) should be performed during treatment in all patients with pre-existing liver disease[21] (see also Chapter 8). Expert consultation should be sought when treating TB patients with advanced or unstable liver disease.

Treatment of Patients with Renal Failure and Severe Renal Insufficiency

The recommended initial TB treatment regimen for patients with renal failure or severe renal insufficiency is two months of INH, RIF, PZA and ethambutol, followed by 4 months of INH and RIF.[3]

INH and RIF are metabolized by the liver; therefore, these drugs may be given in normal dosage to patients with renal failure. In severe renal failure, patients should receive pyridoxine 25–50 mg along with INH in order to prevent peripheral neuropathy. PZA is also metabolized by the liver, but its metabolites (pyrazinoic acid and 5-hydroxy-pyrazinoic acid) may accumulate in patients with renal insufficiency. EMB is about 80% cleared by the kidneys and may accumulate in patients with renal insufficiency, therefore, dosing of these agents when creatinine clearance is <30ml/minute or the patient is on hemodialysis should be as follows:[6,8,22,23]

- PZA 25 mg/kg per oral thrice weekly
- EMB 15 mg/kg per oral thrice weekly

Streptomycin should be avoided in patients with renal failure because of an increased risk of nephrotoxicity and ototoxicity. If streptomycin must be used in a patient with renal failure, the dosage should be 15mg/kg two or three times per week, to a maximum of 1 gram per dose, and serum levels of the drug should be monitored.[3]

References

1. Tuberculosis Coalition for Technical Assistance. International Standards for Tuberculosis Care (ISTC), second edition. Tuberculosis Coalition for Technical Assistance, The Hague, 2009.
2. World Health Organization. Report of the meeting on TB medicines for children. 8-9 July 2008. Geneva: World Health Organization. 1-22. Available at: www.who.int/selection_medicines/committees/subcommittee/2/TB.pdf.
3. World Health Organization. Treatment of Tuberculosis: Guidelines. Fourth Edition. Geneva: World Health Organization, 2009. (WHO/HTM/TB/2009.420).
4. World Health Organization. Unedited draft report of the 17th Expert Committee on the selection and use of essential medicines. May 2009. Ver. 18, 1-157. Available at: www.who.int/selection_medicines/committees/expert/17/WEBuneditedTRS_2009.pdf.
5. World Health Organization. Stop TB Department and the Department of Child and Adolescent Health and Development of the World Health Organization. Ethambutol efficacy and toxicity. Literature review and recommendations for daily and intermittent dosage in children. Geneva, Switzerland: WHO, 2006 (WHO/HTM/TB/2006.365).
6. World Health Organization. Stop TB Dept. Revised guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization; 2008 (WHO/HTM/TB/2008.402).
7. Menzies D, Benedetti A, Paydar A, Martin I, et al. Effect of duration and intermittency of rifampin on tuberculosis treatment outcomes: A systematic review and meta-analysis. PloS Med. 2009 September, 6(9):e1000146.
8. American Thoracic Society. Treatment of Tuberculosis. MMWR Vol. 52 / RR-11. June 20, 2003. American Thoracic Society, CDC, and Infectious Diseases Society.
9. Khan F, Minion J, Pai M, Royce S, Burman W, Harries AD, Menzies D. Treatment of active TB in HIV co-infected patients – a systematic review and meta-analysis. Manuscript in preparation.
10. WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance, World Health Organization. Stop TB Dept. Anti-tuberculosis drug resistance in the world: Fourth global report. Geneva: World Health Organization; 2008.
11. Espinal MA, Kim SJ, Suarez PG, Kam KM, Khomenko AG, Migliori GB, et al. Standard short-course chemotherapy for drug-resistant tuberculosis: Treatment outcomes in 6 countries. JAMA. 2000 May 17;283(19):2537-45.
12. Quy HT, Lan NT, Borgdorff MW, Grosset J, Linh PD, Tung LB, et al. Drug resistance among failure and relapse cases of tuberculosis: Is the standard re-treatment regimen adequate? Int J Tuberc Lung Dis. 2003 Jul;7(7):631-6.
13. Stop TB Partnership, World Health Organization. The global plan to stop TB, 2006-2015. Geneva: World Health Organization; 2006.
14. Sam IC, Drobniewski F, More P, Kemp M, Brown T. Mycobacterium tuberculosis and rifampin resistance, United Kingdom. Emerg Infect Dis. 2006 May;12(5):752-9.
15. World Health Organization. Treatment of Tuberculosis: Guidelines for National Programs, Third Edition. Geneva: World Health Organization, 2003.
16. World Health Organization. Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents: Recommendations for HIV-prevalent and resource-constrained settings. 2007.
17. National Collaborating Centre for Chronic Conditions. Tuberculosis: Clinical diagnosis and management of tuberculosis, and measures for its prevention and control. [NICE National Institute for Health and Clinical Excellence] London (UK): Royal College of Physicians; 2006.
18. Thwaites GE, Nguyen DB, Nguyen HD, Hoang TQ, Do TT, Nguyen TC, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med. 2004 Oct 21;351(17):1741-51.
19. Varpela E, Hietalalahti J, Aro M. Streptomycin and dihydrostreptomycin during pregnancy and their effect on the child's inner ear. Scan J Resp Dis. 50:101-9. 1969.
20. World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. Geneva: World Health Organization, 2006. (WHO/HTM/TB/2006.371).
21. Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, et al. An official ATS statement: Hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med. 2006 Oct 15;174(8):935-52.
22. Malone RS, et al. The effect of hemodialysis on isoniazid, rifampin, pyrazinamide, and ethambutol. Am J Respir Crit Care Med, 1999;159:1580–1584.
23. Strauss I, Erhardt F. Ethambutol absorption, excretion and dosage in patients with renal tuberculosis. Chemotherapy 1970;15:148–157.

Adherence and Monitoring Throughout Treatment

8

Achieving treatment completion and cure of tuberculosis requires close monitoring and encouragement of the patient throughout treatment. The provision of treatment, monitoring, and other related TB care often involves a variety of licensed and non-licensed personnel from both the public and private sectors. Given these complexities, it is recommended that coordination of treatment and care for each TB patient be assigned to a case manager who will have primary responsibility for ensuring that:[1]

- The patient adheres to treatment through to completion
- The patient and significant others in his/her environment receive information on and understand TB disease and how it is transmitted, prevented, and treated
- The patient follows through with all medical evaluations, including routine clinical monitoring
- Individuals in contact with a sputum smear-positive TB case patient are identified, located, prioritized, evaluated, and treated as needed
- Response to treatment is evaluated regularly, and if not in accordance with expected outcomes, is further evaluated

The case manager is the "team leader" of the case management team. The case manager communicates with the treating physician and coordinates the case management efforts of others involved in the delivery of treatment and care to the TB patient, such as the public health nurse, outreach workers, directly observed treatment (DOT) providers, social workers, substance abuse counsellors, correctional facility or jail nurses, school nurses, and those involved in conducting contact investigation activities. The role of the case manager frequently is assigned to a public health nurse or someone connected to the National TB Program.

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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.[2]

Promoting Adherence to Treatment

To ensure the patient does not experience treatment interruptions or default, the case manager must consider all potential barriers to adherence. A plan of care is then developed for the TB patient and includes interventions addressing any barriers identified. Anticipating and addressing potential barriers to adherence cannot always prevent lapses in treatment or nonadherence. The case manager should document all interventions utilized and monitor the success or failure of each in preventing non-adherence.

Developing the Plan of Care for the TB Patient

A strong plan will include the following elements:

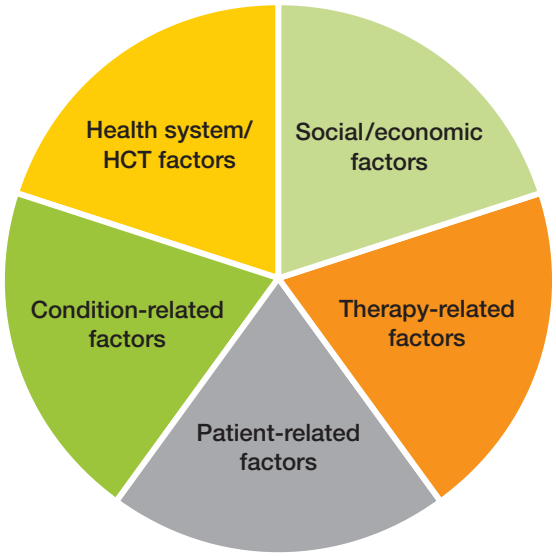
- Assessment of psycho/social and cultural needs
- Provision of education to the patient and patient's family with the goal of obtaining commitment to the plan
- Provision of treatment by DOT
- Use of incentives and enablers
- Use of culturally appropriate resources and supportive measures
- Measures that will be employed if nonadherence is unresolved through lesser restrictive means

Assessing for Barriers to Adherence

The following approach is designed to encourage and facilitate a **positive partnership between providers and patients** working together to improve adherence. Assuming an appropriate drug regimen is prescribed, adherence to the prescribed treatment regimen is the critical factor in determining treatment success.[3] Achieving adherence is not an easy task, either for the patient or the provider.

FIGURE 2.

The five dimensions of adherence



HCT = Healthcare Team

Source: WHO, Adherence to Long-term Therapies. Evidence for Action, 2003.

Anti-tuberculosis drug regimens consist of multiple drugs given for a minimum of six months, often when the patient feels well. Commonly, treatments of this sort are inconsistent with the patient's cultural milieu, belief system, and living circumstances. Consequently, a significant proportion of patients with TB discontinue treatment before completion of the planned duration or are erratic in drug taking. Yet, failure to complete TB treatment leads to prolonged infectiousness, poor outcomes, and drug resistance.

Adherence is a multidimensional phenomenon determined by the interplay of five sets of factors (dimensions), as illustrated in Figure 2.[3]

Despite evidence to the contrary, there is a widespread tendency to focus on patient-related factors as the main cause of poor adherence.[3,4] Sociological and behavioural research during the past 40 years has shown that patients need to be supported, not blamed.[3] Less attention is paid to provider and health system–related factors. Several studies have evaluated various interventions to improve adherence to tuberculosis therapy (see list of interventions in Table 9).

TABLE 9.

Factors affecting adherence and suggested interventions

Tuberculosis	Factors affecting adherence	Interventions to improve adherence
Social/economic factors	(-) Lack of effective social support networks and unstable living circumstances; culture and lay beliefs about illness and treatment; stigma; ethnicity, gender, and age; high cost of medication; high cost of transport; criminal justice involvement; involvement in drug dealing	Assessment of social needs, social support, housing, food tokens, and legal measures; providing transport to treatment settings; peer assistance; mobilization of community-based organizations; optimizing the cooperation between services; education of the community and providers to reduce stigma; family and community support
Health system/healthcare team factors	(-) Poorly developed health services; inadequate relationship between healthcare provider and patient; healthcare providers who are untrained, overworked, inadequately supervised or unsupervised in their tasks; inability to predict potentially nonadherent patients (+) Good relationships between patient and physician; availability of expertise; links with patient support systems; flexibility in the hours of operation	Uninterrupted, ready availability of information; training and management processes that aim to improve the way providers care for patients with tuberculosis; support for local patient organizations/groups; management of disease and treatment in conjunction with the patient; multidisciplinary care; intensive staff supervision; training in adherence monitoring; use of DOT
Condition-related factors	(-) Asymptomatic patients; drug use; altered mental states caused by substance abuse; depression and other psychological disorders, such as psychological stress (+) Knowledge about TB education on use of medications; provision of information about tuberculosis and the need to attend for treatment	Education on use of medications; provision of information about tuberculosis and the need to attend for treatment
Therapy-related factors	(-) Complex treatment regimen; adverse effects of treatment; toxicity	Education on use of medications and adverse effects of medications; adherence education; use of fixed-dose combination preparations; tailor treatment support to needs of patients at risk of nonadherence; agreements (written or verbal) to return for an appointment or course of treatment; continuous monitoring and reassessment
Patient-related factors	(-) Forgetfulness; drug abuse; depression and other psychological disorders, such as psychological stress; isolation due to stigma (+) Belief in the efficacy of treatment; motivation	Therapeutic relationship; mutual goal-setting; memory aids and reminders; incentives and/or reinforcements; reminder letters, telephone reminders or home visits for patients who default

DOT = directly observed therapy; **TB** = tuberculosis;

(+) = factors having a positive effect on adherence; (-) = factors having a negative effect on adherence

Source: Modified from WHO, Adherence to Long-term Therapies. Evidence for Action. 2003.

Other strategies and methods to promote adherence may include:

- Learn as much as possible about your patient's beliefs and attitudes about TB, TB/HIV co-infection and to treatment
- Increase the visibility of TB programs in the community, which may increase knowledge and improve attitudes towards TB
- Provide information about the disease and treatment to patients and communities
- Involve the patient in problem solving and be creative and flexible in determining how the patient can best be brought into planning for successful treatment completion
- Minimize costs and unpleasantness related to clinic visits
- Involve the family, peers, and social networks in providing support and encouragement to the patient
- Provide access to comprehensive primary care, as described in the WHO's Integrated Management of Adolescent and Adult Illness (IMAI)
- Provide or facilitate access to specialized services (e.g., opiate substitution for injection drug users)

ISTC 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.[2]

Directly Observed Treatment

The third component of the global DOTS strategy, now widely utilized worldwide, is the administration of a standardized, rifampicin-based regimen using case management interventions that are appropriate to the individual and the circumstances.[5,6,7,10] Given that nonadherence to anti-TB treatment is a well known risk factor for treatment failure, relapse, and the emergence of drug resistance,[1,5,6,7,8] the use of DOT is highly regarded as one of a range of measures to facilitate adherence and successful completion of treatment.

The main advantage of DOT is that treatment is carried out entirely under close, direct supervision.[9] This provides both a greater assurance that the prescribed medications have actually been ingested and an opportunity to assess whether the patient is clinically improving. Because there is regular contact between the patient and the treatment supporter, adverse drug effects and other complications can be identified quickly and managed appropriately. Moreover, such case management can also serve to identify and as-

sist in addressing the countless other problems experienced by patients with TB, such as poor nutrition, inadequate housing, and loss of income.[2] The provision of anti-TB treatment by DOT also allows for the use of intermittent regimens in the continuation phase for eligible new patients (see Chapter 7).

It is important to note that to successfully carry out DOT, two basic skills are needed:

- **Good communication** is essential since a lapse in communication can have serious consequences and can lead to incomplete or inadequate treatment resulting in:
  - Additional persons exposed to TB
  - Rehospitalisation with serious complications of TB
  - Development of MDR-TB
- **Collaboration** is necessary for conducting good TB surveillance and case management

Administration of treatment by DOT must be prioritized for patients whose sputum smear or culture is positive, re-treatments, unfavorable social conditions such as alcoholism and for administering treatment to children.

DOT Implementation

When implementing any new strategy, it is essential to establish a means for monitoring and evaluating the intervention. Effective implementation of DOT will require procedures to be described, training of personnel, and a process of supervision.

The technical, logistical, operational, and political aspects of DOT implementation work together to ensure its success and applicability in a wide variety of ways.[7]

Supervision of patients at home can involve:

- Responsible and trained friend or a member of a care group
- Outreach workers
- Community health worker
- Community volunteer

Clinical Response Monitoring

Patient monitoring and treatment supervision are two separate functions. Patient monitoring is necessary to evaluate the response of the disease to treatment and to identify adverse drug reactions. For the latter function, contact between the patient and a healthcare provider is necessary (see Monitoring and Recording Adverse Reactions pages 75–76).

ISTC 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 drug susceptibility testing should be performed. In patients with extrapulmonary tuberculosis and in children, the response to treatment is best assessed clinically.[2]

To judge response to treatment in patients with PTB, the most expeditious method is sputum smear microscopy (see Tables 10 and 11 for recommended sputum monitoring of new and retreatment PTB patients).

One-two sputum specimens should be collected for smear microscopy **at each follow-up sputum check** (Tables 10 and 11). One should be collected at the time the patient comes in to the clinic or health center for follow-up evaluation ("spot"). The patient should then be instructed to collect another sputum specimen early the next morning to bring back to the clinic/health center. Specimens should be transported to the laboratory for testing as soon as possible after collection. If a delay is unavoidable, the specimens should be refrigerated or kept in a cool location. Ideally, sputum cultures, as well as smears, should be performed for monitoring.[10]

TB culture and drug susceptibility testing is particularly important when sputum smears remain positive after completion of the initial phase to ensure early identification of unrecognized drug resistance. If present, the treatment regimen can be modified appropriately without waiting until the 5th month (the month when patients remaining sputum smear-positive can first meet the definition for treatment failure). Note that treatment failure is also declared if a patient is found to harbor MDR-TB at any point in time during treatment. Even if eventually fully drug susceptible, a positive culture in the fifth month of treatment confirms poor response and further investigation and intervention should follow.[10]

TABLE 10:

Bacteriological monitoring of new PTB patients

	Sputum smear	TB culture	Drug Sensitivity Testing (DST)
At treatment start	✔	✔	✔
End of month 1	✔		
End of month 2[a]	✔	Repeat if smear is positive	Repeat if culture is positive
Month 3	✔	↓	
Month 4	✔		
Month 5[b]	✔		Repeat if culture is positive
At end of treatment	✔	✔	

a If smear remains positive at end of initial phase (end of month 2), obtain TB culture. If culture is positive, repeat DST. Modify treatment regimen if drug resistance is identified on DST result. If resistance to INH and RIF identified, record as treatment failure, send isolate for second-line DST, seek expert consultation and initiate appropriate MDR-TB regimen

b If smear remains positive at month 5, repeat culture. If smear or culture is positive, patient should be re-registered as a treatment failure with appropriate retreatment regimen initiated. DST should be repeated if culture is positive. Evaluation for non-adherence should be conducted

Delay in sputum smear conversion can occur due to a number of factors including:[11]

- Poor supervision and patient non-adherence
- Extensive cavitation and large initial bacillary load
- Comorbid conditions interfering with adherence, absorption, or with response to treatment
- Inadequate therapy due to the presence of unrecognized drug-resistant *M. tb*
- The AFB seen are due to NTM (in the presence or absence of TB)
- The mycobacteria remaining visible by microscopy represent non-viable organisms

When patients fail to show bacteriological and clinical improvement on treatment, careful review of the patient's support and supervision should occur with prompt intervention when indicated. Patient treatment records should be reviewed with the responsible health-care worker, and reasons for any interruptions explored and addressed.[12]

TABLE 11:

Bacteriological monitoring of retreatment[a] PTB patients

	Sputum smear	TB culture	Drug sensitivity testing (DST)
At treatment start	✔	✔	✔[b]
Month 1	✔		
Month 2	✔		
End of month 3[c]	✔	Repeat if smear remains positive	Repeat if culture remains positive
Month 4	✔		
Month 5	✔	Repeat if smear remains positive	Repeat if culture remains positive
Month 6	✔		
Month 7	✔		
At end of treatment	✔	✔	

a Non-MDR/XDR retreatment only. See Chapter 11 for monitoring MDR/XDR patients

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

c If smear remains positive at end of initial phase (end of month 3), obtain TB culture. If culture is positive, repeat DST. Modify treatment regimen if drug resistance is identified on DST result. If resistance to INH and RIF identified, record as treatment failure, send isolate for second-line DST, seek expert consultation and initiate appropriate MDR-TB regimen

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

- Sputum smear (and culture) examination (see Tables 10 and 11 for frequency)
- Weight at initiation of treatment, then monthly until weight is stable
- Review of TB symptoms present at time of diagnosis and documentation when symptoms resolve

In the WHO Treatment guideline 3rd ed., patients with positive smears at the end of the 2nd month received an extra month of intensive phase treatment before proceeding to the continuation phase. This recommendation made sense at the time given the 8 month regimen only included rifampicin for the first 2 months. Extending the intensive phase for patients that remained smear-positive after 2 months meant they would receive an additional month of rifampicin. After review of all existing data, the WHO Guideline committee for the revised treatment guidelines (4th edition) determined **there was insufficient evidence to justify continuing to recommend this practice for regimens containing 6 months of rifampicin.**[10]

> WHO Recommendation 6. In patients treated with the regimen containing rifampicin throughout treatment, if a positive sputum smear is found at completion of the intensive phase, the extension of the intensive phase is not recommended.[a] (Strong/High grade of evidence)

Criteria for Discharging the Sputum Smear-positive Patient from the Hospital[1]

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

- Clinical improvement noted by decrease in symptoms
- Bacteriological response noted by decrease in number of AFB on smear
- Social capacity in place to ensure successful continuation of treatment as an outpatient

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

New Sputum Smear-negative PTB Patient[10]

It is important to re-check a sputum specimen at the end of the intensive phase in case of disease progression due to non-adherence or drug resistance, or an error at the time of initial diagnosis (i.e. a true smear-positive patient was misdiagnosed as smear-negative). PTB patients whose sputum smear results were negative before treatment and at 2 months (end of initial phase) need no further sputum monitoring. They should be monitored clinically; body weight is a useful progress indicator.

Monitoring the Extrapulmonary TB Patient

In patients with EPTB and in children (see also Chapter 10), clinical evaluation (including weight and symptom monitoring) is the usual means of assessing response to treatment.[10]

Interrupters and Defaulters

Attempts to contact patients who have missed an arranged appointment to receive treatment should be made promptly. The management of such patients must take into consideration multiple factors. Each of these factors, if present, will necessitate more caution and erring on the side of additional treatment.[6]

- The patient is returning to treatment after default (see Chapter 4, page 23)
- Interruption occurs in the intensive rather than the continuation phase
- Interruption occurs early in the continuation phase (rather than later)
- Long duration of treatment interruption
- The patient is immune compromised (living with HIV or another condition)
- The patient had poor response to treatment before the interruption
- Drug-resistant disease is known or suspected

Culture and drug susceptibility testing should be performed upon the return of patients who meet the definition for default. If laboratory capacity permits, additional patients returning after treatment interruption should also have specimens obtained and culture and drug susceptibility testing performed.[10]

a WHO recommends that a positive sputum smear at completion of the intensive phase should trigger a careful review of the quality of patient support and supervision, with prompt intervention if needed. It should also trigger additional sputum monitoring

An interruption in treatment is <1 month and should be handled as follows:

- Conduct efforts to trace patient within 1 day of missing during the initial phase and within 1 week of missing treatment during the continuation phase
- Identify and solve the cause of interruption (see *ISTC* Standard 9)
- Continue treatment and prolong it to compensate for missed doses

The following actions should be taken for a patient whose TB treatment is interrupted for 1 month or more:

- Conduct efforts to trace patient
- Identify and solve the cause of interruption (see *ISTC* Standard 9)
- Collect 2 sputum specimens for AFB smear and culture; continue treatment while waiting for results
  - If smear-negative, obtain TB culture. Continue treatment while awaiting culture result. If culture is negative, complete current course of treatment prolonging it to compensate for missed doses
  - If one or more smears are positive or if culture is positive, **reregister patient as a defaulter** and undertake the following actions:
    - Ensure culture is performed; arrange for DST
    - Investigate the cause of interruption and re-establish treatment plan mutually with the patient (see *ISTC* Standard 9)
    - Re-establish patient on appropriate treatment regimen
      - Start standard retreatment regimen (see Table 8, Chapter 7) if risk of MDR is deemed low or medium; adjust regimen as needed once DST result is available; or
      - Start empiric MDR regimen while awaiting DST result if risk of MDR is deemed to be high; or
      - Hold treatment for culture and/or DST result;[a] re-establish patient on appropriate treatment regimen once DST result is available

Attempts to contact patients who have missed an arranged appointment to receive treatment should be made promptly.

Monitoring and Recording Adverse Reactions

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

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

a Treatment should not be held if a patient's clinical condition is worsening, is known to be HIV-coinfected, or if other factors may result in deterioration of patient's clinical status while awaiting DST result (e.g. access only to conventional agar proportion DST, other co-morbidities, etc.). This option is best suited to conditions where there is ready access to rapid DST or liquid culture and DST methods

These patients should receive pyridoxine 10–25 mg daily along with their anti-tuberculosis drugs.[6,10]

Complaints of drug side effects should be promptly referred for evaluation to identify the offending drug so as to minimize interruptions in treatment and/or unnecessary cessation of important first-line drugs. Physicians and nurses responsible for the management of patients being treated for tuberculosis should be familiar with the common adverse reactions associated with drug therapy (Table 12) and the related management.

Table 13 shows a symptom-based approach to the most common adverse effects of the essential anti-tuberculosis drugs. Adverse effects are classified as minor or major. In general, a patient who develops minor adverse effects should continue the TB treatment. The patient also receives symptomatic treatment. If a patient develops a major side-effect, the treatment or the offending drug is stopped and the patient should be urgently referred to a clinician or healthcare facility for further assessment and treatment. Patients with major adverse reactions should be managed in a hospital.[10]

TABLE 12:

Common adverse reactions to the first-line anti-tuberculosis drugs

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

Note: All drugs may cause rash, nausea, and fever

a For information on managing drug interactions in HIV-related tuberculosis, see www.cdc.gov/tb/tb_hiv_Drugs/default.htm

TABLE 13.

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

Side-effects	Drug(s) probably responsible	Management
Minor		**Continue anti-tuberculosis drugs, check drug doses**
Anorexia, nausea, abdominal pain	Pyrazinamide, rifampicin, isoniazid	Give drugs with small meals or just before bedtime. If symptoms persist or worsen, or there is protracted vomiting, icterus or signs of bleeding, consider the side effect to be major and refer to clinician urgently.
Joint pains	Pyrazinamide	Aspirin or non steroidal anti-inflammatory drug
Burning, numbness or tingling sensation in the hands or feet	Isoniazid	Pyridoxine 50-75 mg daily (3)
Drowsiness	Isoniazid	Reassurance.
Orange/red urine	Rifampicin	Reassurance. Patients should be told when starting treatment that this commonly happens and is normal
Major		**Stop responsible drug(s) and refer to clinician urgently**
Skin rash with or without itching	S, H, R, E, Z	Stop anti-tuberculosis drugs
Deafness (no wax on auroscopy)	Streptomycin	Stop streptomycin; use ethambutol
Dizziness (vertigo and nystagmus)	Streptomycin	Stop streptomycin; use ethambutol
Jaundice (other causes excluded), hepatitis	H, Z, R	Stop anti-tuberculosis drugs
Confusion (suspect drug-induced acute liver failure if jaundice present)	Most anti-tuberculosis drugs	Stop anti-tuberculosis drugs
Visual impairment (other causes excluded)	Ethambutol	Stop ethambutol
Shock, purpura, acute renal failure	Rifampicin	Stop rifampicin
Decreased urine output	Streptomycin	Stop streptomycin

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

Management of Drug-induced Hepatitis

Most anti-tuberculosis drugs can damage the liver. INH, PZA, and RIF are most commonly responsible, ethambutol rarely. Additionally, asymptomatic jaundice without evidence of hepatitis can be caused by RIF. Care should be taken to rule out other possible causes of the hepatitis before deciding that it is drug-induced and modifying the TB regimen.

The management of drug-induced hepatitis depends on:

- Whether the patient is in the intensive or continuation phase of TB treatment,
- The severity of the liver disease
- The severity of the TB, and
- The capacity of the health unit to manage side effects of TB treatment

If the hepatitis is thought to be caused by the anti-tuberculosis drugs, stop all drugs. If the patient is severely ill with TB and it is considered unsafe to stop anti-tuberculosis treatment, the regimen should be changed to a non-hepatotoxic regimen consisting of streptomycin, ethambutol, and a fluoroquinolone.[10]

If the patient is not severely ill, treatment should be held until liver function tests have returned to normal and clinical symptoms (e.g., nausea, abdominal pain) have resolved. If it is not possible to perform liver function tests; wait an extra 2 weeks after the jaundice and upper abdominal tenderness has disappeared before recommencing TB treatment.[10]

Once drug-induced hepatitis has resolved, reintroduce the same drugs one at a time every 3-7 days starting with rifampicin (as it is the least likely to cause hepatotoxicity and is the most effective agent) then isoniazid.[6,14] Serum transaminases and bilirubin should ideally be checked immediately prior to initiation of each drug. In patients who experienced jaundice but who are tolerating the reintroduction of rifampicin and isoniazid, it is advisable to avoid pyrazinamide.[6]

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

- If rifampicin is implicated, a suggested regimen without rifampicin is two months of isoniazid, ethambutol and streptomycin followed by 10 months of isoniazid and ethambutol (2HES/10HE)
- If isoniazid cannot be used, 6 to 9 months of rifampicin, pyrazinamide and ethambutol can be considered
- If pyrazinamide is discontinued before the patient has completed the intensive phase, then the total duration of isoniazid and rifampicin therapy may be extended to 9 months
- If neither isoniazid nor rifampicin can be used, the non-hepatotoxic regimen consisting of streptomycin, ethambutol, and a fluoroquinolone should be continued for a total of 18–24 months.[6,10] Consultation should be sought in these situations

Introducing one drug at a time is the optimal approach, especially if the patient's hepatitis was severe. Therefore, NTPs using fixed-dose combination tablets should stock limited amounts of single anti-TB drugs for use in case of adverse effects of anti-TB drugs.

Management of Cutaneous Reactions

If a patient develops itching without a rash and there is no other obvious cause, the recommended approach is to try symptomatic treatment with anti-histamines and avoiding dry skin, and continue TB treatment while observing the patient closely. However, if a skin rash develops then all anti-tuberculosis drugs must be stopped.[10]

Once the reaction has resolved, anti-tuberculosis drugs are re-introduced one by one, starting with the drug least likely to be responsible for the reaction (rifampicin or isoniazid) and starting with a small challenge dose such as 50 mg isoniazid.[11] The dose is gradually increased over three days. The procedure is repeated, adding in one drug at a time. If a reaction occurs after adding a particular drug, that drug is identified as the offending agent. The alternative regimens listed above can also be considered when a particular drug cannot be used because it was implicated as the cause of a cutaneous reaction.[10]

References

1. Francis J. Curry National Tuberculosis Center. Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, Second Edition. Francis J. Curry National Tuberculosis Center and California Department of Public Health, 2008.
2. Tuberculosis Coalition for Technical Assistance. International Standards for Tuberculosis Care (ISTC), second edition. Tuberculosis Coalition for Technical Assistance, The Hague, 2009.
3. World Health Organization. Adherence to long-term therapies: Evidence for action. Geneva: World Health Organization, 2003 (WHO/MNC/03.01).
4. Munro SA, Lewin SA, Smith HJ, Engel ME, Fretheim A, Volmink J. Patient adherence to tuberculosis treatment: a systematic review of qualitative research. PLoS Med 2007; 4(7):e238.
5. World Health Organization. Treatment of Tuberculosis: Guidelines for National Programs, Third Edition. Geneva: World Health Organization, 2003 (WHO/CDS/TB/2003.313).
6. ATS, CDC and Infectious Diseases Society of America. Treatment of tuberculosis. MMWR. 2003; 52(RR-11):1-77.
7. World Health Organization. Implementing the Stop TB Strategy: A handbook for national tuberculosis control programs. Geneva, 2008 (WHO/HTM/TB/2008.401).
8. Mitchison DA. How drug resistance emerges as a result of poor compliance during short course chemotherapy for tuberculosis. Int J Tuberc Lung Dis 1998;2(1):10-5.
9. Sbarbaro J. What are the advantages of direct observation of treatment? In: Frieden TR, ed. Toman's tuberculosis. Case detection, treatment and monitoring, 2nd Edition. Geneva: World Health Organization, 2004:181-182.
10. World Health Organization. Treatment of Tuberculosis: Guidelines. Fourth Edition. Geneva: World Health Organization, 2009 (WHO/HTM/TB/2009.420).
11. Tomans K, World Health Organization. Toman's tuberculosis. Case detection, treatment and monitoring: Questions and Answers, 2nd Edition. Geneva: World Health Organization, 2004.
12. Williams, G, Alarcon E, Jittimanee S, et al. Best Practice of the care for patients with tuberculosis: A guide for low income countries, 2007. 1st Edition. Paris: International Union Against Tuberculosis and Lung Disease (The Union); 2007.
13. Technical Working Group (TWG) meeting minutes 2008. Kingston, Jamaica. (non-published reference.)
14. Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, et al. An official ATS statement: Hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med. 2006 Oct 15; 174(8):935-52.

9 HIV Infection & Tuberculosis

Tuberculosis is highly associated with HIV infection and with overt HIV disease worldwide. Globally, the percentage of patients with TB and HIV co-infection ranges from less than 1% in low HIV-prevalence countries to 50–70% in countries with a high HIV prevalence, mostly in sub-Saharan Africa.[1] Although the prevalence of HIV infection varies widely among and within countries, in persons with HIV infection, there is always an increased risk that tuberculosis infection can become active TB disease.

In the absence of HIV infection, the lifetime risk of developing TB disease is approximately 10%. However, one out of 10 persons with both HIV infection and TB infection will go on to develop TB disease each year with **over 50% developing TB in their lifetime.**[2]

The increase in TB both globally and in CMCs during the last two decades is largely attributed to the escalating HIV epidemic. HIV affects the progression of TB disease in the following two ways:

- **Reactivation of latent TB infection to TB disease** in HIV-positive individuals. This is the main driving force behind the current TB epidemic and is preventable in the individual patient through isoniazid preventive therapy (IPT)
- **Rapid progression from recent TB infection to TB disease.** If an immune-deficient person is infected with TB bacilli from a patient with infectious PTB, TB disease may develop within a number of weeks

According to the latest available information, a total of 2,135 new TB cases all forms were reported in the CAREC member countries in 2007.[3] 50% of them (1,066) were tested for HIV resulting in 291 TB patients with HIV (27%) doubling the Regional average for the Americas. Compared with data from the period 1997 to 2002, the proportion of TB patients tested for HIV has declined from 59 to 50% and the seroprevalence rate has been kept constant. For 2007, 28% of the co-infected patients were receiving cotrimoxazol (CPT) and 39% anti-retroviral therapy (ART). It is worth noting that between 2006 and 2007 while the percentage of coinfected patients declined in the Bahamas (54 to 30%) and Jamaica (31 to 22%) it greatly increased in Guyana (13 to 28%) and Trinidad & Tobago (5 to 30%) with similar number of TB patients tested for HIV in both years.[3]

TB continues to be the most common opportunistic infection worldwide for people with HIV, including for persons on antiretroviral therapy, and remains a leading cause of death for people living with HIV in low- and middle-income countries.[4] Failure to diagnose and treat TB disease promptly in HIV-infected patients contributes to premature mortality in AIDS patients and increased TB transmission in the community. TB disease can spread quickly in congregate settings where people living with HIV reside. In addition, outbreaks of TB due to HIV/TB have been reported in settings such as hospitals, homeless shelters, jails, and prisons.

Given the global TB and HIV situation, collaboration between national programs (NTP and NAP) is highly recommended to ensure control of both diseases (see Chapter 3, Collaboration between TB and HIV/AIDS Programs for description of the objectives, activities, and threshold for planning and implementing TB/HIV joint activities).

A.[a] Establishing Collaboration Between TB and HIV Programs

TB services are a critical entry point for the promotion of HIV prevention, testing and treatment, as well as for adherence support and antiretroviral drug resistance monitoring. We now have a golden opportunity for HIV and TB programs to work hand-in-hand to ensure comprehensive, high quality care is provided for individuals co-infected with HIV and TB.

Ideally, service delivery should be integrated, providing an accessible continuum of care. It is now accepted that both HIV and TB care require a chronic disease management approach. That being said, most forms of TB are curable upon completing a standard 6 month treatment regimen (see Chapter 7).

For collaboration to be effective, a series of actions should be taken:

A1. **Set up a Coordinating Body for TB/HIV Activities at All Levels**

Collaboration between TB and HIV programs and services must occur at all levels of service delivery (national, sub-national and health facility levels) and would ideally include organizations supporting TB and HIV/AIDS programming (e.g., donors, NGOs, community-based organizations, advocacy groups, etc.). Important areas of responsibility for the joint coordinating body might include:

- Developing joint workplans and defining responsibilities related to shared activities
- Developing country specific guidelines that integrate service delivery (e.g., improving access to TB testing and preventive treatment for persons with HIV; improving HIV counseling, testing and treatment of persons with TB)
- Defining indicators for monitoring and evaluating joint activities
- Mobilizing community involvement in joint TB/HIV activities

A2. **Conduct Surveillance of HIV Prevalence Among Tuberculosis Patients**

Surveillance is essential to provide information for program planning and implementation. Surveillance must contribute to a better understanding of the magnitude of the problem and provide reliable, timely, and cost-efficient information for action. While surveillance for tuberculosis is generally passive and reflects access to the general healthcare services in the public sector, TB/HIV surveillance can also make use of data deriving from specific activities, e.g., prevention of mother-to-child transmission (PMTCT). Generally, in the CAREC member countries, surveillance for TB and TB/HIV is characterized by monitoring on an ongoing basis. WHO recommends HIV testing for patients of all ages, irrespective of epidemic setting, who present with signs or symptoms that suggest tuberculosis,[5] whether TB is suspected or already confirmed.[6]

The following are some suggested objectives for surveillance of TB and TB/HIV:

- To increase political, professional, and community awareness of the situation
- To justify the argument for collaboration between the programs (TB and HIV) at the national level, and for formulation and implementation of a TB/HIV strategy

a Note that the letters introduced to section headers in Chapter 9 correspond to the tool WHO Interim Policy on Collaborative TB/HIV Activities

- To provide information on the HIV epidemic and its impact on TB patients and, conversely, the impact of TB on HIV patients
- To quantify the need for providing ART to TB patients

The structure of the surveillance system for TB/HIV varies widely among countries in the Caribbean. PAHO/WHO recommends that each country ensure routine surveillance is conducted utilizing updated registers that collect co-infection data to help track and monitor local TB and HIV epidemiology. Supervision, training and support is crucial to ensure reporting is accurate and timely from both programs. Surveillance data from both programs should be shared and analyzed jointly and communicated at all levels. This kind of communication will enhance planning and execution of prevention and care programs.

Data Sources and Indicators

- The main sources of data are health centers, hospitals, and laboratories; however, voluntary counseling and testing (VCT) sites and PMTCT clinics may also provide useful data to NTPs
- Specific HIV-related indicators that NTPs might consider adding to TB registers and data collection sources include: CD4, date of ART initiation, date of switching of ARV drugs, and CPT initiation, as these may be useful in integrated case management. WHO has updated many of their reports and registers to include data fields that will capture HIV-related management data (www.who.int/tb/dots/r_and_r_forms/en/index.html)

A3. **Joint TB/HIV Planning**

Joint planning and coordinated management done by the coordinating body at each level is particularly important for:

- **Joint resource mobilization.** Human and financial resources need to be made available at all levels if countries are to succeed in achieving national, Millennium Development Goals (MDG), and global Stop TB targets. Preparation and submission of joint proposals would be helpful in soliciting resources for collaborative activities
- **Capacity building, including training.** Joint capacity building should include training of health workers in both TB and HIV
- **Advocacy, communication and social mobilization.** Advocacy targeted at influencing policy, program implementation and resource mobilization is important. Communication that creates awareness of the interaction between TB and HIV among patients with either disease can increase the likelihood that these persons will actively seek out and avail themselves of the services. From another perspective, commitment among all stakeholders is critical in the national effort to prevent TB and HIV and to mitigate the impact of both diseases
- **Enhancing community involvement in collaborative TB/HIV activities.** Through support groups (for people with HIV, TB, and TB/HIV) and community-based organizations, TB prevention and care can be integrated with HIV prevention, care, and support. Communities can be mobilized to advocate for resources and help implement collaborative TB/HIV activities
- **Operational research.** Operational research can help to determine the most effective and efficient means of delivering collaborative TB/HIV activities. However, this kind of research has to be tailored to take into account cultural, geographical, and resource diversity in order to inform national policy and strategy development

A4. **Monitoring and Evaluation (M&E) of Collaborative TB/HIV Activities**

M&E provides the means to assess quality, effectiveness, coverage, and delivery of collaborative TB/HIV activities in order to inform planning of new activities and adjustment of ongoing initiatives.[7] NTPs and NAPs should agree on a core set of indicators and the data collection tools that will be used (see Chapter 12).

The WHO guidelines for monitoring and evaluation of collaborative TB/HIV activities can serve as a key resource for standardizing country-specific monitoring and evaluation activities (www.who.int/hiv/pub/tb/en).

B. Decreasing the Burden of TB in People with HIV

TB is unique among the many other diseases affecting people with HIV, because:

- It remains a life-long risk for people with HIV, even in the presence of antiretroviral therapy, and can occur at any stage of HIV-related immunodeficiency
- In many countries, it is often the first disease affecting people with HIV during the progression from HIV infection to AIDS
- It most often results in death if not diagnosed early and treated adequately[8]
- It is a major public health problem, given that it is an airborne disease that can be spread to the general population and that can occur more than once despite adequate treatment in settings where TB is endemic

Prevention and treatment of TB in people with HIV must be accepted as an urgent priority for HIV/AIDS and TB programs. The "Three I's", Intensified case-finding for active TB, TB Infection control, and Isoniazid preventive therapy (IPT) are key public health strategies to decrease the impact of TB on people with HIV.[9]

B1. Intensified TB Case-finding in People with HIV

Case-finding involves screening for symptoms and signs of TB in settings where people with HIV seek care and is strongly recommended to be performed by all healthcare workers that provide services to persons with HIV. TB should be suspected in all sick, HIV-infected patients who are not doing well clinically. Early identification of signs and symptoms of TB, followed by pursuit of a confirmed diagnosis and prompt treatment, increase the chances of survival, improve quality of life, and reduce transmission of TB in the community (see Table 14: TB screening questionnaire).

Health staff should be aware that:

- Where there is a high prevalence of TB, a considerable proportion of cases may also be HIV seropositive
- In areas with a high prevalence of HIV, they should look actively for cases of TB
- Signs and symptoms of severe progressive TB are very similar to those of clinical AIDS, particularly chronic fever, loss of body weight, and cough

Staff should know about and use local referral mechanisms for TB and HIV diagnostic and treatment or care services when indicated. Information on where and how to access

these services should be clearly communicated to the public. The following sites should be prioritized for intensified TB case-finding:

- Medical and infectious disease wards
- VCT and PMTCT centers
- Outpatient and emergency room departments
- Prisons and jails

All people with HIV should be screened for TB disease at each encounter;[7] persons with symptoms or signs suggestive of TB disease should undergo further clinical investigation.[10] The TB screening questions in Table 14 should be asked of each and every person with HIV visiting any of the above sites.

TABLE 14:

TB Screening Questionnaire

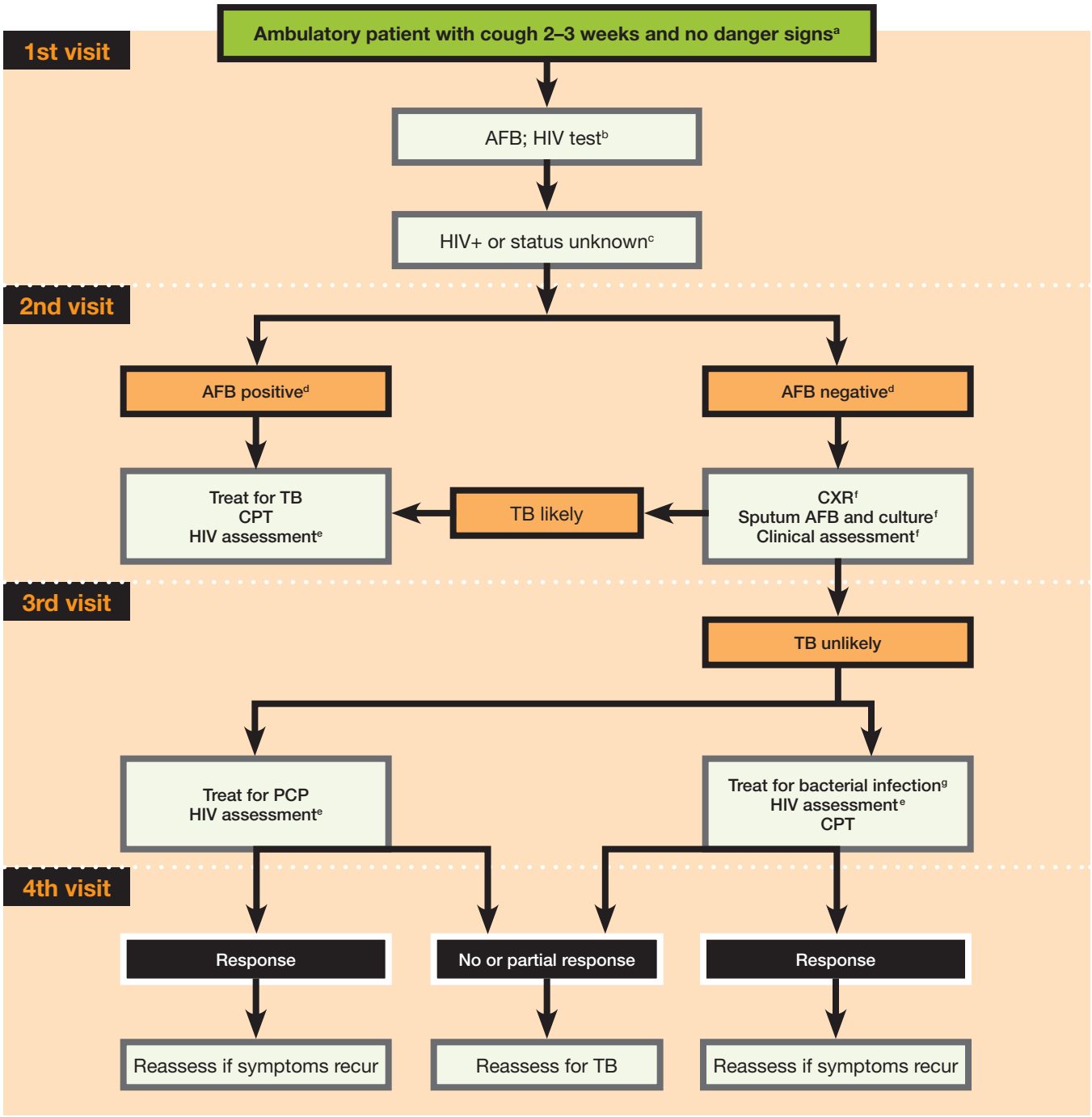
Yes	Questions to ask	No
	1. Have you had a cough for 2–3 weeks?	
	2. Have you had recent contact with another person with active TB? (e.g., share same residence, work or travel together for ≥8 hours)	
	3. Have you lost ≥3 kg in the past 4 months?	
	4. Have you had fever for ≥3 weeks?	
	5. Have you had night sweats for ≥3 weeks?	

- If "yes" to question 1: the patient is a TB suspect, perform sputum collection for AFB smear and culture and continue evaluation for TB per the diagnostic algorithm for pulmonary TB (Figure 3)
- If "no" to question 1 but "yes" to any other question: the patient is a TB suspect; continue evaluation for TB guided by clinical signs and symptoms. Refer to national reference hospital if necessary
- In "no" to all the questions: the patient is not a TB suspect at this time; stop investigations for TB and repeat screening with questionnaire at each health service encounter, whether routine or for treatment[7]

Source: Adapted from the International Center for AIDS Care and Treatment Program Questionnaire.[11]

FIGURE 3:

Algorithm for the diagnosis of TB in ambulatory HIV-positive patient



AFB = Acid fast bacilli; **CPT =** Cotrimoxazole preventive therapy; **PCP =** Pneumocystis carinii pneumonia, also known as *Pneumocystis jirovecii* pneumonia.

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, classify HIV status unknown into HIV-positive depends on clinical assessment or national and/or local policy.

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

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

f 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.

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

Source: Adapted from Improving the Diagnosis and Treatment of Smear-negative Pulmonary and Extrapulmonary Tuberculosis Among Adults and Adolescents. Recommendations for HIV-prevalent and Resource-constrained Settings. Geneva: WHO, 2007.

Evaluation of suspected HIV-related TB ***should always include sputum TB culture and a chest radiograph*** *in addition to smear microscopy and clinical assessment*

Clinical Presentations of HIV related TB[12,13]

- With CD4+ T-cell counts of >350 cells/mm^3, the following apply:
  - HIV-related TB presents like TB among HIV-uninfected persons
  - Disease is frequently limited to the lungs
  - Common chest radiographic manifestations include upper lobe fibronodular infiltrates with or without cavitation
- With increasing immunodeficiency, extrapulmonary TB (with or without pulmonary involvement) becomes increasingly common
- At CD4+ T-cell counts of <50 cells/mm^3, the following apply:
  - Extrapulmonary involvement is common
  - Chest radiographic findings are more likely to involve middle and lower lung zones. Common presentations include intrathoracic adenopathy, focal lower or middle lobe infiltrates, pleural involvement, and diffuse miliary or reticulonodular patterns
  - In severely immunocompromized patients, TB can be a critical systemic disease with high fevers, rapid progression, and sepsis syndrome

TABLE 15:

How pulmonary TB differs in early and late HIV infection

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

Source: Modified from WHO, TB/HIV. A Clinical Manual. 2004.[1]

Evaluation of suspected HIV-related TB **should always include sputum TB culture and a chest radiograph** in addition to smear microscopy and clinical assessment (see Figure 3). However, several pulmonary diseases can mimic PTB on chest X-ray and in signs and symptoms. The clinician should consider the complete differential diagnosis of the presenting illness and take care not to diagnose pulmonary TB in every patient with AIDS who may have an abnormal chest X-ray, signs and symptoms of chest disease, and negative sputum smears (see also Chapter 5, Figure 1: An illustrative approach to the diagnosis of sputum smear-negative PTB in patients presenting with an illness suggestive of PTB).

Table 15 shows how the clinical picture, sputum smear result, and chest X-ray appearance often differ in early and late HIV infection.

ISTC STANDARD **18**

All providers of care for patients with TB should ensure that persons who are in close contact with patients who have infectious TB 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 TB; 2) is at high risk of developing TB if infected; 3) is at risk of having severe TB if the disease develops; 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.[14]

B2. Isoniazid Preventive Therapy

People with HIV that have latent TB infection can be protected from developing TB disease if they receive a daily dose of isoniazid for at least six months.[10] Isoniazid preventive therapy, or IPT, is an economical, relatively simple and highly effective measure that must be taken wherever TB and HIV coexist.[15] Studies suggest that IPT can reduce the incidence of TB disease by at least 40 percent among people with HIV who test positive for TB on skin tests[16] and may decrease the burden of TB in the community at large.

Programs providing care for persons with HIV should provide comprehensive approaches for prevention, diagnosis and treatment. This includes screening for active TB, treating those co-infected with TB and HIV, and providing preventive therapy to those who do not have active disease but who are at risk.

ISTC 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.[14]

WHO/UNAIDS recommendations on IPT in HIV-positive persons

The provision of IPT to persons with HIV should be organized and determined by the TB/HIV coordinating body at each level. For countries that have not yet implemented routine IPT for persons with HIV, the TB/HIV coordinating body should consider the following as prerequisites prior to implementation:[1]

- Adequate capacity for HIV counseling, which should include information, education and counseling about TB
- Sufficiently trained healthcare staff

Rule out TB before IPT!

*IPT should **never** be initiated in a patient with HIV infection who has signs and symptoms consistent with active TB, or in whom TB disease cannot be safely excluded. IPT is used most safely in asymptomatic HIV-infected patients, e.g., those diagnosed early in the course of HIV infection through VCT centers or antenatal clinics.*

- Linkage between HIV care and TB control services
- Good TB control program with high cure rates and combined default/failure rates at the end of treatment of <10%

ISTC 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.[14]

Practical considerations for countries preparing to scale up IPT[17]

- Ensure IPT is an integral part of a package of interventions for persons with HIV
- Start with operational projects in a variety of routine settings (e.g., clinics/settings where pre-ART care and treatment is provided)
- Develop simple flow charts for eligibility for IPT
- Procure, distribute and administer IPT in the simplest way possible
- Integrate IPT monitoring and evaluation into existing treatment cards and registers

Suggested eligibility criteria for IPT in HIV-positive persons

Persons should be motivated for IPT after having been educated about the benefits as well as the possible side effects and risks. Offer IPT for persons with HIV once active TB has been excluded if any of the following apply:[18]

- Exposure to an infectious TB case
- Living in an area with a prevalence of latent TB infection estimated to be >30%
- Healthcare worker, prisoner, miner or other identified group at high risk of acquiring or transmitting TB
- Mantoux tuberculin skin test result is ≥5 mm induration (or interferon gamma release assay test is positive) indicating latent TB infection

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

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

Monthly monitoring

The person receiving IPT should be **evaluated at least monthly** to check three important issues:

- **Signs and symptoms of TB:** If symptoms of tuberculosis should develop while taking IPT, isoniazid should be stopped immediately and patient referred for evaluation

- **Side effects attributable to IPT:** These may include, for example, liver toxicity or peripheral neuropathy.
- **Adherence:** Interruptions in therapy should be followed by counseling and an attempt should be made to understand and remove barriers to adherence.

Dosage of isoniazid

The adult dose of isoniazid is 5 mg/kg (maximum 300 mg) daily for 6–9 months,[18] self-administered or administered under the supervision of a treatment supporter. The use of isoniazid with stavudine (d4T) may increase the risk of peripheral neuropathy. To prevent peripheral neuropathy, administer pyridoxine 25–50 mg daily along with the isoniazid. For children, the isoniazid dose is 10 mg/kg bodyweight.[19] (See Appendix B for additional information on treating latent TB infection.)

ISTC 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 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.[14]

B3. TB Infection Control

Increased transmission of TB may occur in healthcare (clinics and hospitals)[20] and congregate settings (e.g., prisons, jails, and military barracks)[21] where people with TB and HIV are frequently crowded together. Evidence that some patients with MDR-TB and HIV may be highly infectious[22] presents added urgency to ensuring adequate infection control measures are in place to protect against TB transmission in settings where these patients may be seeking care.

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

Measures to reduce TB transmission at facility level[23,24]

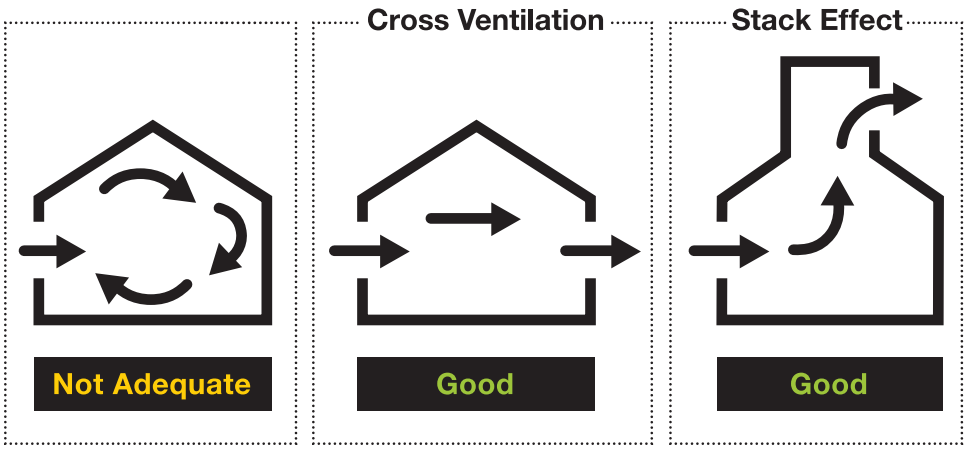
- **Managerial control** measures form the framework for establishing and implementing the other three control measures. Managerial activities ensure political commitment and leadership at both national and facility levels
- **Administrative control measures** should include:
  - Development and maintenance of systems for early recognition, diagnosis, and treatment of TB suspects (particularly those with PTB)

- Development of a facility Infection Control Plan and designation of an Infection Control Officer with responsibility for implementation of the plan
- Policies and procedures for separation of PTB suspects from others until a diagnosis is confirmed or excluded
- TB Infection control training and annual updates for staff
- Preparation and/or display of TB information for patients and the public related to its transmission, treatment and prevention

- **Environmental control measures** should include:
  - Maximizing natural ventilation to help reduce TB transmission indoors (e.g., open windows to promote cross ventilation and "stack effect" [see Figure 4], use of fans where air may be stagnant)
  - Whenever possible, capitalize on sunlight which is a natural source of ultraviolet light and can kill TB bacilli
  - Designate an appropriate location for sputum collection in an adequately ventilated booth or out in the open air, away from other people
- **Personal protection** should include:
  - Provide accessible, acceptable, confidential voluntary HIV counseling and testing
  - Protect HIV-positive persons from possible exposure to TB (e.g., transfer of an HIV-infected worker from medical wards where patients with infectious TB are admitted)
  - Provide isoniazid preventive therapy if indicated
  - Provide a face mask for the TB patient or suspect TB patient to wear when moving from one part of a hospital to another

FIGURE 4:

Promoting Natural Ventilation



Source: Dr. Rod Escombe.

C. Decreasing the Burden of HIV in Tuberculosis Patients

C1. Accessing HIV Testing and Counseling

Even in low-HIV prevalence countries, HIV testing should always be considered in managing individual TB patients, especially among groups in which the prevalence of HIV is higher, such as injecting drug users or men who have sex with men. In countries having a high prevalence of HIV infection, the yield of positive results will be high, and the impact of a positive result will be to increase the responsibility of the healthcare team.

HIV testing should be promoted and offered routinely to all TB patients because of the following benefits:

- Cotrimoxazole prophylaxis and antiretrovirals (ART) have been shown to reduce morbidity and prolong survival following successful TB treatment,[25] but cannot be provided if the TB patient's HIV status remains unknown
- The patient may be worried about being HIV-positive or having AIDS. This is particularly true in areas where TB and HIV co-infection is prevalent. The clinician who is able to discuss HIV with the patient in a non-stigmatising, caring manner, helps to reduce the patient's psychological burden by allowing the patient's fears to be discussed, and by providing an avenue for information and advice to be given to the patient
- When persons know their HIV status, they have clearer opportunities to adopt safe behaviours for their own sake as well as for the sake of others in the community; they can also gain access to care and support services. When persons know their status, they are then in a position to disclose confidentially to family members and professional care givers, which in most cases, is a benefit to the patient

WHO Guiding Principles of Expanded HIV Testing and Counseling[26]

- HIV testing should be voluntary—mandatory HIV testing is not effective for public health purposes, nor is it ethical. Everyone being tested should give informed consent. This involves:
  - Providing pre-test information on the purpose of testing and on the treatment
  - Ensuring support is available once the result is known
  - Ensuring understanding
  - Respecting the individual's autonomy
- Confidentiality must be protected
  - Only health-care staff with a direct role in management should have access to medical information, on a "need to know" basis
- Post-test support services should be offered
  - People who receive positive test results should receive counseling and referral to care, support and treatment

There are several models of HIV counseling and testing currently being used in different settings in the Caribbean:

Provider-Initiated Testing and Counseling (PITC) in Health Facilities

Provider-initiated HIV counseling and testing takes place in clinical settings, such as accident and emergency departments, medical wards, and TB and sexually transmitted–infection clinics. This approach is currently promoted as an important intervention to increase access to HIV testing in the Caribbean region. The PITC model utilizes "routine" or "opt-out" testing at selected healthcare settings, where all patients are counselled and tested for HIV unless they decline. The objective of this approach, which utilizes existing health systems for HIV counseling and testing, is to increase early entry to HIV prevention, treatment and care—particularly in high-prevalence HIV areas.

A patient with active TB disease who is HIV-positive is, by international definition, considered to have WHO Stage III (PTB) or Stage IV (EPTB) HIV disease, and is therefore eligible for antiretroviral therapy.

Voluntary Counseling and Testing

Voluntary HIV counseling and testing (VCT) gives patients an opportunity to confidentially explore their HIV risks and to learn their HIV test results. VCT services can be provided either in free-standing sites or embedded within other facilities, such as health centers, workplace settings, and military facilities. The target audience is individuals who are interested in knowing their HIV status and learning how to reduce their risk. The focus of the counseling sessions is risk assessment, risk reduction, partner referral and linkages to care, treatment, and support.

Prevention of Mother-to-Child Transmission of HIV

Testing and counseling for prevention of mother-to-child transmission of HIV (PMTCT) occurs in reproductive health, prenatal, labour and delivery settings for the purposes of learning a pregnant woman's HIV status and, where necessary, providing a PMTCT intervention. Pre- and post-test counseling sessions focus on recommending and offering the HIV test, obtaining informed consent, using the test results to make decisions about PMTCT, and providing appropriate referrals for follow-up care, treatment and support.

There are many alternative testing algorithms for HIV testing. See "*Guidelines for Implementation of Reliable and Efficient Diagnostic HIV Testing, PAHO*," published June 2006, for more on HIV testing strategies and algorithm guidelines at: www.paho.org/English/AD/FCH/AI/LAB_GUIDE_ENG.PDF

C2. HIV Prevention in TB Patients[6]

TB programs jointly with HIV programs should develop and implement comprehensive HIV prevention strategies for their patients. Appropriate prevention messages and methods should be provided to patients with confirmed or suspected TB, dependent on their HIV status and local knowledge of the modes of transmission or assessment of risk.[27] NTPs should provide harm-reduction measures for TB patients who practice injecting drug use, or should establish a referral linkage with HIV programs to do so.[18]

Clinical Management of HIV-Related TB

All patients diagnosed with tuberculosis (any form) should be screened also for HIV. In patients with HIV-related TB, the priority is to treat TB first, especially in patients with smear-positive PTB, followed by provision of CPT and ART. (See Chapter 7 for standard treatment regimen recommendations for persons with HIV-related TB.) Table 16 lists some of the common clinical features suggestive of HIV co-infection in patients presenting with tuberculosis.

Treatment of HIV-related TB should follow the general principles developed for TB treatment in the HIV uninfected individual. This includes appropriate collection of clinical samples for staining, microscopy, culture and drug sensitivity testing (see Chapters 5 and 6). Wherever possible, sampling must be done before initiating drug treatment. This implies that suitable transportation and affordable diagnostic laboratory facilities are in place.

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All patients with TB and HIV infection should be evaluated to determine if antiretroviral therapy is indicated during the course of treatment for TB. Appropriate arrangements for access to antiretroviral drugs should be made for patients who meet indications for treatment. However, initiation of treatment for TB should not be delayed. Patients with TB and HIV infection should also receive cotrimoxazole as prophylaxis for other infections.[14]

TABLE 16:

Clinical features suggestive of HIV infection in patients with TB

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

Source: Modified from WHO, TB/HIV. A Clinical Manual. 2004.[1]

C3. **Cotrimoxazole Prophylaxis**

CPT substantially reduces mortality in HIV-positive TB patients[25,28] and should be started concurrently with TB treatment as soon as the patient is known to be HIV-positive.[6] Cotrimoxazole should be given throughout the course of TB treatment with continuation post-TB treatment considered in accordance with national guidelines[6] (see *ISTC* Standard 15).

The use of cotrimoxazole (sulfamethoxazole and trimethoprim 5:1) may reduce morbidity and mortality in HIV-infected TB patients through the prevention of other opportunistic infections such as pneumocystis pneumonia, other pneumonias, malaria, diarrhoea, etc. For cotrimoxazole dosages, contraindications, side effects and their management, see the WHO 2006 *Guidelines on Co-trimoxazole Prophylaxis for HIV-Related Infections among Children, Adolescents and Adults* at www.who.int/hiv/pub/guidelines/ctx/en/index.html. Additional information and guidelines on CPT are also available in the *Caribbean Guidelines for the Care and Treatment of Persons with HIV Infection* at www.chartcaribbean.org.

C4. **HIV-related Care and Support for TB/HIV Patients**[6]

TB programs should provide (or refer to HIV/AIDS programs to provide) the recommended package of HIV-related prevention, treatment, care and support services and support for people living with HIV.[25,29] To improve treatment success, the needs of special needs groups (e.g., drug users, prisoners, migrant populations, other marginalized groups) should be assessed and addressed, and their care integrated with other services.

A comprehensive AIDS care strategy includes clinical management (prophylaxis, early diagnosis, treatment and follow-up care for opportunistic infections), nursing care (including promoting hygiene and nutritional support), palliative care, home care (including education for care providers and patients' relatives, promoting universal precautions), counseling and social support.[27,30]

This package of care includes a core set of effective interventions listed below that are simple, relatively inexpensive, can improve the quality of life, prevent further transmission of HIV, and for some interventions, delay progression of HIV disease and prevent mortality. In addition to the 3 "I's", CPT and ART, the following interventions promote health, reduce the risk of HIV transmission to others, and address diseases that most impact the quality and duration of life of adults and adolescents with HIV.[9]

- Psychosocial counseling and support
- Disclosure of HIV status, partner notification and testing and counseling
- Preventing fungal infections
- Preventing sexually transmitted and other reproductive tract infections
- Preventing malaria
- Providing selected vaccines (hepatitis-B, pneumococcal, influenza, and yellow fever)
- Nutrition
- Family planning
- Preventing mother-to-child transmission of HIV
- Needle-syringe programs and opioid substitution therapy, and
- Water, sanitation, and hygiene

Once the patient with TB/HIV completes their course of TB treatment, there should be a continuum of care by HIV programs providing the package mentioned above.

C5. **Antiretroviral Therapy**

ART improves survival in HIV-positive patients.[25] Recommendation 3 in the WHO's Rapid Advice: Antiretroviral therapy for HIV infection in adults and adolescents (2009),[31] provides guidance on the provision of ART for TB/HIV co-infection. The recommendations are as follows:

- Start ART in all HIV-infected individuals with active TB irrespective of CD4 cell count
- Start TB treatment first, followed by ART as soon as possible after starting TB treatment
- Use efavirnenz (EFV) as the preferred non-nucleoside reverse transcriptase inhibitor (NNRTI) in patients starting ART while on TB treatment

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

ART Regimens for Patients Receiving TB Treatment[6]

WHO recommends that the first-line ART regimen contain two nucleoside reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse transcriptase inhibitor (NNRTI). These are efficacious, generally less expensive, have generic and fixed-dose combination formulations, do not require a cold chain, and preserve a potent new class (protease inhibitors) for second-line regimens. The preferred NRTI backbone is zidovudine (AZT) or tenofovir disoproxil fumarate (TDF) combined with either lamivudine (3TC) or emtricitabine (FTC). For the NNRTI, WHO recommends either EFV or nevirapine (NVP).[32]

Efavirenz-containing regimens are the recommended first-line ART regimens for TB patients, since interactions with anti-TB drugs are minimal. In several cohort studies, antiretroviral therapy of standard-dose EFV and two nucleosides was well-tolerated and highly efficacious in achieving complete viral suppression among patients receiving concomitant rifampicin-based TB treatment.[33]

However, alternatives to EFV are needed in the following situations:

- Women of childbearing potential without adequate contraception and in pregnant women in the first trimester of pregnancy because of potential teratogenicity. For further guidance on ART in pregnant women, see Recommendation 5 in the WHO's Rapid Advice: Antiretroviral therapy for HIV infection in adults and adolescents, November 2009 available at: www.who.int/hiv/pub/arv/advice/en/index.html
- Patients who are intolerant to efavirenz
- Patients infected with a strain of HIV that is resistant to NNRTIs

Alternative first-line treatment regimens include NVP and triple NRTIs (TDF or abacavir-based) regimens. For NVP-containing regimens, ALT should be checked at 4, 8 and 12 weeks; directed by symptoms thereafter. In selecting alternatives to EFV for the situations noted above, the NTP manager should consult with the country's HIV program and other experts familiar with the most recent results of ongoing studies or change in policies.

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

Patient Monitoring During TB Treatment[6] (see also Chapter 8)

Adverse effects of medications are common in HIV-positive TB patients, and some toxicities are common to both ART and TB drugs.[25] Overlapping toxicities between ART, TB therapy, and cotrimoxazole include rash (and more rarely hepatic dysfunction), so vigilance in terms of monitoring side-effects is required.[28,34]

TB and ART Drug Interactions

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

Immune Reconstitution Inflammatory Syndrome

As the patient begins to respond to TB treatment, the patient's immunity is also reconstituted and this may result in an exaggerated immune reaction to the TB bacillary material. This reaction, which is called IRIS, can vary in severity from mild to more serious but more commonly presents in a mild to moderate form in patients with TB started on ART.[6] IRIS can occur in non-HIV-infected persons with TB,[35] but is more common among those with HIV infection, particularly those receiving ART. The syndrome typically manifests itself as a worsening of TB-related signs and symptoms (e.g., fever, enlarging lymph nodes, new lymphadenopathy, expanding central nervous system lesions, worsening of pulmonary parenchymal infiltrations, and increasing pleural effusions), generally occurring within 12 weeks of initiating ART and more common when CD4 count is low (<50 cells/mm^3)[6]. TB-related IRIS can be associated with significant morbidity and even mortality if not appropriately managed. In most cases, TB treatment and ART can and should be continued. Mild symptoms usually resolve over time and can often be managed with the use of non-steroidal anti-inflammatory drugs. Moderate to severe symptoms may require the use of corticosteroids to suppress the immune response.[36]

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

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

Treatment Recommendations for Children with TB/HIV Co-infection

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

- **In the ART-naïve child,** TB treatment (by DOT) should be given for 4-8 weeks before initiating ART in order to better monitor and reduce potential toxicities
- **For a child who is already receiving ART,** the ART regimen should be reviewed and altered if necessary to ensure optimal treatment for both TB and HIV and to minimize potential toxicities and drug-drug interactions
- **The initial phase of treatment of TB** should consist of a four-drug regimen: RIF, INH, PZA, and EMB. If the organism is found to be susceptible to the first 3 drugs, EMB can be discontinued and initial phase completed (2 months) using 3 drugs. Streptomycin should replace EMB in the treatment of TB meningitis (see Chapter 10)
- **In the continuation phase,** INH and RIF should then be continued daily to complete 6–9 months therapy. Note that PAHO/WHO do not recommend the 7 month HR continuation phase but it is considered an option by the CTWG. (see Chapter 7 for standard treatment regimen recommendations for persons with HIV-related TB)

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

References

1. World Health Organization. TB/HIV: A Clinical Manual. Geneva: World Health Organization, 2004 (WHO/HTM/TB/2004.334).
2. World Health Organization. IMAI TB/HIV co-management training manual for first-level facilities 2-day clinical course: participant's training manual. Geneva: World Health Organization, 2008.
3. World Health Organization Report 2009. Global Tuberculosis Control: Surveillance, Planning, Financing. Geneva: World Health Organization, 2009 (WHO/HTM/TB/2009.411).
4. UNAIDS. 2008 Report on the Global AIDS Epidemic. Geneva: Joint United Nations Programme on HIV/AIDS, 2008 (http://data.unaids.org/pub/GlobalReport/2008/JC1510_2008GlobalReport_en.zip).
5. WHO, UNAIDS. Guidance on provider-initiated HIV testing and counseling in health facilities. Geneva: World Health Organization, 2007.
6. World Health Organization. Treatment of Tuberculosis: Guidelines. Fourth Edition. Geneva: World Health Organization, 2009 (WHO/HTM/TB/2009.420).
7. World Health Organization. A Guide to monitoring and evaluation for collaborative TB/HIV activities 2009 revision. Geneva: World Health Organization, 2009 (WHO/HTM/TB/2009.414, WHO/HTM/HIV/09.01).
8. Koenig SP, Riviere C, Leger P, Joseph P, et al. High mortality among patients with AIDS who received a diagnosis of tuberculosis in the first 3 months of antiretroviral therapy. CID 2009; 48:829-31.
9. World Health Organization. WHO Three I's Meeting. Intensified case finding (ICF), isoniazid preventive therapy (IPT) and TB infection control (IC) for people living with HIV. Geneva: World Health Organization, 2008.
10. World Health Organization. Essential Prevention and Care Interventions for Adults and Adolescents Living with HIV in Resource-limited Settings. 2008. (www.who.int/hiv/pub/guidelines/EP/en/index.html)
11. ICAP. Screening for tuberculosis in individuals with HIV infection. A clinical guide for HIV care providers in resource-limited settings. New York: Columbia University Mailman School of Public Health, 2007.
12. Burman WJ, Jones BE. Clinical and radiographic features of HIV-related tuberculosis. Seminars in Respiratory Infections 2003; 18(4):263-71.
13. Rabkin M, El-Sadr WM, Abrams EJ. Columbia clinical manual. Care and treatment of HIV/AIDS in resource-limited settings. ICAP, Columbia University Mailman School of Public Health. 2005.
14. Tuberculosis Coalition for Technical Assistance. International Standards for Tuberculosis Care (ISTC), second edition. Tuberculosis Coalition for Technical Assistance, The Hague, 2009.
15. Center for Global Health Policy. Deadly duo: The synergy between HIV/AIDS and tuberculosis. Arlington: Infectious Diseases Society of America and the HIV Medicine Association, 2009.
16. Meldrum J. Treating latent TB. AIDSMAP. October 27, 2005. Available at: www.aidsmap.com/cms1199978.aspx?type=preview (Accessed Oct. 14, 2009).
17. Aït-Khaled N, Alarcon E, Bissell K, et al. Isoniazid preventive therapy for people living with HIV: public health challenges and implementation issues. Int J Tuberc Lung Dis 2009; 13(8):927-935.

18. World Health Organization. Implementing the Stop TB strategy: A handbook for national tuberculosis control programs. Geneva: World Health Organization, 2008 (WHO/HTM/TB/2008.401).

19. World Health Organization. WHO report on TB medicines for children. 8–9 July 2008. Geneva: World Health Organization. 1-22. Available at: www.who.int/selection_medicines/committees/subcommittee/2/TB.pdf.

20. Centers for Disease Control and Prevention. Guidelines for preventing the transmission of Mycobacterium tuberculosis in health-care settings, 2005. MMWR 2005; 54 (No. RR-17); 1-141.

21. Centers for Disease Control and Prevention. Tuberculosis transmission in multiple correctional facilities—Kansas, 2002-2003. MMWR 2004; 53(32); 734-738.

22. Escombe AR, Moore DAJ, Gilman RH, et al. The infectiousness of tuberculosis patients co-infected with HIV. PloS Med 2008. 5(9): e188. doi:10. 1371/journal.pmed.0050188.

23. World Health Organization. WHO policy on TB infection control in health-care facilities congregate settings, and households. Geneva: World Health Organization, 2009.

24. World Health Organization. Tuberculosis infection control in the era of expanding HIV care and treatment. Addendum to WHO guidelines for the prevention of tuberculosis in health care facilities in resource-limited settings. 1999. Geneva: World Health Organization, 2007.

25. Harries AD, Zachariah R, Lawn SD. Providing HIV care for co-infected tuberculosis patients: A perspective from sub-Saharan Africa. Int J Tuberc Lung Dis. 2009 Jan;13(1):6-16.

26. World Health Organization. HIV testing and counseling: the gateway to treatment, care and support. 3 by 5 Technical Brief. Available at: www.who.int/3by5/publications/briefs/hiv_testing_counselling/en/index.html (Accessed Oct. 14, 2009). (WHO/HIV/2003.13).

27. World Health Organization. Interim policy on collaborative TB/HIV activities. Geneva: World Health Organization, 2004 (WHO/HTM/TB/2004.330, WHO/HTM/HIV/2004.1).

28. World Health Organization. Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults in resource-limited settings: Recommendations for a public health approach. Geneva: World Health Organization, 2006.

29. World Health Organization. Dept. of HIV/AIDS, World Health Organization. Stop TB Dept, WHO Integrated Management of Adolescent and Adult Illness Project. Tuberculosis care with TB-HIV co-management: Integrated management of adolescent and adult illness (IMAI). Geneva: World Health Organization, 2007.

30. World Health Organization. Dept. of HIV/AIDS. Towards universal access: Priority interventions for HIV. Geneva: World Health Organization, 2008.

31. World Health Organization. Rapid Advice: Antiretroviral therapy for HIV infection in adults and adolescents. Geneva: World Health Organization; 2009. Available at: www.who.int/hiv/pub/arv/advice/en/index.html (Accessed Dec. 16, 2009).

32. World Health Organization. Dept. of HIV/AIDS. Priority interventions: HIV/AIDS prevention, treatment and care in the health sector. Geneva: World Health Organization, 2009 (available at http://www.who.int/hiv/pub/priority_interventions_web.pdf).

33. Centers for Disease Control and Prevention. Managing drug interactions in the treatment of HIV-related tuberculosis [on-line]. Atlanta: Centers for Disease Control and Prevention, 2007 (available at: www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/PDF/tbhiv.pdf).

34. World Health Organization. Stop TB Dept. Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency Update 2008. Geneva: World Health Organization, 2008. (WHO/HTM/TB/2008.402).

35. Berg J, Leonard A, Clancy CJ, Nguyen MH. Subcutaneous abscesses due to Mycobacterium tuberculosis: paradoxical expansion of disease during therapy for miliary tuberculosis. Clin Infect Dis. 1998;26:231-232.

36. Iseman MD. A Clinician's Guide to Tuberculosis, Chap. 8, Tuberculosis in relation to human immunodeficiency virus and acquired immunodeficiency syndrome. Philadelphia: Lippincott Williams & Wilkins, 2000.

Tuberculosis in Children

10

The WHO estimates that each year, approximately one million cases of tuberculosis occur in children <15 years of age, accounting for 11% of the annual burden of cases diagnosed worldwide.[1]

Children can present with TB at any age. The frequency of childhood TB is influenced by the intensity of the TB epidemic locally, the age structure of the population, the availability of diagnostic tools, and whether contact investigation is routinely conducted.[1]

Transmission of tuberculosis to a child usually results from exposure to an infectious adult or adolescent in her/his close environment, often within the household.[2] On acquiring TB infection, children frequently develop a primary parenchymal lesion, or a Ghon focus, in the lungs, with subsequent spread to the regional lymph nodes. The cell-mediated immune response halts further progression in most situations; however, very young children (<3 years of age) and those with weakened immune systems are at great risk for disease progression.[3] For infants, the time span between infection and disease can be as short as a few weeks.

Clinical Presentations of TB in Children

Most children with TB have PTB; however, PTB is more difficult to recognize because many children present with primary rather than reactivation (cavitary) PTB. Additionally, the majority of children with TB are too young to produce sputum for smear microscopy. The WHO notes that the ratio of reported PTB:EPTB in children is usually around 1:3; however, the ratio varies depending on factors such as age, ability to conduct contact investigations, and also possibly genetic factors.[2]

The most common type of EPTB seen in children is intrathoracic. Other forms of EPTB frequently seen in children include:[2,4]

- TB lymphadenopathy (cervical lymphadenitis being the most common presentation)
- Central nervous system TB (TB meningitis and tuberculoma)
- Disseminated TB
- TB effusions (pleural, pericardial, and peritoneal)
- Spinal TB

Smear-positive PTB is more commonly seen in school-aged children, particularly in adolescents when PTB presents more as it does in adults (i.e., with cavitation).

Presentations of TB in Children[2]

Primary TB Disease

- Uncomplicated primary diseases:
  - Often **unilateral lymphadenopathy**, hilar or mediastinal, without radiographic abnormalities in the lung (no obvious parenchymal involvement). This is the most frequent presentation of TB in children (70–80%) and should be classified as EPTB

    - Sometimes **typical "primary complex"** combining hilar and mediastinal lymph-adenopathy and a small opacity in the lung, 3–10 mm in diameter ("primary lesion"). It is less frequent (20%, usually in children under 5 years of age). This is classified as a case of PTB
- Complicated primary diseases:
    - Rarely, **lobar or segmental opacity** in the lung, combined with unilateral lymph-adenopathy on the same side. When bronchial compression has resulted in atelectasis, corticosteroids in addition to chemotherapy may be helpful
    - Unilateral hyperinflation
    - Cavitation of the primary lesion in the lung is exceptional in children, and is classified as PTB, often smear-positive
    - Tuberculous bronchopneumonia and expansile pneumonia

Acute Disseminated Primary TB (often in children aged under 5 years):

- Miliary with or without meningitis is classified as PTB

Post-primary PTB (usually in children aged over 10 years):

- Without cavitation, smear-negative or with cavitation often smear-positive

Post-primary EPTB

Presentations of TB in Children with HIV

The natural history of TB in a child with HIV depends on the stage of HIV disease

- In early HIV infection, the signs of TB are similar to those of an HIV-uninfected child
- As HIV infection progresses, dissemination of TB becomes more common:
    - Meningitis
    - Miliary TB
    - Widespread tuberculous lymphadenopathy
- Older HIV-infected children with TB may have clinical presentations similar to that seen in HIV-infected adults
- Children with TB/HIV co-infection have:
    - Longer hospital stays
    - Greater likelihood of malnutrition[6]
    - Higher mortality despite initiation of appropriate anti-TB medications

It is essential to have a high index of suspicion for TB disease in HIV-infected children. As with the non-HIV infected child, a definitive diagnosis of TB disease requires isolation of *M. tuberculosis* from any of the following:

- Expectorated sputum
- Bronchoalveolar lavage fluid, induced sputum or aspirated gastric fluid (obtained in the early morning after overnight fast), or pleural fluid
- Biopsied lung, peripheral lymph node, or other tissue

Diagnosing TB in Children

Diagnosing tuberculosis in children is particularly problematic. Children <5 years of age rarely expectorate sputum for evaluation, and even when specimens are obtained they are rarely smear-positive for AFB on routine microscopy. In very young children, gastric aspirate specimens can be collected; however, the yield of positive smear is also fairly low (less than 20%) and the procedure is often not practical outside of urban centers (see Appendix E: Gastric aspirates patient preparation and procedure).

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In all children suspected of having intra-thoracic (i.e., pulmonary, pleural, and mediastinal or hilar lymph node) TB, 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 TB should be based on the presence of abnormalities consistent with TB on chest radiography, a history of exposure to an infectious case, evidence of TB infection (positive tuberculin skin test or interferon gamma-release assay) and clinical findings suggestive of TB. For children suspected of having EPTB, appropriate specimens from the suspected sites of involvement should be obtained for microscopy and for culture and histopathological examination.[7]

Recommended Approach to Diagnose TB in Children

Points to remember:

- Diagnosis of PTB may be difficult in children <6–8 years of age, particularly in low-resource settings
- Diagnostic TB workup in a child should include all of the following:
  - Symptom and contact history
  - Clinical exam (including growth assessment)
  - Mantoux tuberculin skin test result
  - Bacteriological confirmation (whenever possible)
  - Chest radiograph
  - Other specific evaluation indicated by disease site (see Chapter 5, Presentations and Investigations for EPTB) or co-morbidity (e.g., HIV risk)
  - HIV testing

Careful History (including history of TB contact and symptoms consistent with TB)[3]

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

- Children (especially those <5 years of age) who have been in close contact with a case of smear-positive TB must be screened for TB (see Appendix C: Implementing TB Contact Investigation)

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

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

- **Chronic cough:** an unremitting cough that is not improving and has been present for 2–3 weeks
- **Fever:** of 38°C for 14 days after common causes such as malaria or pneumonia have been excluded
- **Weight loss or failure to thrive:** always ask about weight loss or failure to thrive and look at the child's growth chart

Clinical Examination (including growth assessment)[3]

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

Physical signs highly suggestive of EPTB:

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

Physical signs requiring investigation to exclude EPTB:

- Meningitis not responding to antibiotic treatment, with a sub-acute onset or raised intracranial pressure
- Pleural effusion
- Pericardial effusion
- Distended abdomen with ascites
- Non-painful enlarged lymph nodes without fistula formation
- Non-painful enlarged joint
- Signs of tuberculin hypersensitivity: phlyctenular conjunctivitis, erythema nodosum

Documented weight loss or failure to gain weight, especially after being treated in a nutritional rehabilitation program, is a good indicator of chronic disease in children, and TB may be the cause. Table 17 summarizes some of the key history and examination findings that would suggest a diagnosis of tuberculosis in a child.

TABLE 17:

An approach to the diagnosis of tuberculosis in children

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

A history of:	On examination:
• Unexplained weight loss or failure to grow normally • Unexplained fever, especially when it continues for more than two weeks • Chronic cough (i.e. cough 2–3 weeks, with or without wheeze) • Exposure to an adult with probable or definite pulmonary infectious tuberculosis	• Fluid on one side of the chest (reduced air entry, stony 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

Source: Modified from WHO Management of the Child with A Serious Infection or Severe Malnutrition, 2000.[8]

Mantoux Tuberculin Skin Test (TST)[3]

A positive Mantoux TST can occur when a child is infected with *M. tuberculosis*. However, in children, the Mantoux TST can also be used in conjunction with signs and symptoms of TB and other diagnostic tests as an adjunct in diagnosing TB disease. There are a number of TSTs available (e.g., Mantoux, multipuncture, Tine and Heaf), but the Mantoux skin test is the recommended test.

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

- **High-risk children:** TST ≥5 mm induration (high risk includes HIV-infected children, close contacts to active pulmonary TB, children whose chest X-ray is consistent with TB, and severely malnourished children, i.e., those with clinical evidence of marasmus or kwashiorkor)
- **All other children:** TST ≥10 mm induration is regarded as positive (whether or not they have been BCG vaccinated)

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

The TST is useful in HIV-infected children to identify those with dual TB/HIV infection and as an aid in the diagnosis of TB, although fewer HIV-infected children will have a positive test, as a normal immune response is required to produce a positive TST, and many HIV-infected children have immune suppression.

There can be false-positive as well as false-negative TST tests (see Appendix A). It is sometimes useful to repeat the TST in children once their malnutrition has been addressed or their severe illness (including TB) has resolved, as they may be initially TST negative, but positive after 2–3 months on treatment. **A negative Mantoux TST never rules out a diagnosis of TB.**

Bacteriological Confirmation[3]

It is always preferable to make a bacteriological diagnosis of TB in a child using whatever specimens and laboratory methods are available. Samples include sputum, gastric aspirate and other material (e.g., lymph node biopsy or any other material that is biopsied). Fine needle aspiration of enlarged lymph glands for both histology and staining for AFB has been shown to be a useful test with a high bacteriological yield. All specimens that are obtained should be sent for mycobacterial culture whenever possible. This will improve the yield of the test (i.e., it is more sensitive), but it is also the only way to differentiate *M. tuberculosis* from other non-tuberculous mycobacteria.

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

- Suspected drug resistance
- HIV infection
- Complicated or severe cases of disease
- An uncertain diagnosis

The more common ways of obtaining sputum for microscopy include:

- **Expectoration:** Sputum for smear microscopy is a useful test and should always be obtained in adults and older children ≥10 years of age who are pulmonary TB suspects. Among younger children, especially children <5 years of age, sputum is difficult to obtain and most children are "sputum smear-negative." However, in children who are able to produce a specimen, it is worth sending for smear microscopy (and culture if available). Yields are higher in older children (>5 years of age) and adolescents, and in children of all ages with severe disease. As with adult TB suspects, at least two sputum specimens should be obtained: spot specimen (at first evaluation), followed by an early morning specimen
- **Gastric aspirates:** Gastric aspiration using a nasogastric feeding tube can be performed in young children who are unable or unwilling to expectorate sputum. If performed, gastric aspirates should be sent for smear microscopy and mycobacterial culture. (Procedure detailed in Appendix E.)
- **Sputum induction:** Several recent studies have found that sputum induction can be performed safely and effectively in children of all ages, and the bacteriological yield is as good as or better than for gastric aspirates. However, training and specialized equipment are required to perform this test properly

Investigations relevant for suspected PTB and EPTB[3]

- **Relevant for suspected pulmonary and intrathoracic TB:** In the majority of cases, children with pulmonary or intrathoracic TB have CXR changes suggestive of TB. The most common picture is that of persistent opacification in the lung, together with enlarged hilar or subcarinal lymph glands. A miliary pattern of opacification in non-HIV-infected children is highly suggestive of TB. Patients with persistent opacification that does not improve after a course of antibiotics should be investigated for TB.

  Adolescent patients with TB have CXR changes similar to adult patients, with large pleural effusions and apical infiltrates with cavity formation being the most common forms of presentation. Adolescents may also develop primary disease, with hilar adenopathy and collapse lesions visible on CXR.

  Chest radiography is quite useful in the diagnosis of TB in children. A lateral view may be helpful in situations where the frontal view is difficult to interpret and in very young children (e.g., <5 years of age). The CXR preferably should be read by a radiologist or other healthcare worker trained in their reading. Good quality CXRs are essential for proper evaluation

- **Relevant for suspected extrapulmonary TB:** Chapter 5 addresses the usual investigations for diagnosing common forms of extrapulmonary TB. In most of these cases, TB will be suspected from the clinical picture and confirmed by histology or other special investigations

- **Other tests:** Serological and nucleic acid amplification (e.g., polymerase chain reaction [PCR]) tests are not currently recommended for the routine diagnosis of childhood TB, as they have been inadequately studied in children and they have performed poorly in the few studies that have been done. However, this is an area that requires further research, as they may prove to be useful in the future. Interferon gamma release assay (IGRA) tests are increasingly being used to identify latent TB infection; however, further research is needed regarding their performance in young children and infants.[9]

  Miliary or haematogenously disseminated TB has a high risk (60–70%) of meningeal involvement and should therefore be managed similarly to TB meningitis. For this reason, many experts recommend that all children with miliary TB (or suspected of having miliary TB) should undergo lumbar puncture to evaluate the presence of meningitis[10]

  Note: Other specialized tests, such as computerized chest tomography and bronchoscopy, are not recommended for the routine diagnosis of TB in children.[3]

HIV Testing

HIV counseling and testing should be included as part of routine care and management of children in which TB is diagnosed.

Treating Childhood TB

Treatment Regimens

The recommended treatment regimens for children are based on prior treatment history and clinical presentation (see Table 18). These guidelines present current WHO-recommended options for drug regimen (Table 18) and dosage (Table 5, Chapter 7) for the treatment of tuberculosis in children. There are several points of note pertaining to treatment of TB in children:

- WHO has updated dosage recommendations for children (see Table 5, Chapter 7) based on review of evidence from pharmacokinetic studies and in consultation with pediatric pharmacology and TB experts.[11] Weight should be monitored regularly throughout treatment for all children and adjustment to dosage made as the child gains weight
- Although prior regimen options for children included a thrice weekly continuation phase, pediatric dosing recommendations for intermittent regimens are currently under review and not yet available with the exception of ethambutol.[12] The thrice weekly dose recommendations for INH, rifampicin and pyrazinamide provided in earlier WHO documents[2,10] are likely to be suboptimal for children

TABLE 18:

Recommended regimens for treatment of TB in children

Clinical presentation	Regimen (daily or 3 times weekly)[a]	
	Intensive phase	Continuation phase
New smear-negative PTB and less severe forms of EPTB	2 months HRZ[b]	4 months HR
New smear-positive PTB New smear-negative PTB with extensive parenchymal involvement Severe forms of EPTB (other than TB meningitis—see below) Severe concomitant HIV disease	2HRZE	4 months HR
TB meningitis	2 months HRZS[c]	4 months HR
Previously treated smear-positive PTB:[d] • Relapse • Treatment after interruption • Treatment failure	2 months HRZES followed by 1 month HRZE	5 months HRE
MDR-TB	Specially designed standardised or individualised regimens (recommend consultation with a clinician experienced in MDR-TB treatment and management)	

TB = tuberculosis; **H** = isoniazid; **R** = rifampicin; **Z** = pyrazinamide; **E** = ethambutol; **PTB** = pulmonary TB; **EPTB** = extra-pulmonary TB; **HIV** = human immunodeficiency virus; **S** = streptomycin; **MDR-TB** = multidrug resistant tuberculosis

a Direct observation of drug administration is recommended during the initial treatment phase and whenever the continuation phase contains R

b E may be omitted during the initial phase of treatment for young children with non-cavitary, smear-negative pulmonary or primary TB who are known to be HIV-negative and known to be infected with fully drug-susceptible bacilli

c S replaces E in the treatment of TB meningitis

d TB culture and DST must be attempted to rule out MDR-TB in all previously treated TB patients

Source: Adapted from WHO Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children. 2006.

- Reference to the Diagnostic Categories has been removed from this chapter given the recent removal of the Categories from the revised WHO guidelines, Treatment of Tuberculosis, Fourth edition. which provides guidance on treatment of TB in adults[13]
- TB meningitis and miliary TB are more common in children and are associated with high rates of death and disability.[1] There are several approaches to treatment of TB meningitis presented in this chapter as there remains some controversy on the optimal approach (see Table 19). While many TB drugs have suboptimal transfer across uninflamed meninges, streptomycin may penetrate better than ethambutol across inflamed meninges and should be used in place of EMB in the initial phase.[1] Corticosteriods should also be used for all children with TB meningitis (see section on Management of TB Meningitis and Miliary TB on page 110)
- The principles for TB treatment are the same in the HIV-infected as in the HIV-uninfected child. Modified treatment durations, schedules and medications are recommended for specific instances (see Chapter 9: HIV Infection and Tuberculosis for information on management of HIV-related TB)

TABLE 19:

Selected regimens for treatment of TB meningitis in children

Intensive phase	Continuation phase	Reference
2HRZS	4HR	WHO (WHO/HTM/TB/2006.371)[1]
2HRZ(S or Eth[a])	7–10HR[b]	American Academy of Pediatrics[18]

TB = tuberculosis; **H** = isoniazid; **R** = rifampicin; **Z** = pyrazinamide; **S** = streptomycin; **Eth** = ethionamide

a Some experts (not WHO) recommend ethionamide as the 4th drug as it crosses both healthy and inflamed meninges

b Some experts recommend a longer duration of continuation-phase

Source: Adapted from WHO Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children. 2006.[1]

Management of HIV-related TB

Cotrimoxazole Prophylaxis[14]

Daily CPT (20 mg trimethoprim + 100 mg sulfamethoxazole if aged <6 months; 40 mg trimethoprim + 200 mg sulfamethoxazole if <5 years; 80 mg trimethoprim + 400 mg sulfamethoxazole if ≥5 years) prolongs survival in HIV-infected children and reduces the incidence of respiratory infections and hospitalisation. No studies have been done in HIV-infected children with TB, but a number of studies of CPT in HIV-infected adults with TB have shown clear and consistent benefit. WHO and the Joint United Nations Program on HIV/AIDS (UNAIDS) have recently revised provisional recommendations for HIV-infected children.[15] All HIV-infected children with advanced immunosuppression should be started on cotrimoxazole. There is no consensus yet on whether children on ART who have immune reconstitution can safely stop cotrimoxazole.

Antiretroviral Therapy

In the HIV-infected child with confirmed or presumptive TB, initiation of anti-TB treatment is the priority.[16] Treatment of TB in HIV-infected children on ART or who will start on ART needs careful consideration. There are many drug-drug interactions between ARVs and rifampicin as well as the adverse events of anti-TB drugs and ARVs are similar and can cause confusion as to which drug may need to be stopped.[1] (See also Chapter 9, section on Clinical Management of HIV-related TB.)

Although the optimal timing for the initiation of ART during anti-TB treatment is not known, the decision to initiate ART should take into consideration the degree of immune suppression[16] and the child's progress during anti-TB treatment. Table 21 shows the recommendations for the timing of ART following the initiation of anti-TB treatment in children who are co-infected with HIV. The clinical and immunological condition of the HIV-infected child should guide the decision whether to:[1]

- Start ART treatment soon (2–8 weeks) after the start of anti-TB treatment
- Delay ART until after completion of the initial phase of anti-TB treatment
- Delay start of ART until anti-TB treatment is completed

Where possible, the initiation of ART should be deferred for at least 2–8 weeks in children starting anti-TB treatment who have not yet started ART (e.g. antiretroviral "naive" patients). A careful review of any possible drug interactions between ART and anti-TB medications should be carried out, and any modifications should be determined with the guidance of an HIV treatment expert.[1]

TABLE 20:

Proposed classification of HIV-associated immunodeficiency in children

Classification of HIV-associated immunodeficiency	Age-related CD4 values			
	≤11 months (%)	12–35 months (%)	36–59 months (%)	≥5 years (cells/mm3)
Not significant	>35	>30	>25	>500
Mild	30 - 35	25 – 30	20 – 25	350 – 499
Advanced	25 – 30	20 – 25	15 – 20	200 – 349
Severe	<25	<20	<15	<200[a]

a Or <15%

Source: Adapted from Antiretroviral Therapy of HIV Infection in Infants and Children in Resource-limited Settings: Towards Universal Access. Recommendations for a Public Health Approach. WHO.[16]

TABLE 21:

Recommended timing of ART following the start of anti-TB treatment with a rifampicin-containing regimen in HIV-infected children

WHO pediatric clinical stage[a]	Timing of ART following start of anti-TB treatment[b,c]	Recommended ART regimen
4[d] (EPTB other than lymph node TB)	**Start ART soon after anti-TB treatment** (between 2 and 8 weeks following start of anti-TB treatment)	**In children aged <3 years:** • Preferred: triple NRTI first-line regimen d4T or AZT + 3TC + ABC • Alternative: standard first-line regimen two NRTIs + NVP[e] **In children aged 3 years and above**[f] • Preferred: triple NRTI first-line regimen d4T or AZT + 3TC + ABC • Alternative: standard first-line regimen two NRTIs + EFV[g] Following completion of anti-TB treatment, it is preferable to remain on the ART regimen outlined above
3 (PTB and lymph node TB)	**With clinical management alone:** • **Start ART soon after start of anti-TB treatment** (between 2–8 weeks following start of anti-TB treatment) • **Consider delaying start of ART until anti-TB treatment is completed** If excellent clinical response to anti-TB treatment in first 2–8 weeks of anti-TB therapy and child is stable and on cotrimoxazole preventive therapy, it may be reasonable to delay start of ART	
	Where CD4 values are available: evaluation of the possibility of delaying start of ART will depend on assessment of clinical status, CD4 values, and clinical and immunological response to anti-TB therapy • **Severe and advanced immunodeficiency:**[h] **start ART soon after start of anti-TB treatment** (between 2–8 weeks following start of anti-TB treatment) • **Mild or no immunodeficiency:**[i] **consider delaying start of ART until anti-TB treatment is completed** Closely monitor response to anti-TB therapy and reassess for need for ART after anti-TB therapy; if no improvement, consider starting ART	Regimens as recommended above Where ART can be delayed until after completion of anti-TB treatment, starting with a standard two NRTIs + NNRTI first-line regimen is recommended

ART = antiretroviral therapy; **NRTI** = nucleoside reverse transcriptase inhibitor; **d4T** = stavudine; **AZT** = zidovudine; **3TC** = lamivudine; **ABC** = abacavir; **NVP** = nevirapine; **EFV** = efavirenz; **NNRTI** = non-nucleoside reverse transcriptase inhibitor.

a Clinical stage of child with TB (as an event indicating need for ART)

b Anti-TB treatment: a rifampicin-containing regimen

c Administration of cotrimoxazole preventive therapy is important in children with TB/HIV co-infection

d All children with clinical stage 4 should be started on ART regardless of CD4 values

e Careful clinical monitoring with laboratory support, if available, is recommended where NVP is administered concurrently with rifampicin

f Because of lack of data, the ranking of preferred or alternative antiretroviral regimens is not a consensus recommendation

g EFV is not currently recommended for children <3 years of age or <10 kg, and should not be given to post-pubertal adolescent girls who are either in the first trimester of pregnancy or are sexually active and not using adequate contraception

h Advanced immunodeficiency is assumed to be up to 5% above the age-specific CD4 threshold for severe immunodeficiency or 200–349 CD4 cells/mm3 for children ≥5 years of age (see Table 20)

i Mild or no immunodeficiency is assumed at CD4 levels above those defining advanced immunodeficiency (see Table 20)

Source: Adapted from Antiretroviral Therapy of HIV Infection in Infants and Children in Resource-limited Settings: Towards Universal Access. Recommendations for a Public Health Approach. WHO.[16]

Immune Reconstitution[1]

Sometimes referred to as a paradoxical reaction, this temporary exacerbation of symptoms, signs, or radiographic manifestations sometimes occurs after beginning anti-TB treatment. This can simulate worsening disease, with fever, and increased size of lymph nodes or tuberculomas. Immune reconstitution can be brought about by improved nutritional status or by the anti-TB treatment itself. Clinical deterioration due to immune reconstitution can occur after initiation of ART in HIV-infected children with TB, and is known as the IRIS.[17] The reaction may occur during the first 3–6 months of ART, is generally self-limiting and lasts 10–40 days. Anti-tuberculosis treatment should be continued, although in some cases the addition of corticosteroids might be useful.

Management of TB Meningitis and Miliary TB

Miliary or haematogenously disseminated TB has a high risk (60-70%) of meningeal involvement and should therefore be managed similarly to TB meningitis. For this reason, many experts recommend that all children with miliary TB should undergo a lumbar puncture to test for the presence of meningitis.[1] (See also Chapter 5 for additional information on presentation and diagnostic investigations for TB meningitis.)

Children with TB meningitis or miliary TB should be hospitalized, preferably for at least the first 2 months. Table 19 summarizes the commonly recommended treatment regimens for TB meningitis. Because penetration of some drugs (e.g., RIF and streptomycin) into the cerebrospinal fluid is poor, these forms of TB may benefit from the upper end of the recommended dose ranges (see Table 5, Chapter 7). Corticosteroids are recommended for all children with TB meningities (see below).[1]

Adjunctive Treatment with Corticosteroids[1]

Corticosteroids may be used for the management of some complicated forms of TB (e.g., tuberculous meningitis, the complications of airway obstruction by TB lymph glands, and TB pericarditis). In advanced TB meningitis cases, corticosteroids have been shown to improve survival and reduce morbidity and are thus recommended in all cases of TB meningitis. The drug most frequently used is prednisone, in a dosage of 2 mg/kg/day (maximum dosage 60 mg/day) for 4 weeks. The dose should then be slowly reduced (tapered off) over 1–2 weeks before stopping, with vigilance for subsequent worsening due to rebound inflammation or IRIS.

Treatment Administration and Adherence[1]

Children, their parents, and other family members and other caregivers should be educated about TB and the importance of completing treatment. The support of the child's parents and immediate family is vital to ensure a satisfactory outcome of treatment. Preferably someone other than the child's parent or immediate family should observe or administer treatment and all doses recorded on the patient treatment card. All children should receive treatment free of charge, and fixed-dose combinations should be used whenever possible to improve simplicity and adherence.

Children with severe forms of TB should be hospitalized for intensive management where possible. This is particularly important in situations of suspect TB meningitis where com-

plications may result from meningeal irritation, local vasculitis, tuberculoma formation or increased intracranial pressure and hydrocephalus. In addition to treatment with anti-tuberculosis drugs and corticosteroids, treatment may require anti-convulsants for seizures, nutrition, fluid and electrolyte management and occasionally acute ventriculostomy tube placement for acute hydrocephalus. In general, conditions that merit hospitalisation include:

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

Monitoring Throughout Treatment

Ideally, each child should be assessed by the National Tuberculosis Program (NTP) (or those designated by the NTP to provide treatment) **at least** at the following intervals:

- 2 weeks after treatment initiation
- Monthly, especially until the end of the intensive phase
- Every 2 months until treatment completion

The assessment should include, at a minimum:

- A symptom assessment
- An assessment of adherence
- Enquiry about any adverse events
- Weight measurement with medication dosages adjusted to account for weight gain
- Adherence including reviewing the treatment card
- A follow-up sputum collected for AFB smear microscopy, especially at 2 months for any child who was sputum smear-positive at diagnosis

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

The NTP is responsible for organizing treatment in line with the Stop TB Strategy, and ensuring the recording and reporting of cases and their outcomes. Good communication is necessary between the NTP and clinicians treating children with TB. Adverse events noted by clinicians should be reported to the NTP.

High priority should be given to examining contacts who are children or people with HIV.

ISTC STANDARD **18**

All providers of care for patients with TB should ensure that persons who are in close contact with patients who have infectious TB 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 TB; 2) is at high risk of developing TB if infected; 3) is at risk of having severe TB if the disease develops; 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.[7]

Child Contact

Children who are newly infected with tuberculosis are at high risk for miliary TB and possibly meningitis, which can develop within weeks unless the child is given preventive therapy.

Close contact screening and management is recommended by most NTPs, but it rarely happens in low-resource settings where the majority of childhood TB occurs. For most child contacts, however, assessment can be a straightforward procedure that simply requires clinical evaluation[1] (see Appendix C: Implementing TB contact investigation).

Ideally, responsibility for contact tracing and subsequent management would reside with the same healthcare worker who registers and/or supervises the treatment of the source case. This would provide consistency, convenience for the household or family and enables the healthcare worker to better understand areas where support can be offered to improve adherence. Once screened and active TB ruled out, children recommended for IPT should be registered separately and have their own IPT card. Additionally, a prophylaxis register could be used to keep track of contacts that initiate IPT.

ISTC 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.[7]

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

Recommendations for management of child contacts (<5 years) to infectious PTB

Mantoux tuberculin skin test–positive children:

- If well, (child asymptomatic with normal CXR and growth parameters), offer IPT for 6–9 months
- If unwell, further evaluate for TB disease (see the section on Diagnosing TB in Children, pages 101–105)
- Provide treatment for disease if tuberculosis is evidenced

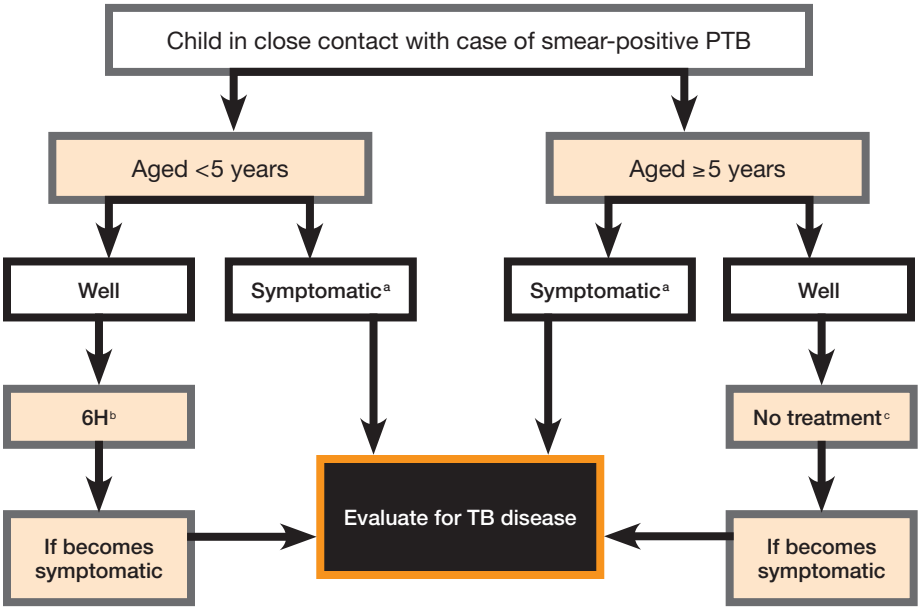
Mantoux tuberculin skin test–negative children:

If well (e.g., child asymptomatic with normal chest X-ray and growth parameters):

- Offer IPT for 2 months, then repeat the tuberculin skin test
- If positive at two months, continue IPT for a total of 6–9 months
- If negative at two months, discontinue IPT

FIGURE 5:

Approach to contact management when chest X-ray and Mantoux TST are not readily available



PTB = pulmonary tuberculosis; **H** = isoniazid; **TST** = tuberculin skin test; **HIV** = human immunodeficiency virus

a If TB is suspected, refer to the guidelines on diagnosis of childhood TB (pages 101–105).

b Isoniazid 10 mg/kg daily for 6 months

c Unless the child is HIV-infected (in which case isoniazid 5 mg/kg daily is indicated)

Source: Modified from Figure 1 in WHO Guidance for National Tuberculosis Programs on the Management of Tuberculosis in Children. 2006.

If unwell:

- Further evaluate for possible or probable disease, including a detailed history and physical exam (see the section on Diagnosing TB in Children, pages 101–105)
- Provide treatment for disease if tuberculosis is evidenced

When the Mantoux tuberculin skin test is not possible:

If well:

- Exclude active disease and provide IPT for 6 months (WHO recommendations)[1]
- Educate the caregiver to return with the child should the child become ill
- Initiate routine follow-up monthly while on IPT

If unwell:

- Obtain a history and physical examination for TB as well as a CXR (Figure 5 suggests a decision pathway algorithm for evaluation when Mantoux TST and CXR are not available)[1]
- Treat for tuberculosis if evidenced

Special Circumstances

Child contact is known to be HIV-infected[1]

If the child contact is HIV-infected and otherwise well, consider IPT for all ages, including those ≥5 years. As with other contacts, active disease should be ruled out, and only HIV-infected children who are healthy should be offered IPT. HIV-infected children who have symptoms should be carefully evaluated for TB, and if found to have TB disease, they should be referred to the NTP for registration and initiation of treatment.

Suspected HIV infection of source case and contact[1]

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

Child contacts of infectious multidrug-resistant tuberculosis (MDR-TB) cases[1]

The only chemoprophylaxis regimens to have been studied are based on INH, and to a lesser extent, rifampicin. Since by definition MDR-TB is resistant to both of these drugs, it is unlikely that using them to treat latent infection caused by an MDR-TB strain will prevent the development of active TB disease. Close contacts of MDR-TB patients should receive careful clinical follow-up for at least two years. If active disease develops, prompt initiation of treatment with a regimen designed to treat MDR-TB is recommended. On the basis of the currently available evidence, the WHO does not recommend second-line drugs for chemoprophylaxis in MDR-TB contacts.

Management of a baby born to a mother diagnosed with infectious PTB[1]

Once a pregnant woman has been on appropriate treatment for at least two–three weeks, she is generally considered no longer infectious. If a pregnant woman with TB has been on treatment for TB for several weeks before delivery, it is less likely that the baby will become infected. The risk is highest if a mother is diagnosed at the time of delivery or shortly thereafter. If a pregnant woman is found to have pulmonary TB shortly before delivery, then the baby, and if possible the placenta, should be investigated for evidence of congenital TB infection and, if found, the baby should be treated.

A breastfeeding infant has a high risk of infection from a mother with smear-positive PTB, and has a high risk of developing TB disease. In this situation, one of the following two actions should be taken:

- Provide the infant 6 months of IPT, followed by BCG immunization. Breastfeeding can be continued safely during this period; or
- Give the infant 3 months of IPT, then perform a TST
  - If the test is negative, INH should be stopped and BCG vaccination given[a]
  - If the test is positive, INH should be continued for another 3 to 6 months, after which it should be stopped and BCG given[a]

Immunizations

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

BCG Vaccination in Children

Bacille Calmette-Guérin (BCG) is a live attenuated vaccine derived from *Mycobacterium bovis*. In 2007, the WHO revised the BCG vaccination guidelines for infants at risk for HIV infection following a review of relevant data by the Global Advisory Committee on Vaccine Safety (GACVS). HIV Infection in infants is now a full contraindication to BCG vaccination.[20] WHO had previously recommended that in countries with a high TB burden, a single dose of BCG vaccine should be given to all healthy infants as soon as possible after birth, unless the child presented with symptoms suggestive of HIV infection.

Recent evidence shows that children who were HIV-infected when vaccinated with BCG at birth, and who later developed AIDS, were at increased risk of developing disseminated BCG disease.[21,22,23] Among these children, the benefits of potentially preventing severe TB are outweighed by the risks associated with the use of BCG vaccine. GACVS therefore advised WHO to change its recommendation such that children who are known to be HIV-infected, even if asymptomatic, should no longer be immunized with BCG vaccine.

However, there are a number of issues that must be considered by national programs in the implementation of the recommendations of GACVS. The following guidance has been provided to facilitate national and local decisions on the use of BCG vaccine in infants at risk for HIV infection:[24]

- In general, populations with high prevalence of HIV infection also have the greatest burden of TB; in such populations, HIV-uninfected children will benefit from the use of BCG vaccine
- Benefits outweigh risks for BCG vaccination for infants born to women of unknown HIV status. These infants should be immunized
- Benefits usually outweigh risks for BCG vaccination for infants whose HIV infection status is unknown and who demonstrate no signs or reported symptoms suggestive of HIV infection but who are born to known HIV-infected women

a BCG is contraindicated and should not be given to an infant known to be HIV-infected (see section on BCG Vaccination in Children)

- Risks outweigh benefits for BCG vaccination for infants who are known to be HIV-infected with or without signs or reported symptoms of HIV infection. **These infants should not be immunized**
- Risks usually outweigh benefits for BCG vaccination for infants whose HIV infection status is unknown but who have signs or reported symptoms suggestive of HIV infection and who are born to HIV-infected mothers. **These children should not be immunized.** However, this guidance can only be applicable to children who have not yet received BCG in the first few weeks of life, since clinical manifestations typically occur after 3 months of age

With the increasing availability of effective interventions to prevent vertical transmission of HIV from mother to child, the majority of HIV exposed infants are not infected and would therefore benefit from BCG vaccination. Maternal HIV antibodies are transferred to the infant *in utero* and can persist up to 18 months of age; the HIV antibody test may be positive although the infant is uninfected. Early infant diagnosis is limited by the availability of more expensive virological tests-HIV DNA PCR or HIV RNA PCR (viral load) or p24 antigen tests which can detect the presence of the HIV virus. In the Caribbean, these tests are becoming increasingly available and earlier infant diagnosis is possible. BCG may then be administered once HIV infection has been ruled out. WHO recommends that these virological tests are first performed at or around 6 weeks of age and this is often after BCG vaccination has already been administered.[25] Infant testing with HIV DNA PCR at 48 hours and two weeks of birth may be recommended to determine the HIV status in HIV exposed infants earlier. However, the sensitivity of a single HIV DNA PCR at 48 hours is only 38%.[26]

IUATLD BCG Working Group supports the revised WHO BCG vaccination policy, but recommends that current universal BCG immunization of infants continue in countries highly endemic for TB until countries have all programs in place for implementing selective deferral of HIV-exposed infants.[27] Successful implementation of a selective delayed BCG vaccination policy in HIV-exposed infants will require that the following conditions are met:

- High uptake of maternal HIV testing coupled with effective PMTCT strategies, including maternal ART
- Early virological diagnosis of HIV infection in infants coupled with institution of ART
- Coordination of PMTCT, vaccination and TB programs to minimize loss to follow-up; implement alternative TB preventive strategies; and deliver successful vaccination following selective non-vaccination at birth
- Improved surveillance of BCG adverse events in settings highly endemic for TB and HIV
- Research on improved TB preventive strategies in HIV-exposed and -infected infants; the safety and feasibility of delayed BCG vaccination strategies; BCG benefits in HIV-exposed non-infected infants and new vaccines that are effective and safe in immune-compromised children

In the Caribbean, the following factors will be important in the interpretation of the recommendations and national decisions on the use of BCG:

- National PMTCT programs are being scaled up and there are fewer infants being born with HIV infection- information on the coverage and efficacy of interventions to prevent MTCT of HIV
- The capacity for earlier infant diagnosis in the Caribbean is increasing

- The estimated HIV prevalence: this may be less than 2% in most countries
- TB prevalence in the country-which continues to be low in some Caribbean countries
- Capacity to conduct follow-up of immunized children; this is already part of existing EPI programs
- BCG is not given in all countries, and the use of BCG in a child that is not infected is dependent on the policy of the country

Because the prevalence of TB in most Caribbean countries is not high, the Expanded Program on Immunization recommendations are:

- **For the HIV exposed infant:** The child should not receive BCG until their HIV status is known. If the baby tests HIV negative then the baby can receive BCG vaccine. This requires a process for selective deferral of HIV-exposed infants in Caribbean countries where BCG is still given
- **For the HIV infected infant:** The child should not receive BCG vaccine regardless of the status of the baby (symptomatic or asymptomatic)

References

1. World Health Organization. Guidance for national tuberculosis programs on the management of tuberculosis in children. Geneva: World Health Organization, 2006 (WHO/HTM/TB/2006.371).
2. World Health Organization. Treatment of tuberculosis: Guidelines for national programs, Third Edition. Geneva: World Health Organization, 2003 (WHO/CDS/TB/2003.313).
3. World Health Organization. Guidance for national tuberculosis programs on the management of tuberculosis in children, "Introduction and diagnosis of TB in children" [Chapter 1]. Int J Tuberc Lung Dis 10(10):1091-1097. The Union, Stop TB Partnership Childhood TB Subgroup, Geneva: World Health Organization, 2006.
4. Marais BJ, Gie RP, Schaaf HS, et. al. The spectrum of disease in children treated for tuberculosis in a highly endemic area. Int J Tuberc Lung Dis 10(7):732-738. The Union, 2006.
5. Gie R. Diagnostic Atlas of Intrathoracic TB in Children, A Guide For Low Income Countries. 2003. Paris: International Union Against Tuberculosis and Lung Disease.
6. Cotton MF, Schaaf HS, Hesseling AC, Madhi SA. HIV and childhood tuberculosis: the way forward. Int J Tuberc Lung Dis 8(5):675–682. IUATLD, 2004.
7. Tuberculosis Coalition for Technical Assistance. International Standards for Tuberculosis Care (ISTC), second edition. Tuberculosis Coalition for Technical Assistance, The Hague, 2009.
8. World Health Organization. Integrated Management of Childhood Illenss. Management of the child with a serious infection or severe malnutrition. Guidelines for care at the first-referral level in developing countries. Geneva: World Health Organization, 2000 (WHO/FCH/CAH/00.1).
9. Centers for Disease Control and Prevention. Guidelines for Using the QuantiFERON®-TB Gold Test for Detecting Mycobacterium tuberculosis Infection, United States. Morbidity and Mortality Weekly Report 2005;54(No. RR-15):49-54.
10. World Health Organization. Guidance for National Tuberculosis Programs on the management of tuberculosis in children, "Anti-tuberculosis treatment in children" [Chapter 2]. *Int J Tuberc Lung Dis* 10(11), 2006:1205–1211. The Union, Stop TB Partnership Childhood TB Subgroup. Geneva: World Health Organization, 2006.
11. World Health Organization. WHO report on TB medicines for children. 8-9 July 2008. Geneva: World Health Organization, 2008. 1-22. Available at: www.who.int/selection_medicines/committees/subcommittee/2/TB.pdf.
12. World Health Organization. Stop TB Department and the Department of Child and Adolescent Health and Development of the World Health Organization. Ethambutol efficacy and toxicity. Literature review and recommendations for daily and intermittent dosage in children. Geneva: World Health Organization, 2006 (WHO/HTM/TB/2006.365).
13. World Health Organization. Treatment of Tuberculosis: Guidelines. Fourth Edition. Geneva: World Health Organization, 2009 (WHO/HTM/TB/2009.420).
14. World Health Organization. Guidance for National Tuberculosis Programs on the management of tuberculosis in children, "Management of TB in the HIV-infected child" [Chapter 3], Int J Tuberc Lung Dis 10(12):1331–133vx6. The Union, Stop TB Partnership Childhood TB Subgroup, Geneva: World Health Organization, 2006.

15. World Health Organization. Guidelines for cotrimoxazole prophylaxis for HIV-related infections in children, adolescents and adults in resource-limited settings. Recommendations for a public health approach. Geneva: World Health Organization, 2006. (www.who.int/hiv/pub/guidelines/en/index.html).

16. World Health Organization. Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access. Recommendations for a public health approach. Geneva: World Health Organization, 2006. (www.who.int/hiv/pub/guidelines/WHOpaediatric.pdf).

17. Shelburne SA, Hamill RJ, Rodriguez-Barradas MC, et al. Immune reconstitution inflammatory syndrome. Emergence of a unique syndrome during highly active antiretroviral therapy. Medicine 2002; 81: 213-27.

18. American Academy of Pediatrics. Tuberculosis. In: Pickering LK, Baker C J, Long SS, McMillan JA, eds. Red Book: 2006 Report of the Committee on Infectious Diseases. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2006: 678-698.

19. Donald P R, et al. Intensive short course chemotherapy in the management of tuberculous meningitis. Int J Tuberc Lung Dis 1998; 2:704–711.

20. World Health Organization. Revised BCG vaccination guidelines for infants at risk for HIV infection. Wkly Epidemiol Rec, 2007; 82:193–196.

21. Trunz B B, Fine P, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. Lancet 2006; 367: 1173–1180.

22. Fine P E M, Carneiro I A M, Milstien J B, Clements C J. Issues relating to the use of BCG immunization programmes—a discussion document. Geneva: World Health Organization, 1999 (WHO/V&B/99.23).

23. Hesseling A C, Marais B J, Gie R P, et al. The risk of disseminated bacille Calmette-Guérin (BCG) disease in HIV-infected children. Vaccine 2007; 25:14–18.

24. Global Advisory Committee on Vaccine Safety. Meeting of the Global Advisory Committee on Vaccine Safety, 29–30 November, 2006. Wkly Epidemiol Rec 2007; 82:18–24.

25. World Health Organization. Report of the WHO Technical Reference Group, Pediatric HIV/ART Care Guideline Group Meeting, WHO HQ, Geneva, Switzerland, April 10-11, 2008, http://who.int/hiv/pub//paediatric/WHO_Paediatric_ART_guideline_rev_mreport_2008.pdf (accessed October 9, 2009).

26. Dunn DT, Brandt CD, Kirvine A, et al. The sensitivity of HIV-1 DNA polymerase chain reaction in the neonatal period and the relative contributions of intra-uterine and intra-partum transmission. AIDS, 1995. 9(9):F7-11. www.ncbi.nlm.nih.gov/pubmed/8527070.

27. Hesseling AC, Cotton MF, Fordham von Reyn C, Graham SM, Gie R, Hussey GD. Consensus statement on the revised World Health Organization recommendations for BCG vaccination in HIV-infected infants. Int J Tuberc Lung Dis 12(12):1376-1379, 2008.

Drug-resistant Tuberculosis 11

This chapter outlines the basic principles for addressing drug resistant (including MDR/XDR) TB and is intended to serve as a brief overview. References to sources of more detailed information are provided throughout. For more comprehensive information on MDR-TB (with or without HIV infection, pediatric and other special populations) refer to the WHO publication *Guidelines for the programmatic management of drug-resistant tuberculosis (WHO/HTM/TB/2008.402)*. It is strongly recommended that expert consultation be sought when undertaking the treatment and management of MDR and XDR-TB.[1,2]

In countries where drug resistance has been identified, the NTP must undertake specific measures to identify and address areas of practice or program weakness in order to prevent the propagation and dissemination of drug-resistant TB, including MDR-TB. Obtaining DST results for every patient, well-administered first-line treatment for susceptible cases, and full implementation of DOTS are the best prevention against chronic disease and extension of MDR-TB.[2]

Definitions

Anti-tuberculosis drug resistance is classified as follows:

- **Mono-resistance:** isolates of *M. tb* confirmed to be resistant *in vitro* to one first-line anti-tuberculosis drug
- **Poly-resistance:** isolates are resistant *in vitro* to more than one first-line anti-tuberculosis drug other than both isoniazid and rifampicin
- **Multidrug-resistant TB (MDR-TB):** isolate with *in vitro* resistance to at least isoniazid and rifampicin
- **Extensively Drug-resistant TB (XDR-TB):** *In vitro* resistance to at least isoniazid and rifampicin (i.e., MDR-TB) plus resistance to any fluoroquinolone and any one of the second-line anti-tuberculosis injectable drugs (kanamycin, amikacin or capreomycin)

Background

MDR-TB can occur in new cases, although it occurs more frequently in re-treatment cases, especially in those who are treatment failures. Worldwide, 15% of previously treated patients have MDR,[3] whereas the global average of MDR-TB in new patients is 3%.[2] MDR-TB is one of the main causes of treatment failure in new cases treated under strict DOT.

ISTC 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 (see Table 13), culture and testing for susceptibility 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.[4]

Drug resistance is largely man-made and is a consequence of suboptimal regimens and treatment interruptions. **Clinical errors** that commonly lead to the emergence of drug resistance include:[4,5]

- Failure to provide effective treatment support and assurance of adherence
- Failure to recognize and address patient nonadherence
- Inadequate drug regimens
- Failure to recognize existing drug resistance
- Adding a single new drug to a failing regimen

In addition, **co-morbid conditions** associated with reduced serum levels of anti-TB drugs (e.g., malabsorption, diarrhea, HIV infection, or use of antifungal agents) may also lead to the acquisition of drug resistance.[5]

Programmatic causes of drug resistance include:

- Drug shortages and stock-outs
- Administration of poor-quality drugs
- Lack of appropriate supervision to prevent erratic drug intake

The strongest factor associated with drug resistance is previous anti-tuberculosis treatment. In previously treated patients, the odds of any resistance are at least fourfold higher, and that of MDR-TB at least tenfold higher than in new (untreated) patients.[3]

Patients who fail treatment (i.e., sputum-positive after five months of treatment) are at highest risk of having MDR-TB, especially if rifampicin was used throughout the course of treatment.[3]

Persons who are in close contact with confirmed MDR-TB patients, especially children and HIV-infected individuals, also are at high risk of being infected with MDR strains. In some closed settings, prisoners, persons staying in homeless shelters, and certain categories of immigrants and migrants are at increased risk of MDR-TB.[3,6]

Identifying Drug Resistance

Although drug-resistant TB in the Caribbean exists, the true burden in CMCs is unknown, as the means for systematic surveillance has not yet been established. From 1999–2005, drug-resistant tuberculosis cases were identified in at least 6 of the 21 member countries. Resistance to isoniazid was reported in 5 CMCs, and MDR-TB in 4 of these countries.[7]

Drug-resistant TB must be diagnosed correctly before it can be treated effectively. DST should be prioritized for patients with risk factors for drug resistance. This includes TB patients:

- With a history of previous anti-tuberculosis treatment (patients who have failed treatment, especially those who have failed a standardized re-treatment regimen, and chronic cases are the highest priority)
- Known to have been in close contact with persons confirmed to have MDR-TB
- Known to have had contact with a patient who died of TB while under treatment
- With HIV infection, given the high mortality rates in persons with MDR and XDR-TB and HIV infection[5,8]

Management Principles

The main priority for TB control is the identification and cure of sputum smear-positive pulmonary TB cases. The decision to use second-line regimens (reserve anti-tuberculosis drugs) should thus be based on:[9]

- The availability of additional financial resources for reserve drugs
- The capacity of the NTP to maintain patients on regular treatment
- Access to a laboratory that can perform high-quality drug susceptibility testing
- Prevention of uncontrolled use of reserve drugs
- Special registration of MDR-TB cases and expert committee(s) for decisions on treatment and monitoring
- Special cohort analysis

Without an effective organizational framework, such as the one suggested in the Stop TB Strategy, and without knowledge of the operational requirements of treatment with reserve regimens, the chances of success will be minimal.[5,9]

Second-line drugs are more expensive and have greater toxicities associated with their use than do the first-line drugs. Therefore, many programs will choose to hospitalize the patient to enable closer monitoring and follow-up, at least for the initial phase of therapy. After tolerance of the drug regimen has been ascertained and the patient's cooperation has been secured, the patient can be started on ambulatory treatment.[9] The drawback with hospitalization, however, is the increased risk of nosocomial transmission of MDR-TB to both staff and patients, especially those infected with HIV. Infection control must be addressed in settings where patients with suspected or confirmed MDR-TB will be hospitalized.[4]

Programs with strong home-based care, well-trained visiting healthcare workers, and/or capable healthcare centers may choose to have ambulatory treatment from the outset.[1,9] Ambulatory treatment reduces the cost and the risk of MDR-TB transmission in hospitals, which often lack adequate infection control capacity.[9]

Infection control must be addressed in settings where patients with suspected or confirmed MDR-TB will be hospitalized.

Treatment Principles

Although the goals for treatment of MDR and XDR-TB are similar to those of all other TB cases, achieving successful treatment outcomes is much more difficult, given the need to use less effective and more toxic drugs for a substantially longer time. Experience and dedicated resources are required to successfully manage and treat patients with MDR-TB. An appropriate treatment strategy must be in place for use of reserve (second-line) drugs under proper management conditions.

ISTC 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 18–24 months beyond culture conversion. Patient-centered measures, including observation of treatment, are required to ensure adherence. Consultation with a provider experienced in treatment of patients with MDR/XDR tuberculosis should be obtained.[4]

Current treatment recommendations for MDR-TB patients are based on observational studies, general microbiological and therapeutic principles, extrapolation from available evidence from pilot MDR tuberculosis treatment projects, and expert opinion.[10,11]

The WHO recommends two strategic options for treatment of MDR-TB:

- Standard regimen (standardized approach); or
- Individualized regimen based on DST results

Determining which strategic option is most appropriate for the NTP and for the individual patient depends in part on the type of laboratory method available to confirm MDR-TB (i.e., rapid molecular or conventional methods). The basic principles involved in the design of an MDR treatment regimen include:[1,2,4]

- The use of at least four drugs with either certain or highly likely effectiveness
- Include drugs from Groups 1–5 in a hierarchical order based on potency (Table 24)
  - Use any Group 1 (first-line) likely to be effective
  - Use an effective Group 2 injectable drug[a]
  - Use a Group 3 fluoroquinolone
  - Use the remaining Group 4 drugs to complete a regimen of at least 4 effective drugs (total number drugs based on degree of uncertainty of effectiveness/ extent of resistance and extent of disease; regimens often contain 5–7 drugs)
  - For regimens with fewer than 4 effective drugs, consider adding two Group 5 drugs

a Avoid streptomycin even if DST suggests susceptibility because of high rates of resistance with drug-resistant TB strains, patient is likely to have received this drug in the past, and because of higher incidence of ototoxicity.[2]

- Avoid using drugs for which there is the possibility of cross resistance (see Table 22 on cross resistance)
- Eliminate drugs that are not safe (quality of drug is unknown or unable to safely monitor)

- Drug administration at least six days a week with each dose given by DOT
- Drug dosage determined by patient weight
- The use of an injectable agent (an aminoglycoside or capreomycin) during the initial phase (for at least six months after culture conversion)
- Treatment duration of 18–24 months beyond culture conversion

TABLE 22.

Cross-resistance for anti-tuberculosis drugs

Drug	Cross-Resistance	Comments
Isoniazid	**Ethionamide**	Cross-resistance to ethionamide may occur when there is low-level resistance to isoniazid.
Rifampin	**Rifamycins**	Cross-resistance among the rifamycin class of drugs is typical. In a few strains that are resistant to rifampin, rifabutin may retain susceptibility *in vitro*.
Ethambutol	**None**	
Pyrazinamide	**None**	
Streptomcyin	**None**	
Amikacin	**Kanamycin**	High likelihood of cross-resistance since it is associated with the same mutation.
Kanamycin	**Amikacin**	High likelihood of cross-resistance since it is associated with the same mutation.
Capreomycin	**Amikacin/Kanamycin**	Variable frequency of cross resistance has been reported.
Fluoroquinolones	**Other fluoroquinolones**	In general, there is a complete class effect cross-resistance among fluoroquinolones *in vitro*. However, data suggest that moxifloxacin may continue to demonstrate some activity despite *in vitro* resistance to ofloxacin.
Cycloserine	**None**	
PAS	**None**	
Ethionamide	**Isoniazid**	Cross-resistance to isoniazid may occur when there is low-level resistance to ethionamide.
Clofazimine	**None**	

Source: Francis J. Curry National Tuberculosis Center. Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 2nd ed., 2008.

Standard Regimen Approach

In countries where DST is not readily available and may take months before results return to confirm or exclude MDR-TB, an empiric treatment regimen (see examples in Table 23) will be required, at least initially, for patients with a high likelihood of MDR (e.g., those whose prior treatment has failed).[2] Once MDR is confirmed, the regimen may be continued (use of standard regimen), or may be tailored (individualized) on the basis of susceptibility to drugs other than isoniazid and rifampicin.

Advantages of standardized treatment regimens include:

- Facilitates standard approach to treatment for suspect MDR-TB despite limitations in laboratory technical capacity in country
- Easier operational implementation (estimation of drug needs, purchasing, distribution, training personnel on how to treat MDR-TB, etc.)

Empiric and Standard regimens should be based on representative drug-resistance surveillance data or on the history of drug usage in the country.[2] In selecting the country's standard MDR regimen, NTP managers are strongly urged to seek expert consultation and to review planned regimens.[2,5]

A standardized approach is useful in settings where second-line drugs have not been used extensively and, consequently, where resistance levels to these drugs are low or absent. In patients who fail the standardized regimen, second-line DST should be obtained and expert consultation sought.

Individualized Treatment Regimens

Individually designed regimens are based on the patient's history of past drug use and DST to isoniazid, rifampicin, the second-line injectable agents, and a fluoroquinolone. Every effort should be made to verify prior treatment (drug regimen, administration method and adherence) with objective records from previous healthcare providers. A detailed clinical history can help suggest which drugs are likely to be ineffective. As a general rule, if a patient has used a drug for over a month with persistently positive smears or cultures, the strain should be considered as "potentially resistant" to that drug, even if by DST it is reported as susceptible.[2] This is not to say that resistance cannot develop in times shorter than one month.

DST results should complement rather than invalidate other sources of data about the likely effectiveness of a specific drug. For example, if a history of prior anti-tuberculosis drug use suggests that a drug is likely to be ineffective, this drug should not be relied on as one of the four core drugs in the regimen, even if the strain is susceptible by DST.[2] Alternatively, if the strain is resistant to a drug by DST, but the patient has never taken the drug and resistance to it is extremely uncommon in the community, this may be a case of a laboratory error or a result of the limited specificity of DST for some second-line drugs.[a]

Another important pitfall is that due to the turnaround time necessary for DST, the patient may have already received months of treatment by the time DST results become available from the laboratory. The possibility of further acquired resistance during this time must be considered. If there is a high probability of acquired resistance to a drug after the specimen for DST was collected, this drug should not be counted as one of the four drugs in the core regimen, but can be included as an adjunctive agent.[2]

a Since a fluoroquinolone and an injectable agent form the backbone of MDR treatment, they should be used even if the patient's *M. tuberculosis* demonstrates resistance to all available drugs in these two classes[3,4]

TABLE 23.

Treatment regimens for the management of patients with multidrug-resistant TB

Pattern of Drug Resistance	Suggested Regimen	Minimum Duration of Treatment	Comments
INH and RIF (± SM)	PZA, EMB, FQN, injectable agent ± another second-line agent.	18–24 months beyond culture conversion	Extended treatment is necessary to lessen the risk of relapse.
INH, RIF (± SM), and EMB or PZA	FQN, (EMB or PZA if available), injectable agent, plus 2 other second-line agents.	18–24 months beyond culture conversion	Consider surgery. Consider high-dose INH treatment if low-level resistance is documented.
INH, RIF, EMB, PZA (± SM)	FQN, injectable agent, 3 other second-line drugs	24 months beyond culture conversion	Consider surgery. Consider high-dose INH treatment if low-level resistance is documented.
INH, RIF, EMB, PZA, FQN	3 second-line drugs, an injectable agent, plus consider third-line agent.	24 months beyond culture conversion	Consider surgery. Consider high-dose INH treatment if low-level resistance is documented.
INH, RIF, EMB, PZA, injectables	FQN, 3 other second-line drugs, ± additional third-line agents. Include an injectable drug if there is one available to which the isolate is susceptible.	24 months beyond culture conversion	Surgery should be performed if possible. Consider high-dose INH treatment if low-level resistance is documented.
INH, RIF, FQN injectable	EMB, PZA, 3 second-line drugs ± additional third-line agent. Include an injectable drug if there is one available to which the isolate is susceptible.	24 months beyond culture conversion	Surgery should be performed if possible. Consider high-dose INH treatment if low-level resistance is documented
INH, RIF, EMB, FQN, injectable	PZA, 3 second-line drugs, plus a third-line agent. Include an injectable drug if there is one available to which the isolate is susceptible.	24 months beyond culture conversion	Surgery should be performed if possible. Consider high-dose INH treatment if low-level resistance is documented
INH, RIF, PZA, FQN, injectable	EMB, 3 second-line drugs, plus a third-line agent. Include an injectable drug if there is one available to which the isolate is susceptible.	24 months beyond culture conversion	Surgery should be performed if possible. Consider high-dose INH treatment if low-level resistance is documented
INH, RIF, EMB, PZA, FQN, injectable	3 second-line drugs, plus 2-3 third-line agents. Include an injectable drug if there is one available to which the isolate is susceptible.	24 months beyond culture conversion	Surgery should be performed if possible. Consider high-dose INH treatment if low-level resistance is documented

Source: Francis J. Curry National Tuberculosis Center. Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 2nd ed., 2008.

When available, centers of excellence, to which patients may be referred for treatment, could utilize individualized regimens tailored to the drug susceptibility pattern of the patient. Referral to such facilities may also be the best option for patients whose cooperation is not easy to achieve, such as individuals suffering from alcoholism or drug dependence, prisoners, and homeless persons. Special efforts are needed to persuade such patients to complete the long and arduous treatment regimens required.

Current WHO recommendations for treatment of MDR-TB can be found at (www.who.int/tb/en/). MDR-TB treatment is a complex health intervention, and medical practitioners are strongly advised to consult colleagues experienced in the management of these patients.[4,5]

Reserve Anti-tuberculosis Drugs

Reserve drugs (commonly referred to as second and third-line drugs) are most useful for treating MDR and XDR-TB cases. The WHO *Guidelines for the Programmatic Management of Drug-resistant Tuberculosis (2006)* introduced a group system based on efficacy, experience of use and drug class that is very useful when describing the design of MDR and XDR-TB treatment regimens. These groups are referred to in Table 24 which lists the drugs under each group, their mode of action, dosage, and notes other special considerations and monitoring required (Group 1 drugs are not listed in Table 24 but include the oral first-line anti-tuberculous agents described in Table 5, Chapter 7). Not all drugs in the same group have the same efficacy or safety. More information on each drug is available in Annex 1 of WHO's *Guidelines for the Programmatic Management of Drug-resistant Tuberculosis, Emergency Update 2008* (http://whqlibdoc.who.int/publications/2008/9789241547581_eng.pdf)[5] and in Chapter 4 of the Francis J. Curry National Tuberculosis Center and California Department of Public Health, 2008: *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, Second Edition* (www.nationaltbcenter.ucsf.edu/drtb).[1]

The Green Light Committee and the global response to MDR-TB

In designing the country's MDR treatment component and integrating it into the national program, NTP managers are strongly encouraged to make full use of the Green Light Committee. The Green Light Committee is a subgroup of the MDR-TB Working Group of the Stop TB Partnership, and an advisory body of WHO that promotes access to quality-assured, life-saving MDR-TB treatment, and ensures and monitors its use to protect against incurable TB.[2] A well-functioning DOTS program is a prerequisite for Green Light Committee endorsement and for continuation of their support. (www.who.int/tb/challenges/mdr/greenlightcommittee)

Through the Green Light Committee Initiative, NTPs may have access to:

- Expertise in programmatic management of drug-resistant TB based on best available evidence and collective experience
- High-quality drugs to treat drug-resistant TB at concessional prices
- Support through a wide network of technical partners
- Peer support and knowledge-sharing with other Green Light Committee -approved programs; and
- Independent external monitoring and evaluation

TABLE 24.

Reserve anti-tuberculosis drugs by drug group

Drug (Abbreviation)	**Recommended Daily Dosage**[a]			**Special Considerations and Monitoring**
	Average (mg/kg)	**Children** (mg/kg)	**Max** (mg/day)	
Group 2 – Injectable agents (bactericidal)				
kanamycin (Km)	(15)[a]	(15-30)[a]	1000[a]	Adjust dose and frequency for renal insufficiency and age >59 Monitor creatinine, electrolytes and vestibular function monthly Obtain baseline and monthly audiology exam
amikacin (Am)	(15)[a]	(15-30)[a]	1000[a]	
capreomycin (Cm)	(15)[a]	(15-30)[a]	1000[a]	
streptomycin (S)	(15)[a]	(20-40)[a]	1000[a]	
Group 3 – Fluoroquinolones (bactericidal)				
ofloxacin (Ofx)	400 bid[b] (15-20)[b]	(15-20)[c]	800 - 1000[b]	Adjust dose and frequency for renal insufficiency Maximum daily dose for children is 800mg
levofloxacin (Lfx)	750-1000[b]	(15-20)*[a]	1000[b]	Adjust frequency for renal insufficiency *younger children: divide daily dose in two
moxifloxacin (Mfx)	400[b] (7.5-10)	(7.5-10)[c]	400[b]	Symptom-based monitoring; may cause QTc prolongation
Group 4 – Oral bacteriostatic				
cycloserine (Cs)	500-750[a] (10-15)[a]	(10-20)[a]	1000[a]	Children: divide daily dose in two every 12 hr. Check serum peak concentration 1-2 weeks after initiation (desired peak = 20-30mcG/ml)
ethionamide (Eto) **protionamide** (Pto)	500-750[a] (15-20)[a]	(15-20)[a,c]	1000[a]	Divide daily dose into two or three; slowly increase to target dose over several days Monitor TSH and liver function Avoid during pregnancy
***p*-aminosalycilic acid** (PAS)	8-12g[a] (150)[b]	(200-300)[a]	12g	Divide daily dose into two or three; slowly increase to target dose over several days Monitor TSH, electrolytes, liver function, CBC
Group 5 – Agents with unclear efficacy (not recommended by WHO for routine use in MDR-TB patients)				
clofazimine (Cfz)	100-300[a]		300[a]	Some clinicians begin at 200-300 mg daily and decrease to 100 mg after 4 to 8 weeks. Use with caution in patients with severe hepatic insufficiency
linezolid (Lzd)	600[a]	(10)[a] every 8 hours	600	Give with pyridoxine Monitor for peripheral neuropathy & optic neuritis Monitor CBC weekly initially then monthly
amoxicillin/clavulanate (Amx/Clv)	2000/125[a]	(80)[a] divided 2x/d		Dose twice daily Adjust dose and frequency for renal insufficiency
Imipenem (Ipm) **Cilastatin** (Cln)	Usual adult dose is 500–1000 mg IV every 6 hours.[b]			
High-dose INH	(16-20)‡[b]	(20-30)‡[a]	1500 3x/wk	Monitor liver function monthly Give with pyridoxine ‡Dosing is twice or thrice weekly (900-1500mg)[a]

a Francis J. Curry National Tuberculosis Center. Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 2nd ed., 2008

b WHO's Guidelines for the Programmatic Management of Drug-resistant Tuberculosis, Emergency Update 2008

c WHO Guidance for national tuberculosis programmes on the management of tuberculosis in children, 2006[12]

Monitoring the MDR/XDR-TB Patient[2]

Patients with MDR- or XDR-TB must be monitored closely throughout treatment. Sputum smears and cultures should be performed monthly until both become consistently negative (conversion). Conversion is defined as two consecutive negative smears and cultures taken 30 days apart and is a key marker for assessing response to treatment. Once conversion is documented, sputum monitoring at a minimum should continue monthly for smears and quarterly for cultures until completion of treatment. Patients with MDR or XDR-TB should be seen and evaluated by a clinician at least monthly until sputum conversion, then every 2-3 months throughout treatment. Weight should be documented monthly until stable. This is particularly important for those patients presenting with significant weight loss at the time of TB diagnosis as weight gain may signify clinical response early in the course of treatment for these patients.

Reserve drugs have many more adverse effects than the first-line anti-tuberculosis drugs, but management of these adverse effects is possible. Screening for medication side effects should occur at every DOT and clinician encounter. Patients should be aware of and understand the possible side effects, have access to clinical and laboratory services to help detect side effects, and access to medications to treat adverse effects when they occur (see Table 24 for recommended toxicity monitoring of the reserve drugs). Prompt management of adverse effects caused by reserve drugs is essential for successful treatment of MDR and XDR-TB.

Considerations for Contacts of MDR-TB Index Cases

The only chemoprophylaxis regimens to have been studied are based on isoniazid, and to a lesser extent, rifampicin. Since by definition, MDR-TB is resistant to both of these drugs, it is unlikely that use of these drugs to treat latent infection caused by an MDR-TB strain will prevent the development of active TB disease.[5,a]

In addition to the lack of evidence related to the efficacy of non-isoniazid- and rifampicin-based regimens for preventing TB progression in patients with LTBI, there are no tests currently available to determine the susceptibility profile of the infecting strain in contacts found to have a positive Mantoux. Contacts of MDR-TB patients in whom latent infection is newly diagnosed may be infected with isoniazid-susceptible strains, particularly in high-burden areas where many different strains of TB may circulate in the community. Studies from high-burden TB areas have shown that approximately one-half to two-thirds of household members had the same strain of TB, as determined by genetic testing. (The degree of strain concordance could be higher in contacts who are children under 5 years of age because they have less exposure to strains circulating outside the household.)[13,14,15]

Close contacts of MDR-TB patients should receive careful clinical follow-up for a period of at least two years. If active disease develops, prompt initiation of treatment with a regimen designed to treat MDR-TB is recommended, and culture and drug susceptibility testing should be expedited to confirm or rule-out MDR-TB.[5]

On the basis of the currently available evidence, WHO does not recommend the universal use of second-line drugs for chemoprophylaxis in MDR-TB contacts;[5] however, treatment may be indicated in certain high risk situations. For persons who are likely to be infected with an MDR-TB strain (isoniazid- and rifampicin-resistant) and who are at high risk for

a Tuberculin skin tests become positive in most patients infected with TB irrespective of whether the strain is susceptible or resistant

developing TB, pyrazinamide and ethambutol or pyrazinamide and a fluoroquinolone (i.e., levofloxacin or moxifloxacin) for 6–12 months may be considered.[1] Close monitoring for hepatitis should occur if treating such contacts with a two-drug regimen that includes pyrazinamide. Contacts who are immune-compromised (e.g., HIV-infected persons) should be treated for 12 months. It is advisable in these situations to **consult with a clinician familiar with the treatment and management of MDR-TB.**[1]

References

1. Francis J. Curry National Tuberculosis Center. Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, Second Edition. Francis J. Curry National Tuberculosis Center and California Department of Public Health, 2008.
2. World Health Organization. Treatment of Tuberculosis: Guidelines. Fourth Edition. Geneva: World Health Organization, 2009 (WHO/HTM/TB/2009.420).
3. WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance, World Health Organization. Stop TB Dept. Anti-tuberculosis drug resistance in the world: Fourth global report. Geneva: World Health Organization; 2008 (WHO/HTM/TB/2008.394).
4. Tuberculosis Coalition for Technical Assistance. International Standards for Tuberculosis Care (ISTC), second edition. Tuberculosis Coalition for Technical Assistance, The Hague, 2009.
5. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency update 2008. Geneva: World Health Organization, 2008 (WHO/HTM/TB/2008.402).
6. Caminero JA. Likelihood of generating MDR-TB and XDR-TB under adequate National Tuberculosis Control Programme implementation. Int J Tuberc Lung Dis 2008;12(8):869-77.
7. CAREC Surveillance Report. Vol. 26, No. 3. Oct. 2006.
8. Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet 2006;368(9547): 1575-80.
9. World Health Organization. Treatment of Tuberculosis: Guidelines for National Programs, Third Edition. Geneva: World Health Organization, 2003 (WHO/CDS/TB/2003.313).
10. Caminero JA. Management of multidrug-resistant tuberculosis and patients in retreatment. Eur Respir J 2005;25(5):928–36.
11. Mukherjee JS, et al. Programs and principles in treatment of multidrug-resistant tuberculosis. Lancet 2004;363(9407):474–81.
12. World Health Organization. Guidance for national tuberculosis programs on the management of tuberculosis in children. Geneva: World Health Organization, 2006 (WHO/HTM/TB/2006.371).
13. Verver S, et al. Proportion of tuberculosis transmission that takes place in households in a high-incidence area. Lancet, 2004, 363(9404):212–214.
14. Schaaf HS, et al. Evaluation of young children in household contact with adult multidrug-resistant pulmonary tuberculosis cases. Pediatric Infectious Disease Journal, 1999, 18(6):494–500.
15. Steiner P, Rao M. Drug-resistant tuberculosis in children. Seminars in Pediatric Infectious Diseases, 1993, 4:275–282.

12 Monitoring and Evaluation

Establishing a reliable monitoring and evaluation system is one of the key elements of pursuing high quality DOTS within the Stop TB Strategy.[1] Such a system is useful not only to monitor progress and treatment outcomes of individual patients, but also to evaluate the overall performance of tuberculosis control programs at the local, national, and global levels, and to indicate programmatic weaknesses.[1] A monitoring and evaluation system:

- Allows for targeted, individualized follow-up to help patients who are not making adequate progress (i.e., failing therapy)[2]
- Allows for evaluation of the performance of the practitioner, the hospital or institution, local health system, and the country as a whole[3]
- Ensures accountability[3]

Monitoring refers to the *routine* tracking of services and program performance.[4] Monitoring is conducted to assess to what extent a policy or program is achieving its intended target(s).

Evaluation is the *episodic* assessment of results that can be attributed to program activities.[4] There are many methods of evaluation; however, the more common types utilized in NTPs and related project activities generally fall into two categories:

- **Process evaluation** which assesses the progress in program implementation and coverage[4]
- **Outcome and impact evaluation** which measures the effect of the program activity on the target population[4]

Indicators

An indicator is a variable used to measure progress towards a goal, objective or target of the program.[4] Table 25 lists the standard selection criteria for judging the relevance of specific indicators.

Apart from routine monitoring, indicators can be used to:

- Assess the priorities and effectiveness of the Stop TB Strategy
- Compare program performance across and between countries
- Negotiate on policy with interested parties

TABLE 25.

Criteria for indicator selection[a]

Valid	Indicators should measure the condition or event they are intended to measure
Reliable	Indicators should be objective and produce the same results when used more than once to measure the same condition or event, all things being equal (for example, using the same methods/tools/ instruments)
Specific	Indicators should measure only the condition or event they are intended to measure
Sensitive	Indicators should reflect changes in the state of the condition or event under observation
Operational	Indicators should be measured with definitions that are developed and tested at the program level and reference standards
Affordable	The costs of measuring the indicators should be reasonable
Feasible	It should be possible to carry out the proposed data collection under normal program conditions
Measurable	Indicator can be objectively measured
Comparable	Indicators should be comparable over time and across different geographical sites

Source: Table 2 from WHO A Guide to Monitoring and Evaluation for Collaborative TB/HIV Activities. Field Test Version, 2004.[4]

Table 26 includes a list of key TB control indicators that make up a minimum set of M & E indicators for assessing the performance of an NTP. Many of these indicators are process-level indicators that measure the development and implementation of the expanded Stop TB Strategy as well as important program outcomes.

Using and disseminating data:

Monitoring and evaluation systems are worthwhile only if the information collected is used. The following are some points for sharing results of monitoring and evaluation:

- Improve performance and programming
- Increase public awareness about TB
- Encourage communities to support TB patients
- Improve coordination among agencies working with TB
- Advocate for policy changes
- Encourage allocation of resources to TB control

a Tuberculin skin tests become positive in most patients infected with TB irrespective of whether the strain is susceptible or resistant.

TABLE 26:

Key TB Control Indicators

Indicators for Global Reporting

- TB case detection rate
- Treatment success rate
- DOTS coverage
- Surveillance of multidrug-resistant TB
- HIV seroprevalence among TB patients

Indicators for Program Outcomes

- New adult smear-positive cases

Political Commitment

- National TB policy
- National TB program manual
- NTP medium-term development plan and budget
- NTP annual work plan and budget
- National TB control policy addresses links between TB and HIV

Diagnosis and Laboratories

- Existence of comprehensive laboratory network
- TB microscopy units submitting slides for rechecking

Case Management and Treatment

- Patients under direct observation of therapy

Drug Management

- Existence of a quality assurance system for drug management
- Anti-TB drugs meeting international minimum quality standards
- Existence of buffer stock at central, regional, or district-level facility

Recording and Reporting

- Completeness of reporting to NTP

Supervision

- Supervision of DOTS implementation
- Existence of supervision guidelines

Human Resources Development

- TB microscopy units with at least one laboratory technician trained in AFB microscopy
- Health care units with at least one health care professional trained in TB case detection and treatment

Health Systems

- Equitable distribution of DOTS

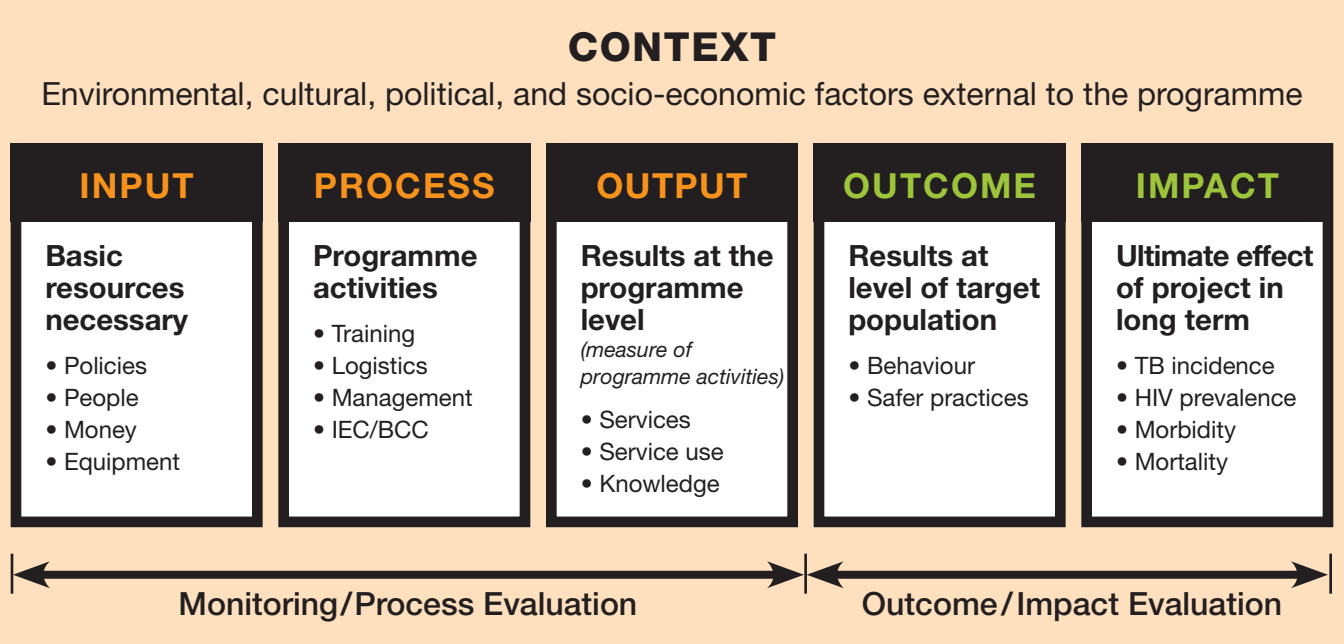
Source: Adapted from WHO. Compendium of Indicators for Monitoring and Evaluating National Tuberculosis Programs, 2004.[5]

M&E Framework and Components[4]

The elements of monitoring and evaluation described above are brought together into a framework (Figure 6). This framework is a visual concept of how the various program or project elements fit together to achieve monitoring and evaluation information.

FIGURE 6:

Monitoring and evaluation framework



IEC = Information, Education, Communication; **BCC** = Behavior Change Communication

Source: Adapted from WHO. A Guide to Monitoring and Evaluation for Collaborative TB/HIV Activities, 2004.

For a program or project to achieve its goals, **inputs**, such as money, staff time and policies, must result in **outputs**, such as drug stocks and supply systems, new or improved services, or trained staff. These outputs are often the result of specific **processes**, such as training sessions for staff, which are key activities aimed at achieving the outputs. If these outputs are well designed and reach the populations for which they were intended, the program or project is likely to have positive short-term effects or **outcomes**, such as an increased number of people with HIV screened for TB symptoms, or of TB patients tested for HIV. These positive short-term outcomes should lead to changes in the longer-term **impact** of programs, reflected in fewer new cases of TB or HIV.

A strong monitoring and evaluation system has three components:

1. A monitoring and evaluation plan (M&E Plan) at the level of the ministry
2. A data management unit
3. Data collection and reporting systems

The Monitoring and Evaluation (M&E) Plan

The M&E Plan should identify how the NTP goals and objectives relate to the country's national health strategy and M&E Plan. The plan should include:

- Indicators selected
- Data sources and methods of data collection
- Target-setting
- Availability of baselines
- Description of how data will be disseminated and results utilized
- Provisions for ensuring confidentiality of sensitive data
- Budget amount allocated to M&E

Data Management

Management of data systems is essential to M&E. Processes must be in place to ensure that the information collected adequately represents the program's activities. This requires training, sufficient oversight, guidance, and support to staff at the various levels where data is collected, analyzed and reported. Ideally, a comprehensive M&E unit would coordinate these activities providing a coherent system within the Ministry of Health that allows sharing of data and reporting across disease specific programs. Table 27 lists some of the elements successful M&E systems have in common.

Data Collection and Reporting System

Collection of data occurs at the level of service delivery. Most program areas associated with the delivery of health services can be grouped depending on whether services are delivered in a health facility or in the community. Data collected must be *accurate* (measuring what we intend to measure) and *reliable* (collected and measured in the same way by all program personnel over time). This allows for meaningful interpretation of the data later on when data is analyzed and reported.

To ensure the same information is being collected in each location, data collection forms and instructions for completing the forms must be standardized and staff responsible for their use must be trained. In 2006, the Stop TB Department of the WHO completed a revision process to align the WHO TB forms and registers to the new Stop TB Strategy (available to download at: www.who.int/tb/dots/r_and_r_forms/en/index.html).[7] These updated forms facilitate the monitoring of the Stop TB Strategy components.

Reporting tuberculosis cases to the local tuberculosis control program is an essential public health function, and in many countries is legally mandated. Ideally, the reporting system design, supported by a legal framework, should be capable of receiving and integrating data from several sources, including laboratories and healthcare institutions, as well as individual practitioners.

ISTC STANDARD 21

All providers must report both new and re-treatment TB cases and their treatment outcomes to local public health authorities, in conformance with applicable legal requirements and policies.[3]

TABLE 27:

Features of a good M&E System

M&E Unit	• An established M&E unit within the Ministry of Health with designated technical and data management staff. This unit should, among other things, coordinate M&E efforts across the three disease areas (HIV/AIDS, TB, and malaria), regardless of where individual disease-specific M&E is housed • A budget for M&E that is between 5 and 10% of the combined national HIV/AIDS, TB, and malaria budgets from all sources. On average, 7% should be used as the reference • A significant national contribution to the national M&E budget (not total reliance on external funding sources) • A formalized (M&E link, particularly with appropriate line ministries, nongovernmental Organizations and donors, and national research institutions aimed at enhancing operations research efforts • A multi-sectoral working group to provide input and achieve consensus on indicator selection and various aspects of M&E design and implementation • Epidemiological expertise in the M&E unit or affiliated with the unit • Behavioural/social science expertise in the M&E unit or affiliated with the unit • Data processing and statistical expertise in the M&E unit or affiliated with the unit • Data dissemination expertise in the M&E unit or affiliated with the unit • Expertise in resource tracking, including both financial and commodity resources
Clear Goals	• Well-defined national programme or project plans with clear goals, targets and operational plans. National M&E plans should be revised every 3–5 years, and M&E operational plans yearly • Regular reviews/evaluations of the progress in implementing national programme or project plans • Guidelines and guidance to districts and regions or provinces for M&E • Guidelines for linking M&E to other sectors such as education, labour, and military • Coordination of national and donor M&E needs
Indicators	• A set of priority indicators and additional indicators at different levels of M&E • Indicators that are comparable over time • A number of key indicators that are comparable with other countries
Data Collection & Analysis	• An overall national level data collection and analysis plan, including data quality assurance • A plan to collect data and periodically analyse indicators and associated data sets at different jurisdictional levels of M&E (including geographical) • Second Generation Surveillance, where behavioural data are linked to HIV/STI surveillance data
Data Dissemination	• An overall national level data dissemination plan • A well-disseminated, informative annual report of the M&E unit • Annual meetings to disseminate and discuss M&E and research findings with policy makers, planners and implementers • A clearinghouse for generation and dissemination of findings • A centralised database or library of all HIV/AIDS, TB and malaria-related data collection, including ongoing research • Coordination of national and donor M&E dissemination needs

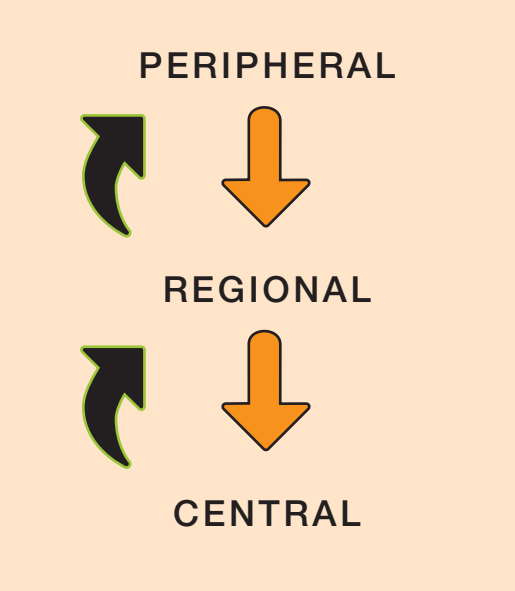
Source: Adapted from Monitoring and Evaluation Toolkit: HIV/AIDS, Tuberculosis and Malaria. WHO, 2004.[6]

The surveillance system structure is usually organized at three levels (Figure 7):

- **The peripheral or district level**—where there is direct supervision and monitoring of disease prevention and control, with data capture at health centers, hospitals or other health facilities
- **The regional level**—with roles for monitoring, supervision and feedback to those within its jurisdiction, and reporting to central level
- **The central level**—with roles for policy development, program planning implementation and national supervision

FIGURE 7:

Surveillance Data Flow



Source: Francis J. Curry National TB Center.

Organizational data flow

- Completion of specified data collection tools in the periphery
- National health authority determines reporting periods for data transfer to the regional/district and central office
- Notification of new cases is usually done the same day on receipt of confirmation
- A minimum set of TB surveillance data is included in the four weekly disease reporting form and sent to CAREC
- Cohort data are requested by the Pan American Health Organization (PAHO)/WHO on an annual basis

Records, Registers, and Reports

Records and **registers** are the primary tools for collecting and recording data that you want to track and report on. These forms prompt for the collection of specific data such as sputum smear result, treatment category (new case or re-treatment), type of patient (default, relapse, treatment failure), etc. This specific data feeds into the indicators you want to measure such as treatment success, incidence and prevalence, and allows for tracking progress towards program or project targets. **Reports** are used for monitoring and evaluation, activity planning, implementation and budgeting purposes. Accurate and timely record keeping on individual patients, maintenance of registers and regular reporting are all core M&E activities.

The following standardized forms are the tools used in tuberculosis control:

- Request for Sputum Examination
- Tuberculosis Treatment Card
- Tuberculosis Identity Card
- Basic Management Unit TB Register
- TB Laboratory Register
- Quarterly Report on TB Case Registration
- Quarterly Report on Sputum Conversion
- Register of TB Suspects
- Quarterly Report on Treatment Outcomes
- Quarterly Report on TB Treatment Outcomes and TB/HIV Activities in BMU
- Yearly Report on Program Management in Basic Management Unit

ISTC STANDARD 13

A written record of all medications given, bacteriologic response, and adverse reactions should be maintained for all patients.[3]

Tuberculosis Treatment Card

This card has been revised and now includes more information relevant to managing patients with TB and HIV.[7] Patient information includes name, age, sex, address, contact details, the TB patient's diagnostic category, results of initial and follow-up sputum smear examinations, treatment regimen, drug doses, initial and follow-up body weight, and medication collection data.

This card is issued after a patient is diagnosed with TB and treatment is started. The card must be completed in full in order for it to be useful both to the patient and for gathering accurate information for program analysis. The Tuberculosis Treatment Card should be kept at the health facility at which the patient obtains TB medicines[8]—it should not be given to the patient. For patients that move, a new card should be issued at the referral TB treatment site when the patient reports and hands in his or her referral form.

Tuberculosis Identity Card

The Tuberculosis Identity Card (previously called the patient identity card) contains an extract of the information found on the Tuberculosis Treatment Card and is handed to the patient at the start of TB treatment.[8] The card identifies at which health facility location the patient is receiving treatment and also contains a space for noting dates of follow-up appointments. Daily DOT can be recorded on this card for the intensive phase of the treatment.

The TB nurse should advise the patient to keep the card even after completing treatment, as it is a reference document for TB for the rest of his or her life. When the patient falls ill, the card should be presented to the doctor or nurse along with other health records.

Basic Management Unit TB Register

The Basic Management Unit TB Register (*TB Register*) is the cornerstone of the NTP M&E system. It records essential information for notification and treatment outcome by unit. Great care should be taken to ensure that the information in the *TB Register* is correctly recorded and regularly updated, showing the most current data on sputum smear examinations and treatment outcome. The revised register now contains fields for capturing important information related to patients with HIV/TB co-infection.[7]

Using the TB Register for patient monitoring

- Every patient on tuberculosis drugs in the clinic must be recorded in the treatment register. Therefore, every clinic which administers tuberculosis treatment must maintain a treatment register
- The *TB Register* must be filled during or immediately after a patient has been diagnosed, attended clinic and/or collected drugs
- Patient monitoring must be effected by immediate entries of laboratory investigation and service appointment dates in pencil. Particular attention should be taken to ensure that the patient is correctly recorded and treated
- The *TB Register* should be scanned daily for appointment dates to ensure timely detection of noncompliance to the services and to initiate immediate action (remember, the card or patient file system of monitoring is inadequate)

Using the TB Register for reporting

- Patients should be recorded in numerical order as they become known to the health worker responsible for the *TB Register*. Numbering commences with number one at the beginning of each calendar year, regardless of when the patient was diagnosed or commenced treatment
- The results of treatment must be recorded at least 12 months after the commencement of treatment
- Disseminate quarterly and annual reports to all stakeholders, including those at the regional and parishes, and NAP

Recording and Evaluating TB Treatment Response

TABLE 28:

Standardized definitions of treatment outcomes[a]

Cure	Patient whose sputum smear or culture was positive at the beginning of treatment but who was smear-negative or culture-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 have a negative sputum smear or culture result in the last month of treatment and on at least one previous occasion[b]
Treatment failure	Patient who is sputum smear-positive at five months or later during treatment Also included in this definition are patients found to harbor a MDR strain at any point of time during the treatment, whether they are smear-negative or -positive
Died	Patient who dies for any reason during the course of treatment
Default	Patient whose treatment was interrupted for 1 month or more[c]
Transfer out	Patient who has been transferred to another recording and reporting unit and whose treatment outcome is unknown
Treatment success	A sum of cured and completed treatment[c]

a These definitions apply to pulmonary smear-positive and smear-negative patients, and to patients with EPTB disease. Outcomes in these patients need to be evaluated separately

b The sputum examination may not have been done or the results may not be available

c This is PAHO's definition for Default for countries in the WHO region of the Americas

d For smear-positive or culture-positive patients only

Source: Adapted from WHO Treatment of Tuberculosis, Guidelines; 4th ed., 2009[9]

Cohort Analysis of Treatment Outcomes

Cohort analysis of treatment should be done at least annually (every quarter and/or at year end). A cohort of TB patients consists of all those sputum smear-positive PTB patients registered during a certain time, usually a quarter of a year (i.e., 1 January to 31 March; 1 April to 30 June; 1 July to 30 September and 1 October to 31 December). New and previously treated patients form separate cohorts. Evaluation of the end of treatment (6 or 8 months) outcome takes place about 3 months after all patients in the cohort have completed their course of treatment.[9]

Data (in absolute numbers) are extracted from the register according to the following indicators:

- New sputum smear-positive and smear-negative cases according to HIV antibody results
- New smear-positive cases according to age group, sex, HIV antibody results and other risk factors

- Relapses; failures; defaulters; return after default and deaths
- Extrapulmonary TB cases
- Culture-positive and negative cases
- Cases on treatment and re-treatment
- Cases on antiretroviral therapy
- Referrals for administration of ART to the TB/HIV co-infected
- Determine outcome in relation to cure, treatment completion, failure, default, transfer or deaths

Results of culture and antimicrobial susceptibility testing, atypical mycobacteria identification, as well as the documentation of HIV/TB co-infection with CD4 counts in the quarterly report will also aid in monitoring the magnitude of the problem. Programs should strive to achieve documentation of HIV status (positive or negative) being recorded on the *TB Register* for all TB patients and vice versa.

This very useful method of evaluation is recommended for managers and coordinators and can be used for decisions in adjusting and modifying program activities.

References

1. World Health Organization. An expanded DOTS framework for effective tuberculosis control. Geneva: World Health Organization, 2002 (WHO/CDS/TB/2002.297).
2. Maher D, Raviglione MC. Why is a recording and reporting system needed, and what system is recommended? In: Frieden TR, ed. Toman's Tuberculosis. Case Detection, Treatment and Monitoring, 2nd Edition. Geneva: World Health Organization, 2004: 270–273.
3. Tuberculosis Coalition for Technical Assistance. International Standards for Tuberculosis Care (ISTC), second edition. Tuberculosis Coalition for Technical Assistance, The Hague, 2009.
4. World Health Organization. A Guide to Monitoring and Evaluation for collaborative TB/HIV Activities. Geneva: World Health Organization, 2004 (WHO/HTM/TB/2004.342, WHO/HIV/2004.092004).
5. World Health Organization. Compendium of Indicators for Monitoring and Evaluating Tuberculosis Programs. Geneva: World Health Organization, 2004 (WHO/HTM/TB/2004.344).
6. The Global Fund to Fight AIDS, Tuberculosis & Malaria. Monitoring and Evaluation Toolkit: HIV, Tuberculosis and Malaria. Part 2: Tools for monitoring programs for HIV, tuberculosis, malaria and health systems strengthening. Tuberculosis. The Global Fund to Fight AIDS, Tuberculosis & Malaria. 2009; 155-167 (www.theglobalfund.org).
7. World Health Organization. Revised TB recording and reporting forms and registers: version 2006. Geneva: Word Health Organization, 2006 (WHO/HTM/TB/2006.373).
8. International Union Against Tuberculosis and Lung Disease. Management of Tuberculosis: A Guide for Low Income Countries, Fifth Edition. IUATLD, 2000.
9. World Health Organization. Treatment of Tuberculosis: Guidelines. Fourth Edition. Geneva: World Health Organization, 2009 (WHO/HTM/TB/2009.420).

Managing Drug Supply

13

Management of medicines is an essential part of any healthcare system, but even more critical to the success of a TB program. TB can be cured using multi-drug regimens. It is essential that ALL the necessary TB medicines are available in the right quantities at the right time. Non-availability of any of the TB medicines at any time would be a serious weakness in the TB program and would contribute to the emergence of TB drug resistance in a patient.

Selecting and packaging the appropriate drug formulations of the essential anti-TB drugs are some of the most important responsibilities of NTP officials, and may require the assistance of consultants.[1]

Several fixed-dose combinations of 2, 3, and 4 anti-TB drugs are available on the market; however, not all combinations contain the correct dose of each prescription drug. A number of studies have shown some combinations to be incorrect or incompletely absorbed. WHO and IUATLD, therefore, recommend that use of these fixed-dose combinations be restricted to combinations whose bioavailability has been demonstrated by laboratories that are independent from the manufacturers.[1]

Determining Appropriate Quantities[1]

A more complex task than selecting the drugs is deciding on the quantities needed. Calculation of these quantities should be based on the number of cases in the different treatment categories notified the previous year, the standardized treatment regimens used in the NTP, and the existing and required stocks. It is essential to plan for reserve stocks for each level (e.g., three months at local/district level, three months at regional level, and six months at central level). Practical methods to quantify drug needs are fully described in the *Tuberculosis Handbook*.[2]

A more precise estimate is required if different formulations are used, depending on the patients' age and weight. As a rule, weight categories should be limited to 2–4 for adult patients, and the number of children among TB patients should be taken into account.

Ensuring the Quality of Anti-tuberculosis Drugs

National TB control programs should ensure that anti-TB drugs are of good quality by making sure that the drugs:[1]

- Are produced following the good manufacturing practices recommended by WHO
- Are imported with a PAHO/WHO certificate (certification scheme on the quality of pharmaceutical products moving in international commerce)
- When bought by competitive tender, are ordered with the appropriate specifications
- Are stored properly following good storage practice and the first expiry, first out (FEFO) principle

Stock Control

A stock control system serves two main purposes and it is effectively implemented if:

- It ensures that the correct items are available in the right amounts, at the time when they are needed
- It improves accountability

A properly functioning stock control system has many advantages:

- It ensures efficient use of financial resources
- It prevents under-stocking and "stock outs"
- It prevents overstocking and wastage
- It prevents shortages in case of delays in delivery
- It keeps medicine stores going even when there are staff changes
- It allows identification of security problems

Ordering Supplies

New supplies of medicines need to be ordered at regular intervals. Whether this takes place weekly, every two weeks or once every month depends on how the system is set up in each particular country. The purpose of ordering supplies is to replace stock which has been used. This ensures the availability of TB medicines in all health facilities at all times. The order should always be prepared carefully. If too much of an item is ordered, then medicines which might be needed urgently elsewhere will pile up on shelves and eventually expire. If too little is ordered, then patients will suffer because they will not receive the necessary medication. This can have disastrous consequences for the TB patients, like treatment failure, or development of MDR-TB. It also leads to a loss of credibility for the health facility and NTP.

Guiding Principles when Ordering Supplies

Anticipate changes in demand

The quantity of TB medicines required by a health facility is directly related to the number of TB patients registered at the facility. Any increase or decrease in the number of registered TB patients will necessitate an increase or decrease in future orders.

- Estimation of stock required should be determined by the previous year's usage
- Extrapolation based on the average percent increase of stock over the previous several years will assist in predictions for ordering the following year's stock
- If no TB patients are receiving treatment, then it is only necessary to keep a small amount of TB medication in stock for emergencies (e.g., if a TB patient is a visitor to the area and needs his or her medication refilled). If a healthcare facility is very near its supply source, then it may not be necessary to stock any TB medication at all
- Do not forget that if pediatric TB patients receive treatment or prophylaxis at your health facility, it may be necessary to order TB drugs of different formulations
- Know when the order is to be placed and ensure that the order is submitted in good time

Be systematic

Follow the steps below to ensure that appropriate quantities are ordered.

Step 1: Perform a physical stock count. This should be done for every item that is normally stocked, not only items that are known to be needed.

Step 2: Decide whether or not to order a particular item. Check whether the physical stock is equal to or less than the minimum stock indicated on the stock card. If it is, order enough units to make up the minimum stock. If the physical stock is greater than the minimum stock, do not order the item!

Step 3: Complete your order book. Fill in the appropriate amount for the items you want to order (reorder enough quantity to equal minimum stock level).

Stock management definitions

- **Lead time:** The lead time is the time it takes between the first step in the procurement process until the supplies arrive in the country's central medical stores. It is important that this is known for all items that need procurement, so that they are ordered before country stocks reach the minimum level
- **Order interval:** This is the time between two orders. If orders are placed once a month, then the order interval is one month
- **Minimum stock (reorder level):** This is the stock amount which represents the average consumption of a particular item during a period that is twice the order interval. If three units of isoniazid tablets are used per order interval, then the minimum stock level is 3 x 2 = 6 units. If the stock level equals or falls below the minimum stock value, the item should be reordered. Wherever drugs are stored (health center site locally, district site, regional site, etc.) a minimum stock level should be clearly marked at the storage site
- **Maximum stock:** This number defines the maximum number of units of a particular item there should be in stock—do not stock more than this. The number should equal the average consumption of that item in a time covering four times the order interval. This means that if the average consumption is 3 units of isoniazid tablets per order interval, then the maximum stock for isoniazid is 3 x 4 = 12 units. In this example, you should not store more than 12 units of isoniazid at a time! This number should also be clearly marked at each site where drugs are stored

Minimum and maximum stock levels can both change over time according to changes in consumption. For TB medicines, these levels will change as the number of TB patients change. The initial calculations should be done by the person in charge of the central storage site *together with* the Chief Medical Officer, Chief Pharmacist and NTP Director or Manager.

When these numbers are used for ordering the first time, they should be recalculated at the latest after two months. After this, the minimum and maximum stock levels should be recalculated on a regular cycle (e.g., every three or four months, or annually).

Receiving Supplies

When receiving supplies from the district hospital or medical stores, the following must be carefully checked:[3]

- Does the number of boxes received agree with the number indicated on the delivery note?
- Are all the boxes sealed and intact?
- Does the number of items received agree with the number recorded on the "Goods Received" note? (In other words, have the right items in the right unit size and in the right quantity been supplied?)
- Do the medicines have satisfactory expiry dates (at least four times the order interval from the date of receipt)?
- Are all containers intact (nothing damaged or tampered with)?
- Was the cold chain maintained where applicable?

If there are any problems with the quantity, type, expiry date or condition of any items received, then contact the supplying facility immediately by telephone to report the problem. In addition, make a written statement detailing the problems found; keep one copy for your reference and send one copy to the supplying facility.

Storage[1,4]

The following factors are all of crucial importance for storing drugs and supplies:

- Adequate storage conditions (adhere to manufacturer or shipper's directions for stacking and storing—temperature and humidity, away from the elements, free from rodents and pests)
  - Place liquid products on the lower shelves or bottom of stacks
  - Store products that require cold storage in appropriate temperature-controlled zones
  - Store high security/high value products in appropriate security zones
  - Separate damaged or expired products from the usable stock without delay and dispose of, using established disposal procedures
  - Arrange cartons so arrows point up and identification labels, expiry dates, and manufacturing dates are visible. If this is not possible, write the product name and expiry date clearly on the visible side
- Management inside the storage facility/location (appropriate space for stocks, clear cataloguing for easy access and movement, control of expiry date, implementation of FEFO principle, reserve stocks)
- Implementation of a drug accounting system at all levels where the drugs are stored or administered

Stock Records

The minimal information that should be collected on stock records for medicines and other health products includes:

- Product name/description (including the form [e.g., capsule, tablet, liquid suspension, etc.] and strength)
- Stock on hand/beginning stock balance
- Receipts
- Issues
- Losses/adjustments
- Closing/ending balance
- Transaction reference (e.g., issue voucher number or name of supplier or recipient)

Depending on the system, stock records might also include additional product information, such as:

- Special storage conditions (e.g., 2°–8°C)
- Unit prices
- Lot numbers/bin locations
- Item codes
- Expiry dates

*Always follow the **FEFO rule (first expiry first out)**: always issue the stock with the closest expiry date.*

Distributing Anti-tuberculosis Drugs

Special consideration should be given to the distribution of anti-TB drugs (as with other essential drugs) at the intermediate and peripheral levels. Drug stocks should be distributed from national to intermediate level on predetermined intervals, rather than yearly, to ensure even distribution.[1]

Issuing supplies involves the following:

- Moving stock from the shelf and transporting to the dispensing sites (issue older stock first)
- Ensuring that the expiry dates correspond with the demand of the drug required by the peripheral sites
- Ensuring medications issued to peripheral sites match the order sheet
- Removing stock of fast-moving items for pre-packing
- Sending stock which is not needed (excess stock) back to the regional or central store/pharmacy
- Removing expired or unsuitable medicines from the shelf and sending them for disposal as per country protocol
- Removing broken containers from the shelf

How to avoid wastage due to expired stock

Following the basic rules described above will help avoid wastage of medicines due to expiry.

FEFO Rule

This stands for First Expiry First Out. When new supplies are received, put them at the back of the shelf and always issue stock from the front first. However, if the expiry date of new stock is earlier than that of the older stock, put the new stock in front so that it is used up first. This will prevent expiry of medicines.

In addition, the following should also be done routinely:

- **Clearly mark containers of medicines with close expiry dates (<12 months).** This will bring these items to your attention when you are placing an order and dispensing medicines
- **Return excess stock to your supplying facility as soon as you are aware of it.** Once you realize that you cannot use all of an item before its expiry date, or that you have more than the calculated maximum stock of an item, return the stock to your supplying facility with documentation to show who is returning it

Conclusion

The supply and use of anti-TB drugs do not occur in a vacuum. Nearly all countries have a general national drug supply system. When feasible, anti-TB drug supply and training of staff should be integrated into the essential drugs program and into the national system (e.g., procedures for tender bids, storage and distribution, and drug quality control). This should lead to increased efficiency and long-term sustainability.

References

1. World Health Organization. Treatment of Tuberculosis: Guidelines for National Programs, Third Edition. Geneva: World Health Organization, 2003 (WHO/CDS/TB/2003.313).
2. Pio A, Chaulet P. Tuberculosis Handbook, Second Edition Geneva: World Health Organization, 2003 (WHO/CDS/TB/2003.320).
3. Rational Pharmaceutical Management Plus. Managing pharmaceuticals and commodities for tuberculosis: a guide for national tuberculosis programs. Arlington, VA: Rational Pharmaceutical Management Plus, for the U.S. Agency for International Development, 2005. Available at: http://erc.msh.org/toolkit/toolkitfiles/file/TB-Guidelines_English-final-Aug-2008-w-cover.pdf; (accessed December 15, 2009).
4. John Snow, Inc./DELIVER in collaboration with the World Health Organization. Guidelines for the Storage of Essential Medicines and Other Health Commodities. Arlington, VA: John Snow, Inc./DELIVER, for the U.S. Agency for International Development, in collaboration with the World Health Organization, 2003.

APPENDIX A

Screening

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

Screening for TB is **active or planned (as opposed to passive or incidental) case-finding.** It can be done in the general population, but is particularly useful for the following high-risk groups:

- People with HIV (see Chapter 9, HIV Infection and TB)
- Healthcare workers and laboratory staff
- Prison inmates and staff
- Elderly in long-stay institutions
- Other immunocompromized persons
- Household contacts and other close contacts of known cases of TB
- Persons who will be undergoing immunosuppressive treatment (e.g., organ transplant candidates; some cancer patients; patients with autoimmune illnesses who will begin treatment with tumour necrosis factor alpha antagonists)

The tuberculin skin test (TST) is used in many TB control programs as part of the procedure for identifying individuals who may be infected with TB.

Mantoux Tuberculin Skin Test

The Mantoux TST is the recommended method of skin testing to determine whether a person could be infected with *M. tuberculosis*. Multiple puncture tests (e.g., the Tine test) should not be used because they are harder to standardize and the results are less reliable. The Mantoux TST is performed by injecting 0.1 ml of 5 tuberculin units of purified protein derivative (PPD) intradermally, using a 1 ml. tuberculin syringe and a fine-bore (27-gauge) hypodermic needle. The preferred injection site is the front (ventral surface) of the forearm. Given the importance of the injection technique to obtaining an accurate result, instruction and training should be provided to those who will be required to place, read and interpret the Mantoux TST.

As vaccination with a live virus vaccine can interfere with the Mantoux TST reaction, testing should be done as follows:

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

Procedure for placing the Mantoux TST

- Explain the procedure to the person
- Wash and dry your hands

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

Mark the site and make a record of the date and time of the injection. The next step is to read the result of the Mantoux skin test by examining the patient's arm for induration (palpable swelling). This is done 48 to 72 hours after giving the PPD injection.

Using a ruler with millimeter measurements (preferably a transparent ruler), measure the *largest* transverse (horizontal) diameter of the indurated area at the site of the test on the person's forearm. The area of erythema (redness) around the indurated area is not included in the measurement.

TABLE 29:

Defining positive Mantoux TST reaction

≥5 mm Induration	• HIV-infected persons
	• Recent contacts of infectious TB cases
	• Persons with fibrotic changes on CXR consistent with prior TB
	• Organ transplant recipients
	• Persons who are immunosuppressed for other reasons, such as:
	  ◦ Taking the equivalent of ≥15 mg/day of prednisone for 1 month or more
	  ◦ Taking tumour necrosis factor alpha antagonists

≥10mm Induration	• Recent immigrants (within last 5 years) from a high TB-prevalence country • Injection drug users • Residents or employees of high-risk congregate settings • Mycobacteriology laboratory personnel • Children <5 years of age, or children or adolescents exposed to adults at high risk • Persons with clinical conditions that increase the risk for TB infection progressing to disease (see pages 7–8)
≥15mm Induration	• Persons with no known risk factors for TB

CXR = Chest x-ray

Source: Modified from Targeting Testing and Treatment of LTBI, CDC, 2000.

Interpretation of the Mantoux skin test

As there are many factors that can affect the result of the Mantoux TST, it is important to ensure that the test has been placed and read correctly and a thorough history taken to help you interpret the result.

- A positive reaction to the TST is taken to indicate that the person could be infected with TB
- A negative test result, in the absence of immunocompromising conditions (e.g. HIV infection and AIDS, post-measles syndrome, malnutrition, corticosteroid treatment and miliary tuberculosis) should be taken to indicate no previous contact with *Mycobacterium tuberculosis*

False-negative Mantoux TST result

Some persons may not react to the TST even though they are infected with *M. tuberculosis*. The reasons for these false-negative reactions may include, but are not limited to, the following:

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

False-positive Mantoux TST result

Some persons may react to the TST even though they are not infected with *M. tuberculosis*. The causes of these false-positive reactions may include, but are not limited to, the following:

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

Recommended PPD Preparations

USA:

Purified protein derivative (PPD-S) (MT5)

Dosage 0.1 ml containing 5 tuberculin units of PPD

UK:

PPD-RT23 (Statens Serum Institute)

Dosage 0.1 ml containing 2 tuberculin units

Note: *2 tuberculin units of PPD-RT23 is equivalent to 5 tuberculin units of PPD-S*

Tuberculin surveys can be used to estimate the prevalence of tuberculosis infection in the community.

APPENDIX B

Treating Latent TB Infection

In persons infected with *Mycobacterium tuberculosis*, the risk of progression to active TB disease varies according to the time since infection, age and other host factors. In healthy adults with TB infection but without risk factors, active TB disease will develop in about 10% (5% within 2 years of infection and 5% after 2 years). For young children, the risk for disease after infection is substantially higher and is inversely correlated with age (up to 40% risk in infants). In children and adults, conditions that compromise the immune system will also increase the risk of disease after infection (see Chapter 2, Tuberculosis Transmission and Pathogenesis). Treating TB infection, however, can significantly decrease the number of persons who might otherwise go on to develop active TB disease.

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

1. **Primary prophylaxis (window period prophylaxis):** the drug is given to an individual who is exposed to a known source of infection and who is considered to be very susceptible to becoming infected and at greater risk for progressing to active TB disease. This would include children <5 years of age and persons known to be significantly immunosuppressed. Treatment during the "window period" is recommended for contacts at high risk for rapid progression of infection to disease. Treatment may be discontinued if, after a period of eight weeks, the repeat Mantoux TST is negative and the contact remains asymptomatic and is immunocompetent. If the individual is unable to mount a delayed-type hypersensitivity reaction (e.g., an infant who is too young or individual with severe immunosuppression), consideration should be given to extending treatment for the full duration (9 months for INH)

2. **Treatment of Latent TB Infection (LTBI):** the drug is used to prevent progression to disease in people who have already been infected, as demonstrated by a positive Mantoux TST result (see Appendix A for induration size indicating a positive TST result) or positive blood assay for *Mycobacterium tuberculosis*

Drugs and Regimens for Treating LTBI

- In general, INH for 6–9 months is most frequently used to treat LTBI, as it is relatively inexpensive, well tolerated and is proven effective
- Rifampicin daily for 4 months would be the preferred drug in situations of exposure to an INH-resistant TB source case or when isoniazid is not tolerated. The duration must be extended from four months to six months when treating children
- The American Thoracic Society and Centers for Disease Control and Prevention now recommend that the 2-month regimen of rifampicin and pyrazinamide (RIF/PZA) should generally not be offered to persons with LTBI due to this regimen's association with severe liver injury (www.cdc.gov/mmwr/preview/mmwrhtml/mm5231a4.htm)
- **The use of thiacetazone is no longer recommended!**

In 2000, the American Thoracic Society and the Centers for Disease Control and Prevention published updated recommendations for treatment regimens for persons with LTBI. To help clinicians make informed treatment decisions based on the most current research results, evidence-based ratings are assigned to the drug treatment recommendations (general recommendations have no rating). These ratings were updated in 2003 in response to reports of severe liver injury associated with the use of the 2-month RIF/PZA regimen and are shown in Table 30.

Dosage of Isoniazid

The adult dose of isoniazid is 300 mg daily, self-administered or administered under the supervision of a treatment supporter. The current WHO guideline for treating child contacts to infectious PTB is isoniazid at a dose of 10mg/kg bodyweight (maximum 300mg daily) for a total of 6 months.

Use of Supplemental Pyridoxine (B_6)

In HIV-infected persons taking antiretroviral treatment, the use of isoniazid with stavudine (d4T) may increase the risk of peripheral neuropathy; therefore, for these individuals, administer pyridoxine (B_6) 25–50 mg daily along with the isoniazid.

Routine administration of pyridoxine is not recommended for children taking isoniazid, but could be considered in the following circumstances:

- Children and adolescents with diets likely to be deficient in pyridoxine
- Children who experience paraesthesia while taking isoniazid

Treatment for latent TB infection should be offered to:

- Mantoux TST–positive contacts of patients with sputum smear-positive PTB, especially children under five years of age, after evaluating with CXR, medical history and physical exam to rule out active TB disease
- Adults and children with Mantoux TST-positive reactions (see Appendix A) and who have been evaluated for clinical manifestation of the disease and found to be disease free (particularly those with HIV infection). This would include individuals who have had BCG vaccination but are found to be Mantoux TS-positive and who are without clinical manifestations of TB disease

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

- When isoniazid is chosen for treatment of LTBI in persons with HIV infection or those with radiographic evidence of prior TB, 9 months rather than 6 months is recommended.
- For pregnant, HIV-negative women, isoniazid given daily or twice weekly for 9 or 6 months is recommended. For women at risk for progression of LTBI to disease—especially those who are HIV-infected or who have likely been infected recently—initiation of therapy should not be delayed on the basis of pregnancy alone, even during the first trimester. For women whose risk for active TB is lower, some experts recommend waiting until after delivery to start treatment
- Breastfeeding **is not contraindicated** when the mother is being treated for LTBI. The Centers for Disease Control and Prevention (CDC) recommends infants whose breastfeeding mothers are taking INH should receive supplemental pyridoxine (see CDC. Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection, *MMWR* 2000 www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm). The amount of INH provided by breast milk is inadequate for treatment of the infant

- For contacts to an index patient with isoniazid-resistant, rifampicin-susceptible TB, rifampicin given daily for 4 months is recommended (6 months for children)
- Active hepatitis and end-stage liver disease are relative contraindications to the use of isoniazid or pyrazinamide for treatment of LTBI
- Currently, there are no drug regimens that have been proven effective for treating LTBI resulting from exposure to a multidrug-resistant TB (MDR-TB) source case; however, treatment may be indicated in certain high-risk situations (see Chapter 11: Drug-resistant TB)

TABLE 30:

Revised drug regimens for treatment of latent TB infection in adults

Drug	Interval and duration	Comments†	Rating§ (Evidence)	
			HIV negative	HIV infected
Isoniazid	Daily for 9 months**††	In HIV-infected persons, isoniazid may be administered concurrently with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors, or non-nucleoside reverse transcriptase inhibitors (NNRTIs).	A (II)	A (II)
	Twice-weekly for 9 months**††	Directly observed therapy (DOT) must be used with twice-weekly dosing.	B (II)	B (II)
Isoniazid	Daily for 6 months††	Not indicated for HIV-infected persons, those with fibrotic lesions on chest radiographs, or children.	B (I)	C (I)
	Twice-weekly for 6 months††	DOT must be used with twice-weekly dosing.	B (II)	C (I)
Rifampin§§	Daily for 4 months	Used for persons who are contacts of patients with isoniazid-resistant, rifampin-susceptible TB. In HIV-infected persons, most protease inhibitors or delavirdine should not be administered concurrently with rifampin. Rifabutin with appropriate dose adjustments can be used with protease inhibitors (saquinavir should be augmented with ritonavir) and NNRTIs (except delavirdine). Clinicians should consult web-based updates for the latest specific recommendations.	B (II)	B (III)
Rifampin plus pyrazinamide (RZ)	Daily for 2 months Twice- weekly for 2–3 months	RZ generally should not be offered for treatment of LTBI for HIV-infected or HIV-negative persons.	D (II) D (III)	D (II) D (III)

Strength of the recommendation:

A Both strong evidence of efficacy and substantial clinical benefit support recommendation for use. Should always be offered.

B Moderate evidence for efficacy or strong evidence for efficacy, but only limited clinical benefit supports recommendation for use. Should generally be offered.

C Evidence for efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy might not outweigh adverse consequences (e.g., drug toxicity, drug interactions) or cost of the treatment or alternative approaches. Optional.

D Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered.

E Good evidence for lack of efficacy or for adverse outcome support a recommendation against use. Should never be offered.

Quality of evidence supporting the recommendation:

I Evidence from at least one properly randomized controlled trial.

II Evidence from at least one well-designed clinical trial without randomization from cohort or case-controlled analytic studies (preferably from more than one center), from multiple time-series studies, or from dramatic results from uncontrolled experiments.

III Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

† Interactions with human immunodeficiency virus (HIV)–related drugs are updated frequently and are available at www.aidsinfo.nih.gov/guidelines.

** Recommended regimen for persons aged <18 years.

†† Recommended regimens for pregnant women.

§§ The substitution of rifapentine for rifampin is not recommended because rifapentine's safety and effectiveness have not been established for patients with LTBI.

Source: Adapted from CDC. Targeted Tuberculin Testing and Treatment of LTBI, 2000.

Clinical and Laboratory Monitoring

Before Treatment Initiation

Baseline laboratory testing is not routinely indicated for all patients at the start of treatment for LTBI; however, persons at greater risk for hepatitis should have baseline hepatic measurements of serum aspartate aminotransferase (serum glutamic oxaloacetic transaminase) (AST [SGOT]) or alanine aminotransferase (serum glutamic pyruvic transaminase) (ALT [SGPT]) and bilirubin.

Patients should not be given isoniazid (INH) if monthly monitoring is not possible.

Baseline laboratory evaluation should be obtained for:

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

Baseline testing is not routinely indicated in older persons. However, such testing may be considered on an individual basis, particularly for patients who are taking other medications for chronic medical conditions.

Monitoring Throughout Treatment

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

Monthly evaluation should include:

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

Monthly laboratory monitoring:

- Indicated for persons whose baseline liver function tests are abnormal
- Other persons at risk for hepatic disease
- Laboratory testing may also be indicated for the evaluation of possible adverse effects that occur during the course of treatment (e.g., liver function studies for patients with symptoms compatible with hepatotoxicity, or a uric acid measurement to evaluate complaints of joint pain)

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

APPENDIX C

Implementing TB Contact Investigation

For some NTPs, conducting TB contact investigations will be a new initiative. If so, the NTP should ensure all of the following are met prior to initiating contact investigation activities:

- Adequate staffing is in place
- DOT approach to case management is well established and satisfactory outcome measures for all TB cases are being met
- Training can be provided to all impacted healthcare workers to explain the rationale and potential benefit of contact investigation, as well as the steps involved and appropriate management of contacts

TB contact investigation provides an opportunity to prevent future cases of tuberculosis, particularly among children. At a minimum, NTPs should strive to implement a process for **evaluation of high-risk contacts** (children <5 years of age and persons with HIV infection) **to the most infectious TB patients** (sputum smear-positive). In consultation with stakeholders, the NTP should decide the means of introducing and monitoring contact investigation and management that will be most effective in its setting. Methods that could be utilized to accomplish this might include:

- Utilizing a phased-in approach, starting with a limited number of districts and then progressively scaling up over time
- NTPs can utilize the existing structure in country and establish a "contact clinic" (i.e., a set time and place each week where contacts can be assessed clinically). This clinic can be at the first referral level, whether district hospital, TB management unit or health center, depending on the local situation
- In high HIV-prevalence settings (i.e., in generalized HIV epidemics or in defined subpopulations in which HIV is concentrated) TB contact investigations can be an important opportunity for both TB and HIV case-finding (e.g., joint TB/HIV contact investigations)

A fully implemented contact investigation process would include the following steps:

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

Decide whether to initiate a contact investigation

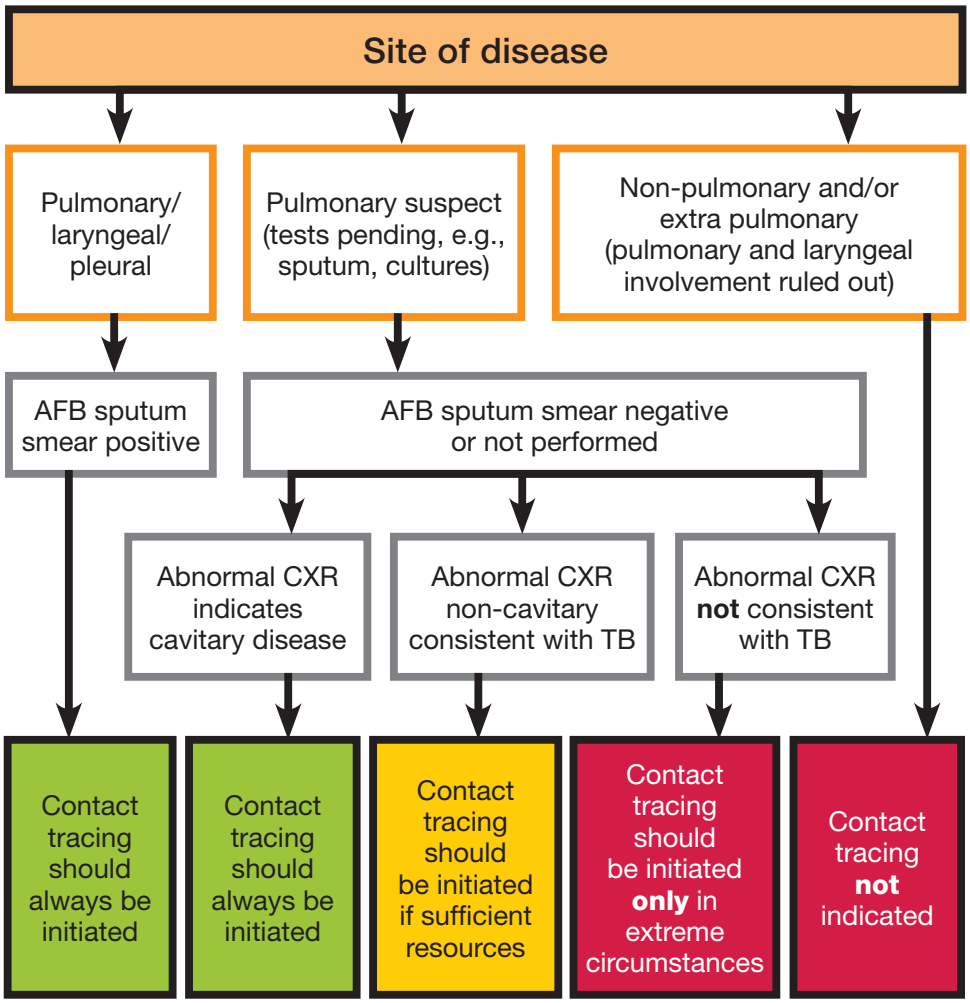
In general, the decision to identify and evaluate contacts should be based on the likelihood that transmission of TB has occurred (see Figure 8). This depends in part on factors associated with the TB patient, but also depends on factors related to the environment of the exposure as well as to the contact's ability to ward off infection.

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

- TB patient is sputum smear-positive (confirmed case once culture returns positive), or
- TB patient is sputum smear-negative, and
  - PTB is highly suspect, or
  - Vulnerable contacts exposed (e.g., neonates, HIV-infected persons, etc.)

FIGURE 8:

Decision to initiate a TB contact investigation



AFB = Acid-fast bacilli; **CXR** = Chest radiograph

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

Interview the TB patient

The purpose of the interview is to obtain information from the patient related to onset of symptoms in order to help establish the potential infectious period as well as to identify persons and places where the TB patient spent time prior to diagnosis. Generally, several interviews will be needed to obtain this information.

Elements of the TB Interview:

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

Determine the Infectious Period

Establishing an "infectious period" helps to focus the investigation on persons most likely to have been exposed and infected. Published guidelines on estimating onset of infectious period are essentially based on expert opinion, but give some parameters for NTPs to consider for establishing country-specific guidelines.

The infectious period onset (see Table 31) is estimated based on TB patient factors, which include:

- Date when TB symptoms began
- Date of first diagnostic test consistent with TB (e.g., sputum or CXR)

TABLE 31:

Estimating onset of infectious period

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

Source: Modified from the California Department of Health Services Tuberculosis Control Branch; California Tuberculosis Controllers Association. Contact Investigation Guidelines. Berkeley, CA. California Department of Health Services; 1998, page 23.

The infectious period is generally considered closed when the TB patient:

- Has 3 consecutive sputum smears that are negative; and
- Has been on appropriate TB treatment for ≥2 weeks; and
- Is showing clinical response to treatment, with symptoms diminishing

Conduct a Field Investigation

In short, the field investigation includes visiting each site where the TB patient spent time during the infectious period (e.g., homes, work settings, schools, clinics, jails, etc.). Performing a field investigation is the most reliable method for assessing the risk for transmission to contacts at that setting.

The visit should be made shortly following the initial TB patient interview. The site visit creates an opportunity to test contacts, make referrals for further evaluation, schedule clinic visits, and provide education. Sometimes additional contacts are identified during these site visits.

Prioritize Contacts

High-priority contacts include those most likely to have become infected due to the quality of exposure or those most likely to progress to TB disease once infected (see list on pages 7–8). These are the individuals to target for evaluation when implementing contact investigation in the NTP.

In general, contacts who may pose a greater risk to others (e.g., teachers, hospital nursery workers, other healthcare workers) or who are at greater risk themselves (e.g., HIV-infected persons and children <5 years of age) should be prioritized for testing even though they may not have had close contact.

For larger setting investigations (e.g., school and work sites), it is advisable to give priority classifications of high, medium and low, with criteria for each classification clearly defined. This will enable the NTP to keep the focus on those with a high-priority classification (see the CDC *Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis,* 2005 for an example of prioritization criteria).

Evaluate Contacts

The Mantoux TST is used to test contacts deemed at risk for TB infection (see Appendix A for TST procedure). Additionally, all high-priority contacts should be assessed for evidence of active TB with a symptom evaluation and clinical exam (see Chapter 10 on TB in Children, pages 101–105, for recommendations on the management of child contacts to infectious PTB).

Contacts with a positive skin test result (≥5 mm) or signs or symptoms of TB disease should be evaluated carefully to rule out disease before isoniazid preventive therapy (IPT) is started. This requires:

- A CXR, a medical history, and examination by a medical officer
- Contacts with abnormal CXR findings suggestive of active TB, and those with symptoms of active TB should also have sputum collected for AFB smear microscopy

Contacts found to have a negative initial TST should be told they will require a follow-up TST 8–10 weeks after the date of their last TB exposure and should have a clinic appointment scheduled within that timeframe.

Follow-up and Treatment of Contacts

All contacts whose initial TST was negative must have a follow-up TST performed 8–10 weeks following their last TB exposure. Those whose TST is found to be positive during the follow-up testing should be evaluated as described above.

ISTC 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.

Treating LTBI is an important TB prevention activity:

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

It takes several weeks between the time of infection and when the body can produce a response to the TST. This time period is called the "window period." Vulnerable contacts whose initial TST is negative should be considered for IPT during the window period until the follow-up TST is placed and read 8–10 weeks after last contact:

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

The WHO does not recommend use of second-line drugs for treatment of contacts to MDR-TB. In these situations, close contacts should receive careful clinical follow-up for at least two years following date of last exposure.

See Chapter 10 on TB in Children for recommendations on management of child contacts to infectious PTB cases.

Evaluate Contact Investigation Activities

Monitoring and analysing outcome data is critical, both from a patient management perspective and to identify possible shortfalls in the system that could be addressed and corrected. Important information could be gathered locally and then sent to central office for analysis:

- Number of contacts evaluated, categorized by age group (e.g., 0–4; 5–14, etc.)
- Number treated for TB disease and outcome
- Number given IPT and outcome, including treatment completion
- Adverse reactions to medications

Each contact (on whatever treatment) should have an individual card on which is also recorded the details of the source case. The information could be kept at the local level and provided to the central office with the quarterly case-finding report. It would be useful to have a separate registration book for the contacts on IPT. Once the process has started, there should be regular dissemination of information relating to contact management by the NTP to pediatricians, government health departments, and district health and district TB officers.

References

1. Centers for Disease Control and Prevention. Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis. *MMWR* Recommendations and Reports: December 16, 2005 / Vol. 54(RR15): 1-37.

Supervision

Supervision is an essential activity which must be conducted on a regular basis by the National Tuberculosis Program. In order to consolidate TB/HIV collaborative efforts, where possible, this activity can be conducted jointly. The aim of supervision is to identify factors that inhibit or enhance implementation of NTP policies and to ensure that weaknesses are corrected so as to provide motivation for staff and ultimate achievement of the programs goals and objectives.

Profile of Competence of NTP Staff

Attitude
- An interest and concern for patients with tuberculosis
- An interest in fieldwork
- A preference for facilitating approach to problems

Knowledge
- The clinical aspects of tuberculosis
- NTP control policies
- Epidemiology and control
- The operational area
- Ministry of Health structure and regulations

Skills
- Clinical practice
- Organization
- Accounting
- Supervision
- Communication
- Maintenance and distribution of NTP supplies
- Training
- Recording and reporting

National Tuberculosis Control Unit

For effective and efficient implementation of NTP policies, the National Tuberculosis Control Unit must ensure the following:

- Appropriate management for planning, implementation, monitoring and evaluation of NTP activities, including all curative and preventive aspects of tuberculosis
- Monitor the progress of the control measures, and where necessary, adjust the policy of the NTP in collaboration with external experts in the field of TB control
- Ensure appropriate training for all categories of staff, adequate supervision of the network of laboratories, and that quality control activities are conducted
- Conduct supervision and supporting visits to health facilities in the periphery level and advise medical officers involved on NTP matters
- Ensure the procurement and distribution of drugs, supplies and funds, as well as monitor the proper use and consumption, based on quarterly reports
- Collect, analyze, and submit statistical data and activity reports to the chief medical officer

- Collaborate with the NAP to ensure that a patient's TB/HIV co-infection receives adequate care and that exposure of HIV-infected individuals to TB is well controlled
- Initiate, coordinate, and advise on research in relation to tuberculosis control
- Collaborate and maintain active contact with donor or other related agencies

Job Descriptions

General Health Staff

- Suspect/detect tuberculosis among patients reporting to a clinic and take measures for the examination of those patients
- Educate and examine household contacts of patients diagnosed with tuberculosis
- Treat patients upon instructions by the medical officer and TB control coordinator
- Encourage and supervise patients regarding DOT
- Educate tuberculosis patients on the need for regular attendance and on the importance of treatment compliance
- Engage in measures of collaboration regarding TB and HIV for the benefit of the patients
- Ensure that treatment progress is monitored through AFB sputum smear examination
- Identify patients who need to be referred to a medical officer regarding complications of tuberculosis, according to the guidelines of the NTP
- Maintain the *Tuberculosis Register*
- Trace patients who are irregular in attendance
- Keep records of the attendance, treatment, and sputum results in the appropriate registers and files
- Conduct health education for new patients and their household contacts
- Conduct health education on the importance of early diagnosis and the possibilities of cure
- Maintain a three-month stock supply of tuberculosis drugs (see Chapter 13)

National Program Coordinator

- Implement program policies and strategies for planning, implementation, monitoring, and evaluation of the NTP in the region/district/parish, under the technical guidance of the program manager or other responsible offices appointed by Ministry of Health
- Assist healthcare workers in tuberculosis case-finding, diagnosis, and classification
- Ensure that:
  - Patients receive treatment as prescribed
  - Patients taking treatment irregularly are located and reasons for treatment interruption are addressed
  - Registers are kept up to date
  - Laboratory examinations of sputum are done at the required intervals, with appropriate management and/or referrals for patients with complications
  - TB patients are investigated for HIV
  - There is collaboration of efforts between NTP and NAP

    - Policies for DOT are developed and implemented; facilitate the involvement of outreach workers and other community members in the use of DOTS
- Facilitate the involvement of nongovernmental organizations in TB prevention and control efforts
- Supervise the general health staff by:
    - Conducting visits (weekly/monthly) where short-course chemotherapy is administered; health staff should be observed as the clinic is being conducted
    - Visiting all health facilities once every 2 to 3 months (according to conditions)
    - Visiting treatment centers and microscopy units/centers every four weeks
    - Provide annual schedules of visits well in advance to units
- Ensure the procurement of drugs, laboratory supplies, and stationery; ensure their distribution and appropriate use in the health facilities
- Maintain regular contact with health facilities, including nongovernmental organization hospitals and NAP where patients may be referred
- Initiate and coordinate health education through learning institutions and on-the-job activities, for healthcare workers and the general public
- Collect and analyze correct data on TB control activities; compile quarterly reports on case notifications and annual reports on treatment outcome; and give feedback to staff in the periphery
- Cooperate with operational research activities necessary for the control of TB
- Ensure a representative sample of all sputum specimens of TB patients is sent to the reference laboratory for quality control
- Ensure that sputum samples of patients with TB/HIV co-infection and newly diagnosed patients with tuberculosis are sent for culture
- Ensure adequate sputum samples (expectorated or induced) are obtained for diagnostic smear microscopy for all suspects and that sputum samples are sent to the appropriate laboratory for culture, identification, and antimicrobial susceptibility testing of *M. tb* prior to the commencement of re-treatment regimen for patients requiring re-treatment
- Initiate and coordinate control activities for TB/HIV co-infection by liaising with specialized services such as the NAP and services for the control of nosocomial infection
- Assist and advise the tuberculosis control manager and other health staff in the diagnosis, treatment, and prevention of tuberculosis

Microbiologist/Laboratory Advisor (TB)

The incumbent should possess a B.Sc. (BS) in microbiology or a Fellow (Canadian Medical Technology/CASMET), and function as a part of the team in the national program in tuberculosis prevention and control:

- Assist the tuberculosis control unit in ensuring that adequate policy and standards regarding microbiological diagnosis of *M. tb* / MOTT are maintained
- Supervise all procedures at the regional/district/parish level; perform isolation and identification of *M. tb*, or ensure appropriate testing at a reference laboratory
- Determine and conduct surveillance of resistance of *M. tuberculosis* and submit data to the tuberculosis control unit
- Build skills for the conduct of AFB smear activities in the periphery and central laboratories, organize for culture and ensure that quality control procedures on smears

and culture techniques are conducted, and results are recorded and reported; provide regular feedback to the NTP coordinator/manager

- Provide technical cooperation for training relevant staff and networking, both in-country and with external partners
- Collect, compile and analyse smear, culture and antimicrobial susceptibility test results and provide a report to the NTP coordinator/manager
- Procure and provide laboratory supplies for all AFB microscopy centers and the reference laboratories
- Collaborate with NAPs in TB/HIV efforts and in operational research programs organized by the NTP

Laboratory Technician/Microscopist
(health centers/health posts)

- Ensure adequate sputum collection, reception, and registration
- Ensure the practice of good microscopy techniques and careful recording in the laboratory request forms and registers (a manual on sputum smear microscopy is available to the laboratory)
- Work with the NTP to ensure coordination between laboratory and program activities
- Maintain and practice safe techniques while collecting, handling, and transporting specimens
- Keep all positive and negative slides until a sample is selected for quality control
- Ensure safe disposal of infected material and proper care and use of the microscopes

Supervision Instructions

The following are points to check when conducting supervisory visits to hospitals and peripheral health units. A checklist can be designed to guide the supervisory process.

Registers

- Check one quarterly case notification report from the district register
- Check cards and registers for up-to-date completeness and accuracy of entries
- Check treatment outcome report from the district register
- Check for patients in the unit register who may not be in the district register
- Check for patients continuing treatment while declared “cured” or “treatment completed” in the district register

Staff Performance

- Check knowledge of staff on essential matters regarding diagnosis, treatment, and follow-up
- Observe the staff performance while conducting a clinic regarding diagnosis and treatment
- Check knowledge of the patients regarding all aspects of the disease and management
- Compare the number of patients attending with the number registered for that particular day

- Assess the retrieving of defaulters, when done, by whom, the results, and the weaknesses of this activity
- Assess regularity of patients' attendance (in relation to treatment compliance) and procedures used to encourage directly observed short-course chemotherapy
- Assess staff attitudes towards the clinic as well as patients

ISTC STANDARD 20

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

Hospitals/Clinics

In collaboration with the infection control officer in the hospital, check:

- The facility has an Infection Control Plan
- The condition of the wards (i.e., ventilation, isolation, etc.)
- Accommodation for patients with HIV infection
- Whether according to policy, patients with tuberculosis are screened for HIV and vice-versa
- Appropriate management and care are administered
- Whether case notifications are compatible with those in the unit register
- Check starting times of the clinics and the waiting times of patients

Laboratory

- Check for clean water and the general condition (space, ventilation, and cleanliness) of the laboratory
- Check that three specimens are collected within 24 hours by the spot, morning, spot collection procedure
- Check the transit times of specimens sent to the reference laboratory
- Spot-check a few positive and negative slides for quality and for presence of AFBs, take 3 smears for rereading to the reference laboratory
- Count the number of specimens examined over the past 3 months and divide by number of working days per microscopist
- Check whether the last 5 patients diagnosed as AFB negative have had 3 negative smears each
- Note the number of new suspects examined

Drugs and Supplies etc.

- Check the physical condition, safety, and administrative procedures of the drug store (see Chapter 13)
- Check for expired drugs
- Spot-check the stock position of a random sample of drugs and supplies
- Check all ledgers for completeness and good order; spot-check some entries by comparing with supporting documents
- Spot-check store's ledger balances of drugs supplies by physically counting and verifying balances
- Spot-check copies of issue notes with originals issued to coordinator to verify that they agree

Transport

- Check that the quarterly vehicle reports correspond correctly with the logbook entries for the period
- Verify that the visit entered in the logbook has been made by checking the visitors book of the hospital/health unit when visiting the facility
- Check that the logbook is up to date, and that the mileage agrees with the reading on the speedometer

Discuss the weaknesses and strong points of current performance assessment. Compare with previous assessment. Give praise and recognition where it is due. Cite action points for further improvement and indicate actions for resolution of problems.

APPENDIX E

Gastric Aspirates: Patient Preparation and Procedure

Supportive Data

Gastric aspiration is a technique used to collect gastric contents that can be used in the diagnosis of tuberculosis. Tuberculosis continues to be a problem and children are disproportionately affected, in part because they are more likely to get sick when they are infected with the TB organism. The increase in drug-resistant strains of TB makes it important to try to culture and identify each patient's TB organism.

Since many young children have difficulty in expectorating sputum, gastric aspirates are frequently required to culture the organism in a pediatric patient. When children with pneumonia sleep, their mucociliary mechanism sweeps mucus up their airways into their throat. They swallow the mucus and unless the stomach empties, a pool of mucus in the stomach may be a source of the TB organism.

Ideally the patient being prepared for an early morning gastric aspirate should sleep for at least six hours without interruption. They should not eat or drink anything overnight to prevent the stomach from emptying.

Patient Preparation

- Patient to be nothing per oral (NPO) after midnight
- The family should come to the clinic first thing in the morning. Any family members who could possibly have active TB should wear masks to prevent transmission to healthcare workers
- Place nasogastric (NG) tube in patient. Do not use a lubricant that is bacteriostatic. Use as large a bore NG tube as is comfortable (minimum 10F). Avoid too deep a placement to prevent passage through the pylorus

Sample Collection

- Aspirate the stomach contents. If less than about 10 cc of mucus is aspirated, instill 20–30 cc of sterile water into the tube and quickly withdraw. (Note: the organism is most viable when not exposed to saline or preservatives; the kind of sterile water used for infant feeding is fine). Reposition the tube and/or the patient to maximize the yield of gastric contents
- Place the gastric aspirates in a special bicarbonate-containing gastric aspirate tube or regular specimen cup. If a special bicarbonate-containing tube or cup is not available, the lab must neutralize the stomach acid with bicarbonate within 1/2 hour from the time of specimen collection
- Transport the specimen to the microbiology lab as per standard procedure

Pan American Health Organization
Regional Office of the World Health Organization

I-TECH
International Training & Education Center for Health

CHART

Institut Pasteur de la Guadeloupe

Francis J. Curry National Tuberculosis Center

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