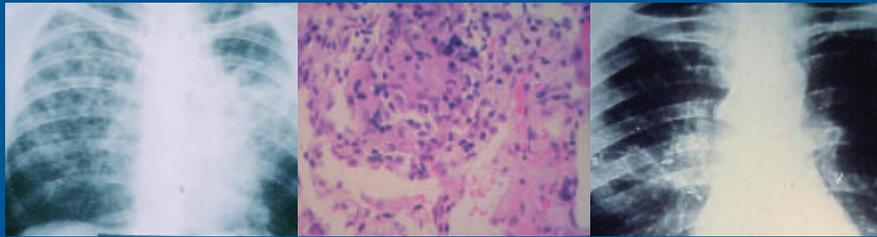


Tuberculosis Verem
Consumption Tibèkilož
결핵 Gruzlica
Tuberkulozi 結核



Kgotlota Ethuna
Batuk 肺結核
Kering
Sanba Nekersa Phthisis Qaaxo
Tuberculose Tuberkuloosi

CLINICAL POLICIES AND PROTOCOLS

Bureau of Tuberculosis Control
New York City Department of Health and Mental Hygiene

Abbreviations

AAP	American Academy of Pediatrics	MAC	<i>Mycobacterium avium</i> complex
ACH	air changes per hour	MAI	<i>Mycobacterium avium intracellulare</i>
AFB	acid-fast bacilli	M. bovis	<i>Mycobacterium bovis</i>
AII	airborne infection isolation	MDRTB	multidrug-resistant tuberculosis
ALT	alanine transaminase	MGIT	Mycobacterial Growth Indicator Tube
AMA	against medical advice	MIRU	mycobacterial interspersal repetitive units
ANA	antinuclear antibody	MOTT	mycobacterium other than tuberculosis, NTM
ATS	American Thoracic Society	MMR	measles, mumps and/or rubella
BCG	Bacille Calmette-Guérin	MRI	magnetic resonance imaging
BP	base pairs	M. tb	<i>Mycobacterium tuberculosis</i>
BTBC	Bureau of Tuberculosis Control	MTD	Mycobacterium Tuberculosis Direct®
CBC	complete blood count	NAA	nucleic acid amplification
CDC	Centers for Disease Control and Prevention	NIOSH	National Institute for Occupational Safety and Health
CDC/DGMQ	CDC Division of Global Migration and Quarantine	NJMRC	National Jewish Medical and Research Center
CFM	cubic feet per minute	NNRTIs	non-nucleoside reverse transcriptase inhibitors
CFP-10	culture filtrate protein-10	NTM	nontuberculosis mycobacterium, MOTT
CI	contact investigation	NYCDOHMH	New York City Department of Health and Mental Hygiene
CNS	central nervous system	NYPHL	New York City Bureau of Public Health Laboratories
CSF	cerebrospinal fluid	PCR	polymerase chain reaction
CT	computed tomography	PHA	public health advisor
CXR	chest X-ray	PHI	protected health information
DOS	Department of State	PIs	protease inhibitors
DOT	directly observed therapy	PPD	purified protein derivative
DR	direct repeat	QFT-G	QuantiFERON®-TB Gold
DRTB	drug resistant tuberculosis	RFLP	restriction fragment length polymorphism
ECLRS	Electronic Clinical Laboratory Reporting System	RTS	return to supervision
EDN	Electronic Disease Notification	SDN	Secure Data Network
EDTA	ethylenediaminetetraacetic acid	SLE	systemic lupus erythematosus
ELISA	enzyme-linked immunosorbent assay	SPC	single positive culture
ESAT-6	Early Secretory Antigenic Target-6	SSRIs	selective serotonin reuptake inhibitors
FP	false-positive	SST	serum separator tubes
HAART	highly active antiretroviral therapy	TB	tuberculosis
HEPA	high-efficiency particulate air	TDM	therapeutic drug monitoring
HHS	U.S. Department of Health and Human Services	TI	Technical Instructions for Medical Examination of Aliens
HIPAA	The Health Insurance Portability and Accountability Act of 1996	TST	tuberculin skin test
HIV	Human Immunodeficiency Virus	TTBI	test for tuberculosis infection
IDPL	Infectious Diseases Pharmacokinetics Laboratory	UGVI	ultraviolet germicidal irradiation
IDSA	Infectious Diseases Society of America	ULN	upper limits normal
INA	Immigration and Naturalization Act	URF	Universal Reporting Form
IND	investigational new drug	USCIS	United States Citizenship and Immigration Services
IFN-g	interferon-gamma	WHO	World Health Organization
IRIS	immune reconstitution syndrome	XDRTB	extremely drug resistant tuberculosis
IRU	Immigration and Refugee Unit		
LFTs	liver function tests		
LTBI	latent tuberculosis infection		

Clinical Policies and Protocols

Bureau of Tuberculosis Control

New York City Department of Health and Mental Hygiene

4th Edition March 2008

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**International Classification of
Tuberculosis**.....inside back cover

Section I.

Introduction to the 4th Edition

Tuberculosis

Section I.

Introduction to the 4th Edition

Director's Statement

This manual describes policies, protocols and recommendations for the prevention, treatment and control of tuberculosis from the New York City Department of Health and Mental Hygiene (NYC DOHMH). It was written primarily for the medical providers of the New York City Bureau of Tuberculosis Control (BTBC) as a reference guide on tuberculosis diagnosis, treatment and prevention. Originally published in 1993, with subsequent editions in 1997 and 1999, the 4th edition of the manual has been updated to reflect changes in national recommendations and BTBC protocols. We continue to use our modified version of the International Classification of Tuberculosis (see inside back cover) for patient classification.

While this manual is comprehensive and covers both routine and complex issues, it cannot and should not be substituted for the best judgement of individual physicians in specific clinical situations. Strict adherence to clinical protocols, however, will result in improved care and consequent control of TB for most patients. Clinicians in the BTBC chest centers and others who use this manual are strongly encouraged to seek expert consultation when needed, particularly in special situations such as drug-resistant tuberculosis.

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About the 4th Edition

This manual was first published in 1993 to guide New York City in our struggle to bring the tuberculosis epidemic under control. Based on national guidelines and the best current consensus of clinical and published data, subsequent editions were published in 1997 and 1999 for use in our chest centers and by New York City physicians for the diagnosis, treatment and prevention of tuberculosis (TB). The 4th Edition incorporates national guidelines published in 2003.

Like most areas of medical treatment, TB control is an evolving field. New medications and treatment protocols continue to be researched and introduced. This edition includes new policies and procedures for diagnosing and treating active TB, and screening and treatment of latent tuberculosis infection (LTBI) adopted by the Centers for Disease Control and Prevention (CDC), American Thoracic Society (ATS), Infectious Diseases Society of America (IDSA) and American Academy of Pediatrics. The CDC now refers to preventive treatment as treatment of LTBI—this change in terminology is reflected in the current edition of the manual.

Treating TB is beneficial to individuals and to the community as a whole as it reduces transmission. Physicians who properly treat TB and ensure successful completion of therapy are therefore performing an essential public health service.

This version of the provider manual has been reorganized to prioritize TB control activities. The sections on the evaluation and treatment of patients with active TB are presented first because the principal strategy for controlling TB is (1) to promptly identify individuals with infectious TB and (2) to quickly and permanently render them noninfectious through effective treatment.

Keeping patients under care until they complete treatment can be very challenging; therefore, an extensive case management section is included to reflect this important public health aspect of TB control. Contact investigation remains the next most important priority, and updated and detailed BTBC guidelines are included herein. Targeted testing and treatment of LTBI guidelines have been moved to the end of the manual and incorporate the most recent ATS/CDC/IDSA recommendations.

Note: In this manual, *M. tb* generally refers to all the organisms of the *M. tb* complex, not just *M. tuberculosis*.

For information not included in this manual, consult one of the individuals listed on p. 11.

The 2003 National Guidelines

The ATS, CDC and the IDSA published revised guidelines for the treatment of TB in 2003 (visit: www.cdc.gov/MMWR/PDF/rr/rr5211.pdf). New features include:

- Patient-centered case management, with an adherence plan that emphasizes directly observed therapy (DOT) as the initial treatment strategy
- Use of rifapentine and isoniazid once weekly in the continuation phase of treatment (months 3–6) for select HIV-negative patients
- Recommendations to obtain sputum cultures at the end of the intensive phase of treatment (end of month 2) to identify those at increased risk of subsequent relapse. If cultures are positive, the continuation phase of treatment should be prolonged for certain individuals (see p. 43).

The 2003 national guidelines clearly assign responsibility for successful treatment to private providers and public health programs, **not** to the patient. Physicians should ensure that every TB treatment plan stresses the use of DOT. For patients with drug-susceptible TB, providers should use intermittent regimens to facilitate the provision of DOT. To achieve TB treatment goals, physicians and the BTBC need to increase their commitment to collaborate. By coordinating care with local public health authorities, physicians are more likely to achieve better outcomes for their patients.

Rifapentine

Rifapentine is a recently approved anti-TB drug that is not yet widely used in clinical settings. Clinical data support intermittent use of rifapentine with isoniazid during the continuation phase of TB treatment for patients with culture-positive non-cavitary pulmonary TB whose sputum is smear negative for acid-fast bacilli (AFB) at the end of the 2-month intensive phase.

Rifapentine (600 mg) is administered once weekly with isoniazid (900 mg) in the continuation phase of treatment. This combination should only be given under direct observation. As with rifampin, drug-drug interactions are common and patients should be monitored regularly. Ease of administration makes this regimen attractive for both TB control programs and patients.

Rifapentine should not be used in HIV-infected patients, given their increased risk of developing rifampin resistance on currently recommended dosages. Data are inadequate to recommend rifapentine in children younger than 12 years of age, pregnant or lactating women, or individuals with culture-negative or extrapulmonary tuberculosis.

Use of Fluoroquinolones in the Treatment of Tuberculosis

The use of fluoroquinolones in the treatment of TB has become more common. They are preferable for use because they are oral agents, have few major side effects and the newer fluoroquinolones appear to be as potent as certain first-line TB drugs. Fluoroquinolones are indicated when first-line TB drugs are not tolerated, in liver sparing regimens and for disease with strains resistant to first-line TB drugs.

The most commonly used agents in patients with active TB are levofloxacin and moxifloxacin. This manual provides recommendations for the use of old and new agents, and highlights adverse effects, especially the newly recognized blood sugar control issues with the use of fluoroquinolones (see p. 91).

BTBC Guidelines vs. ATS/CDC/IDSA Guidelines

The BTBC guidelines are similar to the national guidelines. Differences are summarized below.

- **Prolonged treatment for patients with a positive culture at 2 months.** CDC/ATS/IDSA guidelines recommend 9 months of treatment for individuals with drug-susceptible TB who have a cavity on initial chest X-ray (CXR) and who are still culture positive at 2 months. In addition, they recommend that anyone with cavitation or positive culture at 2 months receive 9 months of treatment at the discretion of their physician.

The BTBC agrees with the former, but in addition recommends prolonged treatment for anyone with a positive culture at 2 months regardless of CXR results. Cavitation alone is not given as a criterion for prolonged treatment.

- **Intermittent therapy for HIV-infected patients.** The 2003 national guidelines recommend either daily or 3 times a week intermittent therapy for patients who are HIV infected, with a CD4 T-lymphocyte cell count of less than 100/mm³.

However, BTBC recommends that such patients be treated with a daily regimen in the intensive phase of TB treatment, and either daily or 3 times a week in the continuation phase.

For patients with CD4 count greater than or equal to 100 cells/mm³ at the time of TB diagnosis, the BTBC recommends a daily regimen in the intensive phase and regimens of either 2 times or 3 times a week in the continuation phase. All patients who are HIV infected should receive TB treatment with DOT.

- **Duration of therapy for smear- and culture-negative active pulmonary TB.** The BTBC now follows the CDC/ATS/IDSA recommendations with respect to treatment for smear- and culture-negative TB by recommending that patients with smear- and culture-negative TB be started initially on 4 drugs (isoniazid, rifampin, pyrazinamide and ethambutol), in the intensive phase. At the 2-month assessment, if the patient is responding to therapy and no other etiology is identified, treatment can continue with only isoniazid and rifampin under certain conditions (e.g., patient has never been treated before). The common BTBC term for this regimen is "4 for 2 and 2 for 2."

The ATS/CDC/IDSA guidelines recommend an initial CXR and a repeat CXR at 2 months. The BTBC follows these recommendations and, in addition, recommends a CXR at the completion of 4 months of therapy.

- **Evaluation and management of patient with old fibrotic changes on CXR consistent with TB.** A "4 for 2 and 2 for 2" regimen is considered acceptable for old TB, and is preferred over the 9-month isoniazid regimen.
- **Use of pyrazinamide in pregnancy.** The ATS/CDC/IDSA guidelines do not recommend the use of pyrazinamide during pregnancy, although the World Health

Organization does. In this manual, the BTBC recommends treating pregnant women with isoniazid-resistant tuberculosis with rifampin, pyrazinamide and ethambutol.

- **Use of ethambutol in children.** The BTBC recommends treating children with standard 4-drug therapy, provided that visual testing can be done or if they are at high risk of having drug-resistant TB. In addition, ethambutol dosage in children should be 20 mg/kg daily, based on new literature (see p. 59).
- **Sputum and chest X-ray at completion of therapy for drug-sensitive patients.** The BTBC recommends collecting sputum at the end of treatment to document cure, plus a new baseline CXR in case the patient relapses or develops another pulmonary disorder. The BTBC also recommends a CXR at the completion of treatment to provide a baseline for comparison with future CXRs.

There is no specific recommendation for sputum collection at the end of treatment according to ATS/CDC/IDSA guidelines; the guidelines suggest that a CXR at the end of treatment is useful, but not essential.

- **Follow-up after treatment completion.** At the end of treatment for multidrug-resistant TB (MDRTB), the BTBC recommends that all patients with MDRTB be followed for 2 years, including clinical evaluation, sputum collection and CXR every 3 months in the first year after completion of therapy, and every 6 months during the second year. Patients who did not receive rifampin or rifabutin should also be followed in this manner. Recommendations for follow-up care of non-MDRTB patients who received non-standard regimens are also provided (see pp. 115-16, including Table VI-2).

Treatment of Patients Who Are Co-Infected with Tuberculosis and HIV

Treatment of patients co-infected with TB and HIV should be coordinated between the TB and HIV providers to ensure optimal treatment for both diseases.

Treatment of TB in the presence of HIV infection is complicated by drug-drug interactions between rifamycins and the protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) used to treat HIV infection.

Specific recommendations related to rifampin:

- Previous recommendations specifically contraindicate the use of rifampin with any PIs or NNRTIs.
- New data indicate that rifampin can be used for treating active TB in patients whose anti-retroviral regimen includes efavirenz with 2 or more nucleoside/nucleotide reverse transcriptase inhibitors. Nevirapine may be used with rifampin in selected patients (see p. 51).
- Use of rifampin with boosted saquinavir at any dose seems to be contraindicated.

Specific recommendations related to rifabutin:

- Rifabutin can be used with regimens containing efavirenz or nevirapine, or a single PI (except saquinavir alone), with some dose adjustments.
- It can also be used with several ritonavir-boosted combinations.
- Data is lacking on the use of rifabutin in antiretroviral regimens containing combinations of NNRTIs and PIs, or multiple PIs, and should be used with caution.

Hospitalization and Discharge Guidelines

Diagnostic assessment and treatment of TB can be achieved in an outpatient setting for most individuals. The decision to admit a patient to a hospital should take into account all relevant aspects of care, including the costs associated with unnecessary admissions. With the advent of modern anti-TB chemotherapy, hospitalization is no longer necessary for effective TB treatment. Studies have shown outpatient TB treatment achieves cure rates that are comparable to inpatient care, and that outpatient therapy is not associated with an increase in TB transmission in the community.

This manual provides detailed guidelines for patients with infectious TB, regarding admission, airborne isolation, discharge and return to work, school and other congregate settings (see p. 121).

Targeted Testing and Latent Tuberculosis Infection

Despite the dramatic decline in the number of reported cases of TB in New York City, many New Yorkers remain at high risk for developing active tuberculosis disease once they are infected with *Mycobacterium tuberculosis* (*M. tb*). Groups at especially high risk include contacts of persons with active TB, HIV-infected persons, individuals with certain predisposing medical conditions and recent immigrants from countries with high rates of TB.

In April 2000, the ATS and CDC revised their guidelines for the treatment of LTBI, which were subsequently endorsed by IDSA and the American College of Physicians: www.cdc.gov/mmwr/preview/mmwrhtml/mm5231a4.htm; sections on infants and children were endorsed by the AAP. New developments since that time are detailed below.

- In 2003, the CDC revised its guidelines on the use of rifampin and pyrazinamide for the treatment of LTBI due to unacceptable levels of hepatotoxicity: www.cdc.gov/mmwr/preview/mmwrhtml/mm5231a4.htm.
- In October 2004, the Pediatrics Tuberculosis Collaborative Group published revised recommendations on targeted tuberculin skin testing and treatment of LTBI in children and adolescents: <http://pediatrics.aappublications.org/cgi/content/full/114/4/S2/1175>.
- The tuberculin skin test (TST) performed by the Mantoux method is the most commonly used method for identifying TB infection. Since 2001, blood-based testing has become available as an alternative to the TB skin test (see p. 183).

This manual provides updated recommendations based on all of the above guidelines and summarizes fundamental aspects of testing and treatment of LTBI. Topics covered include whom to test for TB, revised LTBI treatment regimens, updated recommendations on the treatment of individuals who are HIV-positive and who are receiving antiretroviral agents and rifamycins, screening and treatment of children and information on the use of blood-based TB tests.

Terminology in this manual has been changed to reflect the availability of blood-based tests for TB infection. The term TST is only used in this

manual in specific instances that reference the tuberculin skin test. A more general term, test for TB infection, is generally used instead. The manual also covers new recommendations on the treatment of LTBI in certain groups of patients.

Key Sources

The key sources included in this manual have served as the basis for most of the BTBC guidelines and provide readers with sources for further information on managing the many difficult issues around the treatment of patients with TB. The references are listed by section and are arranged alphabetically; none are cited individually in the text of the manual. Drug monographs and manuals from manufacturers are **not** listed and should always be consulted as needed. An extensive reference list is available at www.nyc.gov/health/tb.

Appendices

Many of the appendices in prior versions have been removed as the national guidelines are easily accessible online. BTBC forms are available on the BTBC Intranet www.nyc.gov/html/doh/html/tb/tb-hcp.shtml#form, and others are on the BTBC Web site. Important aspects of management, previously located in the appendices, have been incorporated into the various sections.

Tuberculosis Surveillance and Epidemiology

Surveillance

Surveillance is a key component of TB control; it is the ongoing collection, analysis, interpretation and dissemination of health data essential to the development and evaluation of public health programs. The objectives of TB surveillance are to:

- Ensure complete reporting of patients suspected of having or confirmed to have tuberculosis
- Maintain and improve the quality and integrity of information on persons with TB
- Facilitate the management of patients with TB
- Ensure the prevention of the transmission of *M. tb* via timely contact investigations

Surveillance data are validated and verified using case review, data validation checks, analysis of timeliness of reporting and audits at microbiology and pathology laboratories. Surveillance data are used to produce data reports and outcome indicators, answer research questions and evaluate interventions.

The reporting of tuberculosis by laboratories and clinical providers is mandated by the New York City Health Code and New York State regulations. Reports must be received at the Health Department within 24 hours of diagnosis, specimen collection or start of anti-TB treatment. Providers can provide reports via telephone, fax, overnight mail or electronic “Universal Reporting Form” (URF) (**Form PD-6**), available online at www.nyc.gov/html/doh/html/hcp/hcp-urf.shtml. Click “Information & Services for Health Care Providers.” As of July 1, 2006, all laboratories in New York City must report electronically, either via file transfer or via direct entry into a Web page. See p. 229, Appendix II-A for reporting requirements.

The Office of Surveillance also ensures the transfer of patients suspected or confirmed with TB to and from NYC. As patients with TB travel or relocate, it is essential that their care continues to be coordinated when travel is long term or involves permanent relocation.

Tuberculosis Epidemiology in New York City

Since the peak of the most recent TB epidemic in 1992, the **number** of TB cases has declined by more than 74%, from 3,811 in 1992 to 984 in 2005 (the first time there have been less than 1,000 cases). The **rate** of TB declined from 51.1 cases per 100,000 in 1992 to 12.3 per 100,000 in 2005. The dramatic decrease in cases is attributable to improved case finding strategies, standard treatment with 4 anti-TB drugs, comprehensive patient management practices and DOT. In addition to reducing active TB cases, the intensive effort by BTBC to control the epidemic in the city has also led to decreases in drug resistance and TB deaths — there were 95% fewer MDRTB cases in 2005 than in 1992 and almost 90% fewer patients co-infected with HIV.

While TB has decreased considerably in NYC both overall and among U.S.-born individuals, the proportion of non-U.S.-born persons increased substantially, from about 18% in 1992 to 70% in 2005. The cases originate from all over the world, but the greatest numbers are from Asia, and Central and South America.

Similar to the U.S., most TB cases in NYC (almost 80%) are among adults aged 25 to 64 years, two-thirds are male and cases are nearly equally divided among Hispanic, black-non-Hispanic and Asian people. From 2001 to 2005, 76% of TB cases were culture positive, half were AFB smear positive from any site, 80% had pulmonary disease and 16% were HIV infected. Of culture-positive patients, 2% to 4% had MDRTB, while 12% to 15% had other drug-resistance patterns. In the last few years, approximately 32% of TB cases were residents of Queens, 32% of Brooklyn, 20% of Manhattan and 16% of the Bronx; these numbers include some 18 to 30 inmates of correctional facilities with TB each year.

The continued immigration of large numbers of people from countries with a high incidence of TB, and the plethora of homeless and HIV-infected persons in NYC pose a serious challenge to TB control in the city.

Confidentiality and Health Insurance Portability and Accountability Act Regulations

Protection of patient confidentiality is of the utmost importance to public health. Maintaining confidentiality assures that patients, their families and their communities have the trust necessary to collaborate with the Department of Health regarding patient treatment, contact investigation and other issues. Violation of a patient’s confidentiality is a very serious infraction of New York State Public Health Law, New York City Health Code, Policies and Procedures of the BTBC and Standards of Conduct of the City of New York.

Laws Governing Confidentiality

- **Article 11 (Reportable Disease and Conditions) of the NYC Health Code:** Lists basic provisions related to reporting, control and confidentiality of communicable diseases, including TB.

Section 11.07 also allows the DOHMH to furnish “appropriate information... to any person when necessary for the protection of health.”

- **Public Health Law 2221:** Outlines confidentiality of TB records and information obtained or maintained by state and local health departments.
- **State Sanitary Codes 2.17 and 2.18:** Outlines laws regarding the confidentiality of general medical records.
- **State Sanitary Code, Part 2, Section 2.6(c):** Directs public health personnel to “instruct a responsible member of the household of the means to be taken to prevent further spread of the disease and to put into effect those other recognized measures which tend to reduce morbidity and mortality.”
- **Public Health Officers Law, Code of Ethics, Section 74.3.C:** Provides that an employee who knowingly and intentionally violates its provisions may be fined, suspended or removed from employment.
- **New York State HIV Confidentiality Law, Article 27F:** Requires that information about AIDS and HIV be kept confidential and anyone receiving an HIV test must sign a consent form first. The law strictly limits disclosure of HIV-related information. When disclosure of HIV-related information is authorized by a release signed by the patient, the person who has been given the information must keep it confidential; new disclosure may occur only with another authorized signed release from the patient. The law only applies to people and facilities providing health or social services.
- **The Health Insurance Portability and Accountability Act of 1996 (HIPAA):** A privacy rule that protects all individually identifiable health information in any form (electronic or non-electronic) that is held or transmitted by a covered (e.g., hospitals, physicians) entity. It gives individuals the right to inspect, copy and request amendment to their medical record.

HIPAA Privacy Rule

On August 14, 2002, the U.S. Department of Health and Human Services (HHS) published final HIPAA Privacy regulations. Most providers

covered by HIPAA Privacy regulations were required to comply with these regulations as of April 14, 2003. These rules provide the first national standards for protecting the privacy of health information and certain individually identifiable health data, referred to as protected health information (PHI). PHI is individually identifiable health information that is transmitted or maintained in any form or medium (e.g., electronically, on paper, or orally), but excludes certain educational records and employment records.

In enacting HIPAA, Congress was very clear in its intent that the regulations not impede public health practice [42 USCA Section 1320d-7(b)]. HHS similarly recognized the importance of continuing to authorize the sharing of protected health information for public health purposes. The federal regulations authorize covered entities to disclose protected health information without an individual’s authorization or the opportunity for the individual to agree or object, to a public health authority “...authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability, including, but not limited to, the reporting of disease, injury, vital events such as birth or death, and the conduct of public health surveillance, public health investigations, and public health interventions...” [45 CFR Section 164.512(b)(1)(i)].

Furthermore, the privacy regulations authorize providers to disclose protected health information without an individual’s authorization or the opportunity for the individual to agree or object when disclosure is required by law [45 CFR Section 164.512(a)]. The New York City Health Code, the New York State Sanitary Code (effective in New York City) and the New York State Public Health Law authorize and in fact require the reporting of numerous diseases or conditions (for example, communicable diseases such as TB, severe acute respiratory syndrome [SARS], immunizations administered to a child under the age of 7 years and HIV/AIDS [Health Code Sections 11.03 and 11.04, 10 NYCRR Section 2.10 and Public Health Law Section 2130]).

In addition to the information routinely required to be reported to DOHMH, there may be instances when DOHMH may request information necessary for a public health activity. Privacy

regulations, with limited exceptions, require covered entities to limit the amount of information disclosed to the minimum necessary to accomplish the intended purpose. Disclosing the minimum necessary is not applicable to disclosures required by law [45 CFR Section 164.502(b)(2)(v)]. As per the Privacy regulations, when the Department requests information as authorized by law, the covered entity may rely on the Department's representation that the information requested is the minimum amount of information necessary to carry out the authorized public health activity [45 CFR Section 164.514(d)(3)(iii)].

To ensure compliance and cooperation, access to paper and electronic medical records as necessary should be provided to DOHMH staff with appropriate credentials. Failure to report information to NYC DOHMH, as required by law, would be a violation of the public health laws outlined above and may result in legal sanctions.

NYC DOHMH is legally mandated to ensure the confidentiality of all information received from providers, and continues to attach the highest level of confidentiality to reported information.

Talking to Tuberculosis Patients and Contacts

The laws and regulations about confidentiality and tuberculosis should be explained to every patient at the beginning of treatment and reinforced when appropriate. The explanation should help ensure protection of the patient's confidentiality. If translation is necessary, it is advisable to use BTBC employees or a language translation service, since using a family member or outside translator may breach confidentiality.

When evaluating contacts, BTBC employees may not disclose the source case's identity, address or any medical conditions, including TB. Contacts may be told that the DOHMH believes they have been exposed to someone with infectious TB. However, if an infectious person is going to be treated as an outpatient, the household members need to be told of this and be taught how to minimize their exposure. (See p. 126 and Appendices III-E and III-F.)

Often family, friends and co-workers already know that the patient is on treatment; however, BTBC employees cannot confirm that information.

In these situations BTBC employees should say, "I am sorry, but I am legally bound by laws of confidentiality and cannot reveal any information."

It is BTBC policy that rules of confidentiality apply to patients even if they have died; an exception may be made when doing the initial interview of the next of kin. In that circumstance, the diagnosis and transmission of tuberculosis must be explained to the next of kin in order to obtain information regarding contacts. Beyond that initial interview, BTBC employees may not disclose any confidential information regarding the deceased when talking to contacts of a person who is diagnosed with TB at death.

Exceptions to Confidentiality Rules

Confidentiality protection is not absolute. Generally, the exceptions to the rule are based on a "need-to-know"—either to treat the individual patient or to protect the public health. When questions arise about disclosure of protected health information, the decision to disclose should be made in consultation with the employee's supervisor and with the approval of a BTBC authorized staff who is acting on a need-to-know basis and under the guidance of the DOHMH law unit. Such release of information must be carefully documented in the patient record and other relevant documents such as a case investigation record.

The following are the general areas of exception:

Protection of the Public Health

This is a broad exception that requires the patient's right to confidentiality balanced against the threat to the public health. The risk of transmission must be so great that a breach of confidentiality is warranted. Exceptions may occur when the patient provides consent or staff is confronted with an exceptional situation in which the patient is knowingly endangering the health of others. In these instances, the decision to disclose information should be made in consultation with a supervisor.

Reporting

Physicians are required to report every suspected or confirmed case of TB and the BTBC is required to monitor the TB treatment of all

reported cases. Physicians are also required to examine all household contacts or refer them to the BTBC for examination. Therefore, even though it may seem like a breach of confidentiality to obtain information about patients from private doctors, this is an essential part of the BTBC's work and is required by law.

Contact Investigations

When conducting TB exposure evaluations, it may be necessary to reveal the identity of a patient to a site administrator. This might occur when there is a need to identify a TB patient's working area or school classes to determine specifically which co-workers or students have had close contact with the patient. The patient's name may only be revealed to an administrator or school principal with the understanding that the information will not be released to other

employees or students. The administrator or principal is bound by the Americans with Disabilities Act to protect the identity of the worker or student.

Sharing of Information with Other Agencies

The law allows the release of TB information to physicians or institutions providing examination of or treatment to a patient. When there is an ongoing need to share information to protect the public health, agreements may be negotiated between agencies, establishing the type of information to be shared and who will have access to it. There must be a legitimate medical or public health need for the information—and these organizations are not permitted to re-disclose the information unless necessary to treat the patient or protect the public health.

Mission Statement, New York City Bureau of Tuberculosis Control

The mission of the Bureau of Tuberculosis Control (BTBC) is to prevent the spread of tuberculosis and eliminate it as a public health problem in New York City.

The goals of the BTBC are:

1. To identify all individuals with suspected or confirmed tuberculosis (TB) disease and ensure their appropriate treatment, ideally on a regimen of directly observed therapy.
2. To ensure that individuals who are at high risk for progression from latent infection to active disease (e.g., contacts of active cases, immunocompromised individuals and recent immigrants from areas where TB is widespread) receive treatment for latent TB infection and do not develop disease.

The BTBC achieves its goals through direct patient care, education, surveillance and outreach. Its mandated activities include the following:

- Ensuring that suspected and confirmed cases of TB identified in all facilities in New York City are reported to the BTBC and documented on the computerized, confidential TB Registry.
- Conducting intensive case interviews and maintaining an effective outreach program so that TB cases remain under medical supervision until completion of a full course of treatment and identified contacts receive appropriate medical care.
- Monitoring and documenting the treatment status of all patients with active TB.
- Setting standards and guidelines, and providing consultation on the prevention, diagnosis and treatment of latent TB infection and disease in New York City.
- Operating clinical sites throughout New York City that provide state-of-the-art care for persons with suspected or confirmed TB disease and their close contacts, at no cost to the patient.
- Ensuring care for persons who have or are suspected of having active TB disease, in accordance with New York State Public Health Law §2202, Article 22, Title 1, at no cost to the patient.
- Collaborating with community-based organizations and health and social agencies in New York City and New York State to improve case-finding and the prevention and control of TB through education, outreach and targeted screening in communities at high risk for TB.

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Section II.

Initial Evaluation of Suspected Tuberculosis

Tuberculosis

Section II.

Initial Evaluation of Suspected Tuberculosis

Pathogenesis of Tuberculosis

Transmission, Infection and Proliferation

Transmission of tuberculosis (TB) occurs when infected patients expel small droplets containing tubercle bacilli into the air (when they cough, sing or speak) and a susceptible person inhales the bacilli and becomes infected. These tiny droplet nuclei (1-5 μm in diameter) float in air, the fluid evaporates and the living tubercle bacillus may remain airborne for long periods until inhaled.

Initially, there is rapid inflammation at the alveolar site where the tubercle bacillus is deposited, usually in the subpleural and in the mid-lung zones where greater air flow favors bacilli deposition. The initial inflammation does not usually inhibit the growth of the organism—bacilli are engulfed by alveolar macrophages, and therein replicate and destroy the host cell in the process. Tubercle bacilli drain via lung lymphatics to the hilar lymph nodes, then the thoracic duct, and ultimately may gain entry to the systemic venous circulation where they circulate and can disseminate, causing additional local foci of infection, particularly seeding the apices of the lungs, kidneys, bone growth plates and vertebrae.

Host Immune Response

After a period of 6 to 12 weeks, cellular immunity directed to the tubercle bacillus develops. Stimulated by antigens from the organism, T-lymphocytes become specifically sensitized and activated; these in turn activate macrophages that become capable of antibacterial action against the tubercle bacillus. The cellular immune reaction is the basis for the tuberculin skin test (TST) and the blood based assays currently in use, and for the characteristic pathologic lesion (the granuloma) that is typical of tuberculosis infection.

The granuloma is composed of a roughly spherical collection of lymphocytes, macrophages and epithelioid cells with a small area of central caseous necrosis. In up to 90% of individuals who become infected with the tubercle bacilli, these small granulomas remain localized and quiescent, become encapsulated with fibrous tissue and may ultimately show calcification of the central caseum, a highly acidic milieu which inhibits mycobacterial proliferation.

Inflammation, Necrosis and Cavity Formation

Primary tuberculosis is progressive disease without a period of latency in the weeks to months following primary infection. It occurs most commonly in infants with immature immune systems, elderly people with waning immunity and HIV-infected persons. The site of disease reflects the path of infection, appearing as enlarged hilar or mediastinal lymph nodes and lower or middle lung field infiltrates on chest X-ray (CXR).

Reactivation tuberculosis occurs more than a year and sometimes decades after primary infection; in this type, the site of disease is most commonly the apices of the lungs but may also include other sites seeded years earlier by the primary infection.

As disease progresses in the lung, the caseous material in the center of the granuloma may undergo liquefaction. This leads to the release of proteolytic enzymes and cytokines (including TNF- α) which cause tubercle bacilli to proliferate and produce more antigen at the site, causing an increased cellular immune response, and lesion enlargement. Ultimately, the necrotic zone may rupture into a neighboring bronchus, the liquefied debris drains into the bronchus and the site of necrosis is replaced by air, resulting in a small tuberculous cavity. This liquefied material (sputum) may be expectorated by the host, leading to the release of infectious droplet nuclei and the potential for further tuberculosis transmission.

Within the host, the liquefied material may travel endobronchially to other regions of the lungs, spreading disease and causing inflammatory tissue damage to other lobes. Examination of sputum and CXRs are the recommended evaluation tools because of these pathologic and clinical characteristics.

Physical Evaluation of Adults and Children

Examination of individuals suspected of having active TB should include:

- A medical evaluation, including a detailed history of the current illness
- Past Medical history
- Symptom review
- Social history
- Physical examination

In addition:

- If there is no documentation of prior test for TB infection, order one unless cultures for *M. tuberculosis* (*M. tb*) are already positive.
- Ask patients about history of TB treatment. If the patient has previously been treated, determine the drugs used, the duration of treatment, the history of adverse reactions, the reasons for discontinuing treatment and the previous drug susceptibility results.
- Ask female patients whether they may be pregnant; order a pregnancy test for women with menses more than 2 weeks late. Offer pregnant women who are HIV negative or whose HIV status is unknown HIV counseling and testing, unless HIV testing has been done within the past 6 months. Manage pregnant women with TB disease according to the guidelines on p. 56.
- If the patient is a child under 18 years of age, identify the source patient's sputum culture and susceptibility results to ensure treatment is appropriate. If the source patient has not been identified, initiate a source case investigation (see p. 167).

- Search the TB Registry to see if the patient has a record of TB disease or latent tuberculosis infection (LTBI)
- Ask about the following risk factors for multidrug-resistant tuberculosis (MDRTB):
 - Previous (especially incomplete) treatment for TB
 - Close contact with a person who has MDRTB
 - Previous hospitalization in a facility with an outbreak of a drug-resistant strain of TB (especially if housed on the ward where the outbreak occurred)
 - Incarceration in the New York State prison system since 1990
 - Country of origin

If a patient has one or more risk factors, other anti-TB medication should be considered in addition to isoniazid, rifampin, pyrazinamide and ethambutol.

Note: There is nothing about the initial clinical presentation of patients with MDRTB to distinguish them from patients who have a susceptible strain.

- Patients aged 18 to 64 years, including those without behavioral risk factors for HIV, should be counseled and offered HIV testing unless they have (1) a positive HIV antibody test or (2) a negative result to an HIV antibody test given less than 6 months previously.
- Patients younger than 18 years of age or who are 65 years and older should be counseled and offered testing if they have behavioral risk factors for HIV and have no documented positive HIV test.
- According to New York State law, adolescents over age 13 may be tested for HIV without parental consent. Parental consent for HIV testing is advised for patients younger than 18 years of age, although these patients may be tested without parental consent at the discretion of the physician-in-charge of the chest center. For young children, the results of maternal HIV testing can be used to determine the child's HIV status. In New York State, maternal HIV testing is universal through testing of cord blood.

- Individuals who are HIV negative and who remain at risk for HIV infection during TB treatment should be retested during the course of treatment.
- If ethambutol is being considered for treatment, a baseline visual acuity exam and Ishihara's test for color blindness should be performed.
- If an aminoglycoside or capreomycin is being considered for treatment, a baseline audiogram should be performed.

Radiographic Evaluation

- A baseline chest X-ray (CXR) should be obtained for all patients, except those who show proof of a CXR, taken in the past month, which can be filed in the chest center. An oral report alone is not acceptable.
- Children younger than 5 years of age should undergo both posterior-anterior and lateral CXR. (For children with an equivocal posterior-anterior CXR, computed tomography of the chest (CT) with contrast can assist in the evaluation of possible adenopathy.)
- All other individuals should receive a posterior-anterior CXR only; additional views should be ordered at the physician's discretion.
- Pregnant women who are being evaluated for active TB disease should undergo CXR without delay, even during the first trimester. A lead shield should be used.
- Patients suspected of having extrapulmonary TB should also undergo CXR to rule out pulmonary TB. (Diagnosis and treatment of extrapulmonary TB is discussed p. 71.)
 - If the CXR is abnormal (including pleural TB), smears for acid-fast bacilli (AFB), as well as cultures and drug susceptibilities, should be ordered from sputum samples collected on 2 to 3 separate days.
 - Three sputa should be obtained from patients who are HIV positive and other patients who are immunosuppressed, even if they have a normal CXR.
- Sputa should be obtained for all patients with suspected pulmonary or pleural TB.

Microbiologic Evaluation

The diagnosis of TB disease is mainly bacteriologic in adults. In children it is usually epidemiologic and thus indirect. In addition to AFB smear and culture results, there are new rapid diagnostic tests which may be helpful. Once the diagnosis of TB is established, several molecular techniques (genotyping) are available for distinguishing among strains of *M. tb* complex.

If the patient is suspected of having TB disease, treatment of TB should not be delayed while the laboratory diagnosis is being established.

Specimen Collection

Sputum should always be obtained in adults and children who are suspected of having pulmonary TB.

- Three sputum samples should be collected over 2 to 3 separate days for AFB smears and drug susceptibilities. At least 1 of them should be an early morning specimen.
- Unless failure of treatment or relapse is suspected, obtain only 1 sputum sample in the chest center if several samples have recently been obtained by a hospital, or if the patient's sputum cultures have already converted to negative.
- In addition to common specimens such as sputum (natural or induced) and gastric aspirate, the following specimens are appropriate for laboratory submission:
 - Urine
 - Stool
 - Cerebrospinal fluid (CSF)
 - Pleural, peritoneal or pericardial fluid
 - Bronchial washings
 - Material from abscesses
 - Endometrial scrapings
 - Bone marrow
 - Other biopsy specimens

All specimen collection procedures that produce aerosols that may contain *M. tb* (e.g., sputum induction, bronchoscopy) should be performed in properly ventilated areas or booths by personnel using adequate respiratory protection.

Sputum collection. Patients should be instructed on the proper method of sputum collection (the material brought up from the lungs after a productive cough is what is desired, and not nasopharyngeal discharge and saliva).

- The sputum should be collected in a sterile, wide-mouthed specimen container with a tightly fitting screw-top lid. Alternatively, commercially available sputum collection devices using a 50-ml plastic, disposable centrifuge tube can be used.
- Specimens should be clearly labeled with patient-identifying information and the date of collection. The container should be placed in a paper bag and refrigerated until transported to the laboratory. A TN50 form should be filled out properly and sent with the specimen to the Public Health Laboratory. The form is available at www.nyc.gov/html/doh/downloads/pdf/tb/tb-form-tn50.pdf
- Patients who have difficulty producing sputum should undergo sputum induction by inhalation of an aerosol of sterile hypertonic saline (3%) or sterile water produced by a nebulizer that causes coughing. The procedure should be done in areas with adequate environmental controls such as a hood or booth fitted with a high-efficiency particulate air (HEPA) filter to prevent transmission, and patients undergoing the procedure should be attended by qualified personnel using appropriate respiratory protection (see p. 132).
 - Aerosol-induced specimens may appear thin and watery and should be clearly labeled as “induced sputum” so it will not be discarded by the laboratory as an inadequate specimen.
 - Among younger children, especially children under 5 years of age, sputum is difficult to obtain; most children are sputum smear negative. In children who are able to produce a specimen, however, it is worth sending it for AFB smear microscopy and mycobacterial culture.

- Bacterial yields are higher in older children (more than 5 years of age) and adolescents, and in children of all ages with severe disease.
- Induced sputum may be obtained from young children who cannot produce sputum spontaneously.
- Several recent studies have found that sputum induction is safe and effective in children of all ages and the bacterial yields are as good as or better than those from gastric aspirates. However, training and specialized equipment are required to perform this procedure properly.

Gastric aspiration. This method is used for children who cannot produce sputum either spontaneously or with aerosol inhalation. Children who are contacts of a source case susceptible to isoniazid and rifampin will usually have the same susceptibility; treatment should be adjusted accordingly as the concordance between the susceptibility of the source case and the contact is high for drug-sensitive TB. Gastric aspirates may not be needed for such children.

Note: Children not fasting for at least 4 to 8 hours before gastric aspiration and children with a low platelet count or tendency to bleed should not undergo the procedure.

- Gastric aspirates should be obtained from children who are contacts of MDRTB cases as there is not 100 % susceptibility concordance.
- Hospitalize the patient and, for highest yield, take the specimens when the patient awakens in the morning and is still in bed. There is little experience with outpatient collection.

Note: A negative result does not exclude TB—a positive culture occurs in only 25% to 50% of children with active TB.

- Aspirate approximately 50 ml of gastric contents via nasogastric feeding tube on 3 consecutive mornings for maximum smear-positivity (the first aspirate will have the highest yield).
- Send gastric aspirates for AFB smear microscopy and mycobacterial culture. Rapid diagnostic tests should not be used due to poor sensitivity and specificity.

Bronchial washings, bronchoalveolar lavage and transbronchial biopsy. Bronchoalveolar lavage and/or transbronchial biopsy performed with fiberoptic bronchoscopy may be needed to establish diagnosis in some patients.

- The topical agents used to anesthetize the airway lining may be lethal to *M. tb*; these agents should be used judiciously.
- The procedure may cause the patient to continue producing sputum for several days; these specimens should also be collected and examined.

Urine. Collect the first morning, voided-midstream specimen; multiple specimens are sometimes necessary to detect mycobacteria.

- Urine smears are usually negative and therefore performing them may not be cost-effective.
- The patient should not be under treatment with broad-spectrum antibiotics at the time of collection — many antibiotics are concentrated in the urine and may reach levels that inhibit growth of mycobacteria.

Blood. Collect the blood in a heparinized tube (e.g., Isolator® tube) and process with a centrifugation system or inoculate into broth media for mycobacterial blood cultures. Blood collected in ethylenediaminetetraacetic acid (EDTA), the “purple top tube,” is not suitable for mycobacterial culture.

Cerebrospinal fluid. Analyze CSF for protein and glucose, and obtain total white blood cell and differential counts.

- High protein (at least 50% of the serum protein concentration), high white blood cell count and low glucose are typical of meningeal TB.
- Submit a minimum of 5 ml of fluid in a sterile container for mycobacterial culture. AFB smear of CSF is usually, but not always, negative.
- If the laboratory concentrates the fluid before smear and culture, a larger sample (10 ml) can lead to increased yield.

Tissue and other body fluids. Consider invasive procedures to obtain specimens from the lung, pleura, pericardium, lymph nodes, bones and joints, bowel, peritoneum, fallopian tubes,

epididymis and from other involved sites when noninvasive techniques do not provide a diagnosis. Many of these areas are suitable for closed techniques such as percutaneous needle biopsy or aspiration.

- In patients with disseminated disease, consider bone marrow biopsy, lung biopsy or liver biopsy for examination and culture.
- The portion of the specimen placed in solution for histologic examination cannot be used for culture. If the specimen cannot be shipped promptly to the laboratory, refrigerate it until shipped.
- Analyze pleural, peritoneal and pericardial fluids for protein and glucose, and obtain white blood cell and differential counts.
 - High protein, high white blood cell count and low glucose are usually found in tuberculous infections, but neither their presence nor their absence is diagnostic.
 - The number of organisms in the pleural fluid from most cases of pleural TB is low, with positive cultures found in 23% to 67% of cases.
 - Pleural biopsy shows granulomatous inflammation in approximately 60% of patients, and *M. tb* can be cultured from up to 80% of pleural biopsies.
 - The combined yield of AFB stains of pleural fluid and biopsy tissue, coupled with mycobacterial culture of pleural fluid and biopsy tissue, is greater than 90%.

Microscopic Examination (Acid-Fast Bacilli Smear)

The smear is vitally important, both clinically and epidemiologically, to assess the patient's infectiousness because it gives a quantitative estimate of the number of bacilli being excreted. The detection of AFB in stained smears examined microscopically also provides the physician with a preliminary confirmation of the diagnosis.

Guidelines for preparing smears:

- Prepare directly from clinical specimens or from concentrated preparations.
- The acid-fast staining procedure depends on the ability of mycobacteria to retain dye

when treated with mineral acid or an acid–alcohol solution; 2 types of techniques are commonly used for acid–fast staining:

- The carbolfuchsin methods (which include the Ziehl–Neelsen and Kinyoun methods)
- Fluorochrome procedures using auramine–O or auramine–rhodamine dyes
- At least 5,000 to 10,000 bacilli per milliliter of specimen must be present to detect bacteria in stained smears. In contrast, only 10 to 100 organisms are needed to obtain a positive culture.
- Concentrate a liquefied specimen by centrifuging and use the sediment for staining to increase the sensitivity of the test. (The sensitivity of sputum smear is 50% – 80% among patients with pulmonary tuberculosis.)
- Factors influencing the sensitivity of smears include:
 - Staining technique (fluorochrome technique has a higher sensitivity than carbolfuchsin-based techniques)
 - Experience of the microscopist
 - The prevalence of TB disease in the population being tested
- In reading smears, the microscopist should provide the clinician with a rough estimate of the number of AFB detected. (See Table II-1 below for the scale used to quantify organisms on AFB smear.)

Nucleic Acid Amplification

Detecting *M. tb* complex with traditional laboratory culture methods takes 1 to 8 weeks; however, direct molecular methods using nucleic acid amplification (NAA) can detect *M. tb* complex genetic material directly from clinical specimens within 3 to 5 hours.

NAA tests identify genetic material unique to *M. tb* complex directly in pre-processed clinical samples. During 1995 and 1996, the FDA approved 2 rapid diagnostic tests based on NAA assays: (1) the Gen-Probe AMPLIFIED MTD (*Mycobacteria Tuberculosis Direct*) Test and (2) the Roche AMPLICOR MTB Test. In 1998, the FDA approved a modified version of the MTD (Gen-Probe MTD-2) that is faster and more sensitive.

- Both types of the MTD test are FDA-approved for use in respiratory specimens from smear-positive, previously untreated patients with high clinical suspicion for TB. Under these circumstances, sensitivity is 95% and specificity is 98%.
- The MTD-2 is also approved for smear-negative cases when clinical suspicion is high, but the sensitivity decreases to as low as 66%, with specificity remaining close to 100%.
- When used in extrapulmonary specimens, sensitivity may be as low as 64% in smear-negative specimens, but specificity remains close to 100%.
- For AFB smear-positive respiratory specimens, NAA should be used to confirm that a

Table II-1

Quantitation Scale for Acid-Fast Bacillus Smears by Stain Used.*

Carbolfuchsin (x 1,000)	Fluorochrome (x 250)	Quantity Reported
No AFB/300 fields	No AFB/30 fields	No AFB seen
1-2 AFB/300 fields	1-2 AFB/30 fields	Doubtful or Suspicious, repeat test
1-9 AFB/100 fields	1-9 AFB/10 fields	Rare (1+)
1-9 AFB/10 fields	1-9 AFB/field	Few (2+)
1-9 AFB/field	10-90 AFB/field	Moderate (3+)
>9 AFB/field	>90 AFB/field	Numerous (4+)

* Adapted from American Thoracic Society. Diagnostic Standards and Classification of Tuberculosis in Adults and Children. *Am J Respir Crit Care Med* 2000;161:1376-1395.

positive AFB smear represents *M. tb*. If the NAA is negative, it may be appropriate to delay starting of anti-TB therapy and contact investigation until culture results are available. However, if a patient lives in a congregate setting or with young children, it may be justified to start treatment pending culture results. (see p. 156, Table IX-1).

- Recent New York State regulations require laboratories to perform rapid diagnostic tests using NAA methods on initial AFB smear-positive sputa or respiratory specimens.
- For AFB smear-negative respiratory specimens, NAA should be used if the clinical suspicion for TB is high. If the NAA test is positive, diagnosis of TB is presumed, and should be confirmed by culture. If the NAA test is negative, diagnosis of TB may not be excluded, and decisions about treatment must be based on clinical assessment.
- For extrapulmonary specimens, NAA should be used if the clinical suspicion of TB is high; if the NAA is positive, diagnosis of TB is presumed and should be confirmed by culture. As with smear-negative specimens, if the NAA test is negative, diagnosis of TB may not be excluded.
- NAA tests must be interpreted within the context of the patient's signs and symptoms, and should always be performed in conjunction with AFB smear and culture.
- NAA procedures can detect nucleic acids from dead as well as live organisms and, therefore, can remain positive for long periods in patients who are taking anti-TB medications or have completed TB treatment. Thus, this method should be used only for initial diagnosis and not for follow-up evaluation of patients.
- If an NAA test is positive, but the patient has no positive cultures, the treating physician must determine TB diagnosis based on clinical response.

Two laboratories—the NYC Public Health Laboratory and the Wadsworth Center of the New York State Department of Health—provide the MTD test at no charge when TB is newly suspected. The provider or the hospital lab can send the specimens to the appropriate lab. Call the Provider TB Hotline at (212) 788-4162 for more information.

Criteria for Requesting NAA Tests

- High clinical suspicion of TB, previously untreated or less than 7 days of treatment*
- Respiratory specimen, or
- Non-respiratory specimens (request from the lab on a case-by-case basis if clinical suspicion is high)

* Since the NAA test can amplify rRNA from both viable and nonviable organisms, and therefore may detect nonviable tubercle bacilli expelled by an individual being treated for TB, the test result may be positive even though the treatment has decreased the likelihood that the TB is infectious.

Culture

All clinical specimens suspected of containing mycobacteria should be cultured for the following 4 reasons:

- Culture is much more sensitive than microscopy and is able to detect as few as 10 bacteria/ml of material
- Growth of the organisms is necessary for precise species identification
- Current drug susceptibility testing methods require pure culture of the organisms
- Genotyping of cultured organisms may be useful to identify epidemiological links between patients or to detect laboratory cross-contamination

In adults, the sensitivity of sputum culture is 80% to 85% with a specificity of approximately 98%. The sensitivity of sputum culture is much lower in children, although the rate may be higher in HIV-infected pediatric patients, adolescents and children with adult type disease.

Three different types of traditional culture media are available:

- Egg-based (Löwenstein–Jensen)
- Agar-based (Middlebrook 7H10 or 7H11 medium)
- Liquid (Middlebrook 7H12 and other commercially available broths). Liquid systems (BACTEC, MGIT, MB/Bact, Septi-check, ESP) allow for rapid growth—detection of mycobacterial growth within 1 to 3 weeks compared with solid media (3 to 8 weeks growth). Agar media provide an opportunity to examine colony structure and detect mixed cultures. (See p. 32 and p. 33, Table II-2).

Species Identification

The genus *mycobacterium* consists of more than 80 different species of organisms, all of which appear similar on acid-fast staining.

Two identification procedures that examine distinctive molecular characteristics of *Mycobacterium tuberculosis* (*M. tb*) have gained widespread use:

- Nucleic acid hybridization, which uses molecular probes that can hybridize specifically with *M. tb* complex, *M. avium* complex, *M. kansasii* and *M. goodii*. Probes for other specific mycobacterial species are not yet commercially available.
- High performance liquid chromatography, which:
 - Is based on the fact that most *mycobacterium* species synthesize a unique set of mycolic acids as components of the cell wall
 - Can produce a pattern that reliably identifies and distinguishes 50 *mycobacterium* species; however, it cannot differentiate *M. tb* from wild type *M. bovis*, although it can differentiate *bacille Calmette-Guérin* (BCG) strain of *M. bovis* from *M. tb* complex

These assays have sensitivities and specificities approaching 100% when at least 10^5 organisms are present; this requirement is easily met when pure cultures are used. Thus, nucleic acid hybridization is typically used after the organisms are grown in culture.

Drug Susceptibility Testing

To formulate an effective anti-TB regimen, drug susceptibility tests are needed on initial isolates from all patients. These tests should be repeated if the patient continues to produce culture-positive sputum after 2 to 3 months of treatment or develops positive cultures after a period of negative cultures. The critical concentrations used by these different methods are listed on p. 33, Table II-2.

There are 2 laboratory methods used in the United States for detecting mycobacterial resistance: (1) the agar proportion method (also known as the conventional method) and (2) the liquid broth method. A smear-positive specimen may be used for drug susceptibility testing when

a moderately large number of organisms is seen on stained smears—at least 3+ or more (direct method), or growth from a primary culture or subculture may be used (indirect method).

- The agar proportion method allows for the calculation of the proportion of organisms that is resistant to a given drug at a specified concentration.
 - Countable colonies (50–150) are obtained on the drug-free medium.
 - The number of colonies observed on the drug-containing medium is then compared with the number on the drug-free medium.
 - The proportion of bacilli that is resistant to a given drug is determined and expressed as a percentage of the total population tested. (This proportion has been set at 1%. When 1% or more of the mycobacterial population is resistant to the critical concentration of a drug, that agent is not — or soon will not be — useful for therapy.)
- The liquid method provides a rapid alternative to conventional drug susceptibility testing.
- The 2 methods may have different critical concentrations for different drugs; attention to the method used to interpret the results of drug susceptibility testing is important.

Testing of susceptibility to pyrazinamide.

Pyrazinamide testing is different from that of other first-line drugs. Activity must be measured at pH 5.5 rather than pH 6.8, the usual pH of the growth medium. As a compromise between testing at the pH for optimum pyrazinimide activity vs. optimum growth, pH 6.0 has been chosen for testing pyrazinimide in liquid and solid media.

If an isolate shows resistance to pyrazinimide, especially if the isolate is resistant to pyrazinimide alone, the identity of the isolate should be confirmed since *M. bovis* and *M. bovis* BCG are naturally pyrazinimide-resistant, whereas the majority of *M. tb* isolates are pyrazinimide-susceptible. This is especially important if the laboratory identifies isolates only to the level of the *M. tb* complex.

Table II-2

Drug Concentrations* for Various Methods Used by New York City Reference Laboratories for *M. tb* Complex Susceptibility Testing

Drug	Broth-based Systems ¹			Solid Media-Agar Proportion Method			Other		
	MGIT (Fluorescence)	Bactec (Radiometric)		Conventional Methods ¹		MIC-Bactec 7H12 Broth ²			
		NYC-PHL	NYS	NJMRC	7H10 Agar	7H11 Agar	Susceptible	Intermediate	Resistant
First-line Drugs				PHL	NYS	NJMRC	NJMRC		
Isoniazid	0.1	0.1 ³	0.1 ³	0.2 ³	0.2 ³	0.2 ³			
Isoniazid (high)	NT	0.4	0.4	1.0, (5.0)	1.0	1.0			
Rifampin ⁴	1.0	2.0	0.5, 2.0	1.0 ³	1.0 ³	1.0			
Pyrazinamide	100.0 ³	100.0 ³	300.0	-	-	-			
Streptomycin	-	-	-	2.0	2.0	2.0			
Streptomycin (high)	4.0	6.0	5.0	10.0	10.0	4.0			
Ethambutol	5.0 ³	7.5	5.0	5.0	5.0	7.5			
Other Drugs									
Amikacin					2.0, 4.0	6.0			
Capreomycin				10.0	10.0	10.0			
Ciprofloxacin ⁵				2.0	-	-			
Clofazimine							≤0.12	0.25	≥0.5
Cycloserine				30.0	30.0	60.0			
Ethionamide				5.0	5.0	10.0			
Kanamycin				6.0	5.0	6.0			
Levofloxacin ⁵							≤1.0	2.0	≥4.0
Linezolid							≤4.0	8.0	≥16.0
Moxifloxacin ⁵							≤1.0	2.0	≥4.0
Ofloxacin ⁵				-	2.0, 4.0	-	≤2.0	4.0	≥8.0
Para-aminosalicylic acid				2.0, 10.0	2.0	8.0			
Rifabutin ⁶				0.5	0.5, 1.0, 2.0	-			

Abbreviations: PHL = MGIT = Mycobacterial Growth Indicator Tube; NJMRC = National Jewish Medical & Research Center; NYS = New York State; New York City Public Health Lab

* Concentration in micrograms per milliliter

¹ Broth-based testing or conventional method testing: any drug resistance found for either method usually means the drug should not be used in the treatment regimen

² MIC-minimal inhibitory concentration-the lowest drug concentration that produces inhibition of more than 99% bacterial growth *in vitro*. Interpretation is based on susceptible, intermediate or resistant strain, and is reflected by that concentration of drug tested at NJMRC.

³ Critical concentration of the drug in this medium is the MIC concentration that inhibited the growth of all wild strains. The critical concentration to separate a susceptible from a resistant strain is reflected by the highest MIC found for the wild *M. tb* strain.

⁴ Rifampin is the class agent for rifapentine and results for rifampin reflect rifapentine susceptibility.

⁵ Fluoroquinolone testing – each laboratory generally tests one member of the class.

⁶ Some investigators also test a higher concentration (usually 1.0 or 2.0 mg/ml) of rifabutin.

Source: Drug susceptibility in the chemotherapy of mycobacterial infections. Leonid B. Heifets. CRC Press, Inc 1991

All susceptibility testing reports should include the method used, the name of the drug, the concentration tested and the result (susceptible or resistant for the liquid method, susceptible or percent resistant for the agar proportion method). Clinician concerns about discrepancies between susceptibility test results and clinical response or status must be communicated back to the laboratory as part of an effective quality assurance program.

Genotyping

Genotyping or DNA fingerprinting of *M. tb* is used to determine clonality of bacterial cultures. Briefly, cultured organisms are heat-killed and their DNA is isolated, cut with specific restriction enzymes, separated in an agarose gel by electrophoresis, transferred to a membrane and probed for specific genetic sequences. A standardized protocol has been developed to permit comparison of genotypes from different laboratories around the world.

Genotyping is useful for:

- Confirming laboratory cross-contamination
- Investigating outbreaks of TB
- Evaluating the efficacy of contact investigations
- Determining whether new episodes of TB are due to reinfection or reactivation

There are 3 methods of genotyping that are currently being used by the BTBC to determine the relatedness of specific *M. tb* strains: (1) restriction fragment length polymorphism (RFLP); (2) spoligotyping; and (3) variable-number tandem repeats of mycobacterial interspersed repetitive units. Since 2001, initial isolates of all culture-positive TB patients in NYC have had genotyping performed by RFLP and spoligotyping analysis.

Restriction fragment length polymorphism (RFLP). *M. tb* complex contains a conserved sequence of DNA called IS6110. Usually there are several copies (generally ranging from 5-20 copies) of this stretch of nucleotides in each strain of *M. tb* complex. When the genome is digested by a specific enzyme and then treated with probes that attach specifically to IS6110 sequences, the digested DNA appears on an electrophoresis gel in distinct bands corresponding to DNA fragments of various sizes that contain the IS6110 element in the genomic DNA. Since the number of these IS6110

sequences varies from one strain to the next, *M. tb* complex strains can be distinguished from one another by the number and size of the fragments of DNA that were created by the enzymatic digestion and visualization of the probes. This process has been standardized to allow universal comparisons of patterns; however, nomenclature may differ across laboratories.

Spoligotyping. Spacer oligonucleotide (spoligotyping) takes advantage of the properties of the direct repeat (DR) region of the *M. tb* complex genome. The DR region consists of a number of copies of repeated sequences consisting of 36 base pairs (bp) interspersed with non-repetitive spacer elements that are each 35 to 41 bp long; there are 43 known spacer elements (spacers). Differences between strains arise by variation in the number and identity of these spacers.

Spoligotyping employs a filter membrane to which short sequences of DNA corresponding to each set of the 43 known spacers are attached. The entire DR region of an isolate to be tested is amplified by a polymerase chain reaction (PCR) and is radiolabeled so that hybridization to the filter shows a pattern of spots corresponding to those spacers that are present in the isolate's genome. Comparison of these patterns enables differentiation between strains.

Variable-number tandem repeats of mycobacterial interspersed repetitive units (MIRU). This is a high-resolution, automated typing technique that involves multiple PCR assays and focuses on 12 defined regions of the TB genome (called loci) that contain variable number of repeats of genetic elements, known as MIRU. The repeated units are 51 to 77 bp long, and the number of repeated units in a locus is determined by the size of the PCR products, which have specific primers that hybridize to the contiguous MIRU regions. The number of repeated units represents a specific allele for each locus and the variation at the 12 MIRU loci generates an allele profile for each strain of TB; the resulting 12-digit output allows for easy comparison of results across laboratories.

The level of strain differentiation provided by this technique is intermediate between that of RFLP and spoligotyping, and thus may have higher or lower utility in some areas than others, depending on the diversity of strains in the population. TB isolates from NYC have only been sent for MIRU since 2004.

These comparisons can be done manually for small databases. But for large databases, some form of shorter designation is necessary to refer to specific patterns. When RFLP and spoligotyping are used together, differentiation between *M. tb* strains can be achieved with a high degree of accuracy. The use of genetic fingerprinting has increased our understanding of the epidemiology of TB transmission, rates of laboratory contamination (see below) and the role of reinfection vs. reactivation among those who relapse.

False-Positive Results

The definitive diagnosis of TB depends on the isolation and identification of the etiologic agent *M. tb* from clinical specimens. The methods currently used may at times lead to a false-positive *M. tb* culture.

A false-positive *M. tb* specimen is a positive culture that is not the result of disease in a patient but is due to either contamination of a clinical device, clerical error or laboratory cross-contamination during processing.

Laboratory cross-contamination is the inadvertent transfer of bacilli from a specimen or culture to another specimen or culture not containing bacilli. This occurs in almost every mycobacteriology laboratory, yet it is difficult to confirm. The reported rate of false-positive cultures varies considerably. The use of highly sensitive culture systems, using both solid and liquid media, may detect a relatively small inoculum. In addition, *M. tb* is relatively stable in the laboratory environment and can remain viable for long periods.

Identifying cross-contamination affords the opportunity to:

- Correct equipment or procedural errors responsible for the false-positive cultures
- Correct an erroneous diagnosis and stop needless therapy
- Avoid unnecessary source/contact investigations, cost of incentives and DOT
- Remove an erroneously diagnosed patient from local and national surveillance systems

Our ability to identify false-positive cultures has greatly improved through the use of DNA

analysis by both spoligotyping and the IS6110-based RFLP methods on isolates from all culture-positive cases of tuberculosis in NYC.

Objectives of False-Positive *M. tb* Specimen Investigations

- Identify patients with false-positive *M. tb* cultures
- Discontinue unnecessary treatment if indicated
- Identify the most likely source/mechanism for every confirmed false-positive event
- Determine the impact of misdiagnosed TB based on false-positive cultures, including the extent of unnecessary patient treatment, hospitalizations, tests and examinations, contact investigations and other BTBC activities
- Disseminate information on rate/source/mechanism of the false-positive event and/or laboratory cross-contamination to participating laboratories

Methods Used to Identify False-Positive *M. tb* Cultures

The retrospective identification of false-positive *M. tb* cultures is achieved by both active and passive surveillance. Active surveillance is accomplished through the following:

1. Review of patients with single, positive cultures

- Cases of TB with only a single positive culture (SPC) for *M. tb* are identified bimonthly. BTBC physicians review each patient with an SPC to determine if the patient's clinical presentation is consistent with TB. Patients with a clinical picture inconsistent with TB are referred for a false-positive culture investigation.
- Patients are investigated under 1 or more of the following circumstances:
 - The patient has a normal CXR with a positive *M. tb* sputum culture.
 - No anti-TB medications were given or anti-TB medications were started after culture result became available (at least 14 days after the date of collection of the positive *M. tb* culture).

- CXR did not improve after the patient received 2 or more months of anti-TB medications.
- Three or more sputum samples were taken and only 1 result was culture positive for *M. tb*.

2. Cases identified through the Molecular Epidemiology Database

Identical matches of spoligotype and/or RFLP can trigger potential false-positive culture investigations by:

- Identifying matching spoligotypes on a batch of specimens analyzed
- Identifying spoligotypes consistent with laboratory proficiency strains
- Periodic queries of identical DNA patterns (both spoligotype and RFLP) in the molecular epidemiology database

3. Clinician referral

- An investigation of potential false-positive cultures can also be initiated by physicians and laboratories. Justification should be provided regarding the need for such an investigation, including a summary of the patient's overall clinical status and the reason the physician or laboratory believes an investigation is warranted.

Interpreting Results of the False-Positive Investigation

If DNA analysis does not identify a match of isolates within concurrent processing or does not indicate contamination with a proficiency, or laboratory, strain, then cross-contamination may be ruled out unless the treating provider requests further investigation into non-laboratory contamination causes of a false-positive result. In that case, further investigation may be warranted to rule out mislabeling or another source of false-positive results.

If DNA analysis identifies a match of isolates with the exact spoligotype and RFLP pattern within concurrent processing, or if DNA indicates contamination with a laboratory proficiency strain, the treating physician may be requested to re-evaluate the patient in light of the laboratory findings to decide on the patient's diagnosis. The processing laboratory also is informed of the findings and asked to investigate the matter within the laboratory.

A suspected false-positive culture is considered to be confirmed as false if there is a spoligotype/RFLP match between the suspected false-positive and another isolate processed concurrently or with a laboratory proficiency strain.

A suspected false-positive culture is considered to be unlikely if there is no DNA fingerprint match between the suspected false-positive and any other isolate(s) processed concurrently or with a laboratory proficiency strain. If the physician treating the patient feels that TB is not the correct diagnosis, that physician must present other clinical information to support his or her decision not to treat the patient for TB disease.

Other Laboratory Tests

The following laboratory tests should be ordered for all patients:

- Complete blood count including platelets.
- Chemistry panel (blood urea nitrogen, creatinine, uric acid, and liver function tests: SGOT/AST, SGPT/ALT, alkaline phosphatase, and total direct bilirubin)
- Viral hepatitis screen
- HIV testing and counseling, and, if HIV-positive, CD4 lymphocyte count (if not done within previous 6 months)

Classification of Suspected Tuberculosis Patients

Patients highly suspected of having current TB disease and expected to evolve as a Class III, active disease should be classified as Class V (High). (This classification would include, for example, a patient whose CXR shows a cavitory lesion and infiltrates typical of active pulmonary TB. In contrast, patients suspected of having old, healed TB and expected to evolve as a Class IV, or non-TB, patient should be classified as Class V [Low]. This would include, for example, a patient who has a positive test for TB infection and has only nodules or linear shadows on CXR.)

All patients initially classified as Class V (High) or Class V (Low) should be reported to BTBC Surveillance Office as a "suspect" and should be reclassified within 4 months of the initiation

of TB evaluation based on their clinical improvement, AFB culture and/or CXR results. (See p. 114).

Tuberculosis in Childhood

In the United States, most children are asymptomatic when they are diagnosed with TB and present as part of an investigation of contacts of an adult case. The test for TB infection plays a very important role in the diagnosis of TB in children. Older children and adolescents who are symptomatic may present with the protean symptoms of TB—fever, weight loss and night sweats. Younger children may have disseminated disease, meningitis or a “pneumonia” that is unresponsive to antibiotics.

Children usually have paucibacillary pulmonary disease, as cavitating disease is relatively rare (about 6% of cases or fewer) in those younger than 13 years of age. In contrast, children develop extrapulmonary TB more often than adults do. Severe and disseminated TB (e.g. TB meningitis and disseminated TB) occur more frequently in young children (less than 3 years) and can occur relatively quickly once the child is infected.

The following areas of evaluation and presentation of disease merit special attention in children:

Medical Evaluation

Obtain a detailed history and physical examination

- Review family history and include history of possible contacts, including non-household care givers, visitors and foreign travel. Specific information about contact may allow retrieval of the isolate and its susceptibilities.
- Enquire about missed milestones, behavioral changes, headache, gastrointestinal disturbance, weight loss, lack of weight gain and night sweats.
- Do a thorough exam, beginning with weight and height.
- Always keep in mind extrapulmonary sites when evaluating children for TB, such as peripheral lymph nodes, central nervous system, bones and joints, liver and spleen (in addition to evaluation for chest disease).

Chest X-ray in Children

CXR is useful in the diagnosis of TB in children; they should receive a posterior-anterior and lateral CXR which should be read by a radiologist experienced in pediatric radiography. In the majority of cases, children with pulmonary TB have CXR changes suggestive of TB.

The most common finding is persistent opacification in the lung in conjunction with enlarged hilar or subcarinal lymph glands. A miliary pattern of opacification in HIV-uninfected children is highly suggestive of TB. Patients with persistent opacification which does not improve after a course of antibiotics should be investigated for TB.

Some characteristics of childhood TB include:

- More than half of children with radiologic pulmonary disease are asymptomatic (identified through contact tracing).
- The CXR is typically “sicker” than the child.
- Children of any age with complicated intrathoracic disease and adolescents more typically have adult-type reactivation TB (upper lobe disease which may cavitate) with positive AFB-sputum smear. (However, adolescents with significant radiographic findings, including cavitory disease, may have surprisingly few symptoms.)
- Wheezing is an occasional manifestation of TB in an infant due to endobronchial disease or lymph nodes compressing a bronchus.
- Children should be regarded as infectious if they have sputum smear-positive pulmonary TB or cavitory TB on CXR. Airborne isolation should be initiated (see p. 122).
- If the child is not AFB smear-positive, diagnostic criteria for sputum smear-negative pulmonary TB should include:
 - At least 3 sputum specimens negative for AFB
 - Radiological abnormalities consistent with active pulmonary TB
 - No response to a course of broad-spectrum antibiotics
 - Decision by a clinician to treat with a full course of anti-TB chemotherapy

Congenital and Neonatal Tuberculosis

The distinction between congenital and early (neonatal) TB is primarily epidemiological. Presentation, management and prognosis are similar.

Congenital TB is uncommon, with about 300 reported cases in the English language literature (only 29 cases from 1980 to 2000); however, the incidence is probably underestimated due to the difficulty in making the diagnosis. It is important to keep a high index of suspicion, as fewer than 50% of the mothers of children with congenital TB were known to have active TB at the time of delivery. A significant percentage of pregnant women with pulmonary tuberculosis are unaware of their disease and may have few, if any, symptoms.

Often, diagnosis in the newborn leads to the retrospective diagnosis of active disease in the mother. Women who have only pulmonary TB are not likely to infect the fetus, but may infect their infant after delivery. If neonatal or congenital TB is suspected and the mother has a normal CXR, evaluation for gynecological or other forms of extrapulmonary TB should be performed in the mother.

Neonatal TB symptoms typically are nonspecific and may overlap with those of other congenitally or neonatally acquired infections. The diagnosis of congenital TB should be considered in infants in whom pulmonary symptoms do not respond to empiric antibiotic therapy or who have evidence of sepsis or fungemia that is unresponsive for treatment.

Evaluating Neonates for Tuberculosis

If the mother had untreated or very recently diagnosed TB, the newborn should be assessed for signs of congenital TB. Initial assessment should include:

- Medical evaluation
- TST and CXR (TST is usually negative in newborn infants with congenitally or perinatally acquired infection)
- Three gastric aspirates on 3 consecutive days

- Lumbar puncture if there is a high clinical suspicion for active TB
- In pregnant woman, regardless of TB treatment status during pregnancy, examination of the placenta microscopically for granuloma, staining for AFB and sending for AFB culture

In infants suspected of having congenital TB, begin treatment with isoniazid, rifamycin, pyrazinamide and an injectable agent (amikacin is recommended, but streptomycin or kanamycin can be used).

- Add corticosteroids if the neonate has meningitis.
- If no granulomas are found in placenta and the infant does not have clinical evidence of active tuberculosis, administer isoniazid for 3 months or until mother is culture-negative.

About 50% of children born to mothers with active untreated disease will develop TB in their first year of life if treatment for LTBI is not given to the baby.

At age 4-6 months:

- Repeat TST if negative at initial assessment.
- If positive, re-evaluate for active disease and treat with isoniazid for a total of 9 months, once active disease has been excluded.

Bacille Calmette-Guérin Vaccination

If the mother (or primary care taker or other family member) is suspected of being non-compliant with TB treatment or is infectious and has MDRTB, Bacille Calmette-Guérin (BCG) vaccination may be considered to protect the infant (Appendix I-G, p. 227), who should also be separated from the mother until the mother's disease activity is determined.

BCG should be considered in the newborn with a negative TST if he/she:

- Is going to be exposed continually to an untreated mother or caretaker and cannot be separated from the mother/caretaker
- Cannot be given long-term treatment with isoniazid for LTBI

- Is going to be continually exposed to a mother with MDRTB and cannot be separated from the mother

If the mother has completed treatment for active TB during pregnancy and there is no evidence of active disease at the time of birth, there is

minimal risk to the infant and no need for specific therapy or separation from the mother. The child should have a TST at birth and at age 6 months, but needs no treatment or further evaluation unless the TST is positive.

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Section III.

Treatment of Pulmonary Tuberculosis

Tuberculosis

Section III.

Treatment of Pulmonary Tuberculosis

Regimens for Treatment of Drug-Susceptible Tuberculosis

All individuals with highly suspected or confirmed tuberculosis should receive initial treatment as soon as appropriate specimens are collected. Treatment should not be delayed while waiting for confirmation by culture and susceptibility results.

Most patients with TB can be treated with a standard 6-month drug regimen. Treatment is divided into 2 phases: the intensive phase and the continuation phase. The intensive phase consists of the first 2 months of treatment, which begins empirically with a standard 4-drug regimen. This is done since susceptibility results are not available at the start of most patients' treatment. Regimens can be adjusted as susceptibility results become available. The continuation phase usually lasts 4 months and consists of fewer drugs. Under certain circumstances, the continuation phase may be extended beyond 4 months.

There are 4 recommended regimens for treating patients with TB caused by drug-susceptible organisms. Although these regimens are broadly applicable, modifications should be made under certain circumstances. Each regimen has an initial phase of 2 months, followed by several options for the continuation phase, which may last either 4 or 7 months.

Current recommendations for treatment of TB in adults who are HIV infected are, with few exceptions, the same as for the rest of the population.

Standard Regimen

The standard regimen should begin with isoniazid, rifampin, ethambutol and pyrazinamide unless there are absolute contraindications.

Use Rifamate® (capsules combining isoniazid and rifampin) for patients who are not receiving directly observed therapy (DOT).

- Discontinue ethambutol and pyrazinamide at the end of the intensive phase of treatment unless:

- Drug susceptibility results show resistance to isoniazid or rifampin.
- Drug susceptibility results are not available and drug resistance is suspected. This may be either because of a history of TB treatment or because of a high rate of resistance in the community.
- Ethambutol can be discontinued earlier, if drug susceptibility results show susceptibility to isoniazid and rifampin.

If clinical response is not adequate in 2 weeks, consider adding additional drugs to the regimen, since drug resistance may be present.

It is important to make sure that patients being treated for TB receive the appropriate number of doses within the recommended length of treatment (see p. 45, Table III-1).

See p. 208, Appendix I-A for dosages of primary medications used in the treatment of TB.

Length of Treatment

Culture-positive pulmonary disease. The standard 6-month treatment (short-course chemotherapy) for drug-susceptible TB consists of a 2-month intensive phase followed by a 4-month continuation phase. However, clinical trials have shown that selected patients have a higher rate of relapse with a 6-month regimen (see p. 46, Table III-2) and may benefit from longer treatment as noted below. (If the strain is drug-resistant, see p. 86, Table V-1 for guidelines on length of treatment.)

- The 4-month continuation phase of treatment should be used for most patients. However, a 7-month continuation phase should be given to the following 4 groups:
 - Patients who have drug-susceptible pulmonary TB, with **initial** cavitation on chest X-ray (CXR), whose sputum cultures remain positive after the intensive phase (i.e., the first 2 months of treatment).
 - Other patients who are still culture positive at 2 months, regardless of CXR results.

- Patients whose treatment regimen did not include pyrazinamide in the intensive phase, or whose organism was resistant to pyrazinamide.
- Patients being treated with once-weekly isoniazid and rifapentine, whose sputum culture remains positive after the 2-month intensive phase of treatment.

Susceptibility results for first-line drugs are usually available within 2 weeks of culture confirmation. If results are delayed, contact the lab and ask the reason for the delay. If it is related to technical issues, continue all 4 drugs until the lab confirms the results. If the delay is due to a mixed or non-viable culture, make sure that the lab tests another specimen.

For patients who are *Mycobacterium tuberculosis* (*M. tb*) culture positive without available susceptibilities at the end of the intensive phase, discontinue pyrazinamide and ethambutol unless drug resistance is suspected.

The patient receiving treatment for tuberculosis may have sputa that are smear positive but culture negative. In patients with drug-susceptible organisms, this may occur during initial treatment, when the patient is beginning to culture convert. It may also occur later in treatment, as a result of dead organisms. This can be verified when cultures come back negative.

In the meantime, a clinical decision must be made regarding the management of these patients. If the patient is on a standard regimen, is tolerating TB medications and has clinically improved (e.g., there is resolution of fever and cough, plus weight gain and an improved CXR), it may not be necessary to change treatment.

Culture-negative pulmonary disease. Multiple studies have shown that clinically confirmed or culture-negative pulmonary TB can be treated successfully in only 4 months, as the bacillary load is believed to be decreased in such patients. As a result, for patients whose initial sputum cultures are negative, the intensive phase of treatment should be followed by a 2-month continuation phase of isoniazid and rifampin only, as long as the patient has not received treatment for TB in the past.

- If the patient has received treatment in the past, isoniazid, rifampin, pyrazinamide and ethambutol should be continued for the full 4 months, as drug resistance may be present.

Intermittent Regimens

For most patients with drug-susceptible TB, intermittent therapy (i.e., regimens given 2 or 3 times a week, or even once weekly when rifapentine is used, [see below]) is well documented to be at least as effective as a daily regimen. Intermittent therapy is easier to supervise than daily therapy, helps ensure adherence and should be offered to all eligible patients (see p. 45, Table III-1).

- Intermittent therapy should be given only under a DOT program.
- If adherence to 2 or 3 times a week DOT falls below 80%, the patient should be put on daily DOT until it is established they can be placed on intermittent DOT.
- Recent data show that patients with cavitary pulmonary TB may be at increased risk of relapse if treated with intermittent regimens in the intensive phase. Such patients should be treated with a daily regimen during this time. Intermittent regimens can be given in the continuation phase.
- Three-times-a-week intermittent therapy may be given in the intensive phase with isoniazid, rifampin, pyrazinamide and ethambutol—with all 4 drugs continued throughout the intensive phase. Isoniazid and rifampin can be continued 3 times a week in the continuation phase.
- Rifapentine should be used in specific instances (see p. 47, Figure III-1) after the patient has completed the 2-month intensive phase.
- Patients who are HIV infected, with CD4 counts lower than 100 should only be treated with either daily or 3-times-a-week regimens. The Bureau of Tuberculosis Control (BTBC) recommends daily treatment in the intensive phase.
- Patients with TB that is resistant only to isoniazid or that is resistant to isoniazid and any of the second-line medications (including streptomycin) can be treated with intermittent regimens as indicated on p. 87. However, if resistance only to isoniazid is discovered, the drug should be removed from the regimen.
- Patients with TB resistant to rifampin alone, or to both isoniazid and rifampin, should not be treated with an intermittent treatment regimen.

Table III-1

Drug Regimens for Culture-Positive Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

Regimen	Drugs	Intensive Phase Interval ¹ and Doses ² (minimal duration)	Drugs	Continuation Phase Interval ¹ and Doses ^{2,3} (minimal duration)
1	Isoniazid Rifampin Pyrazinamide Ethambutol	7 days per week for 56 doses (8 wk) or 5 days per week for 40 doses (8 wk) ⁴	Isoniazid/ Rifampin Isoniazid/ Rifapentine ⁶	7 days per week for 126 doses (18 wk) or 5 days per week for 90 doses (18 wk) ⁴ or 3 times per week for 54 doses (18 wk) or 2 times per week for 36 doses (18 wk) ⁵ 1 time per week for 18 doses (18 wk)
2	Isoniazid Rifampin Pyrazinamide Ethambutol	7 days per week for 14 doses (2 wk), then 2 times per week for 12 doses (6 wk) or 5 days per week for 10 doses (2 wk) ⁴ then 2 times per week for 12 doses (6 wk)	Isoniazid/ Rifampin Isoniazid/ Rifapentine ⁶	2 times per week for 36 ⁵ doses (18 wk) 1 time per week for 18 doses (18 wk)
3	Isoniazid Rifampin Pyrazinamide Ethambutol	3 times per week for 24 doses (8 wk)	Isoniazid/ Rifampin Isoniazid/ Rifapentine ⁶	3 times per week for 54 doses (18 wk) 1 time per week for 18 doses (18 wk)
4	Isoniazid Rifampin Ethambutol	7 days per week for 56 doses (8 wk)	Isoniazid/ Rifampin	7 days per week for 217 doses (31 wk) or 5 days per week for 155 doses (31 wk) ⁴ or 3 times per week for 93 doses (31 wk) or 2 times per week for 62 doses (31 wk) ⁵

Adapted from The American Thoracic Society, Center for Disease Control and the Infectious Disease Society of America. Treatment of Tuberculosis. 2003 (see Key Sources for full citation)

¹ For missed dose, extend treatment to make up the doses, unless there has been prolonged treatment interruption.

² When DOT is used, drugs may be given 5 days per week and the necessary number of doses adjusted accordingly. Although there are no studies that compare 5 with 7 daily doses per week, extensive experience indicates this would be an effective practice.

³ Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month continuation phase regimen (31 weeks; either 217 doses daily or 93 doses 3 times per week or 62 doses 2 times per week).

⁴ Five-day-a-week administration is always given by DOT.

⁵ Not recommended for patients who are HIV infected, with CD4+ cell counts of less than 100 cells/mm³

⁶ Rifapentine should be used only in patients who are HIV negative, older than 12 years of age, not pregnant and have negative sputum smears at the time of completion of 2 months of therapy, and who do not have cavitation on the initial chest radiograph. For patients started on this regimen and found to have a positive 2-month sputum culture, treatment should be extended an extra 3 months.

See p.47, Figure III-1.

Table III-2

Percentage of Culture-Positive Relapse¹ by Continuation Phase Regimen, Radiographic Status and 2-Month Sputum Culture: USPHS Study 22

Continuation Phase					
Isoniazid-Rifampin twice weekly ²			Isoniazid-Rifapentine once weekly ²		
Culture positive at 2 months			Culture positive at 2 months		
Cavity	Yes	No	Cavity	Yes	No
Yes	20.8 (48) ³	4.7 (15)	Yes	22.2 (72)	9.1 (154)
No	5.9 (17)	1.7 (181)	No	11.8 (17)	1.9 (162)

¹ Culture-positive relapse with restriction fragment length polymorphism match to initial isolate

² Isoniazid-rifampin twice weekly-isoniazid-rifampin for 18 weeks: isoniazid-rifapentine once weekly-isoniazid-rifapentine for 18 weeks

³ Denominators in parentheses: number enrolled, completed treatment per protocol and assessed for relapse

Source: Tuberculosis Trials Consortium. Rifapentine and isoniazid once a week versus rifampin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomized clinical trial. *Lancet* 2002; 360; 28-34 and additional data (A. Vernon, personal communication).

Rifapentine

Patient Selection

An intermittent regimen that utilizes rifapentine, a long-acting rifamycin, is available. Rifapentine should only be used in carefully selected patients to avoid relapse or development of acquired rifamycin resistance. Potential candidates for rifapentine/isoniazid must be educated about the availability of this option early in their therapy. Patient brochures about this treatment are available. See p. 45, Table III-1 for more information.

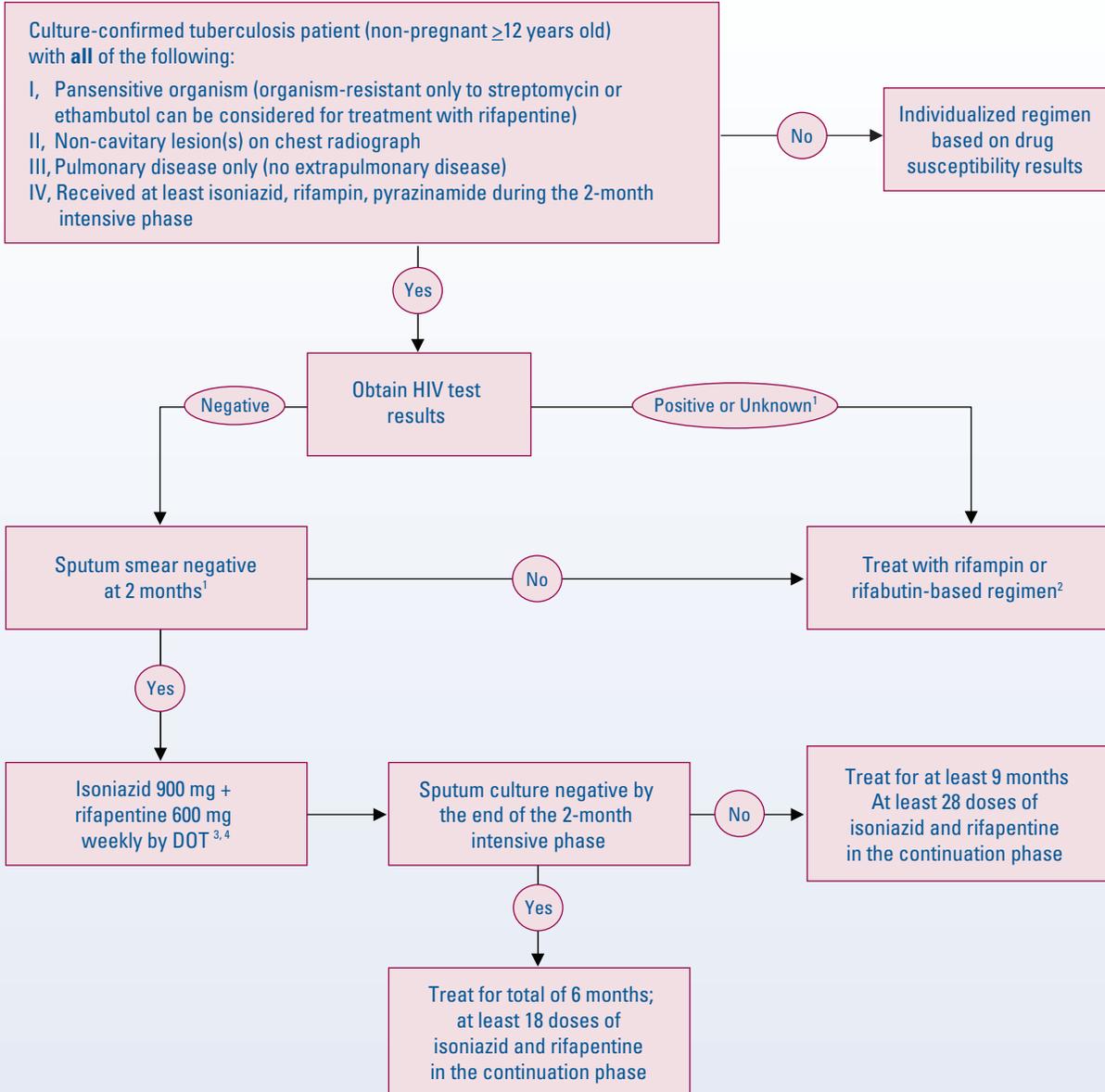
- Patients who are HIV-positive should not receive rifapentine, due to risk of developing rifampin resistance. Therefore, a negative HIV test must be documented before initiating this therapy.
- Sputum must be AFB smear negative at the end of the 2-month intensive phase.
- Patients with any form of extrapulmonary TB are not candidates for this regimen; mediastinal and hilar lymphadenopathy accompanying an infiltrate is not considered to be extrapulmonary TB.

- Patients with a cavitory lesion on CXR are at increased risk of relapsing if treated intermittently with rifapentine and isoniazid at currently recommended doses; therefore we recommend these patients not be given this regimen.
- Clinically confirmed cases of pulmonary TB are not candidates for once a week rifapentine plus isoniazid as this regimen has not been studied.
- Patients who are pregnant or younger than 12 years of age should not be offered this regimen.
- Patients must have received isoniazid, rifampin and pyrazinamide with or without ethambutol for the entire intensive phase.

One to 2 weeks prior to the end of the 2-month intensive phase of therapy, sputum samples must be obtained to demonstrate that sputum smears are negative before the rifapentine/isoniazid regimen is initiated. Offering a once weekly regimen to patients also provides an opportunity to reintroduce DOT if a patient is not already on DOT.

Figure III-1

Treating Tuberculosis with Rifapentine



¹ HIV counseling and testing is recommended if unknown

² A sputum smear should be performed 1 to 2 weeks prior to the end of the 2-month intensive phase

³ Intermittent therapy should only be given under DOT

⁴ Rifampin or rifabutin should not be given biweekly to HIV-infected patients with CD4 count less than 100 mm³. Such patients should receive a daily regimen in the intensive phase and either daily or 3 times per week regimen(s) in the continuation phase.

Treatment Length

Treatment length for this regimen is generally 4 months, for a total 6 months of TB treatment. A patient is considered to have completed an adequate regimen if at least 18 doses of rifapentine/isoniazid are taken during the continuation phase of TB treatment. If an appropriate candidate is started on rifapentine/isoniazid and is later found to have positive cultures on sputum obtained at the end of or after the intensive phase of therapy, the total length of therapy should be 9 months, with at least 28 doses of rifapentine/isoniazid in the continuation phase.

Dosing

The recommended dosage of rifapentine is 600 mg weekly, always in combination with isoniazid 900 mg weekly. Rifapentine is available in 150 mg tablets. Dosing rifapentine with food improves absorption of the drug, so the drug should be administered with food, or patients should be encouraged to eat before a dose is given.

If a patient misses a dose, it can be given on another day during the week as long as the subsequent dose is separated from the last dose by at least 72 hours. Patients who are delinquent for 2 consecutive weeks or more should be switched back to a rifampin-based regimen.

Certain patients receiving isoniazid (900 mg) may require supplementation with pyridoxine (vitamin B₆) 25 mg once daily (this can be self-administered). See p. 62, Table III-4 for list of patients eligible for pyridoxine.

Monitoring

Patients should have baseline liver function tests (LFTs) and a complete blood count (CBC) at the beginning of TB therapy. Monthly follow-up blood testing is not necessary if the baseline is normal, unless a patient develops symptoms consistent with adverse drug reactions (see below). Therapeutic levels of rifampin have been known to interfere with assays for vitamin B₁₂ and folate. Similar interactions should be considered for rifapentine. Clinical monitoring is the same as for all other Class III patients.

Adverse Reactions

Rifapentine, like other rifamycins, may produce a predominantly orange-red discoloration of body fluids and tissues (skin, teeth, tongue, tears,

sputum, saliva, feces, cerebrospinal fluid. Contact lenses may also become permanently stained.

A patient who develops symptoms consistent with hepatitis (anorexia, nausea, vomiting, abdominal pain, jaundice) while taking rifapentine/isoniazid should be instructed to discontinue all medications promptly. The patient should be examined promptly by a physician and have blood drawn for another set of LFTs. (See p. 107.)

If LFTs are normal, drug-induced hepatitis is unlikely. Another cause for the symptoms should be suspected. Depending upon the nature, duration and severity of symptoms, a decision should be made regarding further diagnostic investigation and possible referral.

Use in Pregnant and Breast-Feeding Women

As a precaution, rifapentine should not be used in pregnant women as it has been shown to be teratogenic in rats and rabbits that have been given anywhere from 0.3 to 1.3 times the human dose. There are no adequate data in pregnant women and the effect on the human fetus is unknown. Also, it is not known whether rifapentine is excreted in human milk and therefore should not be used in nursing mothers.

Use in Children

The safety and efficacy of rifapentine in children under the age of 12 has not been established; therefore, rifapentine should not be used in this age group. Children older than 12 years should be prescribed the adult dose of rifapentine and dosed with isoniazid accordingly.

Drug Interactions

Rifapentine is a member of the rifamycin class of drugs and like other rifamycins, it induces the cytochrome p450 system of enzymes, specifically the CY3A4, 2C8 and 2C9 isozymes. Rifapentine increases metabolism and markedly lowers serum concentrations of drugs that are metabolized by these enzymes.

Rifapentine's ability to induce CY3A4 is less than that of rifampin, but greater than that of rifabutin. CY3A4 is important in the metabolism of protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Rifapentine should not be used in persons who are HIV infected, because of the risk of developing rifamycin resistance.

The induction of these enzymes occurs approximately 4 days after the first dose and returns to baseline 14 days after rifapentine is discontinued. The degree of enzyme induction is dose- and frequency-dependent.

Any drug that is known to have an interaction with rifampin should be considered to have similar interactions with rifapentine unless proven otherwise through clinical trials.

See p. 216, Appendix I-F for a list of drugs that interact with rifapentine and the other rifamycins.

Treatment of Co-Existant Tuberculosis and HIV

Given the challenges of managing drug interactions and overlapping toxicities, providers should carefully coordinate treatment of patients with TB and HIV. Close attention should be paid to the possibility of TB treatment failure, antiretroviral treatment failure, paradoxical reactions of TB, unique and synergistic overlapping adverse effects for all drugs used and drug toxicities associated with increased serum concentrations of rifabutin. As new antiretroviral drugs are developed and more information becomes available, recommendations for the use of these drugs with anti-TB medications change.

This section provides updated recommendations for the treatment of TB in patients who are co-infected with TB and HIV. It is based on the BTBC document, *Antiretroviral Drugs and the Treatment of Tuberculosis*, which can be accessed at www.nyc.gov/html/doh/downloads/pdf/tb/tbanti.pdf; it is updated frequently and will have the most recent recommendations.

Antiretroviral Drugs and Rifamycins

Treatment of TB in the setting of HIV infection is complicated by drug-drug interactions between the rifamycin class of antimycobacterial drugs (rifampin, rifabutin and rifapentine) and the PI and NNRTI classes of drugs used to treat HIV infection. Both PIs and NNRTIs are metabolized by hepatic CYP3A, specifically the CYP3A4 isozyme. Rifamycins are inducers of the CYP3A family of enzymes, which includes the CYP3A4 isozyme. Maximal drug levels (represented by C_{max}) or total drug exposure over time (represented by area under the plasma concentration time curve [AUC]) of antiretroviral agents may be

reduced when these drugs are co-administered with rifamycins, adversely affecting the ability of the anti-retroviral regimen to adequately suppress the virus, which is the goal of anti-retroviral treatment regimens.

Rifamycins are inducers of the CYP3A system, but rifampin is not metabolized by this system. Of the 3 available rifamycins, rifampin is the most potent inducer of CYP3A and rifabutin is the least potent, with rifapentine falling somewhere in between. Rifapentine should not be used for the treatment of TB in individuals who are HIV infected, because it can lead to rifamycin resistance at the current recommended dose in this population.

Rifampin is **not** metabolized by the CYP3A system and rifampin exposure is not affected by coadministration of PIs or NNRTIs; rifampin dosing does not need adjustment.

Rifabutin **is** metabolized by the CYP3A system and exposure is usually increased by co-administration of PIs or NNRTIs. Rifabutin dosing must be adjusted according to the choice of the co-administered antiretrovirals (See pp. 54 and 55, Figure III-2 and Table III-2.) Because the exposure of the active metabolite of rifabutin (25-O-desacetyl rifabutin) is also affected, recommended dosages for rifabutin allow for this. Attention must be paid to the adherence of the HAART regimen, as well as the TB regimen, because rifabutin levels will likely be subtherapeutic if the patient stops taking the antiretrovirals.

Protease Inhibitors

The currently approved PIs* and rifamycins have opposite effects on the CYP3A family of enzymes in the liver, causing drug-drug interactions when PIs are taken with rifamycins:

- PI serum concentrations and overall exposure may decrease to sub-therapeutic levels because rifamycins accelerate the metabolism of PIs by inducing the CYP3A enzymes.
- Rifampin levels are not affected since it is not metabolized by CYP3A.
- Rifabutin exposure may increase to toxic levels because PIs decrease its metabolism.

*Indinavir, nelfinavir, saquinavir, ritonavir, amprenavir, fosamprenavir, atazanavir, tipranavir/ritonavir and darunavir/ritonavir administered together, and lopinavir/ritonavir fixed combination.

Rifampin and Protease Inhibitors

Previous recommendations specifically contraindicated the use of rifampin with any of the PIs. However, data indicate that rifampin can be used for the treatment of active TB in patients whose antiretroviral regimen includes ritonavir (600/mg twice daily) as the only PI [plus 2 or more nucleoside-nucleotide reverse transcriptase inhibitor (NRTIs)], although this regimen may lead to loss of virologic response (ritonavir AUC is reduced 30% when co-administered with rifampin). The manufacturer does not make any recommendations on the use of rifampin with ritonavir; the utility of high doses of ritonavir is limited by its poor tolerability in many patients.

Low dose ritonavir (100 mg bid) has gained utility as a booster for other PIs (the combination drug lopinavir/ritonavir is an example). However, low-dose ritonavir does not seem to ameliorate rifampin-mediated reduction in lopinavir concentration; this likely applies to other PIs as well. The administration of rifampin with indinavir and low-dose ritonavir has led to subtherapeutic concentrations of indinavir. Rifampin should not be administered with atazanavir/ritonavir 300 mg/100 mg once per day. Even in the presence of a low dose of ritonavir, there is a clinically significant reaction between atazanavir and rifampin. Some experts have advised against using rifampin with antiretroviral regimens containing low-dose ritonavir.

Tipranavir was FDA-approved for use in a ritonavir-boosted combination and is contraindicated with rifampin. Tipranavir is actually a CYP3A inducer, but when administered with ritonavir, as currently approved, the induction effect is negated by the potent inhibitory effect of ritonavir on CYP3A. Tipranavir can be used with rifabutin at reduced dosage (see p. 54, Figure III-2).

Darunavir is also an inhibitor of CYP3A and is approved for use in a ritonavir-boosted combination. Co-administration of darunavir/ritonavir is contraindicated with rifampin.

Data have indicated that rifampin may be co-administered with ritonavir 400 mg twice daily, given with saquinavir 400 mg twice daily; however, more recent data show that 39.3% of normal subjects exposed to rifampin 600 mg once daily taken with ritonavir 100 mg/saquinavir

1000 mg given twice daily (ritonavir-boosted saquinavir) developed significant hepatocellular toxicity during a 28-day study period. Among these subjects, transaminase elevations of greater than 20 times the upper limit of normal values were noted, and one subject was admitted to the hospital with marked transaminase elevations. Based on this, the manufacturer does not recommend co-administration of rifampin with any ritonavir/saquinavir combinations.

Rifabutin and Protease Inhibitors

Rifabutin can be used with regimens containing a single PI (except saquinavir alone) with some dose adjustments (see p. 54, Figure III-2). Rifabutin can also be used in the following FDA-approved combinations:

- Lopinavir/ritonavir
- Fosamprenavir/ritonavir
- Tipranavir/ritonavir
- Darunavir/ritonavir

Rifabutin should not be used with ritonavir alone because of high rates of adverse effects. For any boosted regimen containing ritonavir, the dose of rifabutin should be reduced to 150 mg 3 times per week.

Non-nucleoside Reverse Transcriptase Inhibitors

The NNRTIs—delavirdine, nevirapine and efavirenz—are all metabolized by the hepatic CYP3A. Therefore, NNRTI levels are adversely affected by the rifamycins. The effect of NNRTIs on the CYP3A is less uniform; delavirdine inhibits the CYP3A, whereas nevirapine and efavirenz induce the CYP3A (see p. 54, Table III-2). Delavirdine should not be used with either rifampin or rifabutin because both rifamycins greatly diminish the levels of delavirdine.

Rifampin and Non-Nucleoside Reverse Transcriptase Inhibitors

Efavirenz. Clinical experience supports the use of efavirenz and rifampin together. Rifampin modestly decreases efavirenz exposure. However, it is safe to use rifampin concomitantly with efavirenz at the 600 mg daily dose, as excellent virologic outcomes have been found in patients on anti-TB treatment with rifampin and efavirenz-based HAART regimens. Some experts recommend the 800 mg dose of efavirenz for patients weighing more than 60 kg.

Nevirapine. Nevirapine exposure is reduced by rifampin. Several small observational studies have shown a favorable clinical response for patients receiving rifampin and nevirapine. Co-administration of nevirapine and rifampin may be particularly useful for pregnant patients in resource-poor countries, since efavirenz cannot be used in pregnancy and use of a PI-based regimen is limited due to general unavailability of rifabutin. If used under these circumstances, close clinical and virologic monitoring is necessary (see p. 53).

Rifabutin and Non-Nucleoside Reverse Transcriptase Inhibitors

Efavirenz. Efavirenz exposure is not significantly affected by rifabutin, but efavirenz does decrease rifabutin exposure. Therefore, rifabutin dosage must be increased (from the usual dosage of 300 mg to a daily dose of 450-600 mg, or 2 or 3 times weekly at a dose of 600 mg) when it is given with efavirenz. An increased dose of rifabutin given daily should be used with caution, since adverse events—including anterior uveitis and reduced white blood cell count—have been reported. Those reports relate to high-dose rifabutin used in regimens that included a macrolide to treat disseminated *Mycobacterium avium* complex infections. Monthly monitoring with a CBC is recommended.

Nevirapine. Nevirapine exposure is slightly decreased by rifabutin, and nevirapine also slightly decreases rifabutin exposure. Therefore, nevirapine can be used with rifabutin, both at their usual doses.

Using More Than 1 PI and/or 1 NNRTI. Drug-drug interactions between rifamycins and antiretroviral regimens containing 2 PIs, 2 NNRTIs, or both a PI and an NNRTI have not been well studied, with the exception of ritonavir (see above). However, based on knowledge of metabolic pathways, some authors have recommended the use of efavirenz or nevirapine plus a PI (other than ritonavir) with rifabutin at its usual dose of 300 mg daily, or 3 times a week. These recommendations are based on theory and not on hard data. Avoiding antiretroviral regimens that contain more than 1 PI (with the exception of ritonavir-boosted regimens) or a PI and an NNRTI, when given simultaneously with a rifamycin-containing regimen for the treatment of TB, is advisable until more data are available.

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs) and Other Antiretroviral Agents

NRTIs include:

- Zidovudine
- Lamivudine
- Didanosine
- Zalcitabine
- Stavudine
- Emticitabine
- Tenofovir
- Abacavir

There is a slight decrease in the level of zidovudine, and probably abacavir, when coadministered with rifampin. The clinical significance of this interaction is not clear. The other NRTIs do not interact significantly with rifamycins. Therefore, rifamycins can be included in the anti-TB regimen if a PI- or NNRTI-sparing antiretroviral regimen is chosen. A small clinical trial comparing 4 NRTIs (zidovudine, lamivudine, abacavir and tenofovir) to efavirenz-based HAART regimen, found both to be equally effective. Triple NRTIs regimens have been shown to be less potent than efavirenz-based HAART. These regimens may be alternatives for patients unable to take NNRTIs because of adverse reaction or HIV drug resistance.

The fusion inhibitor T20, also known as enfuvirtide, is not known to be a substrate for the CYP450 enzymes or to have any effect on the levels of these enzymes. It can be used with all of the anti-TB drugs (see p. 55, Table III-3).

Several new HIV drugs have recently become available. They should be used with caution in TB patients. Raltegravir is a recently approved HIV integrase inhibitor drug. Rifampin decreases the trough concentration of this drug by 60%; however, it is recommended to be used at the standard dose with rifampin.

Rifampin substantially reduces levels of the recently approved CCR5-receptor antagonist, maraviroc, and increased dose of the latter is recommended when co-administered with rifampin. There is no clinical experience at present with this combination.

A newer NNRTI, etravirine, is available through an expanded access program and is predicted to be substantially decreased in the presence of rifampin. No data is available on these interactions.

Other Anti-Tuberculosis Agents

The other major anti-TB drugs (isoniazid, pyrazinamide, ethambutol, the aminoglycosides [streptomycin, kanamycin and amikacin], capreomycin, para-amino salicylic acid, and the fluoroquinolones) are not primarily metabolized by CYP3A. Therefore, they do not have clinically important interactions with current PIs and NNRTIs. However, ethionamide is primarily metabolized by CYP3A, and its AUC may increase if it is co-administered with PIs or delavirdine; efavirenz and nevirapine may decrease levels of ethionamide. The clinical significance of this interaction is unknown.

Treatment Options

For drug-sensitive TB, several rifamycin-containing anti-TB regimens can be safely administered with effective antiretroviral therapy. Rifampin and rifabutin are the preferred rifamycins for patients who are HIV infected and taking PIs or NNRTIs. (See p. 54, Figure III-2.)

The importance of rifamycins must be strongly emphasized. Regimens that include rifampin are much shorter (6-9 months vs. 18-24 months) and have faster sputum conversion rates, higher cure rates and lower relapse rates than regimens that do not include rifampin. Higher mortality has also been reported with non-rifamycin regimens in patients who are HIV positive. Regimens that have used only 2 months of rifampin (or rifamycin) have been shown to have much higher relapse rates, particularly for patients who are HIV infected. Rifabutin may be substituted for rifampin (either initially or during the continuation phase of treatment). Rifabutin should be substituted at least 2 weeks before the planned initiation of a PI or an NNRTI to allow for the resolution of the effect of rifampin on CYP3A. Rifabutin can be administered with all the currently approved PIs (except saquinavir alone), as well as efavirenz and nevirapine. The dose and frequency of rifabutin depends on the PI or NNRTI with which it is being co-administered. (See p. 54, Figure III-2; p. 55, Table III-3.) Rifampin exposure is not affected by the co-administration of the PIs or NNRTIs, and rifampin dosing does not need to be adjusted.

The following regimens can be used:

- Two months isoniazid, rifampin, pyrazinamide, ethambutol, then 4 months isoniazid, rifampin

- Two months isoniazid, rifabutin, pyrazinamide, ethambutol, then 4 months isoniazid, rifabutin
- Two months isoniazid, rifampin, pyrazinamide, ethambutol, then 4 months isoniazid, rifabutin
- Nine months isoniazid, pyrazinamide, streptomycin

General Considerations

Most patients who are HIV positive with TB in NYC have CD4 T-lymphocyte counts below 200 cells/mm³ and are eligible for antiretroviral treatment.

HAART regimens have been shown to be life saving, and many TB patients have advanced AIDS and will benefit from initiation of HAART early in the 2-month intensive phase. (See p. 54, Figure III-2.)

For patients who are not already taking antiretrovirals at the time of TB diagnosis, physicians should consider deferring the initiation of an antiretroviral regimen until after the intensive phase of TB therapy (the first 2 months of treatment for drug-susceptible TB). This allows the clinician to manage the adverse effects associated with TB drugs without having to deal with the complications of antiretroviral drugs, and may minimize the likelihood of immune reconstitution syndrome (IRIS) (see p. 56). Patients may also find the pill burden more tolerable when the antiretroviral drugs are started after some of the anti-TB medications have been discontinued, in the continuation phase. If the patient is unable to tolerate or manage the multiple drugs needed to treat both conditions, it may be necessary to defer HIV treatment until TB treatment is completed.

If a patient is already on a PI- or an NNRTI-containing antiretroviral regimen that is not compatible with rifamycins, consideration should be given to changing the antiretroviral regimen. Currently, treatment interruptions are not recommended for most patients taking antiretroviral therapy—in some patients it may be associated with poorer treatment outcomes. An expert in the management of HIV disease should be consulted.

Alternatively, for patients undergoing therapy with complex combinations of PIs and/or NNRTIs, anti-TB regimens that do not contain rifamycins can be used. Only 1 regimen without a rifamycin—9 months of isoniazid, pyrazinamide and streptomycin—has been shown (in patients who are HIV-seronegative) to have high efficacy in less than 12 months. This regimen is rarely used, however, since the injectable drug has to be administered for the full 9 months.

If an isoniazid-resistant, rifampin-susceptible organism is isolated, it is essential to try to adjust the regimen so that a rifamycin can be used. Otherwise, the patient will need at least 18 to 24 months of treatment with one of the weaker, more toxic regimens used for multidrug-resistant TB.

Women of childbearing age and pregnant women. Treatment of HIV and TB in pregnant women is challenging. Efavirenz is contraindicated both for pregnant women and for women of childbearing potential who are not on adequate contraception. Nevirapine is the only other highly active antiretroviral therapy (HAART) regimen that can be administered with rifampin. However, nevirapine is associated with an increased risk of severe hepatotoxicity in women with CD4 T-lymphocyte counts greater than 250 cells/mm³ and is a relative contraindication. In such women who are pregnant, HAART regimen is difficult to administer during TB treatment when rifabutin is not available. If nevirapine is used with rifampin, close clinical, hepatic and virologic monitoring is necessary.

Length of Therapy. Recommended treatment regimens and length of therapy are similar for individuals who are HIV infected and those who are not. The length of therapy is not affected by antiretroviral use, and short course therapy is possible if a standard rifamycin-containing regimen is used. The clinical, radiographic and microbiologic responses to therapy are similar irrespective of HIV status. Relapse rates are low. Though several studies have shown that relapse rates are higher in individuals who are HIV infected, others have shown similar relapse rates in both groups. If cultures remain positive after 2 months of rifamycin-based treatment, the therapy should be extended to 9 months.

Intermittent Regimens Containing Rifamycins

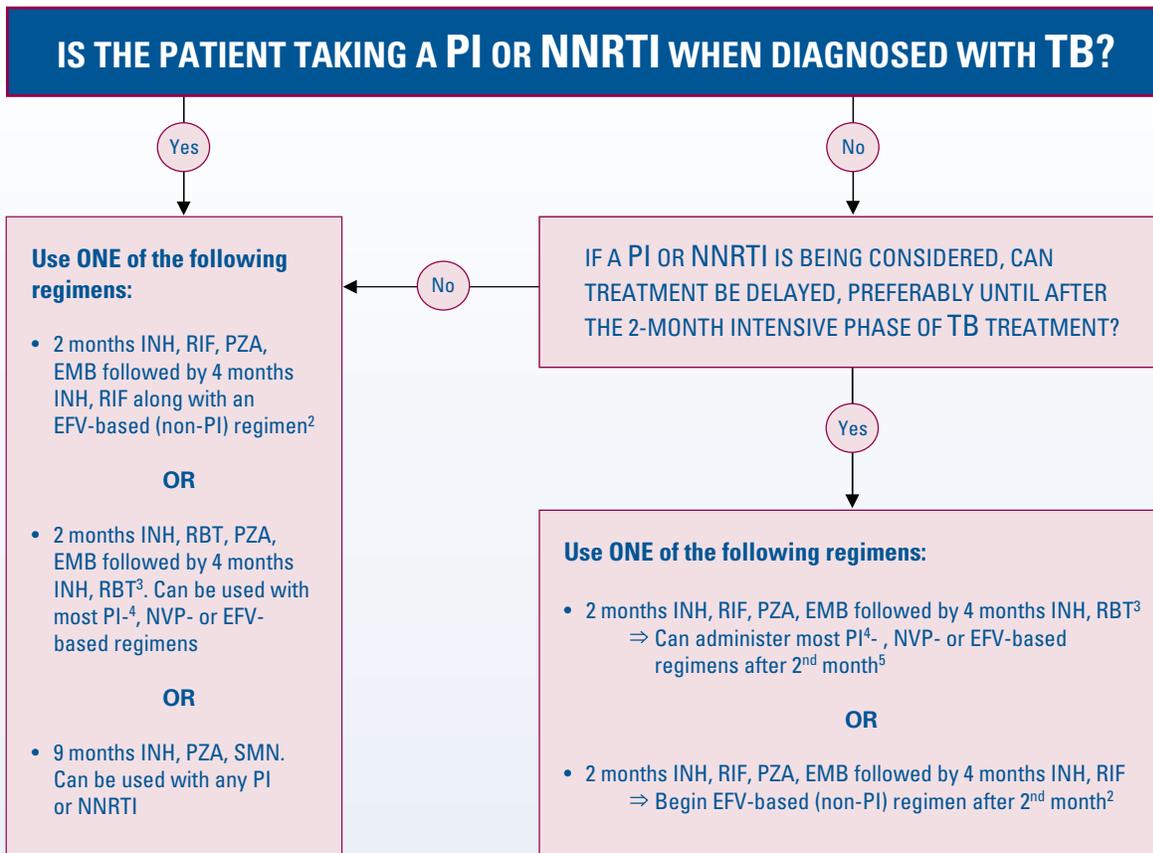
Independent of CD4 counts, all patients with HIV-TB coinfection should be treated with a daily regimen during the intensive phase, regardless of whether they are also receiving antiretroviral drugs. Rifabutin dose may be intermittent, depending on the HAART regimen. (See p. 54, Figure III-2.) During the continuation phase of treatment, the patient's CD4 count is of primary importance in determining frequency of intermittent therapy.

Patients with HIV-associated TB and CD4 cell count of less than 100/mm³ should receive daily therapy during the intensive phase and daily or 3 times per week therapy during the continuation phase. Regimens should not be given at a frequency of less than 3 times per week in HIV-infected TB patients with CD4 cell counts lower than 100/mm³. Administering rifabutin-containing regimens twice a week has been associated with the development of acquired rifamycin resistance. The Centers for Disease Control and Prevention (CDC) suspended enrollment of patients into Study 23 (a study designed to evaluate the efficacy of twice-weekly rifabutin-based regimens for treatment of HIV-associated TB), because 7 cases of acquired rifamycin resistance occurred among study patients. All had received a biweekly rifabutin-containing regimen at some point, during the treatment of TB with a drug-susceptible organism. In addition, NYC experience confirms that use of intermittent rifamycin-containing regimens in the intensive phase of treatment is associated with development of acquired rifampin resistance in patients with very low CD4 cell counts. Rifapentine should not be used at all for the treatment of TB in patients who are HIV infected, because of the increased rate of rifamycin resistance that occurs with highly intermittent therapy.

For patients with a CD4 cell count of less than 100/mm³ receiving lopinavir/ritonavir or any other ritonavir-boosted regimen, TB therapy should be daily during the intensive phase, with the exception of the rifabutin component. Isoniazid, pyrazinamide and ethambutol should be given daily at standard doses. Rifabutin should be given as 150 mg 3 times per week. During the continuation phase of therapy, isoniazid and rifabutin can both be given 3 times per week.

Figure III-2

Treatment Options for Patients Who Have Tuberculosis and Are HIV Infected¹



Abbreviation Key:

EFV efavirenz
EMB ethambutol
IDV indinavir

INH isoniazid
NFV nelfinavir

NNRTI non-nucleoside reverse transcriptase inhibitor

NVP nevirapine
PI protease inhibitor
PZA pyrazinamide

RBT rifabutin
RIF rifampin
SMN streptomycin

NOTES

- Patients who are HIV infected, with a CD4+ count of less than 100 cells/mm³ should receive a daily regimen in the intensive phase and either daily or 3 times per week regimen in the continuation phase.
- With RIF: EFV daily dosage may need to be increased to 800 mg.
- RBT dosage and frequency vary depending on the PI or NNRTI being used.
 - With EFV: RBT 450-600 mg daily or 600 mg 2 or 3 times per week. EFV daily dose is unchanged with RBT.
 - With NVP: RBT 300 mg daily or 300 mg 2 or 3 times per week
 - With amprenavir, fosamprenavir, IDV or NFV: RBT 150 mg daily or 300 mg 2 or 3 times per week
 - With amprenavir/ritonavir, atazanavir, atazanavir/ritonavir, darunavir/ritonavir, fosamprenavir/ritonavir, lopinavir/ritonavir, or tipranavir/ritonavir: RBT 150 mg every other day or 3 times per week. Other anti-TB drugs should be given daily in the intensive phase for patients with a CD4+ count <100 cells/mm³.
- With RBT the following PI dose changes are recommended:
 - Increase NFV to 1000 mg 3 times per day or use standard 1250 mg 2 times/day.
 - Increase IDV to 1000 mg 3 times per day.
- There should be a 2-week washout period after the discontinuation of RIF and before starting a PI or NNRTI.

For further details, see "Antiretroviral Drugs and Treatment of Tuberculosis" at: <http://www.nyc.gov/html/doh/downloads/pdf/tb/tbanti.pdf>

Useful websites:

http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm or www.AIDSinfo.nih.gov

Table III-3

Treatment Adjustments in Patients Who Are HIV Positive and Taking Antiretroviral Agents

Generic Name	Brand Name	OK with rifampin?	OK with rifabutin?*
Protease Inhibitors (PIs)			
Amprenavir	Agenerase®	no	yes
Atazanavir	Reyataz®	no	yes
Darunavir/Ritonavir	Prezista™ & Norvir®	no	yes
Fosamprenavir	Lexiva®	no	yes
Indinavir	Crixivan®	no	yes
Lopinavir/Ritonavir	Kaletra®	no	yes
Nelfinavir	Viracept®	no	yes
Ritonavir	Norvir®	no	yes
Saquinavir	Invirase®, Fortovase®	no	no
Tipranavir/Ritonavir	Aptivus® & Norvir®	no	yes
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
Delavirdine	Rescriptor®	no	no
Efavirenz	Sustiva®	yes	yes
Efavirenz/Emtricitabine/Tenofovir combination	Atripla™	yes	yes
Nevirapine	Viramune®	yes**	yes
Other Antiretroviral Drugs			
Abacavir	Ziagen®	yes	yes
Didanosine	Videx®	yes	yes
Emtricitabine	Emtriva®	yes	yes
Enfuvirtide	Fuzeon®	yes	yes
Lamivudine	Epivir®	yes	yes
Stavudine	Zerit®	yes	yes
Tenofovir	Viread®	yes	yes
Zalcitabine	Hivid®	yes	yes
Zidovudine	Retrovir®	yes	yes
Zidovudine + Lamivudine	Combivir®	yes	yes
Abacavir + Zidovudine + Lamivudine	Trizivir®	yes	yes
Emtricitabine + Tenofovir	Truvada®	yes	yes
Abacavir + Lamivudine	Epziom®	yes	yes

Use of brand names is for informational purposes only and does not imply endorsement by the New York City Department of Health and Mental Hygiene

* When antiretrovirals are used with rifabutin, the dosage of the PI, NNRTI and/or rifabutin may need to be adjusted. Please refer to the text and Figure III-2 on preceding page for details on drug dosages.

** Limited circumstances; refer to text.

For further details, see “Antiretroviral Drugs and Treatment of Tuberculosis” at: www.nyc.gov/html/doh/downloads/pdf/tb/tbanti.pdf

Useful websites:

www.cdc.gov/tb/TB_HIV_Drugs/default.htm or www.AIDSinfo.nih.gov

Patients with CD4 count greater than 100 cells/mm³ at the time of TB diagnosis should be treated with a daily regimen in the intensive phase, and with either 2 or 3 times per week regimens in the continuation phase.

Indinavir, nelfinavir, atazanavir, amprenavir and fosamprenavir can all be administered with daily rifabutin (150 mg/day), as well as with 2 or 3 times per week regimens (during the continuation phase only) at a dose of 300 mg. Efavirenz can be given with rifabutin 450 mg daily or 600 mg 2 or 3 times a week. An increased dose of rifabutin given daily should be used with caution since adverse events, including anterior uveitis and a reduced white blood cell count, have been reported with high-dose rifabutin when it is used in regimens that include a macrolide. Monthly monitoring with a CBC is recommended.

Immune Reconstitution Inflammatory Syndrome

Immune Reconstitution Inflammatory Syndrome (IRIS), also known as paradoxical worsening of TB, is the development of new manifestations of TB or worsening of existing signs and symptoms of TB in patients receiving appropriate medication regimens. IRIS is thought to be an inflammatory response to *M. tb* antigens as the body's immune system recovers while on TB and/or HIV treatment. This theory is strengthened by the observation that patients with HIV-associated TB who are started on antiretroviral regimens seem to be at a particularly increased risk of developing this syndrome.

A number of studies have estimated frequency of IRIS to be 11% to 45%, and find that it occurs more often in patients with lower CD4 counts, extrapulmonary disease, disseminated disease and with a shorter interval from TB diagnosis to HAART administration. Paradoxical reaction occurs within a few weeks of starting HAART, and coincides most closely with viral load decline. Thus the timing of HAART initiation in patients with TB is further complicated by the potential for a paradoxical or IRIS reaction.

Patients may experience substantial morbidity due to IRIS reactions even though the prognosis for survival is favorable. The CDC/ATS/IDSA guidelines suggest delaying HAART initiation until after 4 to 8 weeks of TB therapy. A practical strategy for dually infected patients who were not on HAART prior to TB diagnosis may be to

give TB treatment alone until clinical improvement plateaus, or until the end of the intensive phase. This will also minimize overlapping toxicities, reduce pill burden and make both treatments more tolerable.

Paradoxical worsening can manifest in a wide variety of sites, including cervical or mediastinal adenopathy, worsening infiltrates on CXR or enlarging central nervous system (CNS) lesions. Fever may or may not be present.

The course of paradoxical worsening is often unpredictable. It can be brief or prolonged, with multiple recurrences and exacerbations.

The diagnosis of paradoxical reactions remains a diagnosis of exclusion. Diagnosis relies on negative culture of clinical samples; decrease in HIV viral load and lack of other etiologies, such as relapse of TB, poor adherence to treatment, adverse effects of drugs, worsening TB due to drug resistance or other infections.

Treatment of paradoxical reactions is not well established. Mild and moderate reactions can be managed by reassuring the patients or by non-steroidal anti-inflammatory agents. Repeated aspirations for decompression have been used to avoid surgical drainage. Some experts advocate the use of corticosteroids or discontinuation of antiretroviral therapy for severe cases, such as patients who have lymphadenopathy that may compromise respiration and swallowing, or the development of CNS mass lesions. Prednisone at doses ranging from 20 to 50 mg daily, tapered over as little as 2 weeks, has been used. The use of corticosteroids for short periods of time does not seem to adversely affect the outcome of the TB treatment. Data on the use of corticosteroids for the treatment of paradoxical reactions in HIV-associated TB are limited. Their use should therefore be reserved for severe cases.

Regimens for Pregnant Women

In almost all situations, a pregnant woman who has a positive *M. tb* culture (Class III), or who is suspected of having TB (Class V [High]), should be treated without delay. Very rarely, and with the approval of the Bureau Director or Director of Medical Affairs for the BTBC, treatment for suspected TB may be deferred until the end of the first trimester. This may be done if the pregnant woman is very reluctant to take the treatment, and meets all of the following criteria:

- Sputum smear negative for AFB
- HIV-negative
- No risk factors for HIV infection
- No symptoms of TB (i.e., no cough, fever, night sweats, weight loss)
- No cavities on CXR

Treatment regimens for pregnant women differ from standard treatment regimens because streptomycin is contraindicated and pyrazinamide should be avoided. Streptomycin has been shown to have teratogenic effects on the fetus, and the effect of pyrazinamide on the fetus is not known. However, if treatment is started after the first trimester, pyrazinamide should be included in the initial treatment regimen for: women who are HIV positive; women who have behavioral risk factors for HIV infection but decline HIV testing; and women suspected of having multidrug resistant TB (MDRTB, resistant to at least isoniazid and rifampin). Pyrazinamide should be included in the treatment regimen, regardless of the stage of pregnancy, for women who are HIV positive strongly suspected of having TB resistant to isoniazid and rifampin. Note that despite the lack of data on pyrazinamide, the World Health Organization recommends this drug at all stages of pregnancy for all pregnant women.

TB during pregnancy is rarely, if ever, an indication for a therapeutic abortion. One possible exception, however, is multidrug-resistant tuberculosis (MDRTB). See p. 58 for further discussion.

Whether a mother who has disease should be separated from her infant at delivery depends on how infectious she is. Clinicians should assess the mother's infectiousness. (See p. 130.) If the mother is considered infectious, she should be separated from the infant until she becomes noninfectious on treatment, or until the infant starts treatment for latent tuberculosis infection (LTBI).

Standard Regimen for Pregnant Women

Start with a regimen of isoniazid, rifampin, and ethambutol unless there are absolute contraindications. Use Rifamate® (capsules combining isoniazid and rifampin) for patients who are not receiving DOT. See p. 208,

Appendix I-A for dosages. (See below for treatment for pregnant women who are HIV-negative, and who are suspected of having MDRTB.)

- Use pyrazinamide from initiation of treatment, regardless of month of gestation, if drug resistance is strongly suspected.
- Also give pyrazinamide if the woman is HIV-infected and TB treatment is started after the first trimester.
- Discontinue ethambutol (and pyrazinamide) at the end of the intensive phase of treatment unless:
 - Drug susceptibility results show resistance to isoniazid or rifampin.
 - Drug susceptibility results are not available and drug resistance is suspected because of a history of prior TB treatment.
- Ethambutol can be discontinued earlier once drug susceptibility results are available and show susceptibility to isoniazid and rifampin.

For pregnant women taking isoniazid, give pyridoxine (Vitamin B₆) 25 mg a day unless the patient is already taking a prenatal vitamin that contains the equivalent amount of pyridoxine.

If pregnancy is discovered while the patient is already on a standard 4-drug regimen that includes pyrazinamide, the pyrazinamide can be stopped if the woman is in the first trimester of pregnancy and if the above risk factors are not present. If the first trimester has passed before the pregnancy is discovered, continue all 4 drugs, in order to finish a 2-month intensive phase of treatment. This allows the total duration of treatment to be shortened significantly.

Length of Treatment

Culture-positive pulmonary disease

- If the strain is fully susceptible, treat for a total of 9 months if the patient is treated with isoniazid, rifampin and ethambutol. However, if pyrazinamide was given for the initial 2 months of treatment, (i.e., before the woman was discovered to be pregnant or if the woman was HIV-infected), a total of 6 months of treatment is appropriate. (If the strain is drug resistant, see p. 86, Table V-1 for guidelines on the length of treatment.)

- If the patient is *M. tb* culture positive without available susceptibilities and if drug resistance is not suspected, the patient should be treated with isoniazid, rifampin and ethambutol (and pyrazinamide) during the intensive phase, and then isoniazid and rifampin during the continuation phase.
 - If drug resistance is suspected, the 3-drug regimen of isoniazid, rifampin and ethambutol should be continued for 9 months. The 4-drug regimen that adds pyrazinamide can be given for 6 months.
- If cultures have not converted by 4 months, assess the patient for adherence to treatment, absorption of anti-TB medication(s) and drug resistance. (See p. 84 and p. 214, Appendix I-E.)

Culture-negative pulmonary disease

For patients whose initial sputum cultures are negative and who received only isoniazid, rifampin and ethambutol, the intensive phase of treatment should be followed by:

- A 7-month continuation phase of isoniazid and rifampin only, if the patient has not received treatment for TB in the past, and if drug resistance is not suspected.
- If the patient has received treatment in the past, continue isoniazid, rifampin and ethambutol for the full 9 months, as drug resistance may be present.

If pyrazinamide was used in the intensive phase, than the duration and drug regimen is the following:

- The intensive phase of treatment should be followed by a 2 month continuation phase of isoniazid and rifampin only, if the patient has not received treatment for TB in the past and drug resistance is not suspected.
- If the patient has received treatment in the past, isoniazid, rifampin, pyrazinamide and ethambutol should be continued for an additional 2 months, to complete a 4-month regimen.

Regimen for Pregnant Women Suspected or Known to Have Tuberculosis Resistant to Isoniazid and Rifampin (MDRTB)

Unlike the treatment of drug-susceptible TB, it is not possible to develop standardized protocols for the treatment of known or suspected drug-resistant TB. Physicians treating pregnant women suspected or known to have drug-resistant TB should follow the treatment principles in Section V. As with all drug-resistant TB cases, expert consultation should be sought.

Most of the medications used to treat MDRTB are known to cause fetal abnormalities or have not been studied adequately regarding their safety in pregnancy. (See p. 211, Appendix I-C.) These include streptomycin, kanamycin, amikacin, capreomycin and fluoroquinolones (e.g., ciprofloxacin, levofloxacin, ofloxacin and moxifloxacin), cycloserine, ethionamide and, rarely, clofazimine. Therefore, pregnant women with culture-proven MDRTB should be offered abortion counseling.

In the case that a woman continues the pregnancy, physicians should treat for MDRTB despite the potential toxicities. The risk of TB to the fetus outweighs the risk of toxicities from anti-TB medications. The physician should document all discussion with the patient in the chart.

Anti-Tuberculosis Medications in Breast-feeding Women

The small concentrations of anti-TB drugs in breast milk are not toxic to the nursing newborn (see p. 211, Appendix I-C). Therefore, breast-feeding should not be discouraged for a woman who is HIV negative and who is planning to take, or who is taking, isoniazid or other anti-TB medications. Furthermore, the low concentration of anti-TB medications in breast milk should not be considered effective treatment for disease—or for treatment for LTBI in a nursing infant. Women who are HIV-positive should not breast-feed because of the risk of HIV transmission to the infant.

Regimens for Children

In addition to the standard evaluation listed on p. 26, the following areas of evaluation and presentation of TB merit special attention in children.

Children who can be evaluated for visual acuity or color vision should be managed under the protocol for adults. (See p. 43.) If children cannot identify letters on an eye chart, they may be able to discriminate colors, and this can be used for monitoring for potential ethambutol toxicity. Children who cannot be evaluated for visual acuity or color vision should not be treated with ethambutol unless the child is known or likely to have drug-resistant TB or HIV infection, or immunosuppression from other clinical conditions.

When ethambutol is used as part of the initial regimen, the dosage is 20 mg/kg body weight. The recommended daily dose of ethambutol is higher in children than in adults (15 mg/kg), because the pharmacokinetics are different (peak serum ethambutol concentrations are lower in children than in adults receiving the same mg/kg dose).

Although ethambutol was frequently omitted from treatment regimens for children in the past, due in part to concerns about the difficulty of monitoring for toxicity (particularly optic neuritis, in young children), a literature review indicates that it is safe in children at a dose of 20 mg/kg (range 15–25 mg/kg) daily. Streptomycin should be avoided when possible in children, both 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 for TB meningitis.

Similar to adults with TB, children with confirmed or suspected TB should be given DOT. If DOT is not given, the reason for this must be clearly documented in the medical record. After the intensive phase of daily therapy, children receiving DOT should be switched to an intermittent regimen. Some physicians may prefer to use 3 times a week dosing, as some children may not completely ingest all doses. (See p. 45, Table III-1.) In some situations, however, the physician may prefer daily therapy for adherence reasons. If intermittent therapy is not used, the physician must clearly document the reasons in the medical record.

If cultures have not converted by 4 months, assess the child for adherence to treatment, absorption of anti-TB medication(s) and drug resistance (see p. 84 and p. 214, Appendix I-E.)

Standard Regimen

Start with a regimen of isoniazid, rifampin and pyrazinamide for at least 2 months.

- Use ethambutol at 20 mg/kg if the child's vision can be tested.
- Use ethambutol, regardless of ability to test vision, for children who are:
 - HIV-positive
 - At risk for HIV infection, and whose parent or guardian declines HIV testing
 - Immunosuppressed from other conditions

However, if the exclusive source patient is known to have TB susceptible to isoniazid and rifampin, ethambutol may be omitted from the initial regimen.

Discontinue pyrazinamide (and ethambutol) at the end of the intensive phase of treatment unless:

- Drug susceptibility results of the child's or source case's isolate show resistance to isoniazid or rifampin.
- Drug susceptibility results are not available, and drug resistance is suspected because of a history of prior TB treatment.
- Ethambutol can be discontinued earlier, once drug susceptibility results are available and show susceptibility to isoniazid and rifampin.

See p. 208, Appendix I-A for dosages of primary medications used in the treatment of TB. For younger children, isoniazid or pyrazinamide tablets can be divided, crushed or added to food or liquids such as fruit, juice or gelatin. Also, rifampin may be emptied from the capsule and added to food or liquids just before ingestion. Liquid formulations are available through the BTBC pharmacy.

If the exclusive-source patient is known or strongly suspected to have *M. tb* resistant to isoniazid and/or rifampin, use ethambutol along with other appropriate medications. (See p. 83 and p. 86, Table V-1.)

Length of Treatment Regardless of Culture Results

The standard 6-month treatment (short-course chemotherapy) for drug-susceptible TB in children should consist of a 2-month intensive phase, followed by a 4-month continuation phase. (If the strain is drug-resistant, see p. 86, Table V-1 for guidelines on length of treatment.)

- The 4-month continuation phase of treatment should be used in the large majority of children. However, a 7-month continuation phase should be given to 4 groups:
 - Children with drug-susceptible pulmonary TB with initial cavitation on CXR, whose sputum culture remains positive after the intensive phase (i.e., the first 2 months of treatment).
 - Children who are still culture positive at 2 months, regardless of CXR results.
 - Children whose treatment regimen did not include pyrazinamide in the intensive phase, or whose organism was resistant to pyrazinamide.
 - Children over 12 years of age who are being treated with once-weekly isoniazid and rifapentine, and whose sputum culture remains positive after the 2-month intensive phase of treatment.

If the child is *M. tb* culture positive without available susceptibilities, and drug resistance is not suspected, the patient should be treated with isoniazid, rifampin, pyrazinamide (and ethambutol) during the intensive phase, and then isoniazid and rifampin during the 4-month continuation phase.

For children whose initial sputum cultures are negative, the intensive phase of treatment should be followed by a 4-month continuation phase of isoniazid and rifampin only (if the patient has not received treatment for TB in the past).

- If the patient has received treatment in the past, isoniazid, rifampin, pyrazinamide (and ethambutol) should be continued for the full 6 months, as drug resistance may be present.

For children who have positive gastric aspirates and a favorable clinical response, repeat gastric aspirates to document culture conversion is not recommended.

If the child has hilar adenopathy or extrapulmonary disease, treatment should be for 6 months with the same regimen as for pulmonary TB. However, if meningeal or miliary TB is present, treatment should be extended to 9-12 months, depending on the location of disease. (See p. 74.)

Adverse Events in Children

Adverse events caused by anti-TB drugs are much less common in children than in adults. The most important adverse event is the development of hepatotoxicity, which can be caused by isoniazid, rifampin or pyrazinamide. There are some data suggesting that doses of isoniazid greater than 15 to 20 mg/kg may be associated with a greater risk of hepatotoxicity. Serum liver enzyme levels should not be monitored routinely, as asymptomatic mild elevation of serum liver enzymes (less than 5 times the normal values) is not an indication to stop treatment. However, the occurrence of liver tenderness, hepatomegaly or jaundice should lead to investigation of serum liver enzyme levels and the immediate stopping of all potentially hepatotoxic drugs. Patients should be screened for other causes of hepatitis, and no attempt should be made to reintroduce these drugs until liver function has normalized. An expert experienced in managing drug-induced hepatotoxicity should be involved in the further management of such cases. If treatment for TB needs to be continued for severe forms of TB, nonhepatotoxic anti-TB drugs should be introduced (e.g., ethambutol, an aminoglycoside and a fluoroquinolone).

Regimens for Patients with Chronic Renal Failure

In most patients with chronic renal failure, the regimens for TB treatment must be adjusted. Most experts advise lengthening the interval between conventional doses as the safest method to accomplish adequate but safe serum levels. (see p. 211, Appendix I-C). Three times per week regimens are convenient and should be used. Isoniazid, rifampin, ethionamide and para-aminosalicylic acid (PAS) can be used in conventional doses in patients with chronic renal failure. These medications should be given after hemodialysis.

PAS in its traditional formulations may worsen renal acidosis and provide an excessive sodium load, and should be avoided. However, current formulations of PAS that do not use the sodium salt, (e.g., Paser®), can be used without the hazard of sodium retention.

There is very little information about how to dose patients who are on peritoneal dialysis. While there is some literature on intraperitoneal administration of anti-TB medications, our recommendation at this time is to dose the patient as per hemodialysis dosing.

The following anti-TB medications are eliminated by the kidney and therefore require a dose adjustment:

Aminoglycosides and capreomycin can be used in conventional or 750 mg doses, but only 2 or 3 times per week. The dose should be administered immediately after hemodialysis in patients who are receiving maintenance hemodialysis. Levels of amikacin, if used, may be helpful in guiding therapy.

Pyrazinamide can be used at the usual daily dose in patients with mild to moderate renal insufficiency. In patients with severe renal failure, however, a 3 times a week dose of 30 mg/kg (range 25-35 mg/kg) is recommended. The medication should be given immediately after hemodialysis.

Ethambutol and cycloserine are excreted primarily by the kidney, and excessive and toxic blood levels can occur in patients with chronic renal insufficiency. Both medications should be avoided if possible. If ethambutol is essential to the regimen in patients with MDRTB, a conventional 15 mg/kg dose may be given every 2 or 3 days, but visual acuity and color vision must be very closely monitored and blood levels must be monitored. Cycloserine should be given at a dose of 250 mg/day or 500 mg 3 times a week. Drug levels should be monitored. Doses of both drugs should be given immediately after hemodialysis.

Fluoroquinolones undergo some degree of renal clearance that varies from drug to drug. Levofloxacin at 750-1000 mg 3 times a week is adequate for treatment of TB in patients with end-stage renal disease. Moxifloxacin may be the preferred agent for patients with renal failure, as it is mostly cleared by the liver.

Regimens for Patients with Liver Disease

Many anti-TB drugs are metabolized by the liver. Therefore, patients with underlying liver disease may be more likely to experience liver toxicity from these drugs. In most situations it is not necessary to reduce the dosages of drugs that are metabolized by the liver (isoniazid, rifampin, pyrazinamide and ethionamide). However, closer monitoring of the patient's liver function, and signs and symptoms of toxicity, should be done. Monthly, and in some cases biweekly, LFTs should be done when a patient with chronic liver disease is receiving these drugs.

The administration of rifampin with isoniazid can increase the possibility of isoniazid toxicity. If it is necessary to exclude one of these agents from the regimen, isoniazid should be considered first. In this situation, the patient may be treated with ethambutol, rifampin and pyrazinamide for 6 to 9 months. (See p. 86, Table V-1 and p. 87.) If rifampin must be excluded, the duration of treatment should be prolonged to 18-24 months (see p. 86, Table V-1 and p. 87). Depending on the severity of the hepatitis, a trial of rifabutin should be considered. If pyrazinamide is not used, isoniazid and the rifamycin should be given for at least 9 months for drug-susceptible tuberculosis.

Patients who have viral hepatitis may be difficult to treat because of the underlying hepatic disease and potential drug toxicities. For patients with chronic active hepatitis B, Hepatitis B surface antigen-seropositive individuals with elevated alanine transaminase (ALT) should have hepatitis B e-antigen (HBeAg) testing. If positive, rifampin may be preferred over isoniazid. A gastroenterologist or infectious disease specialist should be consulted regarding further testing and possible pretreatment in individuals with an ALT at least 2 times the upper limits of normal, and who are HBeAg seropositive. In HBeAg-seropositive individuals, clinical and ALT monitoring should occur every 2 to 4 weeks. For patients with chronic hepatitis C, a hepatitis C viral RNA load should be obtained. If it is elevated, the patient should be referred for potential treatment. In these patients, elevated LFTs may be indicative of their underlying liver disease and may not be drug induced.

Table III-4

The Use of Pyridoxine in Tuberculosis Treatment

Drug	Dosage of Pyridoxine	Indicators
Isoniazid	<p>25 mg daily (may be self-administered if patient is on intermittent DOT)</p> <p>50 mg twice weekly, if isoniazid given at 900 mg twice weekly</p> <p>If patient develops peripheral neuropathy, discontinue isoniazid and continue pyridoxine (25 mg daily) until symptoms abate.</p>	<p>Indicated for children on meat- and milk-deficient diets and for breast-feeding infants on isoniazid</p> <p>Also advised for patients with:</p> <ul style="list-style-type: none"> • HIV infection • Malnourishment (more than 10% below ideal body weight or any wasting disease) • Diabetes • Cancer • Chronic renal disease • Pregnancy • Alcoholism • Pre-existing peripheral neuropathy • Chronic liver disease • Other immunosuppressive conditions
Cycloserine	50 mg for each 250 mg of cycloserine to a maximum of 200 mg pyridoxine daily*	Required for all patients taking cycloserine

* If an individual is taking 500 mg of cycloserine at the first dose and 250 mg at the second dose, for simplicity, 100 mg of pyridoxine can be given with each dose of cycloserine, or the entire pyridoxine dose can be given with one of the cycloserine doses.

A recent study found that only excessive alcohol consumption and a high baseline ALT concentration were independently associated with isoniazid hepatotoxicity. The presence of HCV antibody was associated with hepatotoxicity only on univariate analysis in this study.

In patients with acute liver failure, a regimen of nonhepatotoxic drugs—such as an aminoglycoside or capreomycin, ethambutol, cycloserine and a fluoroquinolone—should be used until the liver function improves (see p. 109, Figure VI-2). Levofloxacin is the preferred fluoroquinolone to use in patients with hepatic insufficiency. Moxifloxacin may be used with no change in dosage, however it should be used with caution, especially in cases of severe hepatic insufficiency. A similar regimen can be used in patients with severe chronic liver disease who cannot tolerate isoniazid or rifampin. The duration of therapy depends on whether it is possible eventually to add isoniazid and rifampin to the regimen, and on the final regimen that is tolerated.

The Use of Pyridoxine (Vitamin B₆) in Tuberculosis Treatment

Pyridoxine is often used in conjunction with certain anti-TB medications to prevent side effects in the central and peripheral nervous system (see Table III-4 above.)

Anti-Tuberculosis Drugs and Meals

Rifampin and isoniazid should be taken on an empty stomach whenever possible, as food has been shown to decrease absorption significantly. Absorption of rifapentine is improved when taken with meals. Rifabutin, pyrazinamide and ethambutol can be taken with food. Isoniazid should not be dissolved in, or ingested with, beverages high in glucose or lactose. Isoniazid, ethambutol and fluoroquinolones should not be given with magnesium or calcium-containing antacids, or with medications containing cations, as they may interfere with absorption of these drugs.

Directly Observed Therapy

Directly observed therapy (DOT), the standard of care in TB treatment, is the best way to ensure that patients complete an adequate course of treatment for TB. DOT means that a health care worker, or another responsible individual, directly observes and supervises every dose of anti-TB medication taken by the patient. DOT regimens may be daily, 2 or 3 times a week. Once-a-week DOT is acceptable only when rifapentine is used.

For patients on daily DOT, a 5-days-a-week treatment regimen is acceptable if the patient has drug-susceptible TB, and a standard first-line drug regimen is tolerated. This allows the full treatment to be directly observed. No self-administered doses have to be given to the patient for the weekends and holidays. The necessary number of doses for the duration of the daily treatment should be adjusted accordingly. This should not be attempted for patients on self-administered treatment.

Most patients will adhere to treatment when education, incentives, housing, enhanced social services and home or field DOT are provided. If these less-restrictive measures are likely to fail, or have already failed, the New York City Health Code empowers the Commissioner of Health to issue patients any order deemed necessary to protect the public health (e.g., orders for DOT, isolation or long-term detention). For information on the criteria for a Commissioner's Order, see p. 145.

All HIV-infected patients taking anti-TB treatment should be given DOT. When TB treatment is complicated by drug-drug interactions between drugs used for TB and those used for HIV infection, the need to ensure that patients adhere to their regimens becomes even more paramount. Poor adherence among these patients would be doubly dangerous and catastrophic in that it would create both TB and HIV drug resistance.

In addition to the BTBC, several New York State-sponsored sites provide DOT to TB patients in NYC. DOT can be done either in the clinic or in the field. Arrangements are made to accommodate the patients' schedules. All patient services provided by BTBC are free of charge to the patient.

Non-BTBC physicians who have patients with active TB have 2 treatment options:

1. **Refer the patient to a BTBC Chest Center.** The Health Department will act as the patient's TB care provider. The referring physician remains the primary care provider and receives TB care updates.
2. **Act as the patient's TB care provider.** The physician manages the patient's TB care and treatment. In both cases, all patients can be enrolled in DOT and receive free TB medications. The patient will receive medications through the DOH's Gratis Meds program, where BTBC supplies medications directly to the provider.

The BTBC is required by the CDC to case manage the patient's TB treatment in conjunction with the patient's primary TB provider.

To refer a patient, call the TB Provider Hotline at 212-788-4162.

Protocol for Providing Directly Observed Therapy

- All TB Class III and Class V (High) patients should be given DOT—it is mandatory if intermittent therapy is used. When a patient is not started on DOT, the compelling reason(s) must be clearly documented in the medical record.
- All doses (except those given on weekends and holidays) should be observed; it is not advisable to administer some doses by DOT and allow some to be self-administered.
- TB Class V (Low) patients (patients expected to evolve as TB Class IV) should be treated with an appropriate self-administered regimen. These patients should be monitored by a nurse if they are taking isoniazid alone, or by a physician if they are taking multiple anti-TB medications. If the classification is changed to Class III or Class V (High), DOT should be used.
- DOT should be clinic-based if possible. DOT outside a BTBC chest center should be reserved for patients who (1) are unable to attend the chest center for medical or social reasons; or (2) have failed more than 3 attempts at clinic-based DOT, but are willing to be part of a DOT program outside the chest center.
- A contract should be signed by the patient, the chest center manager or DOT provider (registered nurse or public health advisor)

and the physician who is ordering DOT. There are 2 separate contracts, 1 for field patients and 1 for clinic patients. These are included as Appendix III-C on p. 240 and Appendix III-D on p. 242.

- Patients being cared for by a physician not affiliated with the BTBC may also receive DOT at a BTBC chest center. In this situation, the Physician-in-Charge must review the patient's medical regimen. It is the responsibility of the non-DOH provider to medically follow the patient and order the patient's medication on a monthly basis and provide this information to the chest center.

Priority of Patients for Directly Observed Therapy

In some situations, individuals with suspected or confirmed TB must be assigned priority for DOT. The order of priority for DOT is as follows:

- Drug-resistant TB
- Smear-positive pulmonary TB
- Patients who are HIV positive
- Present or past non-adherence with TB medications
- History of prior treatment of TB
- Disease relapse
- Too ill to self-manage
- History of substance abuse
- Children requiring therapy whose parents are in any of the above categories
- Children and adolescents
- Homeless/shelter residents or unstably housed individuals
- History of being in a correctional facility
- Major psychiatric or memory/cognitive disorder
- Denial of TB diagnosis

- Poor adherence during initial medical management
- Slow sputum conversion or slow clinical improvement
- Clinical deterioration while on TB therapy
- Adverse reaction to TB medication
- At patient's request

Determination of Treatment Completion

It can be difficult to determine when a patient has completed treatment, since not all patients take 100% of prescribed doses, even when on DOT. The 2003 ATS/CDC/IDSA tuberculosis treatment guidelines recommend that treatment should be considered complete after 100% of the prescribed regimen has been taken. Treatment should be lengthened if all prescribed doses have not been taken within the original time frame, although there is limited data to support this recommendation. (See p. 45, Table III-1.)

Most short-course TB chemotherapy trials have considered completion of 80% of the doses prescribed to be adequate. This has been the BTBC guideline for a long time. Though there is little data to show that 100% completion of most short-course chemotherapy regimens is required, some individuals may benefit.

In selected individuals who have not been fully adherent to their treatment, the duration should be extended, to ensure that 100% of the originally recommended doses are given to individuals:

- With cavitary or extensive disease
- With HIV infection
- Who are still culture positive at 2 months after start of treatment
- Who did not receive 2 months of pyrazinamide in the intensive phase

For example, for a patient in the preceding categories who has only taken 80% of the doses in their 6-month regimen, treatment should be extended an additional few weeks to ensure 100% of doses are taken.

For other patients, an attempt should be made to ensure that the full regimen is taken whenever possible. However, if a patient disappears after receiving 6 months of treatment with 80% compliance, and the patient cannot be located, the patient may be considered as having completed treatment.

Interrupted or Incomplete Treatment

General Principles

When a patient has had interrupted or incomplete treatment, the physician must decide the appropriate duration of a new regimen.

Reinstitution of treatment requires a continuation of the regimen originally prescribed (for as long as needed to complete the doses of the original regimen), or a complete renewal of the prescribed treatment. (See p. 66, Figure III-3.)

This decision should be based on an estimate of the load of viable tubercle bacilli remaining in the lungs when treatment is restarted. Continuous treatment is more crucial in the initial, intensive phase of the regimen (e.g., during the first 2 months) because the number of organisms is highest in the beginning of treatment. In the continuation phase (e.g., after 2 months) of TB treatment, there are fewer persisting organisms to kill. Therefore, the possibility is small that a large number of organisms are present after a short lapse in treatment in the continuation phase.

In patients who are HIV-positive or otherwise immunosuppressed, the mycobacterial load can rebound rapidly, even with a short lapse in treatment during the continuation phase. In such patients, consideration should be given to renew treatment, even if the lapse is as short as 1-2 months.

The decision regarding completion of treatment should be based both on the total number of medication doses administered, and on the duration of therapy. If more than 80% of the prescribed doses were taken before a lapse in treatment, the regimen may not need to be renewed. The duration of the regimen should be based on the extent of disease revealed by initial CXR, evaluation of nonpulmonary sites involved, and AFB culture studies at 2 months.

Renewal of Tuberculosis Treatment

The following factors suggest a large mycobacterial load in the patient, and may require that

the patient completely renew the anti-TB regimen (i.e., the previous doses should be disregarded):

- In patients who have had a lapse of 14 days or longer within the intensive phase (i.e., first 2 months) of treatment, the regimen should be completely renewed.
- In patients with a lapse in treatment 3 months or longer, the treatment regimen should be completely renewed. If the patient is HIV positive, treatment renewal should be considered even if the lapse is less than 3 months.

Continuation of Lapsed Treatment

If a lapse in treatment occurs, and a decision is made to continue the regimen, the anti-TB regimen should last as long as needed to complete the doses of the treatment originally prescribed. The decision regarding completion of treatment should be based both on the total number of medication doses administered and on the duration of therapy. For example, a prescribed regimen of 6 months of daily multidrug treatment should include at least 182 doses; a prescribed regimen of 2 months of daily multidrug treatment (56 doses) with 4 months of 2 times per week doses (36 doses) should include at least 92 doses.

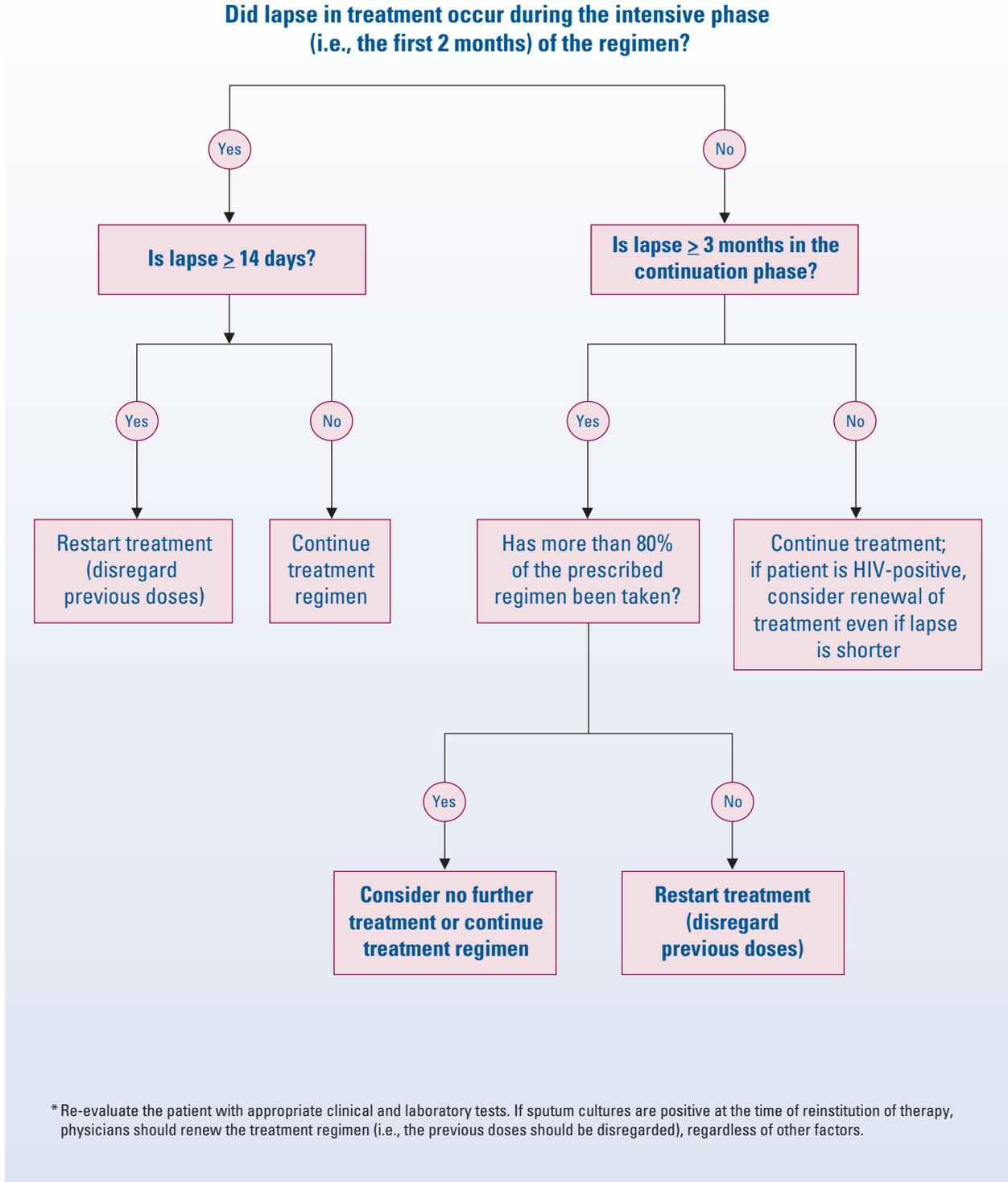
Protocols for Reinstating Treatment

Clinical evaluation and CXR should be done. Sputum samples should also be examined for *M. tb* prior to reinstatement of treatment. If sputum is culture positive at the time of reinstatement, physicians should renew treatment (i.e., the previous doses should be disregarded), regardless of other factors. In addition, drug susceptibility testing should be repeated at this time, even if the pretreatment isolates were pansusceptible.

- If the patient is not currently receiving DOT, it should be instituted. Every attempt should be made to ensure that the patient completes a continuous course of TB treatment.
- If a patient fails to adhere to DOT, a Commissioner's Order for DOT (D3) should be requested.

Figure III-3

Reinstitution of Interrupted or Incomplete Anti-Tuberculosis Treatment*



Treatment Failure

Treatment failure is defined as a positive *M. tb* culture any time after 4 months of appropriate TB treatment in a patient with pansensitive TB. Treatment failure should be suspected in patients whose cultures are pending, and who have clinical deterioration or worsening of the CXR due to TB.

- If sputum smears or cultures are positive after 4 months of appropriate treatment, 3 new consecutive daily sputum samples should be sent for smear, culture and susceptibility testing. For extrapulmonary TB patients, renewed attempts should be made to obtain appropriate specimens for smear, culture and susceptibility testing.
- Never add a single drug to a failing regimen, as it promotes further drug resistance.
- The most recent positive *M. tb* culture, if 1 is available, should be tested for susceptibility.
- Patients who are clinically stable may be maintained on the current anti-TB regimen ("holding regimen"), until susceptibility results are available to guide the choice of medications.
- Patients who are clinically deteriorating should be given at least 2-3 new anti-TB medications, to which the strain is likely to be susceptible. When susceptibility results are available, the regimen should be modified accordingly.
- DOT should be instituted if the patient is not currently receiving it.
- If a patient fails to adhere to DOT, a Commissioner's Order for DOT (D3) should be requested.

Treatment of Coexistent Tuberculosis and Disseminated Mycobacterium Avium-Intracellulare

Severely immunosuppressed individuals can develop TB and disseminated *Mycobacterium avium-intracellulare* (MAI) infection concurrently, and must be treated for both conditions. Also, AIDS patients with TB are candidates for preventative therapy against disseminated MAI infection, when their CD4 counts fall below 50 cells/mm³. Daily clarithromycin and once weekly azithromycin are currently the first-line

agents for preventing MAI infection; however rifabutin can also be used. MAI prophylaxis can be discontinued in patients whose CD4 counts rise to above 100 cells/mm³ on HAART and remain at that level for 6 months to a year. Drugs currently recommended to treat disseminated MAI are clarithromycin and ethambutol, with the possible addition of rifabutin in patients with high mycobacterial loads or in the absence of effective HAART. If rifabutin cannot be used due to drug interactions, fluoroquinolones or parenteral amikacin have been used, despite a lack of documentation of efficacy in clinical trials.

General recommendations are that the patient with disseminated MAI should receive at least 12 months of therapy for MAI, and should maintain 6 months of immune reconstitution (CD4 T cell count greater than 100 mm³ on HAART). Then, MAI treatment can safely be discontinued, but patients should be followed for continued viral load suppression and maintenance of CD4 counts. Lifelong treatment is necessary for disseminated MAI in patients who are HIV infected and patients who are not on HAART, and who do not recover CD4 cell counts above 100 mm³.

When treating concomitant MAI and TB, rifabutin should not be used at the same time as rifampin, due to the added potential for toxicity. Whenever possible, another agent, such as clarithromycin or azithromycin, should be used instead of rifabutin. If another agent is used, rifampin can be continued in the anti-TB regimen. If another agent cannot be used, and rifabutin is required for MAI treatment or prophylaxis, rifampin should be replaced by rifabutin in the anti-TB regimen.

In general, patients with coexistent MAI and TB can be treated at a BTBC chest center for both diseases, until TB treatment is complete. At such time, the patient should be referred to another provider to continue treatment for MAI.

Patients without HIV infection and TB who have MAI should not be treated at a BTBC chest center. If the patient has a positive test for TB infection and an abnormal CXR, sputum smears should be done to assess the activity of the disease. In this case, the patient may receive treatment for TB as a suspect until negative cultures are confirmed. The patient should then finish treatment for LTBI or old TB, if indicated. The patient should be referred to an appropriate provider for the MAI treatment.

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Tuberculosis

Section IV.

Evaluation and Treatment
of Extrapulmonary Tuberculosis

Section IV.

Evaluation and Treatment of Extrapulmonary Tuberculosis

The basic principles that underlie the treatment of pulmonary tuberculosis (TB) also apply to extrapulmonary forms of the disease. As a general rule, regimens that are adequate for treating pulmonary TB in adults and children are also effective for treating extrapulmonary disease since, in most cases, the mycobacterial burden is considerably smaller in this form. However, for certain forms of extrapulmonary disease, such as central nervous system (CNS), disseminated and skeletal TB, the continuation phase of treatment is often prolonged.

This section covers special issues involved in diagnosing and managing certain extrapulmonary forms of TB. The topics herein are typical of those health care providers usually face when diagnosing TB and treating patients in the acute hospitalization phase, before they arrive in the chest center for follow-up care. Therefore, many of these procedures and decisions may not be those made by physicians in the Bureau of Tuberculosis Control (BTBC) chest centers.

About 25% of child and adult TB cases have extrapulmonary manifestations, but as many as 50% of adults who are HIV infected may have extrapulmonary TB. TB meningitis and miliary TB are more common in young children and are associated with high rates of death and disability, particularly if the diagnosis is delayed. It is therefore important to consider these diagnoses in young children as early as possible, especially in children who have a history of contact with an adult with infectious TB.

Table IV-I on p. 72 details the evaluation of extrapulmonary TB in children and adults with suggested appropriate diagnostic procedures, and also contains suggested treatment regimens for various extrapulmonary forms of TB, including follow-up specimens that should be obtained. However, these are only general guidelines. Use additional references for more detail on managing extrapulmonary TB.

Although there are multiple studies showing that clinically confirmed or culture-negative pulmonary TB can be treated successfully in only 4 months, there is little data to suggest this length of treatment can be extrapolated to extrapulmonary TB. Short-course chemotherapy has been shown to be more effective than 18- to 24-month conventional therapy since the 1970s, yet there are few studies exploring treatment of less than 6 months for extrapulmonary TB.

A study has shown that genitourinary TB can be treated in 4 months and posits that, compared to pulmonary TB, there are far fewer organisms in renal than in pulmonary lesions, the kidneys have a very good blood supply, there are high concentrations of the drugs in urine and that drugs penetrate closed cavities in lethal concentrations. This argument, however, cannot be extrapolated to other forms of extrapulmonary TB.

Another small prospective study showed 85% success in treating 68 patients with pleural TB with a 4-month regimen consisting of 2 months of isoniazid, rifampin and pyrazinamide and 2 months of isoniazid and rifampin. Despite this, the BTBC still recommends 6 months treatment for pleural TB.

A recent article reviewed the current trends in chemotherapy for all forms of TB and asserted that treatment of TB in 3 or 4 months would have some significant practical advantages. The article cited research by the Tuberculosis Research Centre in Chennai, India, that showed a 100% favorable response at the end of a 3-month regimen; however, a 20% relapse rate occurred in the subsequent 21 months for patients who had smear-positive pulmonary TB. The study contains comment that while there have been fewer studies focused on extrapulmonary TB, evidence from several trials has shown that all forms of extrapulmonary TB, except meningitis, can be successfully treated in 6 months. A larger, long-term study is needed,

Table IV-1

Evaluation of Extrapulmonary Tuberculosis in Adults and Children

Suspected site	Approach to diagnosis
Bone and joint TB	X-ray, CT, magnetic resonance imaging (MRI), arthrocentesis, synovial or bone biopsy
Disseminated or miliary TB	CXR and lumbar puncture (to test for meningitis). Biopsy of affected sites if possible.
Meningeal TB	CT, MRI and lumbar puncture
Miliary pattern on CXR	Induced sputum, bronchoscopy with bronchial washing and transbronchial biopsy, and gastric aspirates
Pericardial TB	Echocardiogram; pericardiocentesis for biochemical analysis (LDH, protein, glucose concentration and pH), cell count, AFB-smear and culture; or pericardial biopsy
Peripheral lymph nodes (especially cervical)	Fine needle aspiration or lymph node biopsy
Peritoneal TB	Abdominal ultrasound or CT; paracentesis for biochemical analysis (LDH, protein, glucose concentration and pH), cell count, AFB-smear and culture; or peritoneal biopsy
Pleural effusion	CXR; thoracentesis for biochemical analysis (LDH, protein, glucose concentration and pH), cell count, AFB-smear and culture; or pleural biopsy

Abbreviations: AFB=acid-fast bacilli, CT=computed tomography, CXR=chest X-ray, LDH= lactate dehydrogenase test, MRI=magnetic resonance imaging, pH=acid loading test, TB=tuberculosis

however, before treatment recommendations can be changed.

When considering length of treatment for extrapulmonary TB, based on the lack of successful research on 4-month regimens, we cannot endorse the shortening of chemotherapy for extrapulmonary TB to anything less than 6 months. In several forms of TB, corticosteroids have been shown to be useful. (see Table IV-2)

Lymphatic Tuberculosis

Lymphatic TB most commonly affects cervical or supraclavicular lymph nodes, although any lymph node can be involved. However, in children, cervical involvement is most commonly due to non-tuberculous mycobacteria.

Diagnosis

The diagnosis can be established by the culture of *Mycobacterium tuberculosis* (*M. tb*) from lymph node biopsy or aspirate. The presence of acid-fast bacilli (AFB) in tissue (seen in slightly over half

of cases) or aspirate, or pathologic evidence of caseating granuloma, is consistent with TB or non-tuberculous mycobacterial infection. Aspiration is also useful, especially if the node(s) demonstrate fluctuance. Individuals suspected of having tuberculous lymphadenitis should be referred for biopsy or aspiration.

Treatment

Lymphatic TB should be treated according to the regimens for pulmonary TB. Even if lymph node excision is complete, chemotherapy is indicated. The patient's clinical response should be carefully considered in determining the length of treatment; decisions about the duration of treatment should be individualized. Most patients respond well to the standard 6-month regimen.

Pleural Tuberculosis

Small pleural effusions are common as part of primary pulmonary complex in children; larger TB pleural effusions usually occur in children older

than 2 years of age. The patient presents with fairly sudden onset of dyspnea, fever and chest pain, with dullness to percussion and decreased breath sounds (unilaterally or bilaterally) usually present on physical examination. The test for TB infection is often positive.

Diagnosis

Thoracentesis should be done and the pleural fluid sent for white blood count and differential, and measures such as pH, LDH, protein and glucose. A lymphocytic exudate with low glucose typically occurs in TB. AFB stains of the pleural fluid sediment obtained by pleurocentesis are seldom positive (25% to 33% of cases).

A transthoracic needle pleural biopsy is used routinely to establish or support a diagnosis of TB pleuritis based on the presence of caseating granuloma with or without AFB on tissue stains. The combined yield of AFB stains of pleural fluid and biopsy tissue, coupled with mycobacterial culture of pleural fluid and biopsy tissue, is greater than 90%. In nearly 100% of cases, a small open pleural biopsy (usually achieved with video-assisted thoroscopic surgery) is diagnostic of pleural TB. Although a chest X-ray (CXR) may show no visible parenchymal lesions, cultures of sputum or gastric fluid are positive in 25% to 33% of cases. Therefore, 3 sputa for AFB smear and culture should be obtained on all patients with pleural TB.

An individual suspected of having TB pleuritis treated in a BTBC chest center must be referred to an appropriate provider for diagnostic evaluation.

Treatment

Pleural TB should be treated according to a regimen for pulmonary TB. While steroids may decrease pain and hasten the resolution of pleural effusion, we do not recommend their use routinely. If used, a dose of 20 mg to 40 mg per day of prednisone, tapered over 4 to 8 weeks, may be appropriate.

Pericardial Tuberculosis

Pericardial TB is much more common in persons infected with HIV. The onset may be subtle (characterized by cardiovascular consequences of constrictive effusion) or abrupt (fever and precordial pain).

Diagnosis

Fluid from pericardiocentesis is similar to fluid from tuberculous pleural effusion with low glucose and pleocytosis. Positive smears for AFB are not common, and cultures are positive in only 25% to 50% of cases. Some authorities do not advocate pericardiocentesis as part of the diagnostic work-up due to the risks of the procedure and the limited benefit in terms of immediate treatment. Some physicians advocate primary surgical intervention with a pericardial "window" and biopsy in every case of suspected TB pericarditis.

The BTBC recommends pericardiocentesis, or surgical biopsy, to obtain culture and susceptibility data unless there is a positive culture from another source, or the patient urgently requires surgical intervention.

Treatment

Pericardial TB should be treated according to a regimen for pulmonary TB.

Corticosteroids are generally recommended as several studies have shown they improve prognosis. If used, begin prednisone at 60 mg daily and gradually decrease the dosage over a period of 6 to 12 weeks as the effusion subsides. The dose for children is 2 mg/kg of body weight per day to a maximum of 60 mg per day, or its equivalent for 4 to 6 weeks followed by tapering. The dose should be tapered as for adults, and the medication should only be given if the patient is on appropriate anti-tuberculosis therapy. Pericardiectomy is indicated if there is chronic constriction with adverse hemodynamic consequences.

Central Nervous System Tuberculosis

Diagnosis of Meningeal Tuberculosis

Meningeal TB in children and adults has an insidious presentation; it may present as personality changes, irritability and anorexia, then headache, neck stiffness, drowsiness and cranial nerve palsies, and may later progress to coma. Therefore, a detailed history of symptoms should be taken from the patient and family members as the patient may not be able to provide adequate details. The outcome

depends significantly on the stage of disease at presentation (Stage III has the worse outcome):

- Stage I: Isolated meningeal disease without focal neurologic abnormalities
- Stage II: Isolated parenchymal disease and neurologic abnormalities without altered consciousness
- Stage III: Parenchymal and meningeal disease with stupor or obtundation

The key diagnostic procedure is examination of the cerebral spinal fluid (CSF). Characteristic CSF findings are:

- Pleocytosis (65% of cases have white blood cell counts of 100 - 500) with lymphocytic predominance (in 73% of cases in one series)
- Predominance of polymorphonuclear cells is often seen
- Elevated protein and low glucose (common)

These measures may be consistent with TB meningitis but are non-specific. Diagnosis may be supported by positive microscopy (AFB smear) or nucleic acid amplification (NAA) tests, but may not be excluded if these measures are negative.

- AFB are seen in up to 37% of cases on initial examination, and in up to 87% of cases when the fluid from 4 serial spinal taps has been examined. In one recent study, bacteriological diagnosis was made in 107 of 132 (81%) of cases, based on AFB smear or positive culture from CSF collected during a single lumbar puncture. Large volume of CSF (greater than 5 ml) was associated with seeing or culturing *M. tb*.
 - NAA techniques such as polymerase chain reaction (PCR) are more sensitive than AFB smear but are not more sensitive than bacteriology in detecting cases prior to treatment; however, they may be positive and may be useful in cases where antituberculosis therapy has been initiated already.

The diagnosis of TB meningitis cannot be excluded by negative bacteriology and/or negative NAA if clinical criteria are highly suggestive.

Treatment of Meningeal Tuberculosis

Empiric treatment should be started promptly while awaiting results of AFB smears and cultures. Drug-susceptible or culture-negative TB should be treated with isoniazid, rifampin, pyrazinamide and ethambutol in doses the same as those used for pulmonary TB for the first 2 months. This phase should be followed by a regimen of isoniazid and rifampin for 7 to 10 additional months in the continuation phase, as long as drug resistance is not suspected.

- Isoniazid, rifampin and pyrazinamide penetrate the blood-brain barrier efficiently. Ethambutol, the aminoglycosides and capreomycin penetrate only when meninges are inflamed. (For information on the penetration of anti-TB medications in the CNS, see p. 211, Appendix I-C.)

Because penetration of some drugs (e.g., rifampin and streptomycin) into the cerebrospinal fluid is poor, treatment regimens for TB meningitis and miliary TB will most likely benefit from the higher end of the recommended dose ranges. Some experts advocate the addition of pyrazinamide during the continuation phase as CSF concentrations of rifampin are low and pyrazinamide readily penetrates the CNS; however, there are no clinical trials to support this.

- Due to different degrees of drug penetration into the CNS, some experts recommend modifying the standard anti-TB treatment regimen for children. The World Health Organization recommended regimen in children is 2 months of isoniazid, rifampin, pyrazinamide and streptomycin rather than ethambutol. The American Academy of Pediatrics recommends ethionamide as the fourth drug, rather than ethambutol, as it crosses both healthy and inflamed meninges, and is well-tolerated by children.
- Corticosteroids improve survival in children with severe disease and probably reduce neurologic morbidity as well. Many experts advocate the use of corticosteroids in all patients with CNS TB, particularly those with a decreased level of consciousness. Corticosteroids should only be given if the patient is on appropriate antituberculosis therapy. Dexamethasone or prednisone can be given in the following manner:

- **Dexamethasone.** The recommended regimen is an initial dose of 8 mg/day for children weighing less than 25 kg and 12 mg/day for children weighing 25 kg or more and for adults. The initial dose is given for 3 weeks and then decreased gradually during the following 3 weeks.
- **Prednisone.** In children, 2 mg/kg daily for 4 weeks and the dose should be gradually tapered over 1 to 2 weeks before stopping. The dosage of prednisone can be increased to 4 mg/kg daily (maximum 60 mg/day) in the case of seriously ill children, as rifampin decreases corticosteroid concentration. In adults, depending on the site, corticosteroid dosages equivalent to 40-60 mg/day of prednisone are recommended with gradual tapering over 4 to 6 weeks.
- Based on clinical experience, some individuals require a prolonged course of treatment with corticosteroids.
- All children with suspected or confirmed TB meningitis or miliary TB should be hospitalized until their clinical status has stabilized. These patients are at high risk of long-term disability and therefore benefit from specialist care.
- Treatment of drug-resistant TB meningitis is complicated by the pharmacokinetics of antituberculous drugs in the CNS, and intrinsic activity of the drugs. Multidrug-resistant TB meningitis confers a dismal outcome in most cases. In one series, it was associated with an in-hospital case fatality rate of 57% and in another, overall mortality of 100%. Treatment of drug-resistant TB meningitis should be guided by the CNS penetration of first- and second-line agents listed on p. 211, Appendix I-C. Expert consultation should be sought.
- Patients already on appropriate therapy for meningeal, pulmonary or miliary TB may paradoxically develop intracranial tuberculomas on therapy, likely related to immune reconstitution. Tapering of steroids in patients on antituberculous therapy has been associated with the development of intracranial tuberculomas. A recent review described more than 50 cases since 1974 of intracranial tuberculomas progressing or developing while on therapy, most occurring within the first 3 months. Another case series described 22 cases of adult tuberculomas, 8 coexisting with TB meningitis on admission and 14 that developed it while on therapy, mostly within the first 6 weeks. This paradoxical response is generally believed to be due to a recovery of immune function as active TB is controlled, and may be related to a local hypersensitivity response to mycobacterial proteins (see p. 56).
- Usually tuberculomas appear as ring-enhancing lesions on imaging studies. When tuberculomas are identified during the course of treatment, antituberculous therapy generally does not need to be changed, as the lesions reflect enhanced immune response rather than treatment failure. Most authorities recommend treating intracranial tuberculomas for a minimum of 12 months, or longer if they have developed during therapy.
- Most experts use corticosteroids in all symptomatic cases, though there are no randomized trials assessing treatment of tuberculomas with steroids. If corticosteroids are used, dosage and tapering are as above for TB meningitis in preceding section.

Tuberculoma

- Patients with intracranial tuberculoma(s) may present with cranial nerve deficits, altered mental status, hemiparesis, seizures or headache; concomitant meningitis may be present.
- Diagnosis depends on computed tomography (CT) or magnetic resonance imaging (MRI) findings and biopsy of the lesion unless there is a contraindication.

Disseminated Tuberculosis

Disseminated TB is a result of the hematogenous spread of *M. tb* with clinical manifestation of active disease at 2 or more non-contiguous sites and can manifest as discrete involvement of affected sites or as miliary tuberculosis (i.e., when the appearance of tissue within affected organs is similar to millet seeds). If a miliary pattern is noted on the CXR, the radiograph can be described as miliary in the patient's medical record and the patient should be designated as having miliary or disseminated disease. However, miliary should NOT be used to

describe TB involving 2 or more discrete sites, despite the use of these 2 terms interchangeably in the literature.

Diagnosis

Disseminated TB is usually suspected because of the presence of miliary infiltrates on a CXR or involvement of 2 or more sites. Transbronchial biopsy is the highest-yielding procedure for obtaining tissue in miliary TB. In other instances, tissue biopsy of other organs, such as the lymph nodes, liver or bone marrow can confirm the diagnosis.

In children, disseminated TB disease is more common under the age of 5 and affects many organs, including the brain and bone marrow. Enlargement of the spleen and liver is common and the test for TB infection is often negative. Sputum smears and culture are also usually negative, despite the extensive miliary appearance on CXR. CSF should be evaluated if miliary TB is suspected (see p. 72, Table IV-1 for further directed evaluation). Disseminated TB has a high risk (60%–70%) of meningeal involvement and should therefore be managed similarly to TB meningitis; many experts recommend that all children with disseminated TB (or suspected of having disseminated TB) undergo a lumbar puncture to test for the presence of meningitis.

In many patients with AIDS with hematogenous dissemination, urine or blood cultures obtained by appropriate techniques yield *M. tb*. These patients should be assumed to have disseminated TB, even in the absence of radiologically or pathologically demonstrated TB lesions in other organs.

Treatment

A 6-month regimen with standard anti-tuberculosis therapy is recommended for treatment of tuberculosis at multiple sites and for miliary tuberculosis in adults. The American Academy of Pediatrics recommends 9 months of treatment for children with disseminated TB. Corticosteroids may be useful for treating respiratory failure due to disseminated tuberculosis and meningitis. (See p. 79, Table IV-2.)

Skeletal Tuberculosis

Skeletal TB (TB of the bones and joints) usually occurs in the weight-bearing joints; Pott's disease (TB of the spine) is the most common form, followed by TB of the hip and knee. The typical presenting symptoms are pain and difficulty with locomotion. In children, it usually develops in the first year after infection.

Diagnosis

Skeletal TB is diagnosed by X-ray or CT scan of the involved joint, followed by specimen collection and culture. A tissue biopsy is necessary to confirm the diagnosis and obtain cultures for susceptibility testing. All individuals suspected of having bone or joint TB should be referred for appropriate radiologic studies and biopsy or aspiration.

Treatment

Skeletal TB should be treated according to the regimen for pulmonary TB, although some authorities advise 6 to 9 months of treatment for all individuals, regardless of immune status. Most patients with skeletal TB who are treated in a BTBC chest center should also be followed by an orthopedist.

Genitourinary Tuberculosis

Diagnosis

Approximately 90% of patients with genitourinary TB have abnormal urinalysis results (usually gross or microscopic hematuria and/or pyuria). Also, in 90% of patients, *M. tb* can be cultured from 1 of 3 morning urine specimens. Diagnosis of male or female genital tract TB is usually based on biopsies and cultures of affected sites.

Treatment

In general, regimens for treating pulmonary TB are highly successful for treating renal TB. Surgery is indicated only for intractable pain, persistent non-tuberculous infection from obstruction, serious, persistent hematuria or a nonfunctioning or poorly functioning kidney. All patients with renal TB who are treated in a BTBC chest center should be followed by a urologist.

TB of the male or female genitourinary tract responds well to standard chemotherapy, and surgery is necessary only for residual large tubo-ovarian abscesses. Infertility is one of the complications of tuberculosis of the female genital tract. The patient should be referred to a gynecologist if necessary.

Gastrointestinal Tuberculosis

TB can affect any part of the gastrointestinal tract, from the tongue or oropharynx to the anus. The cecum is the most common gastrointestinal site. Evidence of coexistent pulmonary TB is present in about 25% to 50% of cases. The most common symptoms are anorexia, early satiety, abdominal pain or symptoms of intestinal obstruction.

Diagnosis

Many patients with gastrointestinal TB have a stool culture that is positive for *M. tb*; it is important to determine whether the positive culture represents organisms from a gastrointestinal source or organisms that were swallowed from a pulmonary source.

In individuals with confirmed pulmonary TB and no evidence of intestinal obstruction, further evaluation is usually unnecessary to seek the gastrointestinal source since treatment is the same for pulmonary and gastrointestinal TB.

If there is no evidence of pulmonary TB, an upper gastrointestinal series with small-bowel follow-through can detect ulcerative lesions. If there are no lesions in the upper gastrointestinal tract, the lower gastrointestinal tract can be evaluated by air-contrast barium enema. Alternatively, endoscopy and/or colonoscopy can be used to visualize the lumen and obtain specimens for AFB and other cultures.

Most patients will have had a CT scan of the abdomen and pelvis. Common, but not specific, findings are lymphadenopathy, especially in the retroperitoneum, and thickening of the bowel wall with associated lymphadenopathy. The presence of enlarged lymph nodes with hypodense centers is suggestive of necrosis, especially common in patients with HIV.

AFB in stool specimens has no diagnostic significance since water and certain foods are often contaminated by environmental saprophytic mycobacteria that transverse the gastrointestinal tract and are excreted.

Carbolfuchsin, the standard stain for cyclospora in stool specimens, is also a basic stain for mycobacteria. Reports of stool specimens examined for cyclospora and positive for AFB should be assumed to be saprophytes unless a stool culture yields *M. tb*.

Treatment

Gastrointestinal TB should be treated according to a regimen for pulmonary TB. Many patients with gastrointestinal TB treated in a BTBC chest center should have follow-up with a gastroenterologist or surgeon as appropriate.

Peritoneal Tuberculosis

Diagnosis

Peritoneal TB usually presents with 1 of 2 manifestations (1) the presence of ascites, which leads to abdominal pain and distention, with or without gastrointestinal symptoms; or (2) abdominal pain, with or without symptoms suggesting intestinal obstruction. There may be associated systemic symptoms, such as fever, night sweats, fatigue and weight loss. Paracentesis may reveal ascitic fluid with a lymphocytic pleocytosis and elevated protein and low glucose. The diagnosis of tuberculous ascites is made usually by culture of the ascitic fluid or peritoneal or open biopsy; the diagnosis of "dry" tuberculous peritonitis is usually made by laparotomy and biopsy that reveals caseating granulomas, with or without tissue stains positive for AFB.

Treatment

Peritoneal TB should be treated with the same regimen as pulmonary TB. Anyone suspected of having peritoneal TB should be referred to an appropriate gastrointestinal center or hospital for further evaluation; if possible, treatment should not be initiated without such an evaluation.

Cutaneous Tuberculosis

Cutaneous tuberculosis is rare and can be divided into 2 broad categories: (1) cutaneous TB and (2) tuberculids.

Cutaneous TB is *M. tb* infection of the skin that causes disease, and tuberculids are cutaneous manifestations of extracutaneous TB. Cutaneous tuberculosis can be exogenous, with chancres and warty tuberculosis caused by infections of

the skin from outside sources, or endogenous, due to hematogenous or lymphatic spread that may be confused with the cutaneous lesions seen in systemic diseases such as sarcoidosis. Autoinoculation from underlying infected tissues or secretions can also occur. If there is aerosolization of secretions from a skin lesion, the patient should be isolated as per protocol (see p. 122).

Staff who work in mycobacteria labs or who work with autopsy specimens occasionally receive an inoculum of tuberculosis, which can lead to a condition called “Prosecutor’s Wart.” If the individual already has a positive test for TB infection (TTBI) prior to exposure, the individual should be given isoniazid prophylaxis for 9 months; if TTBI negative before exposure, a repeat TTBI should be performed and isoniazid prophylaxis started. If the repeat TTBI at 8 weeks is negative, isoniazid can be discontinued and if positive, isoniazid should be continued for 9 months total.

If active disease develops at the site, it should be treated according to a regimen for pulmonary TB. If the inoculum is known to be due to drug-resistant organisms, treatment should be tailored to the resistance pattern of the organism.

Diagnosis

Diagnosis of skin lesions is usually made by biopsy of the lesion, which is sent for AFB smear and culture, and pathologic analysis.

Treatment

Treatment of cutaneous TB is the same as for pulmonary TB.

Disease Due to Intravesical Bacille Calmette-Guérin for Bladder Cancer

Bacille Calmette-Guérin (BCG) is a live attenuated strain of *Mycobacterium bovis* (*M. bovis*) which is used as immunotherapy for superficial transitional cell carcinoma of the bladder. The mechanism of action appears to be modulation of the immune response in the bladder, with localized inflammation induced by BCG leading to destruction of cancer cells. Occasionally, treatment for bladder cancer is complicated by disseminated or localized BCG-related disease.

A case of *M. bovis* BCG is not counted as a case of TB by CDC criteria.

Diagnosis

BCG-related disease may present early (usually within 12 weeks) or late (usually more than 1 year) following initiation of intravesical therapy.

- Two mechanisms of disease have been postulated—hematogenous dissemination of infection and hypersensitivity reaction. It is likely that both play a role in pathogenesis.
- Early disease may be associated with fever, malaise, chills, sweats, weight loss, shortness of breath and arthralgias. The clinical picture is often consistent with disseminated disease with pneumonitis and/or hepatitis; however, disease may be localized. The diagnosis is supported by the finding of noncaseating granulomas on biopsy of affected organs, and while culture may be positive for *M. bovis* BCG, negative culture does not exclude the diagnosis.
- Late disease is more likely to present locally in the genitourinary tract without associated generalized symptoms of fever, malaise and weight loss, and is the result of reactivation following initial immunologic control. Biopsy uniformly yields noncaseating granulomas. Culture may or may not be positive for *M. bovis*.
- The individual should be tested for TB infection and sputa obtained for AFB smear and culture, as the patient will have an abnormal CXR. Bronchoscopy with biopsy may be indicated. Molecular techniques (genotyping) distinguish *M. bovis* BCG from *M. tb*.

Treatment

No clinical trials have assessed treatment for disease related to intravesical BCG, but most experts recommend treatment for early- and late-presenting disease with isoniazid and rifampin for 9 months (all *M. bovis* strains, including *M. bovis* BCG, are uniformly resistant to pyrazinamide). Some BCG strains are also resistant to isoniazid. Therefore, susceptibility testing should still be done to guide treatment.

Corticosteroids have been used to treat pneumonitis associated with BCG disease; some experts think these drugs contribute to rapid resolution of symptoms.

Table IV-2

Guidelines for Adjunctive Use of Corticosteroids for Extrapulmonary Tuberculosis*§

Type	Length of TB Therapy (mo.)	Corticosteroid Use
Lymphatic	6	Not recommended
Pericardial	6	Strongly recommended
Pleural	6	Not recommended
CNS (including meningitis)	9-12	Strongly recommended
Disseminated	6	Not recommended (unless meningeal or pericardial involvement, or respiratory failure present)
Skeletal	6-9	Not recommended
Genitourinary	6	Not recommended
Abdominal	6	Not recommended
Peritoneal	6	Not recommended

* Adapted from: American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America. Treatment of Tuberculosis. *Am J Respir Crit Care Med.* 2003; 167: 603-662.

§ See text for recommendation of steroid dosage and treatment.

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Section V.

Treatment of Drug-Resistant Tuberculosis

Tuberculosis

Section V.

Treatment of Drug-Resistant Tuberculosis

Principles of Treating Drug-Resistant Tuberculosis

Unlike the treatment of drug-susceptible tuberculosis (TB), developing standardized protocols for the treatment of known or suspected drug-resistant (DRTB) is not possible. Several issues are involved:

- Any treatment recommendation must take into account the drug susceptibility results of the individual isolate and prior treatment history.
- Good data are lacking on the efficacy of non-standard regimens.
- Adverse effects of second-line medications, often serious and intolerable, may preclude the use of these drugs for the recommended period of time.

Multidrug-resistant TB (MDRTB) refers to a strain of *M. tuberculosis* (*M. tb*) resistant to at least isoniazid and rifampin.

Treatment Principles

- Patients with DRTB, particularly MDRTB, should be treated under a program of directly observed therapy (DOT). If the patient is not given DOT, the compelling reason must be documented in the medical record. Some patients will need DOT twice a day.
- MDRTB treatment can be as complex as cancer chemotherapy and should not be attempted without the consultation of a specialist in MDRTB.
- There are no fully intermittent regimens at present for MDRTB treatment. However, the injectable agents may be administered intermittently during part of the treatment, and certain drugs may be given intermittently in patients with renal failure.

- Patients must be treated with a regimen of at least 3 to 5 anti-TB medications to which the strain is likely to be susceptible.
- A single anti-TB medication should never be added to a regimen that is failing (i.e., if the patient is not clinically improving or if the cultures are still positive 4 months after start of therapy). At least 2, and preferably 3, new anti-TB medications to which the strain is likely to be susceptible should be added.
- When an injectable agent is needed, begin with capreomycin as the injectable agent of choice until drug susceptibilities are known. All strain W and strain W variants are streptomycin- and kanamycin-resistant (these strains are still seen in NYC patients).
- Switch to streptomycin if the organism is susceptible. Use kanamycin if strain is susceptible to it and amikacin, but resistant to streptomycin. (Laboratories usually test for either kanamycin or amikacin susceptibility; there is cross-resistance between these 2 agents and resistance to one predicts resistance to the other.)
- Treatment for TB strains resistant to at least rifampin (mono-rifampin, or MDRTB) should be given for at least 18 months after culture conversion to negative. Consider extending therapy to 24 months after culture conversion to negative if:
 - There is cavitory or extensive disease
 - The patient is HIV positive or has risk factors for HIV infection
 - The patient is immunosuppressed
 - Time to culture conversion is prolonged
- In general, any level of resistance to an anti-TB medication, documented by a reliable mycobacteriology laboratory, indicates that the drug is unlikely to be effective. However, susceptibility testing for pyrazinamide,

ethionamide and capreomycin is often inconsistent among laboratories or even within the same laboratory. In cases of partial resistance or inconsistent results, physicians should follow the general dictum, “use the medication, but do not depend on it for success.”

- If there is mono-resistance to pyrazinamide, suspect *Mycobacterium bovis*, another member of the *M. tb* complex.
- Because the continued administration of second-line drugs may be life saving, physicians should not discontinue an anti-TB medication in a patient who has adverse reactions unless the reaction is severe or cannot be ameliorated by supportive treatment.
- Most of the medications used to treat MDRTB are known to cause fetal abnormalities or have not been studied adequately regarding their safety in pregnancy. Therefore, women of child-bearing age who have MDRTB should be strongly encouraged to use birth control methods if they are sexually active. Pregnant women with culture-proven MDRTB on treatment should be offered abortion counseling.
- Children with MDRTB should be treated with the first- and second-line drugs to which their *M. tb* strain, or that of their source case, is susceptible, including streptomycin, ethambutol and pyrazinamide. Ethambutol is bactericidal at higher doses, so daily doses up to 25 mg/kg should be used in children being treated for MDRTB. Some fluoroquinolones are not FDA-approved in children, and must be used after careful consideration of the potential risks and benefits, which should be documented in the patient record. See p. 210, Appendix I-B for dosages of second-line or reserve anti-TB drugs for treatment of MDRTB in children.

Monitoring Principles

- Sputum AFB smear and cultures should be monitored monthly for patients with isoniazid and/or rifampin resistant isolates.
- If a patient has a positive *M. tb* culture after 4 months of treatment, the most recent positive culture must be sent to the clinical laboratory for first- and second-line anti-TB drug-susceptibility testing. There are at least 2 treatment options while the drug-susceptibility results are pending:

1. If the patient is not acutely ill or clinically deteriorating, the current or most recent anti-TB regimen may be continued until the new drug susceptibility results are available. This regimen is often referred to as a “holding regimen”.
 2. If the patient is acutely ill or clinically deteriorating, at least 2 new medications should be started, based on an assessment of the other medications to which the strain is likely to be susceptible. The original medications should be continued until the new drug-susceptibility results are available.
- If a regimen is not failing (i.e., the patient shows clinical improvement and *M. tb* cultures have converted from positive to negative), but the MDRTB patient is having an adverse reaction to a specific, identifiable medication (severe enough to preclude the further use of the medication, e.g., ototoxicity from streptomycin, gout from pyrazinamide, etc.), the following treatment alternatives are available, depending on the length and success of treatment before the adverse reaction:
 1. The medication responsible for the adverse reaction may be omitted and the remainder of the anti-TB treatment regimen continued.
 2. A new, previously unused agent may be substituted for the medication responsible. (This alternative does not increase the risk for drug resistance because the prior anti-TB treatment regimen was not failing.)
 3. If the cause for the adverse reaction (e.g., hepatotoxicity, skin rash) cannot be readily identified, all medications should be discontinued and retested by reintroduction singly into a regimen trial. In some instances of severe toxicity, hospitalization for rechallenge with multiple drugs may be needed.
 - For management of TB patients who are HIV infected, treatment length and regimens are generally the same as for patients not infected with HIV. Nevertheless, HIV status should be determined for all TB patients, as many providers recommend extended treatment for these patients. In addition, if HIV infection is identified, patients can be referred for HIV treatment.

- Monthly, and as needed, clinical and laboratory monitoring should be done as per Bureau of Tuberculosis Control (BTBC) guidelines. (See p. 101; p. 208, Appendix I-A; p. 210, Appendix I-B; and information on individual drugs.)

Principles for Selected Drugs

- Most, but not all, *M. tb* strains that are resistant to rifampin are also resistant to rifabutin. However, a minority of rifampin-resistant organisms, especially those reported to be less than 50% resistant by agar proportion method, will prove sensitive to rifabutin. When there is *in vitro* sensitivity to rifabutin, it can be added to the regimen along with an injectable agent and other oral agents as outlined. However, since the effectiveness of the rifabutin cannot be relied upon due to lack of clinical data, the treatment length should be the same as for a non-rifampin based regimen (18-24 months).
- Aminoglycosides or capreomycin should be used for at least 6 months after culture conversion unless ototoxicity or nephrotoxicity develops. The continuation of aminoglycosides or capreomycin for longer than 6 months after culture conversion may be appropriate if there is extensive disease, extensive resistance to second-line drugs or slow conversion of sputum cultures. Data analyzed by the BTBC indicate that the duration of treatment with an injectable medication is the strongest predictor of culture conversion and survival in patients with MDRTB. With documented MDRTB, over-treatment is much more preferable than under-treatment, which may have dire consequences for the patient and the family.
- Injectable agents should be given 5 days a week initially. After culture conversion, dosing can be 2 to 3 times a week.
- Levofloxacin is currently the preferred fluoroquinolone for TB treatment, even in children. It is the optically active l-isomer of ofloxacin and is more active against *M. tb* than ofloxacin (which consists of equal amounts of the d- and l-isomers).

- The initial dose is 500 mg once daily, which can be increased over a 2-week period to 750-1,000 mg once daily as tolerated, since higher doses may be more bactericidal.
- Levofloxacin has been associated with a decreased incidence of adverse effects compared to the older fluoroquinolones. In general, the adverse effects profile is similar to the other fluoroquinolones.
- Levofloxacin is a category C drug in pregnancy and should only be used if the potential benefit to the mother justifies the potential risk to the fetus.
- When used in children, the potential benefit must justify the potential risk.
- When used in pregnant women and children, the patient and/or caregiver should be educated about the risks and benefits; this should be documented in the medical record.
- Cross-resistance has been demonstrated among levofloxacin, ofloxacin, ciprofloxacin and the newer fluoroquinolones.
- Levofloxacin should not be considered as first-line treatment in patients with drug-susceptible organisms unless they are intolerant of other first-line drugs.

Suggested Regimens for Specific Drug Resistance Patterns

The following suggested regimens are guidelines only (see p. 86, Table V-1). In reality, the options are seldom clear cut, as many patients will have already received trials of some of the medications and may have had them added one at a time to previous regimens. Furthermore, opinions vary on the best medications to use for an individual patient. Expert consultation should be sought for individuals with confirmed or suspected MDRTB.

Table V-1

Suggested Regimens for Treatment of Drug-Resistant Tuberculosis

Resistance Pattern	Initial Phase		Continuation Phase		Total Length
	Drugs	Duration	Drugs	Duration	
Isoniazid ± Streptomycin	Option A: Rifampin/Pyrazinamide/ Ethambutol	2 months	Rifampin/Pyrazinamide/ Ethambutol	4-7 months	6-9 months. Extend to 9 months if still culture positive at 2 months. Preferred regimen even in pregnancy
	If extensive disease, consider adding a 4th agent such as Fluoroquinolone or Injectable Agent				
	Option B: Rifampin/Ethambutol/ Pyrazinamide	2 months	Rifampin/Ethambutol	7 months	9 months
For Isoniazid/Pyrazinamide ± Streptomycin use option C	Option C: Rifampin/Ethambutol + Fluoroquinolone or Injectable Agent	2 months	Rifampin/Ethambutol + Fluoroquinolone or Injectable Agent	10 months	12 months
Rifampin ± Streptomycin	Option A: Isoniazid/Pyrazinamide/ Ethambutol/Injectable Agent + Fluoroquinolone	2-3 months after culture conversion	Isoniazid/Pyrazinamide/ Ethambutol ± Fluoroqui- nolone	12-14 months	18 months Preferred regimen
	Option B: Isoniazid/Pyrazinamide/ Streptomycin (if no Streptomycin resistance) ± Ethambutol	2-3 months after culture conversion	Isoniazid/Pyrazinamide/ Streptomycin ± Ethambutol	3-5 months	9 months
Pyrazinamide ± Streptomycin	Isoniazid/Rifampin/ Ethambutol	2 months	Isoniazid/Rifampin	7 months	9 months
Isoniazid/Ethambutol ± Streptomycin	Rifampin/Pyrazinamide/ Fluoroquinolone ± Injectable Agent	2-3 months after culture conversion	Rifampin/Pyrazinamide/ Fluoroquinolone	7-9 months	9-12 months or 6 months after culture conversion, whichever is longer
Isoniazid/Rifampin ± Streptomycin	Pyrazinamide/Ethambutol/ Fluoroquinolone/Injectable Agent	6 months after culture conversion	Pyrazinamide/Ethambutol/ Fluoroquinolone	12-18 months	18-24 months after culture conversion
Isoniazid/Rifampin/ Ethambutol ± Streptomycin	Pyrazinamide/fluoroquinolone/ Injectable Agent plus at least 1-2 2nd line agents to which strain is susceptible	6 months after culture conversion	Pyrazinamide/ Fluoroquinolone plus at least 1-2 2nd line agents to which strain is susceptible	12-18 months	18-24 months after culture conversion
Isoniazid/Rifampin/ Pyrazinamide ± Streptomycin	Ethambutol/Fluoroquinolone/ Injectable Agent plus at least 1-2 2nd line agents to which strain is susceptible	6 months after culture conversion	Ethambutol/ Fluoroquinolone plus at least 1-2 2nd line agents to which strain is susceptible	12-18 months	18-24 months after culture conversion
Isoniazid/Rifampin/ Pyrazinamide/Ethambutol ± Streptomycin	Fluoroquinolone/Injectable Agent plus at least 2-3 2 nd line agents to which strain is susceptible	6 months after culture conversion	Fluoroquinolone plus at least 2-3 2nd line agents to which strain is susceptible	12-18 months	18-24 months after culture conversion
Isoniazid/Rifampin/Ethambutol/ Streptomycin/Kanamycin/ Ethionamide/Rifabutin ± Pyrazinamide (strain W and W variants)	Fluoroquinolone/Injectable Agent plus at least 2-3 agents to which strain is susceptible	6 months after culture conversion	Fluoroquinolone plus at least 2-3 2nd line agents to which strain is susceptible	12-18 months	18-24 months after culture conversion
Isoniazid/Rifampin/Ethambutol/ Streptomycin/Fluoroquinolone + second-line reserve injectable agent ± Pyrazinamide (i.e. extreme drug resistant TB (XDRTB))	Any 3-4 drugs to which strain is susceptible. Linezolid & Clofazimine may be necessary.	Until culture conversion	Any 3-4 drugs to which strain is susceptible. Linezolid & Clofazimine may be necessary.	Unknown	At least 24 months after culture conversion

Isoniazid Resistance (with or without Streptomycin Resistance)

Regimens

- *Option A.* Use rifampin, pyrazinamide and ethambutol for the duration of treatment. This is the preferred regimen even for pregnant patients, as relapse rates with rifampin and ethambutol are high. Extend to 9 months if the patient is still culture positive at 2 months. If a fluoroquinolone or injectable agent has been used (in patients with extensive disease or slow conversion of sputum cultures), it may be discontinued 2 months after culture conversion.
- *Option B.* If a patient was treated with pyrazinamide for at least 2 months and the drug was discontinued, treat with rifampin and ethambutol for an additional 7 months.
- *Option C.* If pyrazinamide cannot be used because of drug resistance or intolerance, a regimen of rifampin and ethambutol, along with a fluoroquinolone or an injectable agent, should be used for a 12-month period. The use of rifampin and ethambutol alone is not recommended because of high relapse rates on this regimen.

If resistance to isoniazid (with or without streptomycin resistance) is discovered after the patient has been taking isoniazid, rifampin, pyrazinamide and ethambutol for 1 to 3 months, and the patient has extensive disease requiring the addition of a fourth agent, a single medication can be added if the patient has responded to treatment and is smear negative for acid-fast bacilli. **This does not violate the rule of "do not add a single drug to a failing regimen."**

- High dose isoniazid is **not** recommended.

Length of Treatment

For both patients who are HIV negative and HIV positive:

- *Option A.* 6-9-month regimen; the 9-month regimen should be given to those who are still culture positive 2 months after starting treatment. This is the only regimen that can be given intermittently; 3 times a week is preferred for all patients.
- *Option B.* 9-month regimen
- *Option C.* 12-month regimen

Isoniazid and Ethambutol Resistance (with or without Streptomycin Resistance)

Regimens

- Use rifampin, pyrazinamide and a fluoroquinolone, along with an appropriate aminoglycoside or with capreomycin. Use capreomycin or an aminoglycoside other than streptomycin if streptomycin resistance is known at the start of treatment.
- If resistance to isoniazid and ethambutol (with or without streptomycin resistance) is discovered after the patient has been taking isoniazid, rifampin, pyrazinamide and ethambutol for 1-3 months, discontinue isoniazid and ethambutol. Continue rifampin and pyrazinamide, adding at least a fluoroquinolone and possibly an injectable agent such as capreomycin or an appropriate aminoglycoside.

Length of Treatment

- Nine to 12-month regimen, or 6-month regimen after culture conversion, whichever is longer.

An aminoglycoside or capreomycin may be discontinued 2 to 3 months after culture conversion to negative. However, in patients with extensive disease or slow conversion of sputum cultures, the injectable should be used for 6 months after culture conversion.

Rifampin Resistance (with or without Streptomycin Resistance)

Regimens

- *Option A.* Use isoniazid, pyrazinamide and ethambutol, along with an appropriate aminoglycoside or with capreomycin. Use capreomycin or an aminoglycoside other than streptomycin if streptomycin resistance is known at the start of treatment. If the patient has received 10 days or more of isoniazid and rifampin alone, add a fluoroquinolone to the regimen.
- *Option B.* If there is no streptomycin resistance, use isoniazid, pyrazinamide and streptomycin. This regimen, studied in patients who are HIV-negative, is the only non-rifamycin-containing regimen that has been shown to have high efficacy when used for less than 1 year.

Streptomycin was administered daily or intermittently for the entire 9 months in one study. It can be used in patients who are HIV positive with tuberculosis, who are on any antiretroviral treatment, without dose adjustments of anti-TB meds or HIV medications.

Some experts recommend an 18-month regimen of isoniazid/ethambutol as an option, in which streptomycin is used for 2 to 3 months post culture conversion. In NYC, most rifampin-resistant TB is seen in persons infected with HIV in whom this regimen has not been studied. Use pyrazinamide throughout the entire treatment if this regimen is used.

- Isoniazid, pyrazinamide, ethambutol and a fluoroquinolone in a 12-month regimen, while recommended in the new American Thoracic Society/Centers for Disease Control and Prevention (CDC)/Infectious Diseases Society of America guidelines, is not recommended by the BTBC.

Length of Treatment

For both patients who are HIV negative and HIV positive:

- *Option A.* Eighteen months total treatment with isoniazid, pyrazinamide, ethambutol and an aminoglycoside or capreomycin. If an aminoglycoside or capreomycin has been used, it may be discontinued 2 to 3 months after culture conversion. However, in patients with extensive disease or slow conversion of sputum cultures, use the injectable for 4 to 6 months after culture conversion; after this point, dosing for the injectable can be 2 to 3 times per week.
- *Option B.* Use isoniazid, pyrazinamide and streptomycin for a total of 9 months of treatment. After culture conversion, dosing for the injectable can be 2 to 3 times a week for the total duration of treatment.
- Surgery should be considered if a patient's cultures fail to convert to negative after 4 months of appropriate treatment (See p. 95.)

Isoniazid and Rifampin Resistance (with or without Streptomycin Resistance)

Regimens

- Use pyrazinamide, ethambutol and a fluoroquinolone, along with an appropriate aminoglycoside or capreomycin. Use capreomycin or an aminoglycoside other than streptomycin if streptomycin resistance is known at the start of treatment.
- If resistance to isoniazid and rifampin (with or without streptomycin resistance) is discovered after the patient has been taking isoniazid, rifampin, pyrazinamide and ethambutol for 1 to 3 months, discontinue isoniazid and rifampin. Continue pyrazinamide and ethambutol, and add at least 2 drugs — a fluoroquinolone along with an appropriate aminoglycoside or capreomycin to the regimen.

Length of Treatment

- Eighteen months after culture conversion
- Patients with extensive cavitory disease or with prolonged time to culture conversion, patients who are HIV positive, other immunosuppressed patients and patients with behavioral risk factors for HIV infection who decline HIV testing may need to have treatment extended to 24 months after culture conversion.
- The aminoglycoside or capreomycin can usually be discontinued 6 months after culture conversion.
- However, in some patients, especially those with extensive disease, slow conversion of sputum cultures or extensive second-line drug resistance, the injectable can be used for longer than 6 months after culture conversion.
- Intermittent dosing for the injectable may be used after culture conversion.
- Resistance to rifampin is generally associated with cross-resistance to rifabutin and rifapentine. When rifampin resistance is present but *in vitro* susceptibility to rifabutin is reported and this drug is added to the regimen, treatment should be the same as in the case of rifampin resistance.

- Surgery should be considered if a patient's cultures fail to convert to negative after 4 months of appropriate treatment. (See p. 95.)

Isoniazid, Rifampin and Ethambutol Resistance (with or without Streptomycin Resistance)

Regimens

- Use pyrazinamide and a fluoroquinolone, along with an appropriate aminoglycoside or with capreomycin; **in addition**, use 1 to 2 other second-line agents to which the strain is known or likely to be susceptible (e.g., ethionamide, cycloserine or para-aminosalicylic acid). Use capreomycin or an aminoglycoside other than streptomycin if streptomycin-resistance is known at the start of treatment. Use rifabutin if susceptibility to it has been documented.
- If resistance to isoniazid, rifampin and ethambutol (with or without streptomycin resistance) is discovered after the patient has been taking isoniazid, rifampin, pyrazinamide and ethambutol, discontinue isoniazid, rifampin and ethambutol. Continue pyrazinamide and add a fluoroquinolone to the regimen along with an appropriate aminoglycoside or capreomycin, and 1 to 2 other agents to which the strain is known or likely to be susceptible.
- Assess a new specimen, if available, for acquisition of pyrazinamide resistance as this may have been acquired while the patient was being treated with first-line drugs.

Length of Treatment

- Eighteen months after culture conversion
- Patients with extensive cavitory disease or with prolonged time to culture conversion; patients who are HIV positive, immunosuppressed or have behavioral risk factors for HIV infection and decline HIV testing may need to have treatment extended to 24 months after culture conversion.
- The aminoglycoside or capreomycin can usually be discontinued 6 months after culture conversion.

- However, in some patients (especially those with extensive disease, slow conversion of sputum cultures or extensive second-line drug resistance) the injectable can be used for longer than 6 months after culture conversion.
- Intermittent dosing for the injectable may be used after culture conversion.
- Resistance to rifampin is generally associated with cross-resistance to rifabutin and rifapentine. When rifampin resistance is present but *in vitro* susceptibility to rifabutin is reported and this drug is added to the regimen, treatment should be the same as in the case of rifampin resistance.
- Surgery should be considered if a patient's cultures fail to convert to negative after 4 months of appropriate treatment (see p. 95).

Isoniazid, Rifampin and Pyrazinamide Resistance (with or without Streptomycin Resistance)

Regimens

- Use ethambutol and a fluoroquinolone along with an appropriate aminoglycoside or with capreomycin. In addition, use 1 to 2 other second-line agents to which the strain is known or likely to be susceptible. Use capreomycin or an aminoglycoside other than streptomycin if streptomycin resistance is known at the start of treatment. Use rifabutin if susceptibility to the drug has been documented.
- If resistance to isoniazid, rifampin and pyrazinamide (with or without streptomycin resistance) is discovered after the patient has been taking isoniazid, rifampin, pyrazinamide and ethambutol, discontinue isoniazid, rifampin and pyrazinamide. Continue ethambutol, and consider increasing its dosage (25 mg/kg). Add a fluoroquinolone to the regimen, along with an appropriate aminoglycoside or capreomycin, and 1 to 2 other agents to which the strain is known or likely to be susceptible (e.g., ethionamide and para-aminosalicylic acid).

Assess a new specimen, if available, for acquisition of ethambutol resistance as it may have been acquired while the patient was being treated with first-line drugs.

Length of Treatment

- Eighteen months after culture conversion
- Patients with extensive cavitary disease or with prolonged time to culture conversion, patients who are HIV positive, other immunosuppressed patients and patients with behavioral risk factors for HIV infection who decline HIV testing may need to have treatment extended to 24 months after culture conversion.
- The aminoglycoside or capreomycin can usually be discontinued 6 months after culture conversion.
- However, in some patients (especially those with extensive disease, slow conversion of sputum cultures or extensive second-line drug resistance) the injectable can be used for longer than 6 months after culture conversion.
- Intermittent dosing for the injectable may be used after culture conversion.
- Resistance to rifampin is generally associated with cross-resistance to rifabutin and rifapentine. When rifampin resistance is present but *in vitro* susceptibility to rifabutin is reported and this drug is added to the regimen, treatment should be the same as in the case of rifampin resistance.
- Surgery should be considered if a patient's cultures fail to convert to negative after 4 months of appropriate treatment. (See p. 95).

Isoniazid, Rifampin, Pyrazinamide and Ethambutol Resistance (with or without Streptomycin Resistance)

Regimens

- Use a fluoroquinolone, along with an appropriate aminoglycoside or with capreomycin. In addition, use at least 2, and preferably 3, other second-line agents to which the strain is known or likely to be susceptible. Use capreomycin or an aminoglycoside other than streptomycin if streptomycin resistance is known at the start of treatment. Use rifabutin if susceptibility to the drug has been documented.
- If resistance to isoniazid, rifampin, pyrazinamide and ethambutol (with or without streptomycin resistance) is discovered after the patient has been taking isoniazid, rifampin, pyrazinamide

and ethambutol, discontinue all 4 drugs. Start a regimen of a fluoroquinolone, along with an appropriate aminoglycoside or capreomycin, and at least 2, and preferably 3, other agents to which the strain is known or likely to be susceptible (e.g., ethionamide, cycloserine and para-aminosalicylic acid).

Length of Treatment

- Eighteen months after culture conversion
- Patients with extensive cavitary disease or with prolonged time to culture conversion, patients who are HIV positive, other immunosuppressed patients and patients with behavioral risk factors for HIV infection who decline HIV testing may need to have treatment extended to 24 months after culture conversion.
- In both of the above situations, the aminoglycoside or capreomycin may be discontinued 6 months after culture conversion. However, in some patients (especially those with extensive disease or slow conversion of sputum cultures), the injectable should be used for longer than 6 months after culture conversion. Intermittent dosing of the injectable may be used after culture conversion.
- Resistance to rifampin is generally associated with cross-resistance to rifabutin and rifapentine. When rifampin resistance is present but *in vitro* susceptibility to rifabutin is reported and this drug is added to the regimen, treatment should be the same as in the case of rifampin resistance.
- Surgery should be considered if a patient's cultures fail to convert to negative after 4 months of appropriate treatment (See p. 95).

Isoniazid, Rifampin, Ethambutol, Streptomycin, Kanamycin, Ethionamide and Rifabutin Resistance ("Strain W")

Regimens

- In patients suspected of having this strain, start with a regimen of isoniazid, rifampin and pyrazinamide (in the event the strain is found to be susceptible to these medications), plus 3 other anti-TB medications to which the strain is likely to be susceptible. The 3 addi-

tional medications that have been used with success are fluoroquinolones, cycloserine (in conjunction with vitamin B₆) and intramuscular or intravenous capreomycin. Currently, the BTBC uses levofloxacin as the fluoroquinolone of choice.

- If this strain is confirmed, discontinue rifampin and treat with pyrazinamide (if susceptible), levofloxacin, cycloserine and capreomycin. Three other anti-TB medications that may have a role in the treatment of this strain are ethionamide, para-aminosalicylic acid and clofazimine, although the antituberculous activity of the latter is questionable (see p. 95). Do not use amikacin with this strain, as there is cross-resistance to kanamycin. If necessary, use isoniazid intermittently at a high dosage (900 mg twice a week), because this strain is resistant only to low levels of isoniazid. However, do not rely on the effectiveness of isoniazid.

Length of Treatment

- Eighteen months after culture conversion.
- Patients with extensive cavitory disease or with prolonged time to culture conversion, patients who are HIV positive, other immunosuppressed patients and patients with behavioral risk factors for HIV infection who decline HIV testing therapy may need to have treatment extended to 24 months after culture conversion.
- The aminoglycoside or capreomycin can usually be discontinued 6 months after culture conversion. However, in some patients (especially those with extensive disease, slow conversion of sputum cultures or extensive second-line drug resistance), the injectable can be used for longer than 6 months after culture conversion. Intermittent dosing for the injectable may be used after culture conversion.
- This strain is resistant to rifabutin.
- Surgery should be considered if a patient's cultures fail to convert to negative after 4 months of appropriate treatment (see p. 95).

Isoniazid, Rifampin, Ethambutol, Streptomycin, Fluoroquinolone Resistance (with or without either Pyrazinamide or several injectable agents)

Regimen

- Use any 3 to 4 drugs to which the organism is susceptible.
- Inhaled gamma interferon may be considered for select patients with pulmonary disease who are still AFB smear- and culture-positive. Consultation with the BTBC Director must occur.
- Surgical intervention should be considered early in the course of treatment (see p. 95).

Length of Treatment

- At least 24 months after culture conversion

Use of Newer Fluoroquinolones for Treating Tuberculosis

Several fluoroquinolones that have been approved in the last few years have potential use in treating TB. The ones most commonly used in patients with active and latent TB are levofloxacin, moxifloxacin and, until recently, gatifloxacin.

Moxifloxacin was approved in 1999 for the treatment of respiratory tract infections in adults. Many *in vitro* and animal studies have shown its potent activity against *M. tb*. The drug has been chosen by the CDC and the Global Alliance for Tuberculosis Drug Development for further study as an anti-TB agent—Phase II and Phase III clinical trials are underway. The major issue with using moxifloxacin in treating TB is a lack of data on safety and clinical efficacy for prolonged use.

Gatifloxacin also shows *in vitro* activity against *M. tb*; however, it has greater potential for cardiotoxicity than moxifloxacin and can cause hypoglycemia in the elderly and diabetic patients on oral hypoglycemic agents. Therefore, when it is necessary to use a newer generation fluoroquinolone, moxifloxacin is the preferred agent. Furthermore, the manufacturer has recently made a voluntary withdrawal of gatifloxacin from the worldwide market.

Levofloxacin, at present, remains the fluoroquinolone of choice; its safety profile for long-term use is documented over several years in patients with DRTB who are intolerant to isoniazid or a rifamycin.

To provide comparable levofloxacin exposures associated with clinical effectiveness and safety in adults, children 5 years or older need a daily dose of 10 mg/kg whereas children 6 months to younger than 5 years should receive 10 mg/kg every 12 hours.

The following patients are potential candidates for moxifloxacin during TB treatment:

- Adults and children with MDRTB who are not tolerating levofloxacin but may still be a candidate for a fluoroquinolone (e.g., an adverse reaction is unlikely to occur with a different one)
- Adults and children with MDRTB that is resistant to most first- and second-line drugs and for whom a regimen of 3 to 4 drugs cannot be identified.

To date, there is no evidence for the use of fluoroquinolones as a single agent for treatment of latent tuberculosis infection (LTBI) due to a multidrug-resistant organism. It is recommended that if a fluoroquinolone is used for LTBI, it be used in combination with another agent. However, in select situations, moxifloxacin may be used as a single agent after consultation with the BTBC Director.

Toxicities of Fluoroquinolones

Adverse events can vary markedly among the different fluoroquinolones, which most commonly cause nausea, vomiting, diarrhea (*often due to C. difficile*) and abdominal pain. Current data suggest that the newer ones, especially in high-dose regimens, cause a higher incidence of these adverse effects than do older agents such as ciprofloxacin and ofloxacin. Cholestasis, hepatitis and hepatic failure have been infrequently reported. Reversible transaminase elevation may occur in up to 2% to 3% of patients.

Some common adverse effects (phototoxicity, central nervous system effects and inhibition of drug metabolism) are associated with structural

features of the fluoroquinolones. Most adverse effects, including gastrointestinal problems and chondrotoxicity/arthropathy, have not been attributed to specific structural features of the fluoroquinolones.

Of the newer fluoroquinolones in use, levofloxacin is cleared by the kidney and is the preferred agent for patients with hepatic insufficiency; however, it should be used with caution. In patients with renal failure, the interval between doses of levofloxacin should be increased. Moxifloxacin is mostly cleared by the liver and therefore may be the preferred fluoroquinolone in a patient with renal insufficiency.

Fluoroquinolones can cause hypersensitivity reaction either after a single dose or multiple doses. Treatment should be discontinued at the first appearance of a skin rash, jaundice or any other sign of hypersensitivity.

Photosensitivity and Cardiotoxicity

Although fluoroquinolones are generally considered to have favorable adverse event profiles, 2 potentially serious adverse events—photosensitivity and QT interval prolongation—have been associated with certain drugs in the class.

- Photosensitivity is defined as a non-immunological, light-activated irritation that occurs after exposure to a photoactive chemical. This is an infrequent adverse event of most fluoroquinolones; however, the incidence varies according to the individual drug.

Phototoxicity has been described with all fluoroquinolones except moxifloxacin, but appears to occur most frequently in derivatives that have a halogen atom at C-8.

- Some second-generation fluoroquinolones have been associated with prolonged QT intervals and the potential for ventricular tachyarrhythmia. Cardiac events, such as QT prolongation and the potential for ventricular tachyarrhythmia, are most notably associated with the use of levofloxacin and moxifloxacin.

Tendinopathy/Tendinitis

Fluoroquinolone-induced tendinopathy is diagnosed by a sudden onset of swelling and tenderness concurrent with or shortly after fluoroquinolone therapy. There is tendon

rupture in about 33% of all cases. The main site affected is the Achilles tendon: however, it has been reported in the shoulder, knee, hand and plantar aponeuroses. Achilles tendon ruptures have been noted even months after drug discontinuation.

No correlation between duration of treatment and the incidence of tendinopathy has been observed; however, symptom severity is proportional to treatment duration. Uncomplicated tendinitis generally occurs after less than 5 days of therapy and tendon rupture more frequently when therapy lasts longer than 3 weeks.

Concomitant use of corticosteroids is considered to be a risk factor for developing tendinopathy while taking fluoroquinolones, especially in the elderly (older than 65 years). Treatment involves discontinuation of the fluoroquinolone and resting the tendons. Physical therapy may be needed early in treatment and may be prolonged.

Hypoglycemia and Hyperglycemia

All fluoroquinolones can cause hypoglycemia and hyperglycemia: however, such effects on blood sugar are believed to be rare despite the widespread use of these agents. Changes in blood sugar are believed to be due to interaction between ciprofloxacin and glyburide at the cytochrome P450 level. Several recent reports have indicated that the newer generation fluoroquinolones, specifically gatifloxacin, can cause severe symptomatic hypoglycemia in patients with type 2 diabetes who are taking oral hypoglycemic agents, especially the elderly.

There are more recent reports of severe hypoglycemia and hyperglycemia with gatifloxacin alone, particularly in elderly, non-diabetic patients. A possible mechanism for this phenomenon is that gatifloxacin (which is excreted by the kidneys) may accumulate in the elderly, who may experience an age-related decline in renal function. Since fluoroquinolones are generally used for prolonged periods in TB treatment, we do not recommend the use of gatifloxacin for TB. Patients on fluoroquinolones should be closely monitored, including having their blood glucose monitored regularly.

Long-Term Use of Fluoroquinolones

Although fluoroquinolones generally appear to be safe for long-term use, several studies

have documented that the incidence of adverse effects for ciprofloxacin is highest in the first 7 to 10 days of therapy. These studies are limited by the definition of long-term use (usually 1 month or 3 months).

In 1991, the use of first generation fluoroquinolones was reviewed in over 100 patients with mycobacterial disease who were given fluoroquinolones in addition to other drugs for a prolonged period of time. Most reactions were mild and reversible, and were similar for both ciprofloxacin and ofloxacin. Drug therapy was discontinued in 3 patients. Similar results were found in research examining the use of fluoroquinolones for leprosy.

Moxifloxacin

Little data is available on the use of moxifloxacin for prolonged periods. Most adverse events reported in moxifloxacin trials are described as mild to moderate in severity and required no treatment; the drug was discontinued due to adverse reactions thought to be drug-related in 3.8% of patients.

Moxifloxacin has been shown to prolong the QT interval on electrocardiogram in some patients. Due to the lack of clinical experience with the drug in patients with known prolongation of the QT interval, uncorrected hypokalemia and/or patients receiving class IA (e.g., quinidine, procainamide) or class III (e.g., amiodarone, sotalol) antiarrhythmic agents, the drug should be avoided in these populations.

There are no pharmacokinetic studies of moxifloxacin in combination with other drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics and tricyclic antidepressants. An additive effect of moxifloxacin and these drugs cannot be excluded; therefore, it should be used with caution when given concurrently with these drugs.

The effect of moxifloxacin on patients with congenital prolongation of the QT interval has not been studied; however, it is expected that these individuals may be more susceptible to drug-induced QT prolongation. Because of limited clinical experience, moxifloxacin should be used with caution in patients with ongoing pro-arrhythmic conditions such as clinically significant bradycardia and acute myocardial ischemia.

Moxifloxacin is non-formulary at present in the BTBC chest centers and requires approval of the Bureau Director prior to use. The BTBC does not recommend routine EKG testing of patients on moxifloxacin unless clinically indicated.

Adverse reactions occurring in greater than or equal to 1% of moxifloxacin treated patients that may be at least possibly drug-related are:

- Nausea (8%)
- Diarrhea (6%)
- Dizziness (3%)
- Headache (2%)
- Abdominal pain (2%)
- Vomiting (2%)
- Taste alteration (1%)
- Abnormal liver function test results (1%)
- Dyspepsia (1%)

Linezolid

Linezolid belongs to a new class of antibiotics, the oxazolidinones, and was approved by the FDA in 2000 for treatment of infections with resistant gram-positive organisms. *In vitro* studies have shown that linezolid is active against *M. tb*, including strains resistant to many first-line anti-TB drugs. Linezolid may be used as part of a regimen for treating patients with MDRTB and persistent positive sputum cultures (whose treatment options are severely limited) and who also:

- Are already prescribed a regimen to which the organism is susceptible
- Have extensive second-line drug resistance or are intolerant to many second-line drugs
- Are on DOT
- May not be surgical candidates
- Have no other treatment options

Linezolid is available for oral use as well as for intravenous administration. A dose of 600 mg twice a day has been used with good response. Food delays absorption, but does not lower peak plasma concentrations. The drug is partly metabolized in the liver and does not affect the cytochrome P450 enzyme system; it is excreted in the urine. The linezolid oral suspension contains phenylalanine and should not be given to patients with phenylketonuria.

Side effects of linezolid include:

- Myelosuppression (including anemia, leukopenia, pancytopenia and thrombocytopenia)
- Hemolytic anemia
- Diarrhea
- Nausea, vomiting (patients who have recurrent nausea and vomiting, unexplained acidosis or a low bicarbonate level should receive immediate medical attention to rule out lactic acidosis)
- Liver function test elevations
- Tongue discoloration
- Severe hypertension (if taken concomitantly with large amounts of tyramine)
- Peripheral neuropathy, including optic neuritis (in patients who have taken linezolid longer than the maximum recommended 28 days; optic neuropathy may be reversible upon discontinuation, but peripheral neuropathy may be irreversible)

Administration of vitamin B₆ (daily dose, 25 mg/day) may ameliorate some of these adverse reactions, though this remains controversial. A complete blood count should be obtained every 1 to 2 weeks, especially in those with pre-existing myelosuppression, and those receiving concomitant drugs that induce bone marrow suppression. CBC and SMA-18 profile should be monitored every 2 to 4 weeks, vision should be monitored every month and patients should overall be monitored post-treatment per BTBC protocol.

Note: Linezolid is a reversible, non-selective inhibitor of monoamine oxidase and therefore may interact with adrenergic and serotonergic agents. Co-administration of drugs containing:

- Pseudoephedrine
- Phenylpropanolamine
- Selective serotonin reuptake inhibitors
- Possibly other antidepressants

should be undertaken with caution, as serotonin syndrome may occur, manifesting as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination; such patients may need referral to a psychiatrist. The benefit of taking linezolid with these drugs must be weighed against these risks.

In summary, the current cost and high rate of adverse effects of linezolid preclude its widespread use. Linezolid use must be approved by the BTBC Director.

Clofazimine

Clofazimine (an FDA-approved drug previously on the BTBC formulary) has been used, when absolutely necessary, in BTBC chest centers for many years to treat MDRTB. Since it has *in vitro* activity against *M. tb* and some non-mycobacterium TB (*Mycobacterium avium* complex [MAC]), this drug has been used in the treatment of drug-resistant *M. tb* and non-tuberculous mycobacteria patients.

In November of 2004, Novartis Pharmaceutical Corporation discontinued commercial distribution of clofazimine in the United States due to the company's implementation of a compassionate care program for the treatment of leprosy (Hansen's disease). The FDA has now made clofazimine available under an Investigational New Drug (IND) application for these uses and in order to use this drug for a patient, an IND application has to be sent to the FDA.

The Office of Medical Affairs is responsible for obtaining clofazimine for BTBC patients. Once a patient is approved by the FDA to receive it, a unique IND number is assigned to the patient and a 60-day supply of the drug is sent to the BTBC. The bottle with that IND number is specifically for use by that patient only and a new supply has to be requested every 60 days. The Office of Medical Affairs should be contacted 30 days prior to the prescription expiring so that arrangements can be made to have clofazimine available.

Yearly updates must be sent to the FDA for continued use, and the physician caring for the patient must document the continued use of the drug, its risks and benefits, and the patient's agreement to continue with the medication. The patient should be informed of this process (and sign a brief consent form), and monitored monthly or more frequently for sputum conversion, continued need for the drug and side effects, which frequently include:

- Pink to brownish-black discoloration of the skin; the degree of discoloration is dose-related and is most pronounced on exposed parts of the body
- Ichthyosis and dry skin; pruritis and non-specific rash
- Reversible, dose-related red-brown discoloration of the conjunctiva, cornea and lacrimal fluid
- GI side effects such as abdominal and epigastric pain, diarrhea, nausea, vomiting and GI intolerance
- Nervous system effects (reported in less than 1% of patients) such as dizziness, drowsiness, fatigue, headache, giddiness, neuralgia and taste disorders

Monitoring and Post-Treatment Evaluation

Patients being treated for DRTB should be monitored during treatment as outlined on p. 101. For information on adverse reactions in patients taking second-line anti-TB medications, (see p. 210, Appendix I-B). After completing treatment, patients with MDRTB should be evaluated at 4, 8, 12, 18 and 24 months after completion of therapy, as described on p. 115 and on p. 116, Table VI-2.

Surgery for Pulmonary Tuberculosis

Surgery is not a first-line option in the treatment of TB because, in most cases, pulmonary TB is curable using modern drug regimens. Surgery is, however, one of the last alternatives available for individuals with MDRTB strains in whom chemotherapy has failed or is not possible because of a lack of sufficient and effective medications.

Indications for Surgery

In consultation with medical and surgical experts, surgery can and should be considered as an adjunct to chemotherapy when all of the following criteria are met:

- Adequate first- and second-line regimens of anti-TB medications have failed to cure, or to cause *M. tb* cultures to convert to negative within 4 to 6 months.
- Sufficient medications are available to treat the patient post-operatively.
- The disease is sufficiently localized to allow lobectomy or pneumonectomy.
- The remaining lung tissue is relatively free of disease.
- The patient has an acceptable surgical risk, with sufficient pulmonary reserve to tolerate the resection.

Some clinical circumstances, such as major bronchial obstruction, severe hemoptysis or bronchopleural fistula are additional possible indications for surgery.

Protocol for Surgery Referral

- Referrals for surgery should be made on an individual basis, and should be reviewed and coordinated by the BTBC Director or the Director of Medical Affairs.
- Chest center physicians may refer a patient for a CT scan when necessary, after consulting with the physician-in-charge.
- As part of the medical/surgical evaluation, all of the following should be documented:
 - Failure to cure TB, as evidenced by persistent positive *M. tb* sputum cultures or reversion from negative to positive cultures, despite the best treatment regimen possible and every effort to achieve adherence to treatment, including the use of DOT
 - Diagnostic evaluation that shows the majority of disease is anatomically localized, allowing surgical resection
 - Appropriate evaluation proving that the patient has an acceptable surgical risk
- Even after lung resection, the patient must complete a full course of treatment (18 to 24 months after culture conversion) with medications to which the *M. tb* strain is susceptible. If the patient is culture negative after surgery, then the date of surgery is considered to be the conversion date.

Key Sources

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Tuberculosis

Section VI.

Clinical Monitoring and Follow-Up
for Tuberculosis Treatment

Section VI.

Clinical Monitoring and Follow-Up for Tuberculosis Treatment

Monthly Clinical Evaluation

All Class III and Class V patients, as well as Class IV patients on multidrug treatment, should receive at least monthly clinical evaluations by the treating physician and nurse to monitor response and adherence to treatment and to assess for adverse reactions. (See p. 103, Figure VI-1 and p. 105, Table VI-1.)

Physician Assessment

The following should be assessed and discussed with individuals receiving anti-TB treatment and documented in the clinic medical record:

- 1. Signs and symptoms of TB for response to treatment.** All patients should be evaluated for signs and symptoms of TB during the physical examination; if symptoms persist despite treatment, non-adherence or drug resistance should be suspected and frequent sputum specimens should be obtained for culture and drug-susceptibility testing.
 - 2. Chest X-ray (CXR).** Patients who are initially culture negative should have a repeat CXR at 2 and 4 months to document response to treatment or the possibility of non-tuberculous lung disease. (See p. 114.)
 - 3. Adherence to treatment.**
 - The physician should review directly observed therapy (DOT) records if the patient is receiving DOT. Patients who are prescribed intermittent DOT who are less than 80% compliant should be switched to a daily DOT regimen.
 - Patients on self-administered treatment should be instructed at the first visit to bring the last-issued medication bottles to follow-up visits. Pills should be counted by the physician or nurse, and the information recorded in the patient's chart.
 - All patients should be questioned about when and how they take the medications, and to describe the appearance of the medications and the number of pills they take each day.
 - Laboratory tests may be ordered to detect increased uric acid levels in patients taking pyrazinamide.
- 4. Medication side effects and adverse reactions.** Adverse reactions from specific medications should guide the physician's decision regarding the physical exam and laboratory evaluation. (See p. 208, Appendix I-A and p. 210, Appendix I-B, for details and recommended monitoring parameters.)
 - 5. Physical examination.** The nature and extent of the physical exam depends on the patient's symptoms and site of disease (e.g., evaluation of lymph node size, medication side effects). Taking a medical history at each follow-up visit is important to guide the exam, as patients may not reveal certain symptoms or events unless asked.
 - 6. Laboratory tests.** Previous sputum and other laboratory tests requested should be assessed for availability of results to use in treatment decisions. Patients should be told whether their tests show improvement in or a deterioration of their condition and the effect of either on their treatment.

Note: Abnormal test results should be addressed as soon as received, independent of the date of the monthly follow-up visit.

- **Sputum..** Induced sputum should be obtained monthly for smear and culture in patients with drug-susceptible pulmonary disease. For patients with isoniazid- and rifampin-susceptible TB, there is no need to examine sputum monthly once culture conversion is documented (i.e., 2 negative cultures taken at least 2-4 weeks apart).

If sputum specimens remain smear positive for acid-fast bacilli (AFB) after documented culture conversion to negative, continue to collect sputum specimens at least monthly until smear converts. Clinical correlation is recommended. Sputum should be collected from all patients at the end of treatment to document cure.

- For patients who are initially smear positive and are being managed as outpatients, specimens should be collected every 1 to 2 weeks until smear converts to negative. This will allow timely decision-making about when patients may be allowed to leave their home, receive visitors or return to work or school.
- More frequent specimens are unnecessary except on rare occasions when a patient who is already smear or culture negative develops a newly positive AFB smear; in such cases, 2 to 3 specimens may be collected in a week's time as part of clinical reassessment. The specimen collection procedure should also be reviewed to ensure that the result is not falsely positive. Once smears have become negative for AFB on 2 to 3 consecutive specimens, monthly specimens are adequate until culture conversion is documented.
- For hospitalized patients, frequent specimens for smear conversion are vital to determine when airborne isolation can be discontinued or when patients can be safely discharged to the community or a long-term facility (if they are not eligible to be discharged while still AFB smear positive). Daily specimens are unnecessary; specimens should be taken every 3 to 7 days since smear conversion can take many weeks and median time to conversion for most patients is 4 weeks. However, once smears turn negative, specimens can be collected more frequently. Smear conversion is defined as having 3 consecutive negative AFB sputum smear in specimens collected over at least 48 to 72 hours.

- Specimens do not need to have cultures performed every week; cultures can be performed on all initial specimens collected for diagnostic purposes and on specimens taken 2 weeks apart—even for patients with multidrug-resistant TB (MDR-TB). However, if failure or relapse is suspected because smear or culture has reverted to positive after initial conversion, the specimens taken for reassessment should all have cultures done as well. In addition:

- All patients should have a sputum sample taken 1 to 2 weeks before the end of the intensive phase to assess risk of relapse or treatment failure, and to assess eligibility for rifapentine. (See p. 46.)
- More frequent specimens should be taken if the patient is nonadherent to the treatment regimen, there are signs of relapse or the patient is prescribed a nonrifamycin or nonisoniazid regimen. At the end of treatment, a sputum specimen should be taken to document cure; a negative sputum culture at the end of treatment is the only conclusive evidence that the patient has been cured.
- If the patient has isoniazid and/or rifampin-resistant TB, sputum cultures should be examined monthly until the end of treatment (see p. 84), and then evaluated post-treatment according to the guidelines on p. 115.

Sputum should be collected in the clinic setting via induction. Natural sputum collection should be done only in cases where the patient is homebound, has difficulty reaching the clinic or is unable to produce induced sputum during the day. Susceptibility testing on the most recent positive *Mycobacterium tuberculosis* (*M. tb*) culture should be requested if cultures remain positive after 4 months of treatment or if the individual fails to improve clinically.

Physicians who would like to arrange for more frequent susceptibility testing for selected patients should call the New York City Department of Health and Mental Hygiene Bureau of Laboratories at (212) 447-6745.

Figure VI-1

Therapy Evaluation Timeline for Previously Untreated Tuberculosis Patients with Drug-Susceptible Active Disease¹

Months	0	1	2	3	4	5	6	7	8	9
Regimen I²										
Isoniazid ^{3,4}	→									
Rifampin ⁴	→									
Ethambutol ^{5,6}	→									
Pyrazinamide ⁵	→									
Regimen II²										
Isoniazid ³	→									
Rifampin	→									
Rifapentine ⁷	→									
Ethambutol ^{5,6}	→									
Pyrazinamide ⁵	→									
HIV Counseling and Testing	X					O				
Regular Monitoring										
Physician and Nurse Assessment	X	X	X	X	X	X	X	O	O	O
Sputum Smear and Culture ⁸	X	X	X	X	O		O	X	O	O
Nucleic Acid Amplification ⁹	X									
CXR¹⁰	X		O			O		X/O		X
Complete Blood Cell Count with Platelets	X		O	O	O	O	O	O	O	O
Liver Function Tests^{11,12}	X		O	O	O	O	O	O	O	O

- X = Recommended intervention
- O = As needed
- Regular treatment
- Continue treatment if pyrazinamide was not used in the intensive phase or if patient had a cavitary CXR and positive sputum culture at the end of the 2 months intensive phase of treatment
- If sputum cultures are positive at the end of 2-month intensive phase, continue rifapentine and isoniazid for a total of 7 months.

1. This chart applies only to patients whose isolates are found to be drug-susceptible. If drug resistance is documented, consult an expert in its management. To obtain treatment information and susceptibility results, call 212-788-4162 during business hours.
2. Pending the results of drug-susceptibility testing, begin all patients on the first four anti-TB medications listed, unless there are absolute contraindications.
3. Pyridoxine hydrochloride (vitamin B6) 10-25 mg with each dose of isoniazid may decrease peripheral neuritis and CNS effects. See Table III-4.
4. In the continuation phase, isoniazid and rifampin should be given for only 2 months if initial cultures are negative, for a total of 4 months of treatment. The continuation phase should last for 4 months (a total of 6 months of treatment) if initial cultures were positive but susceptibility results are not available.
5. Pyrazinamide and ethambutol can be discontinued at the end of the intensive phase of treatment for all patients with culture negative TB and for those patients with culture positive TB for whom drug-susceptibility is not available, unless drug resistance is strongly suspected, or the patient has been treated in the past.
6. During treatment with ethambutol, monitor visual acuity and color vision monthly.
7. Use rifapentine for pansensitive noncavitary pulmonary TB patients who have received at least isoniazid, rifampin, and pyrazinamide for the 2 month intensive phase of therapy. Rifapentine should not be used in HIV-positive patients, children under 12 years of age, pregnant women, and patients who are sputum AFB-smear positive after 2 months of treatment. It should not be used to treat extrapulmonary TB.
8. Initially at least 3 sputa for AFB smear and culture should be collected over 48 to 72 hours in order to maximize bacteriologic diagnosis. Most patients (e.g., patients on DOT, patients adherent to the treatment regimen, and patients with isoniazid and rifampin-susceptible TB) need monthly sputum tests only until cultures become negative – documented by 2 negative cultures taken 2-4 weeks apart. To document cure, a sputum test should be obtained at the end of treatment. If drug resistance is suspected or documented, seek expert consultation.
9. Nucleic acid amplification testing should be performed on the first sputum that is AFB smear positive and on selected smear negative specimens if the clinical suspicion of TB is high.
10. Obtain CXR after 2 and 4 months to document response to treatment if initial cultures are negative. CXR should be obtained at the end of treatment for all patients as a baseline in the event of suspected relapse in the future.
11. Baseline liver function tests (LFTs) should be done for all patients.
12. Monthly LFTs should be done in patients:
 - Whose baseline LFT results were abnormal;
 - Who are HIV seropositive, regardless of baseline LFT results;
 - Who have a history of heavy alcohol ingestion, liver disease, or chronic hepatitis, regardless of baseline LFT results;
 - Who are pregnant or postpartum (up to 2-3 months after delivery) and are currently taking isoniazid and/or rifampin, regardless of baseline LFT results;
 - Who currently inject drugs or who have documented chronic hepatitis B or C infection, regardless of LFT results;
 - Who are taking hepatotoxic medications

- **Liver function tests**

- Baseline liver function tests (LFTs) and a complete blood count (CBC) including platelets and chemistry panel including creatinine, should be obtained for all patients.
- Monthly LFTs should be done on patients who meet one or more of the following criteria:
 - Have abnormal baseline LFT results
 - Are HIV-positive, regardless of baseline LFT results
 - Have a history of heavy alcohol ingestion, liver disease or chronic hepatitis, regardless of baseline LFT results
 - Are pregnant or postpartum (up to 2-3 months after delivery) who are currently taking isoniazid and/or rifampin, regardless of baseline LFT results
 - Currently inject drugs or have documented chronic hepatitis B or C infection, regardless of baseline LFT results
 - Are treated with second-line medications that may be hepatotoxic (e.g., ethionamide) or with medications that may be hepatotoxic but are unrelated to TB treatment
 - In patients older than 35 years of age, periodic LFTs should also be performed (i.e., 1 and 3 months).

- **Additional Tests.** Other relevant laboratory values should be obtained at appropriate intervals according to the medications used and side effects present. For example, renal function and hearing may be affected by the aminoglycosides and capreomycin; uric acid values are affected by pyrazinamide. (Note: an increase in uric acid is not an indication to discontinue pyrazinamide, as long as the patient remains asymptomatic.) Thyroid function tests should be performed for patients on para-aminosalicylic acid or ethionamide.

HIV counseling and testing should be offered to all patients if HIV status is unknown

7. Formulation of a plan of care based on evaluation of current status.

- Because several medical providers may be involved in the care of one patient, it is important to outline a plan of care that details reasons for decisions, names and dosages of medications, planned length of treatment, etc. in order to ensure continuity of care.
- This plan should be communicated to non-Bureau of Tuberculosis Control (BTBC) providers on a regular basis.
- Changes in treatment plans should be communicated to all providers in a timely manner.

8. Medication orders (to be written on the medication order sheet). Medication must be prescribed on a specific medication order form and be clearly written. To prevent errors, non-standard abbreviations should not be used on the medication order form and the physician's name must be printed along with the signature. A "Hold Medication" order should not be used, as it is not time-specific— a medication should be discontinued, and then restarted when indicated. All medication orders should be time limited. Changes in medication orders due to adverse reaction should be flagged and/or communicated to the nurse who is to execute the order.

Eligible patients should be started on intermittent therapy with DOT, especially after the 2-month intensive phase.

9. Review of non-TB medications. In 1992, New York State amended Section 63.6 of the New York State Education Law, requiring that all medications a patient takes must be reviewed with the patient and noted in his or her medical record at each visit. In addition, a patient must be notified of potential drug interactions to any anti-TB medications that are prescribed in the BTBC.

If there has been no change in the use of non-TB medications from previous visit(s), the documentation in the medical record should read: "no change in medication status." If the patient reports using new medications, if there has been a change in dosage or if any medications have been discontinued, the physician should:

- (1) Enter the name and dosage of the medication(s) in the medical record

Table VI-1

Common Adverse Reactions to First- and Second-Line Anti-Tuberculosis Medications*

Adverse Reaction	Symptoms and Signs	Usual Drug Responsible
Audiovestibular manifestations	Hearing loss, vertigo, new-onset tinnitus	Aminoglycosides, capreomycin
Blood sugar abnormalities	Dizziness, sweating, fainting, poor response to infections	Fluoroquinolones, pyrazinamide, rifampin
Dermatitis	Itching, rash, hives, fever, petechial rash	Pyrazinamide, rifampin, rifapentine, isoniazid (rarely, ethambutol, rifabutin or injectable agents)
Gastritis	Anorexia, nausea, vomiting, epigastric pain	Rifampin, rifapentine, pyrazinamide, rifabutin
Hematologic manifestations	Leucopenia, thrombocytopenia, anemia, eosinophilia	Rifampin, rifabutin, rifapentine, isoniazid, linezolid, capreomycin
Hepatitis	Anorexia, nausea, vomiting, jaundice, abdominal pain	Isoniazid, rifampin, rifapentine, pyrazinamide; rarely ethambutol, rifabutin
Hypothyroidism	Fatigue, weight gain, sluggish reflexes, depression	Para-aminosalicylic acid, ethionamide
Joint and tendon manifestations	Gout-like manifestations, systemic lupus erythematosus-like manifestations; tendinopathies	Pyrazinamide, isoniazid, fluoroquinolones, rifampin
Neurological and psychiatric manifestations	Headaches, depression, agitation, suicidal ideation	Isoniazid, fluoroquinolones, cycloserine
Peripheral neuropathy	Numbness or paresthesias of feet or hands	Isoniazid, linezolid
Renal manifestations	Hematuria, azotemia	Aminoglycosides, capreomycin, rifampin, rifapentine
Visual manifestations	Vision loss and color blindness, uveitis	Ethambutol, rifabutin, rifapentine, linezolid

* This is not a comprehensive list of adverse reactions. Please consult the drug's package insert, *Physicians Desk Reference* or other reference pharmaceutical texts for more information.

- (2) Determine whether the new non-TB medication(s) might interact with the anti-TB medications the patient is currently taking
- (3) Discuss potential drug-to-drug interaction(s) with the patient and document this discussion in the medical record.

Nurse Assessment

The nurse is responsible for performing a monthly nursing assessment of the patient. Nurses should document the following in the clinic medical record:

- Vital signs
- Signs and symptoms of TB disease (for patients with latent tuberculosis infection [LTBI] diagnosis)
- Symptoms of improvement (diseased patients)
- Assessment of adherence
- Monitoring of medication side-effects and adverse reactions, including:
 - Visual acuity testing and Ishihara's color vision testing for patients taking ethambutol
 - Hearing tests for patients receiving injectable agents
 - Check of patient's sclera and nail bed for signs of jaundice
- Review patient's knowledge of medication and dosage, potential side-effects and adverse reactions, and instruct the patient about what to report to the physicians
- Review the physician's plan of care with the patient
- Reinforce need for adherence to treatment and follow-up visit

- Review of non-TB medications
- Ensure that all physician orders were followed
- Perform/facilitate referrals for follow-up of abnormal findings

Management of Adverse Reactions

Anti-TB medications can cause a variety of adverse reactions, summarized on p. 105, Table VI-1; p. 208, Appendix I-A; and p. 210, Appendix I-B.

Dermatitis

Several anti-TB agents can cause rash, including all of the first-line agents; however, the most common culprit in our experience is pyrazinamide (followed by rifampin and isoniazid). Rifampin and the fluoroquinolones can also cause photosensitivity.

History and Examination

- The patient should be questioned about exposure to other medications or skin preparations, environmental contact, etc., that may be responsible.
- HIV-positive patients are subject to a variety of dermatologic diseases (either directly or indirectly related to HIV infection) and to other medications used for therapy or prophylaxis. Consultation with an appropriate infectious disease service or dermatology clinic may be required.
- The patient should be examined for evidence of unrelated skin disease (scabies, contact dermatitis, childhood exanthema, acne, etc.).

Follow-Up

- If the dermatologic reaction is severe and no other cause is found, anti-TB medications should be discontinued promptly and the patient should be examined each week until the skin reaction disappears.
- Patients with a severe dermatologic reaction (e.g., exfoliative dermatitis), or with dermatitis associated with severe systemic reactions should be referred for hospital admission for treatment and the establishment of either a new anti-TB regimen or a rechallenge regimen, under daily surveillance as an inpatient.
- If the drug reaction is mild, the physician may attempt to treat the patient with

antihistamines and topical steroids while continuing TB treatment. Clinical discretion is recommended.

Restarting Anti-TB Medications

- In cases managed in the chest center, rechallenge is appropriate after the skin reaction clears or subsides. It may not be possible to identify the specific causative agent by the characteristics of the skin reaction. Thus, it is appropriate to restart the most important member of the regimen (either isoniazid or rifampin) first, before trying pyrazinamide or ethambutol. (Note: In at least one study, pyrazinamide was found to be a major cause of skin reactions; most reactions occur within the first 4 weeks of treatment.)
- Single daily doses of isoniazid or rifampin should be given alone for 3 days with instructions to discontinue promptly if a reaction recurs. The patient should be examined in 3 to 4 days and in addition:
 - If there is no reaction, an alternate drug (rifampin or isoniazid) should be added with similar instructions. The patient should be re-examined in 3 to 4 days.
 - If the skin reaction does not recur or if it is not severe, ethambutol should be added (if this drug was part of the initial regimen). If there is no reaction to ethambutol, the regimen of isoniazid, rifampin and ethambutol can be continued and pyrazinamide discontinued on the presumption that this caused the skin reaction.
- Treatment should be continued with the original regimen minus the causative agent. A longer period of treatment may be required if the causative agent was isoniazid or rifampin, or pyrazinamide during the initial 2 months of treatment. For patients who are HIV-positive or who have extensive pulmonary or disseminated TB, a single, new drug, such as an injectable agent or a fluoroquinolone, should be added to regimens that lack isoniazid or rifampin. (See p. 83). The new drug should be continued for the duration of therapy. (In such instances, the addition of a single agent to a successful regimen does not violate the rule of “do not add a single drug to a failing regimen.”)
- The same principles of management apply to patients who experience dermatologic reactions while taking “retreatment” regimens for MDRTB.

Hepatitis

Several anti-TB medications can cause hepatotoxicity, which varies from adaptive responses to severe injury. In addition, concomitant use of TB medications increases the risk of developing drug-induced liver damage. Despite these risks, the benefits of TB treatment to the individual far outweigh the risks.

Certain drugs provoke various physiologic adaptive responses in the liver, which may lead to asymptomatic transient elevations of alanine aminotransferase (ALT; formerly known as serum glutamate pyruvate transaminase [SGPT]) or induction of the microsomal enzymes; these rarely lead to hepatic damage. However, certain toxins such as alcohol can interfere with the adaptation processes and augment injury. Concomitant use of other known hepatotoxic agents should be avoided if possible during anti-TB treatment, especially in patients with underlying liver disease.

An increase in serum ALT is more specific for hepatocellular injury than an increase in aspartate aminotransferase (AST-serum glutamic oxaloacetic transaminase [SGOT]), which can also signal abnormalities in muscle, heart or kidney. Populations used to set standard values in the past probably included individuals with occult liver disease, whose exclusion has led to decreases in the upper limit of normal for LFTs. Transaminases tend to be higher in men and in people with greater body mass index. Levels may vary as much as 45% on a single day, with the highest levels occurring in the afternoon, or 10% to 30% on successive days. ALT and AST elevation may occur after exercise, hemolysis or muscle injury.

History and Examination

- Individuals taking anti-TB medication who develop symptoms consistent with hepatitis (anorexia, nausea, vomiting, abdominal pain, jaundice) should be instructed to discontinue all medications promptly and be examined by a physician; have LFTs and a viral hepatitis screen sent immediately.
- In some patients, rifampin or pyrazinamide may cause gastritis with symptoms similar to those of hepatitis. In these patients, LFTs remain normal or stable despite symptoms (see p. 110).

Follow-Up

- If symptoms disappear promptly and LFTs are normal, drug-induced hepatitis is unlikely. Another cause for symptoms should be suspected. Depending upon the nature, duration and severity of symptoms, a decision should be made about further diagnostic study.
- If the LFTs are abnormal (AST or ALT is 3 to 5 times the upper limit of normal) or if serum bilirubin is elevated, with or without symptoms, drug-related hepatitis should be strongly suspected and all anti-TB medication(s) should be discontinued.
- The patient should be examined and have LFTs repeated at least weekly. If symptoms persist for more than 2 weeks without anti-TB medication(s), or if LFTs continue to worsen, the physician should suspect progressive drug-related hepatitis or an unrelated cause of hepatitis. Depending upon the severity of the hepatitis, as indicated by clinical findings and LFTs, hospitalization may be necessary for closer observation and therapy.

Restarting Anti-TB Medications

- If there is strong evidence that the symptoms are not related to hepatitis or anti-TB medication, the entire regimen should be reinstated promptly and the individual followed closely for the recurrence of symptoms.
- If the patient has extensive pulmonary, meningeal or disseminated TB; has HIV infection; or lives in a congregate setting or with young children or immunosuppressed persons, the institution of a new regimen with a lesser potential for hepatotoxicity (e.g., streptomycin, ethambutol, fluoroquinolone) may be indicated even before liver enzymes return to normal.
- For all other patients, anti-TB treatment should be withheld until symptoms disappear and LFTs are normal or have declined and plateaued. During this time, the patient should be followed closely with weekly LFTs; it is then appropriate to rechallenge with a single daily dose of one of the drugs in the prior regimen.
- If hepatitis is caused by any of the drugs in the anti-TB regimen, isoniazid is most likely to be responsible, followed by pyrazinamide, rifampin and ethambutol (in this order).

- Although the specific cause of hepatitis cannot be identified by the pattern of LFT abnormality, rifampin is usually implicated if the pattern is cholestatic (bilirubin and alkaline phosphatase elevated and out of proportion, with little or no changes in ALT, to enzyme elevations). In contrast, isoniazid, rifampin or pyrazinamide may be the cause if the pattern is hepatocellular, with enzymes elevated and out of proportion to bilirubin or alkaline phosphatase. Ethambutol very rarely causes hepatitis.
- In some cases, the treating physician may not want to lose a rifamycin in the treatment regimen. Rifabutin rechallenge may be acceptable with close follow-up of patients.

Cholestatic pattern. If the initial pattern of hepatitis is cholestatic, the patient should be rechallenged with a standard daily dosage of isoniazid and ethambutol after LFTs return to normal or decline to 2 times the upper limit of normal and plateau. The patient should be examined weekly, with LFTs repeated at each visit.

If LFTs remain stable after 1 week of isoniazid and ethambutol, and the patient is asymptomatic, pyrazinamide should be added to the regimen. If there are no subsequent signs of hepatotoxicity, rifampin-induced hepatitis should be assumed, and the patient should be treated with isoniazid, ethambutol and pyrazinamide. Capreomycin or an appropriate aminoglycoside, as well as a fluoroquinolone, should be considered for addition to the regimen (see p. 87).

Hepatocellular pattern. If the pattern is hepatocellular, it is appropriate to rechallenge first with the agent least likely to have been responsible—ethambutol alone for a period of 1 week—after LFTs return to normal or decline and plateau. The patient should be instructed to stop the medication immediately if symptoms of hepatitis occur. The patient should be examined weekly, with LFTs repeated at each visit.

- If LFTs remain stable after 1 week of ethambutol and the patient is asymptomatic, rifampin should be added at the usual dosage, and ethambutol continued. The patient should be followed carefully at weekly intervals as previously.

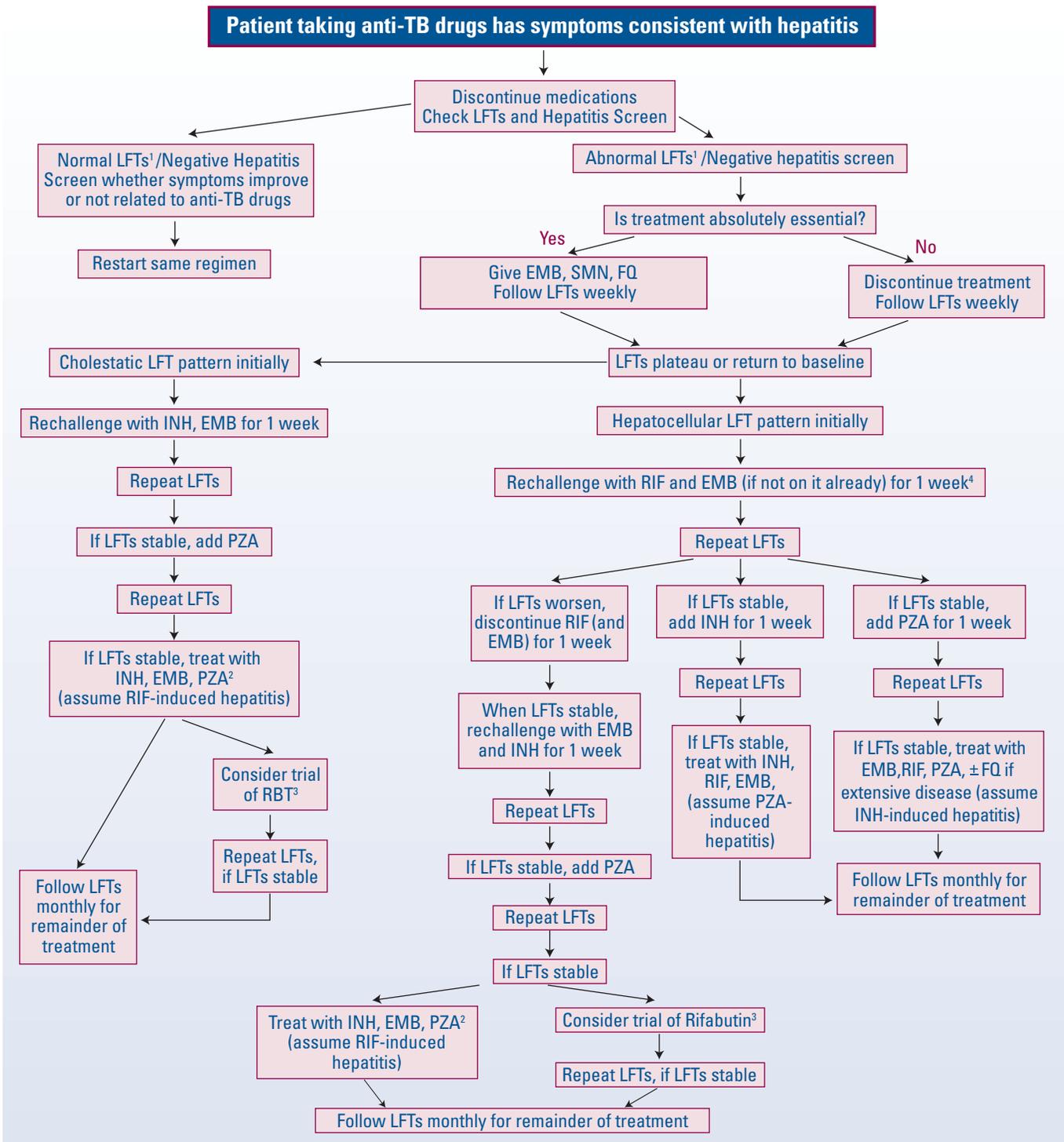
- If LFTs remain stable after 1 week of ethambutol and rifampin, pyrazinamide should be added to the regimen of ethambutol and rifampin. If there are no subsequent signs of hepatotoxicity, isoniazid-induced hepatitis should be assumed, and the patient should be treated with ethambutol, rifampin and pyrazinamide.
- If LFTs worsen after 1 week of ethambutol and rifampin, these medications should be stopped. LFTs should be allowed to return to normal or to decline and plateau, the patient should then be rechallenged with isoniazid and ethambutol.
- If LFTs remain stable after 1 week of isoniazid and ethambutol, pyrazinamide should be added to the regimen. If there are no subsequent signs of hepatotoxicity, rifampin-induced hepatitis should be assumed, and the patient should be treated with isoniazid, ethambutol and pyrazinamide. Capreomycin or an appropriate aminoglycoside, and in selected cases a fluoroquinolone, should be considered for the regimen (see p. 87).

The recommendations for restarting anti-TB medications in patients with drug-induced hepatitis are summarized on p. 109, Figure VI-2.

- Rechallenge with pyrazinamide may be hazardous in patients who tolerate the reintroduction with rifampin and isoniazid. In this circumstance, pyrazinamide may be permanently discontinued, with treatment extended to 9 months. Although pyrazinamide can be reintroduced in some milder cases of hepatotoxicity, the benefit of a shorter treatment course likely does not outweigh the risk of severe hepatotoxicity from pyrazinamide rechallenge.
- Patients who start treatment with a new regimen because of hepatitis should have monthly LFTs for the remainder of treatment.
- Individuals who cannot take either isoniazid or rifampin should be treated with a retreatment regimen—usually pyrazinamide, ethambutol and a fluoroquinolone, along with an appropriate aminoglycoside or with capreomycin, given for 18 to 24 months. (See p. 88.)

Figure VI-2

Restarting Anti-TB Medications in Patients with Drug-Induced Hepatitis



Abbreviations: EMB – Ethambutol; FQ – fluoroquinolone; INH – isoniazid; LFTs – liver function tests; PZA – pyrazinamide; RIF – rifampin; RBT – rifabutin; SMN – streptomycin

1. Abnormal LFTs are ≥ 3 times the upper limit of normal with symptoms or ≥ 5 times the upper limit of normal without symptoms.
2. Capreomycin or an appropriate aminoglycoside, and in selected cases a fluoroquinolone, should be considered for the regimen (see Section V-B). Treatment needs to last for 18 months unless rifabutin is added successfully. An alternate shorter regimen is isoniazid, streptomycin and pyrazinamide, all given for 9 months.
3. There may be times when rifabutin may be tried in an attempt to decrease duration of treatment from 18 months to 6-9 months.
4. Some clinicians may prefer to challenge with ethambutol and rifampin sequentially rather than simultaneously.

- Similar principles of management apply to cases of hepatitis induced by “reserve drugs,” (e.g., para-aminosalicylic acid, rifabutin and, rarely, fluoroquinolones).

Non-Drug Related Hepatitis

Hepatitis from various causes is a common co-morbidity in TB patients. Refer to p. 61 for further details on how to manage such patients.

Gastritis

Almost any medication can cause gastric irritation in susceptible individuals. Of the first-line anti-TB medications, rifampin most often causes gastritis, although pyrazinamide is responsible in some instances. Because rifampin is the most important member of combined chemotherapy, every effort should be made to reintroduce this drug once gastric symptoms resolve.

History and Examination

- Because the symptoms of gastritis (anorexia, nausea, vomiting and epigastric distress) may be due to drug-related hepatitis, LFTs must be done on all individuals who present with such symptoms.

Follow-Up

- Anti-TB medications should be discontinued in symptomatic patients. If LFTs are normal or unchanged from baseline and symptoms persist for 4 to 5 days without medication, unrelated gastrointestinal disease (e.g., peptic ulcer disease, gastritis due to another cause, etc.) should be suspected and appropriate referral made for diagnostic study.

Restarting Anti-TB Medications

- If the individual is taking isoniazid, rifampin, pyrazinamide and ethambutol, rifampin is the most likely cause of gastric symptoms. After symptoms subside, it is appropriate to renew treatment with isoniazid, pyrazinamide and ethambutol.
- If gastric symptoms return, pyrazinamide should be suspected as the cause and treatment should be attempted with isoniazid, rifampin and ethambutol.

- If symptoms do not recur, rifampin may be introduced in most cases without the recurrence of gastric symptoms by modifying the pattern of administration, for example by giving all of the medication before bedtime, preceding the medication with a small meal or renewing rifampin with a smaller dose (300 mg) and increasing to 600 mg over a period of 1 to 2 weeks.
- If rifampin is identified as a cause of gastritis and a rifamycin-containing regimen is appropriate, rifabutin can be attempted.
- Antacids may be useful to help alleviate the symptoms of gastritis, but antacids may interfere with the absorption of isoniazid and fluoroquinolones. If used, antacids should be given 2 hours after isoniazid and a fluoroquinolone have been taken; prolonged use should be avoided. An H₂-blocker or a proton pump inhibitor may be tried. However, patients taking para-aminosalicylic acid granules should take them with acidic foods such as yogurt, applesauce or orange juice rather than with neutral foods such as milk.
- If gastritis is caused by pyrazinamide, it can be omitted from the regimen with less risk than omitting rifampin. If the patient has TB susceptible to isoniazid and rifampin, these 2 medications can be used for a total of 9 months.

Peripheral Neuropathy

Isoniazid may cause peripheral neuropathy, especially in individuals with a predisposing cause, such as alcoholism, diabetes, HIV infection or malnutrition. Pyridoxine usually, but not invariably, prevents the emergence of isoniazid-induced peripheral neuropathy. In rare instances, ethambutol can also cause peripheral neuritis.

History and Examination

- Isoniazid should be assumed to be the primary cause for paresthesias and numbness of the feet and hands (with or without peripheral motor weakness) in isoniazid-treated patients, even if other predisposing causes are present.

Follow-Up

- Isoniazid should be discontinued in patients with peripheral neuropathy and pyridoxine (25 mg per day) should be given until symptoms abate.
- The neuropathy usually subsides over weeks to months, when it is diagnosed early and isoniazid is promptly discontinued. However, neurologic injury may be irreversible if diagnosis is delayed and manifestations become severe; neurologic consultation should be obtained if the diagnosis is not clear.

Linezolid can also cause a peripheral neuropathy and optic neuritis. Vitamin B₆ may or may not help ameliorate the symptoms (see p. 94).

Joint Manifestations

- Isoniazid (and rarely, rifampin) can induce active systemic lupus erythematosus (SLE), especially in patients who have this disease in a subclinical stage. The patient may have only arthralgias or alopecia, or may present with a full-blown pattern of SLE, with arthritis and other systemic manifestations. The diagnosis requires clinical suspicion and positive antinuclear antibody (ANA) markers of SLE. Isoniazid must be discontinued, and these patients should be referred to an appropriate medical or rheumatology clinic. This syndrome has been reported with rifampin as well.
- Pyrazinamide invariably leads to increased levels of serum uric acid because it impairs renal excretion of uric acid; this symptom can be used as a measure of compliance. In rare situations, elevated serum uric acid induces typical bouts of gouty arthritis, especially in patients with a history of gout. Pyrazinamide should be discontinued in such instances, unless it is essential to the anti-TB regimen. Allopurinol can lower the baseline serum uric acid level, but it cannot lower serum uric acid levels that are elevated because of pyrazinamide.
- Hyperuricemia without symptoms of gout is not a reason for discontinuing pyrazinamide.

Renal Manifestations

Renal injury in patients treated for TB is most often due to aminoglycosides or capreomycin. Also, rifampin can cause acute or chronic nephritis (with or without symptoms), evidenced by proteinuria, hematuria and urinary white blood cells. In rare instances, acute or chronic renal failure can occur. Isoniazid and ethambutol are not known to cause renal disease, although the blood levels of ethambutol (and cycloserine, aminoglycosides and capreomycin) may become markedly elevated in patients with renal function impairment. Pyrazinamide is metabolized by the liver, but its metabolites may accumulate in patients with renal insufficiency. Potassium and magnesium losing nephropathy is common with the injectable agents, particularly capreomycin, and can usually be managed with oral supplements.

History and Examination

Urinalysis, blood urea nitrogen serum, creatinine and electrolytes, including magnesium, should be monitored serially in patients with underlying renal disease who are taking ethambutol, cycloserine, an aminoglycoside or capreomycin. Similar studies should be done promptly in any patient who has symptoms consistent with acute or chronic nephritis.

Follow-Up

For information on treatment and follow-up in patients with chronic renal failure, see p. 60.

Hematologic Manifestations

All first-line anti-TB agents can, in rare cases, lead to hematologic abnormalities. Leukopenia can be caused by rifampin, isoniazid, pyrazinamide and rarely, ethambutol. Rifampin is the most common cause of thrombocytopenia, although the other first-line drugs may depress platelets as well. A “flu-like syndrome” has been reported with rifampin, especially when it is used intermittently and has also been seen with rifabutin and rifapentine; it consists of an acute episode with fever, chills and muscle pain that may be associated with severe anemia, thrombocytopenia and leukopenia. Hemolytic syndromes and other types of anemia rarely occur. Eosinophilia is seen with capreomycin and

linezolid can cause pancytopenia and a hemolytic anemia. (See p. 94; p. 105, Table VI-1; and p. 210, Appendix I-B.)

Examination and Follow-Up

If a patient taking anti-TB drugs develops symptoms, signs or laboratory evidence of significant anemia, leukopenia or thrombocytopenia that cannot otherwise be explained, all anti-TB drugs should be discontinued and any non-TB medications that may cause the abnormality should be withheld. The patient should be referred promptly to his/her private physician and to a hematologist for consultation. Blood counts should be allowed to recover with sequential reinstitution of the medications least likely to have caused the hematologic abnormality.

Each medication should be reintroduced on a weekly basis with close follow-up of the CBC and differential. If the medication is absolutely necessary for the patient's regimen and the patient does not have evidence of hemolysis, growth factors, if available, may be used in consultation with a hematologist. In the case of rifampin-induced thrombocytopenia and leukopenia, rifabutin may be tried while following CBC every 1 to 2 weeks.

Visual Manifestations

Ethambutol-induced optic neuritis occurs only rarely, and usually resolves completely when ethambutol is discontinued. However, optic neuritis may progress to severe visual loss if diagnosed late. In general, optic neuritis occurs mostly with elevated serum levels of ethambutol; because the drug is cleared largely by renal excretion, individuals with impaired renal function, especially the elderly, are most susceptible, as are adult patients who receive doses of ethambutol greater than 15 mg/kg body weight per day. Toxic levels of rifabutin may cause uveitis, leading to visual disturbances. Linezolid can also cause optic neuritis.

History and Examination

- The usual symptoms of optic neuritis are loss of visual acuity for small objects (newsprint, sewing, etc.) and/or impairment of red-green color discrimination.
- All patients started on ethambutol should have baseline visual acuity and red-green

color discrimination established at the initiation of therapy.

- All patients at risk for renal disease should have serum blood urea nitrogen and creatinine tested before treatment with ethambutol.
- Ethambutol should be avoided, or used with caution and with frequent monitoring of vision and renal function, in patients with:
 - Renal function abnormalities
 - Risk for renal function abnormalities (e.g., elderly patients and patients with diabetes or hypertension)
 - Patients with preexisting, non-correctable loss of vision
- Patients should be asked about visual changes at each follow-up visit and serial tests of visual acuity and color vision should be performed for early detection of signs of optic neuritis.
- If the patient already has red/green colorblindness at baseline and the use of ethambutol is necessary, the patient should be referred for specialized ophthalmologic evaluation to assess the degree of colorblindness; treatment decisions should be made in conjunction with the ophthalmologist.

Follow-Up

Ethambutol should be discontinued immediately if optic neuritis is suspected and the patient should be referred for ophthalmology consultation if the visual impairment does not reverse promptly. In some patients, visual impairment due to ethambutol may take months to resolve.

Audiovestibular Manifestations

History and Examination

- Patients receiving an aminoglycoside or capreomycin should have a baseline audiogram and a follow-up audiogram during the first and second months of treatment. The audiogram should be repeated every 2 months thereafter or repeated promptly if hearing loss is suspected.
- At each monthly examination, patients receiving an aminoglycoside or capreomycin should be asked about changes in hearing;

most patients will volunteer information about tinnitus or dizziness if these symptoms occur.

Follow-Up

- The aminoglycoside or capreomycin should be discontinued if hearing loss, vertigo or new-onset tinnitus occurs.
 - An ear examination should be done to exclude other sources of these symptoms, such as cerumen or otitis media.
 - An audiogram should be performed and the results compared with the baseline results in order to detect hearing loss.
 - If symptoms or any other evidence of hearing loss is suspected to be unrelated to the aminoglycoside or capreomycin, the patient should be referred to an otolaryngology clinic for consultation.

Restarting Anti-TB Medications

If significant hearing loss, new-onset tinnitus or vertigo is demonstrated and any of these reactions cannot be explained otherwise, the aminoglycoside or capreomycin should be eliminated from the regimen.

Drug Desensitization

Drug desensitization has been tried with most of the first-line agents with varying degrees of success. Rifampin has been the drug most commonly tried. Desensitization is done in a manner similar to penicillin desensitization, with incremental amounts of rifampin given to the patient until a full dose is tolerated. It should only be done in a monitored setting, such as the ICU, after consultation with the Bureau Director or Director of Medical Affairs.

Paradoxical Reactions, Non-HIV-Related

Paradoxical response is defined as the clinical worsening of pre-existing tuberculosis lesions or the development of new lesions after initial clinical improvement on effective antituberculous therapy. Paradoxical response occurs more commonly in patients with HIV coinfection (up to 30% in one series), but also occur in patients who are HIV negative (up to 10%) (see p. 56).

Etiology

The etiology of paradoxical reaction may be related to reversal of the immunosuppression caused by TB disease once antituberculosis therapy has been initiated. The rapid killing of bacilli may cause increased cytokine release, leading to a severe inflammatory response.

Diagnosis

- The diagnosis may only be made after secondary infection, non-compliance with therapy, drug resistance and adverse effects to medication have been excluded.
- In one review of 122 episodes of paradoxical response among patients who are HIV negative, 82% of reactions were associated with extrapulmonary tuberculosis, with a median time from initiation of anti-tuberculous therapy to paradoxical reaction of 60 days. The initial disease site from most common to least common was:

1. Disseminated
2. Central nervous system (CNS)
3. Pulmonary
4. Pleural
5. Lymph node
6. Abdominal
7. Osteoarticular

The paradoxical response occurred in the initial site of infection in 75% of episodes and when the paradoxical response occurred in another anatomical site, the most common site was the CNS (see p. 75).

- In another review among HIV negative patients, 25 (23%) of 109 patients with lymph node TB had paradoxical worsening of disease after a median of 46 days on anti-tuberculous therapy. Episodes lasted a median of 68 days and most patients had cervical lymphadenopathy at diagnosis. Manifestations of paradoxical worsening included expansion of lymphadenopathy or development of new nodes, often pronounced. Some severe cases were associated with sinus tract formation and respiratory compromise.

Treatment

- Many experts advocate the use of corticosteroids in the case of prolonged

or severe paradoxical reactions, although no randomized clinical trials have been done to assess the benefit. If corticosteroids are used, the usual dose is prednisone, 1 mg/kg per day, up to 60 mg/day, gradually tapered over several weeks. Recurrence with tapering is not uncommon.

- Surgical drainage may be indicated in the case of tense, painful lymphadenopathy with impending sinus tract formation. Any drainage should be sent for AFB smear and culture. The patient may need to be on airborne isolation pending the results of the AFB smear.
- The antituberculous regimen rarely needs to be changed once the diagnosis of paradoxical reaction has been established.

Reporting Adverse Events

- All serious adverse reactions to medications in patients followed in the BTBC chest centers must be reported on the DOHMH Reportable Occurrences Form. The form can be accessed

on the intranet at http://healthweb.health.nycnet/pdf/hca/Reportable_Occurrences_Form.pdf.

- The DOHMH Intranet has a detailed document on reportable occurrences at http://healthweb.health.nycnet/pdf/hca/Reportable_Occurrences_Guide.pdf
- A serious adverse reaction is any grade 3 or 4 adverse event that leads to temporary or permanent discontinuation of a drug. Below are general definitions of grades of toxicity. Further details can be found at <http://ctep.cancer.gov/reporting/ctc.html>.
- Any clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 adverse event. The BTBC Director of Medical Affairs and the Quality Assurance Coordinator should be notified and should receive a copy of the Reportable Occurrences Form. The patient should be followed until the adverse reaction is resolved or until transfer to another medical provider or facility has been confirmed.

Grades of Toxicity

GRADE 1 Mild	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required
GRADE 2 Moderate	Mild to moderate limitation in activity — some assistance may be needed; no or minimal medical intervention or therapy required
GRADE 3 Severe	Mark limitation in activity, some assistance usually required; medical intervention or therapy required, hospitalization possible
GRADE 4 Life-threatening	Extreme limitation in activity, significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

Reclassification of Patients Suspected of Having Tuberculosis

All patients initially classified as TB Class V should be reclassified to the appropriate TB class within 4 months of the initiation of evaluation, for example:

- Patients initially classified as TB Class V should be reclassified as TB Class III if they have a positive *M. tb* culture.
- Patients initially designated as TB Class V who do not produce a positive culture for *M. tb* should be reclassified as TB Class III if they meet the following criteria:
 - Resolution of TB symptoms on TB treatment (e.g., cough, fever, sweats, weight loss, chest pains), if initially present, in a time course consistent with TB
 - Improvement of CXR on TB treatment (e.g., improvement or resolution of infiltrates, cavities and effusions) in a time course consistent with TB.

- Patients initially designated as TB Class V (High or Low) who are found to have a negative culture for *M. tb*, should be reclassified as TB Class IV if their CXR is stable after 2 and 4 months of treatment, and is consistent with “old TB.” **A non-TB diagnosis should also be considered.**
- Patients may only be considered Class III when they are classified as “countable” on the Tuberculosis Registry.
- All other TB Class V patients should be given an appropriate International Classification of Tuberculosis based on the test for TB infection result and clinical evaluation.
- In some cases, there may not be enough information to classify patients under the International Classification system; the patient should then be closed out as lost, moved or died, as applicable.

Case Closing and End-of-Treatment Evaluation

- At the end of treatment for pulmonary TB, a sputum culture and a CXR should be obtained.
- A notation should be made in the medical record that the patient has completed treatment and an order should be written indicating that the case should be listed on the TB Registry as completed treatment.
- All patients who complete treatment, except those requiring post-treatment evaluation (see below), should be discharged from the clinic.
- Each patient should be given a document stating that he or she has completed a course of treatment for TB disease.

Post-Treatment Evaluation

- Controlled trials of anti-TB treatment have shown conclusively that the risk of relapse is low in patients with TB susceptible to isoniazid, rifampin and pyrazinamide who complete an optimal treatment regimen. Post-treatment evaluation of patients in this category, therefore, is rarely productive and is not cost-effective. These patients, however, should be advised to return to the chest center for re-evaluation if, in the future, they develop symptoms suggestive of active pulmonary TB

(e.g., fever, night sweats, weight loss, malaise or prolonged cough, with or without sputum).

- Post-treatment evaluation is also not required for most patients who:
 - Have *M. tb* isolates resistant to isoniazid only but susceptible to rifampin, pyrazinamide and ethambutol
 - Have completed 6 months of treatment with all three medications, with or without a fluoroquinolone

Controlled trials have shown low relapse rates for these patients, comparable to rates for patients with isoniazid-susceptible strains.

- Recommendations for the frequency of post-treatment evaluation are summarized on p. 116, Table VI-2.

Candidates and Procedures for Post-Treatment Evaluation

Category 1 and 2 Patients

Certain patients are at greater risk for post-treatment relapse and should be re-evaluated periodically after they complete treatment. Patients in this category include the following:

Category 1. Patients with TB resistant to isoniazid and rifampin, regardless of the regimen used and the duration of treatment.

Category 2. Patients treated with a regimen that did not include rifampin or rifabutin because of resistance or adverse reactions to these drugs.

- Patients in these categories should be scheduled to return for re-evaluation every 4 months for 1 year and at 18 and 24 months. A CXR should be obtained at each visit and compared with the CXR obtained at the end of therapy. At each visit, a single sputum specimen should be obtained for smear and culture. A second appointment is not needed to present the results of the culture, but patients should be told that they will be contacted by telephone if the results are positive.
- If the smear is positive for AFB, the patient should be advised to return for 3 additional sputum specimens. If any specimen is culture positive for *M. tb*, the patient should return promptly for a complete clinical reevaluation and the reinstatement of appropriate therapy.

Table V1-2

Frequency of Post-Treatment Evaluation*

Category of Patient		Frequency of Post-Treatment Evaluation
1	Patients with TB resistant to isoniazid and rifampin (MDRTB)	4, 8, 12, 18 and 24 months**
2	Patients treated without rifampin or rifabutin	4, 8, 12, 18 and 24 months**
3	Selected patients treated with a self-administered regimen whose adherence to therapy is in doubt	At 4, 8 and 12 months**
4	Selected patients who have a history of previous treatment, but who (1) have no details available about the treatment, (2) have negative sputum cultures, (3) have significant changes on CXR consistent with TB, and (4) refuse preventive retreatment	At 4, 8 and 12 months**
5	Selected patients who have no history of previous treatment and who (1) have negative sputum cultures, (2) have significant changes on the CXR consistent with TB, and (3) refuse current treatment	At 4, 8 and 12 months**
6	Selected patients who (1) have a positive test for TB infection (2) have negative sputum cultures (3) have CXR that may be consistent with TB, but also with pulmonary disease other than TB (4) are treated empirically	Refer to general chest clinic if no response to treatment If no referral or patient refuses, re-evaluate with a CXR every 3-4 months for 1 year

Abbreviation: CXR=chest X-ray

* Patients who do not need re-evaluation include those with pan-susceptible TB who complete an optimal regimen and those who have mono-resistance to isoniazid, but who complete 6 to 9 months of treatment with at least rifampin, pyrazinamide and ethambutol.

**Evaluation should include a CXR and the collection of a sputum specimen for AFB smear and culture.

Categories 3, 4, 5 and 6

Patients in the following categories should also receive periodic post-treatment evaluation.

Category 3. Selected patients who were treated with a self-administered regimen and whose adherence to therapy is in doubt.

Category 4. Selected patients who have a history of previous treatment, but who:

- Have no details available about the treatment
- Have negative sputum cultures
- Have significant changes on CXR consistent with TB
- Refuse preventive retreatment

Category 5. Selected patients who have no history of previous treatment and who:

- Have negative sputum cultures
- Have significant changes on CXR consistent with TB
- Refuse current treatment

Patients in categories 3, 4 and 5 should be re-evaluated as described for categories 1 and 2, but only at 4, 8 and 12 months.

Category 6. Category 6 comprises patients who have a positive test for TB infection (TTBI), who have negative sputum cultures for TB and who are treated empirically because a lesion apparent on CXR is believed to be consistent with TB. It is always possible that the lesion is

not the result of TB and is caused by another disease. Lesions are especially important when they appear as a non-calcified spherical lesion, a “segmental” shadow consistent with bronchial obstruction, or enlarged hilar or mediastinal nodes of unknown cause.

In such circumstances, patients who have no clear-cut response to anti-TB therapy should be referred to a general chest center for additional diagnostic evaluation. However, patients who refuse additional investigation should be scheduled for re-evaluation with a CXR at 3- to 4-month intervals for 12 months. If the lesion appears to progress, vigorous efforts should be made to refer the patient to a general chest clinic for additional diagnostic evaluation.

Special Considerations for Patients Who Are HIV Positive

Whenever possible, every patient with TB who is HIV-positive, and who has been treated in a BTBC chest center should be followed concurrently by an appropriate HIV care center; patients who are not attending an HIV care center should be urged to register at one as soon as possible.

After completing TB treatment, patients who are HIV positive should not be routinely followed by the BTBC chest center, unless they belong to one of the above categories 1-5; their care should be provided by an appropriate HIV care center. The basis for this policy is the fact that the occurrence of a respiratory illness in the future is more likely due to disease other than TB. Moreover, BTBC chest centers have limited access to techniques that are generally required for diagnosis in such cases.

When anti-TB treatment is completed, patients who are HIV positive should receive a letter summarizing their treatment in the chest center, to be given to the responsible physician in the HIV care center. The letter should recommend that sputum specimens be obtained for smears and cultures if the patient develops symptoms or signs suggestive of TB, even if the CXR is negative. It should also suggest referral back to the chest center for treatment if evidence of recurrent TB is found.

Patients who are HIV positive and who refuse enrollment in an HIV care center should also receive a summary letter, and they should be advised to report to a general medical clinic or emergency room if they develop symptoms of a recurrent respiratory illness.

Though relapse rates are quite low in HIV-infected persons with drug susceptible TB, most relapses have been associated with development of rifampin resistance. If a HIV-infected person with a history of TB treatment is suspected of having relapse of TB, the person should be assumed to have rifampin resistance, and the treatment regimen should include adequate drugs to appropriately treat rifampin-resistant TB until final susceptibilities become available.

The Use of Isoniazid after Completion of Tuberculosis Treatment

The policy of the BTBC is not to administer anti-TB drugs as prophylaxis after completion of TB treatment. This policy includes patients who are HIV positive. Some patients, however, may need retreatment if there has been new TB exposure (see p. 163 and p. 193).

Key Sources

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Section VII.
Infection Control

Tuberculosis

Section VII.

Infection Control

Guidelines for Hospital Admission and Outpatient Management of Patients with Suspected or Confirmed Tuberculosis

Diagnostic work-up and treatment of TB can be achieved in an outpatient setting for most individuals. Requirements for successful treatment are:

- Administration of correct medications
- Directly observed therapy (DOT) to ensure compliance with medication regimen
- Patient completion of a minimum number of doses considered necessary for cure

The decision to admit a patient to the hospital should include all relevant aspects of care, including costs generated from unnecessary admissions. Some providers believe that treating patients with TB on an outpatient basis leads to increased TB transmission; however, with the advent of modern anti-TB chemotherapy, hospital admission has been shown to be unnecessary for effective treatment.

Since the main determinant of cost in treating TB is hospital stay, outpatient treatment is more cost-effective. Studies have shown that outpatient treatment achieves cure rates comparable to inpatient care, and is not associated with an increase in TB transmission in the community. The risk of transmitting TB to others is related to prolonged exposure to a case with undiagnosed, **untreated**, infectious TB. By the time a case of TB is identified and treatment is started, virtually all transmission to close contacts has already occurred. Also, outpatient treatment is less disruptive for a patient.

Appropriate treatment of sputum acid fast bacilli (AFB) smear-positive cases can render most of

them noninfectious rapidly (generally within 2 weeks) and sometimes in even a few days. The most effective intervention for reducing infectiousness is treatment and providing a mechanism to ensure medication compliance. Therefore, if a patient is being treated and a plan is in place to ensure treatment will continue (i.e., DOT), it is reasonable in most cases to provide outpatient treatment, even if the patient remains sputum AFB smear positive. Patients who are AFB smear/culture positive may be discharged from the hospital as long as certain criteria are met.

The requirements for discharging patients with known or highly suspected multidrug-resistant TB (MDRTB) are more stringent. Since the number of new MDRTB patients in New York City has decreased by over 90% since 1992, there is only a small chance that a patient whose susceptibility results are not yet available upon discharge will have MDRTB.

When to Admit a Patient with Suspected or Confirmed Tuberculosis

Most patients with TB can be diagnosed and treated as outpatients; patients should be admitted to the hospital until they are stable for discharge if they have the following:

- Severe forms of TB, such as:
 - Central nervous system (CNS) and meningeal TB
 - Pericardial TB
 - Disseminated or miliary TB
- Hemodynamic instability
- Severe hemoptysis
- Severe debilitation with weight loss, severe cough, high fevers and inability to care for themselves
- Advanced AIDS
- Comorbid medical conditions that require treatment in the hospital

When **Not** to Admit a Patient with Suspected or Confirmed Tuberculosis

An individual who is clinically stable medically and mentally, and meets **all** of the following 8 criteria should **not** be admitted to the hospital:

1. Has a stable residence at a verified address (form of identification with addresses such as a valid driver's license and state-issued personal ID cards may be used to reasonably verify an address; a phone call to the number given by the patient may also be used to indirectly verify an address). The hospital or clinic provider must verify that the patient lives at the address given.
2. Does not reside in a congregate setting such as a shelter, nursing home or single-room-occupancy hotel.
3. Does not have significant contact with immunosuppressed individuals.
4. Is not actively abusing drugs or alcohol.
5. Is ambulatory and can care for self, and does not need professional home care such as visiting nurse services or a home attendant.
6. Is able to observe risk reduction behaviors such as covering mouth when coughing, and staying at home until no longer infectious according to a physician. The patient should avoid public transportation unless absolutely necessary and should wear a mask in public places.
7. Is competent and willing to follow up with outpatient care (i.e., appointments and necessary tests), and can acknowledge the instructions for follow-up; the patient should be on DOT.
8. If there are children in the home less than 5 years of age and there is an expeditious plan (i.e., to evaluate them by the next business day) for latent TB infection (LTBI) and window period prophylaxis.

If an individual does **not** satisfy **all** of the above criteria, hospital admission may be a reasonable initial approach if the physician is uncertain. Also, if there is going to be a delay in evaluating children in the household or the home situation seems unstable, admission may be advisable until further evaluation. (See p. 123, Figure VII-1.)

Airborne Infection Isolation

Initiating Airborne Infection Isolation

Individuals suspected of having infectious pulmonary or laryngeal TB who are admitted to a hospital should be placed in an airborne infection isolation (AII, formerly called negative pressure or AFB isolation) room which, for new or renovated buildings, has negative air pressure relative to the hall and 12 or more air exchanges per hour, at least 2 of which are outside air. Six or more air exchanges per hour are acceptable for existing structures.

Adults must be placed into an AII room if admitted with **any** of the following:

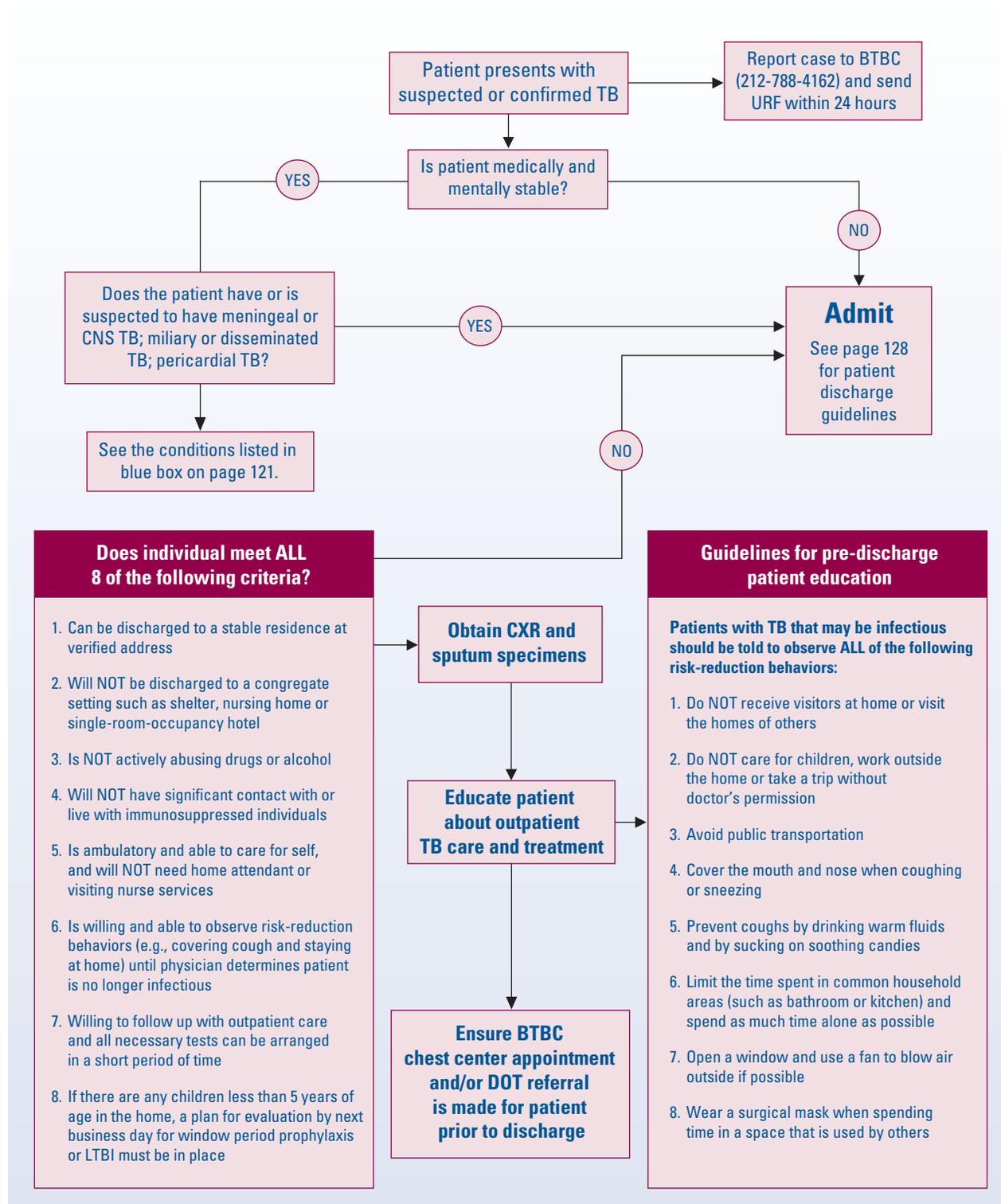
- With or without symptoms of TB and an abnormal chest X-ray (CXR) consistent with TB (i.e., upper lobe infiltrates, miliary pattern, intrathoracic adenopathy, nonresolving infiltrate, pleural effusion; however, almost any parenchymal abnormality that can be seen.)
- Cavitory CXR with or without symptoms
- AFB smear positive from a pulmonary source
- Suspected laryngeal involvement (i.e., hoarseness)
- Extrapulmonary TB with abnormal CXR
- Extrapulmonary TB that includes an open abscess or lesion in which the concentration of organisms is high, especially if drainage is extensive or if aerosolization of drainage fluid is performed
- Extrapulmonary TB with a normal CXR if immunocompromised by disease or treatment (e.g., HIV/AIDS, patients with transplants or patients on chemotherapy, prolonged steroids, TNF-alpha blockers, methotrexate or azathioprine)

Most children with TB are not contagious; however, they must also be placed into an AII room if they display any of the following on admission:

- Cavitory CXR
- AFB smear positive from a pulmonary source
- Suspected laryngeal involvement
- Extensive pulmonary infection
- Congenital TB and undergoing procedures involving oropharyngeal airway

Figure VII-1

Criteria for Admitting Patients with Suspected or Confirmed Tuberculosis to the Hospital



Abbreviations: CNS = central nervous system, CXR = Chest X-ray, TB = tuberculosis, URF = Universal Reporting Form

Plans must immediately be implemented to facilitate eventual outpatient care and follow-up. The DOHMH must be notified of this patient and participate in the discharge planning, ideally early in the patient's hospital stay. Individuals do not necessarily have to be sputum AFB smear negative to be released from the hospital and there is no minimum number of days for treatment prior to discharge if discharge is to an appropriate setting.

If arrangements can be made for outpatient follow-up, the patient may be discharged to home if the 8 criteria on p. 122 are met. The patient should be discharged on home isolation on DOT (see p. 129.) If a patient was admitted over the weekend, she/he should remain hospitalized until plans can be made for follow-up and discharge to an appropriate clinic and DOT.

Discharge from Airborne Infection Isolation

Patients in AII may be transferred to a non-isolation hospital bed or may be discharged from the hospital directly. Because other hospitalized individuals may be especially vulnerable to TB infection, the criteria for transferring patients who are smear positive from isolation to a non-isolation room may be more restrictive than the criteria for discharging smear-positive patients from the hospital (e.g., an individual must be smear negative to be considered for transfer from isolation, but not necessarily for discharge from the hospital).

Transfer to a Nonairborne Isolation Area

If a hospitalized patient has a diagnosis other than TB, and symptoms inconsistent with TB, airborne precautions may be discontinued after collecting 3 negative AFB sputum smear results.

If the patient is suspected to have, or is confirmed to have TB, transfer from airborne isolation to a non-isolation area may be considered when the patient demonstrates both bacteriologic and clinical evidence of response to TB treatment and meets **all 3** of the following criteria:

- Resolution of fever and resolution, or near resolution, of cough

- Is on an appropriate anti-TB regimen to which the strain is known or likely to be susceptible; if the patient is confirmed to have TB, she/he should be on standard multidrug anti-TB treatment for a minimum of 2 weeks.
- Three consecutive negative AFB smears from sputum specimens collected over 48 to 72 hours with at least 1 specimen collected in the early morning. Respiratory secretions pool overnight; this method allows patients with negative sputum smear results to be released from airborne precautions in 2 days.

Patients who have drug-susceptible TB of the lung, airway or larynx who are on standard multidrug anti-TB treatment and have substantial clinical and bacteriologic response to therapy are probably no longer infectious. However, because culture and drug-susceptibility results are not usually known when deciding to discontinue airborne precautions, all patients with suspected TB should remain under such precautions until the above preconditions are met.

The decision to transfer a patient from an AII to a non-AII room must be made by the hospital staff; the patient may be transferred to a single non-isolation room or a multiple-bed room with other smear-negative patients whose TB strain has the same drug resistance pattern. Patients transferred to a non-AII room should have a sputum specimen collected for AFB smear every 1 to 2 weeks during their hospitalization.

If possible, patients suspected of having or known to have MDRTB should remain in an AII room throughout their hospitalization if status is smear and/or culture positive.

Patients with pan-sensitive TB who are hospitalized for reasons unrelated to TB should be isolated until their infectiousness has been assessed. If the patient was sputum smear negative as an outpatient, anti-TB therapy can be continued, and the patient does not need to be isolated.

Patients who are unable to take TB medications for a prolonged period of time should be placed on AII. Sputum smears for AFB should be obtained to assess infectiousness.

Influence of Nucleic Acid Amplification on Airborne Infection Isolation

AFB smear-negative hospitalized patient with positive nucleic acid amplification (NAA) test or *M. tb* culture from a respiratory source

Patients admitted to the hospital for suspected TB who are not yet on treatment may have negative AFB smear results and positive NAA test results. This finding is consistent with a diagnosis of *M. tb*, and culture results are expected to be positive. It is recommended by the Bureau of Tuberculosis Control (BTBC) that the individual remain in airborne isolation until **both** of the following criteria are met:

- There has been clinical improvement (resolution of fever and resolution or near resolution of cough).
- The individual has been on an anti-TB treatment regimen for at least 2 weeks.

Patients may and should be discharged to home before 2 weeks of treatment are completed if appropriate criteria are met as listed in next column, and if the individual is not going to be discharged to one of the congregate settings listed on p. 129, in which case culture conversion is required.

The above recommendations also apply to patients who are AFB smear negative but *M. tb* culture positive from a respiratory source.

AFB smear-positive hospitalized patient with negative NAA test

Many patients may be colonized with, or have disease due to, non-TB mycobacterium (NTM) also known as mycobacterium other than tuberculosis (MOTT). This decision needs to be made by the provider. In such situations, if the patient is still suspected of having TB and is being treated for the disease, the same guidelines should be followed as for TB patients who are AFB smear positive.

Positive NAA test after the patient has been on treatment

If the patient has received treatment for TB for more than 7 days, there is no reason to repeat the NAA test if it was initially positive or do an NAA test if one had not been done already. The reliability of a positive NAA in this situation is not known. If the patient has completed a

course of treatment in the past, the reliability of a positive NAA in this situation is also not known.

If the patient is on treatment for more than 7 days and an NAA test is subsequently done which is positive, there is no need for isolation provided the patient has been on adequate therapy and is clinically improving.

Guidelines for Returning Suspected or Known Tuberculosis Patients to Home

Patients Who Can be Discharged from the Hospital

The following criteria are recommendations of the New York City BTBC; the New York State Department of Health has the responsibility and the authority for regulating hospitals. The decision to discharge an individual who is sputum AFB smear positive from the hospital must be made by the hospital staff in consultation with the BTBC. The patient should not be discharged unless the provider has been in contact with BTBC staff to discuss discharge planning and referral for DOT.

There is no minimum number of days of anti-TB treatment required before a patient may be discharged from the hospital. Patients who are sputum AFB smear positive (including those who are still symptomatic) who are not suspected of having MDRTB and who are well enough to be discharged from the hospital, may be discharged if they meet **all** of the following criteria:

- Currently treated with an appropriate anti-TB regimen to which the strain is known or likely to be susceptible
- Show clinical improvement (i.e., improvement of fever and resolution or near resolution of cough)
- Agree to DOT and this has been arranged in conjunction with NYC DOHMH or a New York State designated DOT program
- An appropriate treatment regimen has been devised, initiated and tolerated.

- Suitable arrangements have been made for the treatment regimen to be continued and properly monitored on an outpatient basis, specifically by DOT.
- Patient agrees to home isolation while still infectious and signs home isolation agreement.
- All 8 of the criteria listed on p. 128 are met.

In compliance with New York State Sanitary Code, Part 2, Section 2.6, the patient and family members should be given written instructions to follow in order to reduce the risk of TB transmission. These instructions are available in several languages at <http://healthweb.health.nycnet/pdf/tb/cpm/tb-cpm-protocol-1.04.pdf>. (See pp. 245, 246, Appendices III-E and III-F.)

Patients Who Should not be Discharged from the Hospital while Still AFB Smear Positive or Moved to a Nonairborne Isolation Room

An individual who is sputum AFB smear positive should not be directly discharged from the hospital to any of the following:

- A congregate living site (e.g., shelter, single-room-occupancy hotel, nursing home, jail, prison, group home, another hospital, etc.)
- A living situation where infants and young children also reside if those children have not been placed on a suitable window period prophylaxis or treatment for LTBI, or there is not an expeditious plan to have them evaluated (less than 1 business day)
- A living situation where immunosuppressed persons (e.g., persons who are HIV infected, persons receiving cancer chemotherapy) also reside if these persons have not been placed on a window period prophylaxis or treatment for LTBI, or there is not an expeditious plan to have them evaluated (less than 1 business day)
- A living situation where home health aides or other social service providers will be present in the home for several hours a day to care for the person or a family member

These patients should be on 2 weeks of standard antituberculosis treatment, clinically improving, and demonstrate sputum AFB smear conversion before they can be discharged from the hospital.

In situations in which an individual will have visitors in the home, refuses to wear a mask or cover his/her mouth when coughing, and/or is less likely to adhere to an anti-TB treatment regimen because of drug or alcohol addiction, it may be prudent to be more conservative and keep the patient in the hospital until sputum is AFB smear negative.

The individual may be transferred to another facility while still sputum AFB smear positive, as long as it is to an AII room. The individual should be transported with appropriate respiratory precautions.

Even after 2 to 3 months of treatment, some patients with advanced pulmonary TB and initially positive smears and cultures may continue to excrete what are believed to be dead mycobacteria. Thus, sputum specimens from these patients may be persistently AFB smear positive and yet culture negative. After discharge from the hospital, these patients should have monthly sputum smears and cultures in order to document the persistence of negative cultures and, ultimately, the appearance of a negative smear.

Discharge of an AFB Smear-Negative Individual Directly from the Hospital (Suspected Non-MDRTB)

Patients with AFB smear-negative pulmonary TB can be discharged to home anytime once clinically stable. However, such suspected and confirmed TB patients should not be discharged to a congregate setting such as a nursing home or a shelter until **both** of the following criteria are met:

- There has been clinical improvement (resolution of fever and resolution or near resolution of cough).
- The individual has been on an anti-TB treatment regimen for at least 2 weeks.

Discharge of an Individual with Known or Suspected MDRTB

For an individual with known or suspected MDRTB, the patient should remain hospitalized in airborne isolation until **all** of the following criteria are met:

- Three consecutive sputum smears are AFB negative taken over at least 48 to 72 hours with at least 1 specimen collected in the early morning.
- Current treatment with an appropriate anti-TB regimen to which the strain is known or likely to be susceptible is started and tolerated.
- There is clinical improvement (lowering of fever and resolution or near resolution of cough).
- The patient agrees to DOT and it has been arranged in conjunction with NYC DOHMH or a New York State-designated DOT program.
- Suitable arrangements have been made for the treatment regimen to be continued and properly monitored on an outpatient basis, specifically by DOT.
- The patient agrees to home isolation while still infectious and signs the home isolation agreement.
- All 8 of the criteria listed on p. 128, Figure VII-2 are met.

These patients may be discharged to home if sputum is AFB smear positive using the same guidelines as on p. 125. The BTBC must evaluate the home so that contacts have been evaluated, and on treatment and environmental controls may be instituted.

If the patient is going to a congregate setting, then AFB culture conversion must be documented; (see p. 129).

Guidelines for Returning Patients to Work, School or Other Congregate Settings

Determining when an individual with TB (class III) or suspected TB (class V) can safely return to work or school is made after reviewing the following:

- Evaluation of the individual with TB (e.g., whether the individual has followed instructions, especially adherence to the anti-TB regimen)

- Characteristics of TB itself (MDR vs. drug-susceptible TB, respiratory AFB smear positive vs. smear negative, cavitary vs. non-cavitary, pulmonary vs. extrapulmonary)
- The work or school environment to which the person will be returning (outdoor work, congregate setting)
- The characteristics of those who may be exposed (i.e., immunocompromised or on chemotherapy)

Sputum AFB Smear-Positive Patients Known or Likely to Have Drug-Susceptible Tuberculosis

Most Class III or Class V (High) patients known or likely to have drug-susceptible pulmonary TB may be considered for return to work (but not school) if they meet **all 3** of the following criteria:

- There is clinical improvement (i.e., improvement of fever and the resolution, or near resolution, of cough).
- Evidence that the number of AFB on consecutive sputum smears taken on different days is consistently decreasing (e.g., from 3+ to rare over 2 weeks).
- Current treatment for 2 weeks with an anti-TB regimen to which the strain is known to be susceptible.
- The worksite or congregate setting to which they are returning is appropriate; patients who work alone or outdoors may return earlier.

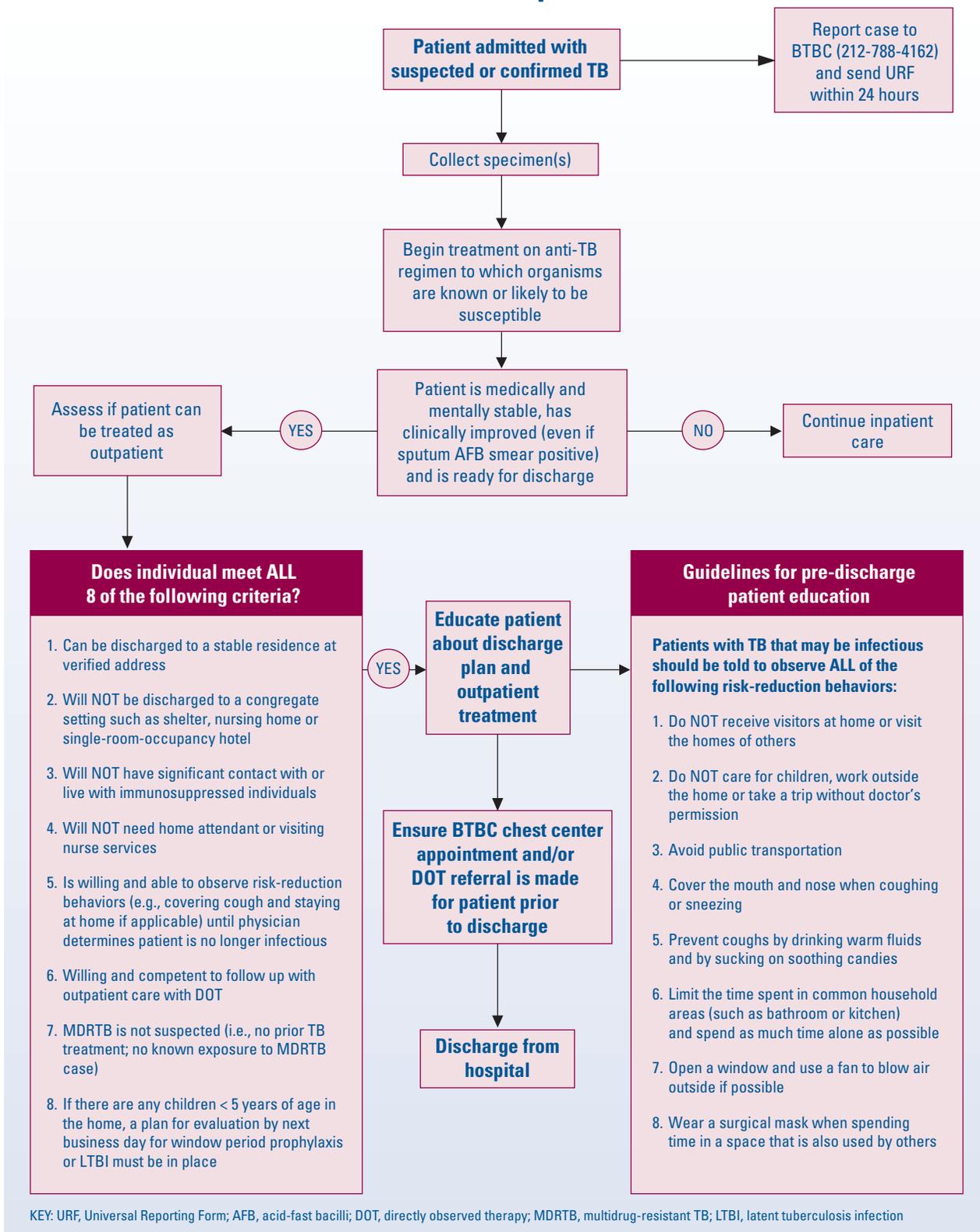
Sputum AFB Smear-Negative Patients Known or Likely to Have Drug-Susceptible Tuberculosis

Individuals with suspected or confirmed AFB smear negative pulmonary TB may return to work or school if **both** of the following criteria are met:

- There has been clinical improvement (i.e., resolution of fever and resolution or near resolution of cough)
- The individual has been on an anti-TB treatment regimen for at least 2 weeks

Figure VII-2

Criteria for Discharging Patients with Suspected or Confirmed Tuberculosis from the Hospital



The following is a list of work sites where individuals with drug-susceptible and drug-resistant TB should be excluded until culture conversion is confirmed:

- Settings where patients who are HIV positive or other immunocompromised patients are present
- Neonatal intensive care units
- Patient care areas
- Nursing homes
- Day care or any setting where there are young children under 5 years of age.

Patients Known or Likely to Have Multidrug-Resistant Tuberculosis

For a known or suspected case of pulmonary MDRTB, the patient should be kept from returning to work or school, and from living or having contact with immunocompromised persons, or transferring to another congregate setting such as a shelter or nursing home until culture conversion is confirmed (i.e., 2 consecutive negative cultures at least 2 weeks apart). Culture conversion is necessary unless the patient will be transferred to a negative pressure isolation room in the congregate setting. (See paragraph above.)

However, exceptions can be made for certain types of work settings. This should be decided in consultation with BTBC Office of Medical Affairs staff.

Home Isolation

The patient who is at home while still sputum AFB smear positive should be on home isolation until at least 2 weeks of treatment are completed, and there is clinical improvement and decrease in AFB on smear. Criteria for return to work or school may be more stringent than the criteria for discontinuation of home isolation. However, for MDRTB patients, home isolation is usually prolonged until culture conversion.

The purpose of home isolation is to provide an alternative to voluntary or compulsory hospitalization (while continuing to prevent transmission of the disease) for patients who remain infectious after appropriate treatment measures have been implemented. Such patients should also be on home DOT until no

longer infectious. Patients should wear a mask when going for medical visits. Exceptions can be made for patients to receive clinic-based DOT while infectious if they use private transportation and wear a mask while in public. Patients pre-discharge information should include education about home isolation. (See p. 128, Figure VII-2.) They should also sign a "Home Isolation Patient Agreement;" a copy should be given to the patient and a copy placed in the patient's medical record. (See p. 246, Appendix III-G.)

For patients who remain infectious for prolonged periods of time, the BTBC can make arrangements to have environmental controls installed in their home. This is particularly useful for patients with MDRTB who may remain infectious for very long periods of time and for whom isolation is often necessary until culture conversion is documented. Environmental controls make the home safer for individuals living with the patient as well as for staff administering DOT.

In order to be on home isolation with a high-efficiency particulate air (HEPA) filter, the following requirements must be met:

- Patient is capable of self-care and does not require hospitalization for other medical condition(s).
- Patient is cooperative and willing to follow infection control practices.
- Patient is not sharing living quarters with immunocompromised persons or children who are negative for TB infection as determined by a tuberculin skin test (TST) or blood-based test for TB infection (TTBI). In this setting, a plan for close follow-up of these individuals must be in place.
- Environmental assessment by the BTBC environmental consultant should indicate that effective isolation would be feasible in the home.
- Patient agrees to DOT in the home while infectious.
- Patient should agree to sign the "Home Isolation Patient Agreement" and to adhere to the conditions of the Agreement.

Adhering to the preceding guidelines will ensure that patients do not remain hospitalized unnecessarily and that members of the public are protected from TB infection.

Infection Control Issues in Pregnancy and the Peripartum Period

Pregnant Women with Latent Tuberculosis Infection

A pregnant woman with risk factors for TB infection should receive a TTBI (either a TST or a blood-based test during pregnancy. See p. 173 and p. 189 for risk factors, determination of a positive result and treatment for LTBI). A pregnant woman with a positive TTBI should have a physical exam and CXR to rule out active TB. For most pregnant women, the CXR can be done with lead shielding after the first trimester to minimize radiation exposure to the fetus **except** in patients who are HIV positive, close contacts of an active TB case or immunocompromised. Treatment of LTBI should be per BTBC policy (see p. 189).

If the medical evaluation and CXR are normal, separation of the mother and the infant at delivery is not indicated since latent TB is not infectious. If there is a contagious family member, that person should be separated until noninfectious from both mother and baby.

Pregnant women with positive TTBI and abnormal CXR not consistent with TB. Chances are low that the mother will transmit tuberculosis to her infant; separation at delivery is not necessary. The mother should be assessed for treatment for LTBI and, if appropriate, given treatment (see p. 193).

Pregnant women with positive TTBI and no CXR during pregnancy. The mother should undergo CXR as soon as she is admitted for delivery; portable CXR is acceptable.

- If CXR is normal, separation of the infant from the mother is not indicated
- If CXR is abnormal and consistent with TB, the mother should deliver the baby under airborne

precautions and immediately postpartum be separated from the infant and undergo evaluation for active TB; the infant should simultaneously undergo evaluation for congenital TB. (See p. 38.)

Pregnant women with positive TTBI and no CXR prior to delivery. The mother should be separated from the infant after delivery and CXR obtained immediately. Airborne precautions should be taken if possible during the delivery and until CXR result is available; at minimum the mother should wear a mask during delivery.

- If CXR is normal, she may be reunited with the baby.
- If CXR is abnormal and consistent with TB, the mother should be separated from the infant and undergo evaluation for active TB; the infant should simultaneously undergo evaluation for congenital TB. (See p. 38.)

Pregnant woman with active TB. If a pregnant woman is being treated for TB during pregnancy and has been compliant with therapy, infectiousness should be assessed at the time of delivery. If the mother was confirmed culture-negative for at least 1 month prior to delivery, there is little risk of infection to the newborn. Three sputa should be analyzed for AFB if culture conversion is not documented or the patient was nonadherent. Specimens should be collected over 48 to 72 hours in the last 2 weeks before delivery. If the mother is not infectious, the infant does not need to be separated from her; however, if the mother is taking rifampin, prophylactic vitamin K is recommended in the infant (there may be an association between rifampin and hemorrhagic disease in newborns).

Pregnant women suspected of having not adequately treated TB at the time of delivery, or who are on treatment but still infectious. Separation of the newborn from the mother may be necessary until the mother is noninfectious (i.e., after at least 3 consecutive negative sputum smears over 48-72 hours). The relative risks vs. benefits of this separation are disputed, but the baby should sleep in a separate room until the mother is noninfectious; the mother should wear a mask when with the baby.

All family members of a mother with active TB should themselves be assessed for active TB before being allowed contact with the infant (including visiting the baby in the hospital). If active untreated TB is found in a family member, that person, until noninfectious, should have no contact with the newborn.

Infection Control in Chest Centers

Triage

All individuals entering a BTBC chest center for diagnostic evaluation or clinical services should be rapidly assessed for the likelihood that they may have infectious TB. As part of this assessment, staff should:

- Evaluate the individual for signs and symptoms of infectious TB as soon as he or she enters the chest center.
- Search for the individual's name (and unique identifiers) on the TB Registry (initial visit only).

For infection control purposes, it is important to determine whether the patient has had previous incomplete treatment for TB. Individuals who have been incompletely treated for TB in the past should be suspected of having infectious TB, pending clinical evaluation. Infection control measures should be considered even if the patient does not appear to be symptomatic.

All individuals identified as likely to be infectious must be seen by a physician as quickly as possible. If a physician cannot see the person immediately, the person must be temporarily isolated from others until he or she is seen.

Temporary Isolation

All individuals identified as possibly infectious must be separated from others while awaiting clinical and diagnostic evaluation or referral. A designated isolation room or a sputum induction room or booth (when not in use) is the most appropriate area for temporarily isolating patients awaiting services.

- Staff should carefully explain to isolated patients the reason for their separation.

Masks and Particulate Respirators

Any individual who is coughing should be provided with a mask and instructed to wear it for the duration of the chest center visit. Also, individuals who have been identified as being likely to be infectious by reason of history, the TB registry or reported symptoms should be given a mask and instructed to wear it, regardless of whether or not they are coughing.

- Most masks are acceptable, except those with an escape valve (e.g., type 3M9970).
- Staff should explain to the patient the reason for wearing the mask.
- To reduce patient discomfort, every effort must be made to limit the amount of time a patient is required to spend in the chest center while wearing a mask.
- Patients who cannot tolerate a mask should be provided with tissues and instructed to cover mouth when coughing. All staff must keep a supply of paper tissues readily available in their work areas.
- Staff should strongly encourage patients to wash their hands after coughing.
- Signs instructing anyone who is coughing to cover his/her mouth should be prominently displayed in all chest center areas.

Physicians and others in contact with a potentially infectious patient should consider the following:

- If the patient suspected of being infectious is seen in a consultation room, the patient should be instructed to wear a mask (staff does not need to wear a particulate respirator while attending a patient who is wearing a mask). However, if the patient cannot tolerate the mask during the examination, the patient should be seen only in an isolation room or a sputum induction booth. Staff attending to a patient in an isolation room or sputum induction booth must use appropriate respiratory protection (e.g., respirator type N95).
- Staff member(s) who have reason to believe that air in a room is contaminated with *M. tb* should wear an appropriate particulate respirator.
- After use by a potentially infectious patient, an isolation room or sputum induction booth should not be used for a certain amount of time (see p. 134). A sign should be posted on the door indicating the time after which the room or booth can be reused.

- Individuals who are temporarily isolated should be instructed to keep their masks on if possible; individuals who cannot tolerate a mask should be provided with tissues and instructed to cover their mouths when coughing.
- Staff attending to a patient who is isolated in the sputum induction room must wear appropriate respiratory protection.
- While a patient is isolated in the sputum induction room, staff should obtain a sputum specimen.
- Clinic staff should frequently check on patients who are being temporarily isolated to ensure these patients are comfortable and compliant with isolation protocols.

Sputum Induction

Sputum induction is a procedure for obtaining sputum from patients who have difficulty producing it spontaneously. In this procedure, patients inhale a mist of nebulized, sterile water (many facilities use hypertonic saline) which irritates their airways, causing them to cough and produce respiratory secretions.

Staff Involved in Sputum Induction

Sputum induction must be ordered by a physician and supervised by a trained staff member.

Equipment

The following equipment is required for sputum induction:

- A room, booth or enclosed area that meets environmental control standards for high-risk procedures, including:
 - Negative pressure relative to other areas (air flow must be from the corridor into the sputum induction room or booth; from there it should be exhausted to the outside or appropriately filtered and safely discharged)
 - 12 or more complete air exchanges per hour
 - For rooms, ultraviolet germicidal irradiation (UVGI)
- Nebulizer and table to support nebulizer
- Disposable tubing with cup and lid
- Sterile sputum collection jar, properly labeled
- Bacteriology slips (TN50)
- Clear plastic biohazard specimen bag and paper bag
- Paper tissues and bag for disposal of tissues
- Sterile water
- Solution of 10% bleach, 90% water
- Disposable gloves
- Refrigerator
- Disposal bags for biohazardous waste
- Disposable drinking cups
- Chair for ambulatory patients

Preparing Equipment and the Sputum Induction Room

Equipment and room should be prepared as follows:

- Assemble and organize the following equipment in quantities sufficient for the anticipated number of patients to be seen that day:
 - Sputum jars
 - Plastic biohazard bags and brown paper bags
 - Disposable plastic nebulizer tubing with cup and lid
 - Sterile water
 - 10% bleach solution, mixed at the start of the shift in an amount sufficient for that shift only
 - Disposable drinking cups
- Check that the ultraviolet light and exhaust fan are on and are functional
- Prepare the nebulizer as follows:
 - Inspect it for cleanliness.
 - If necessary, wipe the nebulizer surfaces with 10% bleach solution.
 - Place sterile water in the nebulizer chamber to the level marked on the chamber.
 - Place a small amount of sterile water in the cup portion of the disposable nebulizer tubing.
 - Insert the cup into the nebulizer.

- Test to make sure the nebulizer is functional by turning it on and checking to see whether it produces a mist.
- Before beginning sputum induction:
 - Label the sputum jar in pencil with the patient's name and address, and the date. Place the completed bacteriology form (TN50) in the lab slip pocket of a biohazard bag with the patient's name facing out. Include the TB Registry number of patients with suspected or confirmed TB on the bacteriology form.

Preparing the Patient

The nurse, public health advisor or public health assistant should prepare the patient for sputum induction by:

- Explaining the purpose of the procedure
- Orienting patients to the nebulizer and demonstrating how it functions; reassure patients that the equipment is clean
- Showing the sputum jar and instructing patients not to open the jar until ready to expectorate into it and telling them to close the jar tightly as soon as the specimen is collected
- Providing water in a disposable cup and explaining that drinking it will help with the procedure
- Explaining not to begin the sputum induction procedure until the staff member has left the room and the door is firmly closed
- Telling patients to:
 - Inhale the aerosol by taking 3 or 4 deep, slow breaths through the mouth without placing his/her mouth on the tubing (the patient is not to demonstrate deep breathing during the instruction).
 - Cough vigorously if they do not cough spontaneously in response to the mist. Ask them to cover their mouth with a tissue when coughing unless expectorating into the sputum jar.
 - Continue trying to cough and to expectorate after inhaling the mist.

- Expectorate all sputum into the sputum jar, without spilling it outside the jar.
- Cover the jar tightly after collecting about 1 tablespoon of sputum.
- Place sputum specimens in the biohazard bag, then the brown paper bag, and give the plastic to the chest center staff.
- Stay in the sputum induction room, remaining in the anteroom until coughing has completely stopped.
- Shut the door after leaving the sputum induction room.

Role of Chest Center Staff during the Induction Procedure

Staff must remain near, but not inside, the sputum induction room during the procedure in order to be available to assist patients if necessary and to ensure that patients remain in the sputum induction room until coughing has stopped.

If a staff member must enter the sputum induction room during the procedure, a properly fitted, National Institute for Occupational Health and Safety (NIOSH)-approved HEPA respirator (e.g., respirator type N95) must be worn.

Handling of Specimen

While in the sputum induction room or booth, patients should place the sputum jar in the ziploc section of the biohazard bag and put the biohazard bag in a brown paper bag. The patient should give the brown paper bag to chest center staff, who should place the bag in the refrigerator until it is delivered to the laboratory.

Care of Equipment and Area Between Uses

The equipment and sputum induction room should be cleaned and restored as follows:

- Before re-entering the sputum induction room, make sure that the door to the room remains closed for the specific amount of time listed in the Box below.

Clinic	Time Door Should Remain Closed
Bedford:	9 minutes
Bushwick:	9 minutes
Chelsea:	13 minutes
Corona:	11 minutes
Fort Greene:	9 minutes
Jamaica:	20-21 minutes
Morrisania:	11 minutes
Richmond:	17 minutes
Washington Hts.:	13 minutes
30th St. Shelter:	9 minutes

These clearance times are calculated for 99% clearance of the sputum induction booth/room with the door closed and the Isol-Aide unit functioning at low fan speed, 150 cubic feet per minute (CFM).

The above clearance times are subject to change based on renovation in the chest center and other factors. Current clearance times are posted in each center.

Clearance times are calculated as follows:

- Determine the cubic volume of the chamber:
cubic volume = length x width x height
- Calculate air changes per hour (ACH):
 $ACH = (CFM \times 60) / \text{cubic volume}$
- Determine air mixing factor: Isol-Aide sputum induction booths/rooms have an effective mixing factor of 1.81 as determined by the manufacturer.
- Extrapolate clearance time from Centers for Disease Control and Prevention's "Guidelines for Preventing the Transmission of Mycobacterium Tuberculosis in Health-Care Facilities, 2005" Table II, available at www.cdc.gov/MMWR/PDF/rr/rr5417.pdf.

- Put on a properly fitted, NIOSH-approved HEPA particulate respirator and disposable gloves before entering the sputum induction room. Do not remove the respirator until after leaving the room. Close the door after entering the sputum induction room.
- Remove the nebulizer tubing with cup and lid and discard it into the disposal bag for biohazardous waste.
- Wipe the nebulizer and table surfaces with a 10% bleach solution and discard any litter in the treatment area.
- Remove gloves, wash hands and prepare the equipment for the next patient.

Care of Room and Nebulizer at the End of the Day

At the end of the day, the nebulizer and the sputum induction room should be restored as follows:

- Before entering the sputum induction room, wait at least 10 minutes after the last patient leaves.
- Put on disposable gloves and a properly fitted, NIOSH-approved particulate respirator prior to entering. Close the door after entering.
- Remove and discard the nebulizer tubing with cup and lid.
- Empty the nebulizer chamber.
- Clean the nebulizer chamber and all exposed surfaces with a 10% bleach solution and wipe the chamber dry.
- Discard the bleach solution.
- Remove and discard the disposable gloves and wash hands.
- Leave the ultraviolet light and the fan on.
- Remove the personal respirator after leaving the room.

Documentation

Document all relevant information in the log book.

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Tuberculosis

Section VIII.

Case Management of
Suspected Cases and
Patients with Tuberculosis
in the Field and Clinic

Section VIII.

Case Management of Suspected Cases and Patients with Tuberculosis in the Field and Clinic

Initial Case Management

In TB control, case management is the system by which an individual (case manager) or a group working together (case management team) has responsibility for the care of a patient. A case management assignment is made as soon as the patient is reported to the program. (See p. 140, Figure VIII-1.)

Objectives of Case Management

The objectives of TB case management are to:

- Render the patient noninfectious by ensuring an adequate course of treatment.
- Provide early intervention to promote continuity of care and treatment adherence.
- Prevent the development of resistant organisms.
- Identify and address other urgent health needs of the patient.
- Identify and remove barriers to adherence to a treatment regime.
- Prevent TB transmission by conducting timely and effective contact investigation.

Case management should begin as soon as a patient suspected of having TB is identified and reported to the local health department. It should not end until the patient completes treatment and is discharged from the clinic. The case manager conducts regular reviews of patient progress and makes plans to address any barriers to treatment adherence, follow-up appointments or referrals, and anticipates problems and plans interventions before problems occur.

Collecting information directly from the patient, the medical record and other sources is crucial to successful case management since appropriate treatment decisions cannot be made without this information. It is imperative that the case manager have as much information (both medical and social) about the patient as possible; information is also essential to deal with problems when they arise.

The Initial Interview

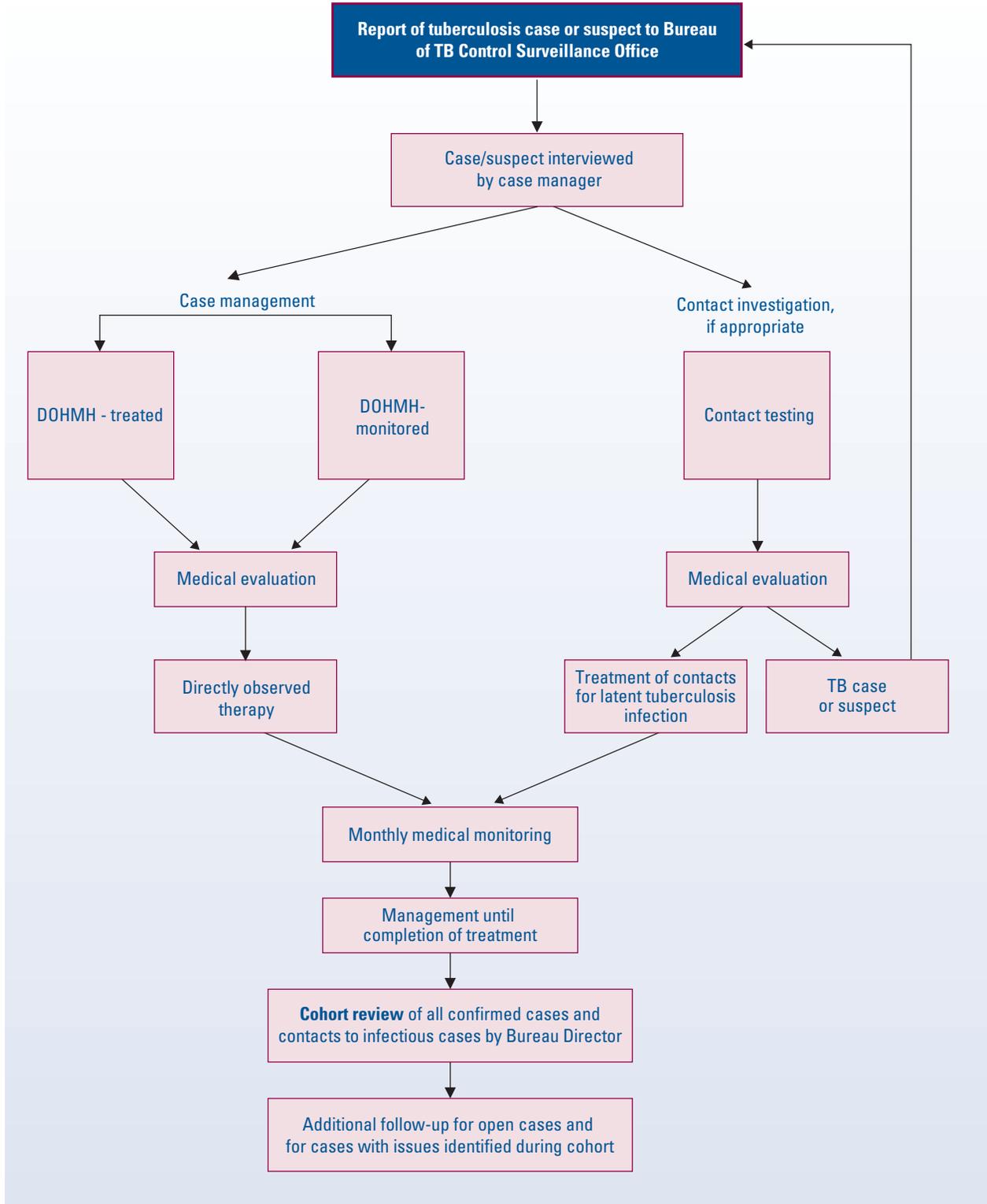
The case manager's initial interview with every patient who has suspected or confirmed TB should involve collecting as much information as possible. See Box on p. 141 for specifics about the initial interview.

Ensuring Effective Case Management

Lack of effective supervision leads to marginal case management and hinders achieving TB control. There must be a systematic review of each case manager's activities and workload. At each review session, follow-up of outstanding issues must be addressed by a supervisor, including identifying barriers to patient adherence and plans must be implemented to counter those barriers. Supervisory reviews should also serve to answer a case manager's questions and address concerns.

Figure VIII-1

Case Management Flow Chart



Abbreviations: DOHMH = Department of Health and Mental Hygiene; TB = tuberculosis

VIII. CASE MANAGEMENT OF SUSPECTED CASES AND PATIENTS WITH TUBERCULOSIS IN THE FIELD AND CLINIC

Case Manager Initial Interview Topics

1. **Educate the patient about TB**, debunking any misconceptions about the disease. The case manager should determine the most appropriate educational intervention and provide appropriate literature. The educational content should include information about:
 - TB transmission and pathogenesis
 - Preventing TB
 - Distinguishing infection from disease
 - How drug resistance develops
 - Length of treatment needed for sensitive vs. drug-resistant TB
 - Standard TB medications, including names, dosages, actions and side effects
 - Directly Observed Therapy (DOT) program and free Department of Health and Mental Hygiene (DOHMH) services for TB
 - How to open prescription packaging and take medication
2. **Establish long-term plans for treatment** (in cases in which the patient will receive treatment/DOT).
3. **Determine whether the patient will stay in NYC** during TB treatment.
4. **Inquire about contacts** and emphasize to the patient why it is important that contacts be identified and evaluated **as soon as possible**.
5. **Establish a trusting relationship**, as this determines how well the patient views the role of the case manager and the health care establishment.
6. **Obtain and document locating information** and agree with the patient on a mode of communication (e.g., beeper, cell phone, home/work number, significant other). Identify who will always know where to find the patient.
7. **Assess understanding of TB** on the part of the family and identified contacts.
8. **Assess social needs** such as access to social services to resolve issues with child care, housing, employment, substance abuse and (if appropriate) legal or immigration issues (tell the patient that all services are provided irrespective of immigration status).
9. **If the patient is diagnosed with TB while in a hospital**, plans for follow-up care upon discharge must be initiated at the outset, and not on the day before discharge. These plans must address issues that will ensure adherence with the treatment regimen.

Case management meetings should be held regularly (once a week is ideal). These meetings must be attended by the physicians overseeing the patient's medical care, the case managers, individuals involved in the supervision of the case manager, individuals involved in contact investigation and others as necessary. Issues to be addressed by the case management team include:

- Mental, emotional and cognitive status (via referral to a social worker)
- Access to transportation
- Usual places of residence, where and how to locate the patient, impending plans to relocate or travel, housing needs and living situation
- Cultural and religious beliefs that may impact adherence
- Language and literacy barriers
- Substance abuse
- Ability to pay for medical care
- Work history/income source
- Support system
- Family dynamics

Ensuring Adherence

Improving adherence to treatment is one important goal of a patient-centered case management strategy—many patients lose the incentive to continue treatment when they start to feel well. Case managers and clinicians should continue to educate the patient about the importance of continuing to take medication longer than the patient thinks is necessary. This message should be restated throughout treatment, even if the patient has not explicitly questioned the need to continue taking medications. The case management team should obtain and document information that may indicate the patient's potential for non-adherence, and address barriers on an ongoing basis. See the Box that follows for information on nonadherence.

Patients should be educated about the causes and effects of TB, the dosing and possible adverse reactions of their medication, and the importance of taking their medication according to the treatment plan. To facilitate adherence, the

plan should use short-course treatment regimens and, for patients whose therapy is not directly observed, fixed-dose combination tablets. A welcoming and respectful atmosphere within the clinic setting is vital to encouraging adherence.

Common Problems with, and Early Indicators of, Poor Adherence

- DOT failure
- Slow sputum conversion or delayed clinical improvement
- Marginal or no acceptance of TB diagnosis
- Clinical deterioration while on TB therapy
- Inability of the case manager to verify pharmacy pick-up
- Failure to attend monthly follow-up appointments
- Pregnancy
- Substance abuse
- Malabsorption of TB medications
- Complaints that TB medications taste bad or make the patient sick.

All patients should be offered directly observed therapy (DOT) as the standard of care. In some cases, electronic cap monitoring may be appropriate; however, it is not a substitute for DOT. Intermittent regimens facilitate DOT for both the provider and the patient, and should be used for most patients on standard TB regimens.

Incentives should be readily available to enhance adherence to therapy. These can range from simple overtures (e.g., offering a cup of coffee or food discount coupons; talking to a patient while waiting in the clinic) to tackling complicated issues (e.g., obtaining food and housing for a homeless patient). Providing transportation to the clinic is also important in promoting adherence.

Clinicians with TB patients who have demonstrated an inability or unwillingness to adhere to a prescribed treatment regimen should consult the Bureau of Tuberculosis Control (BTBC), which provides assistance in evaluating patients to determine causes

of non-adherence. If the patient still fails to adhere, the BTBC may take appropriate legal action, which could entail seeking court-ordered DOT or detention.

Return-to-Supervision Activities

Immediate follow-up is essential for patients who are non-adherent. Chest center staff should initiate the first follow-up contact; patients who cannot be located by chest center staff must be referred to field staff for further return to supervision (RTS) activities.

Follow-Up for Patients with Tuberculosis Who Have Missed Visits and for Suspected Cases Not on Directly Observed Therapy

A telephone call should be made to the patient within 1 working day of a missed appointment and the chart should be reviewed for appropriate action. A new appointment can be mailed to a DOHMH chest center patient if:

- The patient has enough medication to last at least until the new appointment and confirms by phone that he or she is taking the medication.
- The patient is at a low priority level compared with other TB clients requiring home visits.
- The patient specifically requests not to be visited.
- The only means of contacting the patient is a mailing address (i.e., post office box).

For all DOHMH patients, a home visit should follow the telephone call within 3 working days. If the patient has no telephone number and does not fall into the above categories, a home visit **must** be made within 3 working days. Patients who cannot be located by chest center staff must be referred to field staff for further RTS follow-up.

Follow-Up for Missed Directly Observed Therapy Visits

DOT patients should be called within 1 working day of a missed appointment. If the phone call is unsuccessful, or if the patient has no phone

number, a home visit should be made within 1 working day of a missed appointment. Daily DOT patients are considered nonadherent after missing 3 daily doses, or 1 to 2 doses per week, for 2 consecutive weeks. DOT patients on intermittent therapy are considered nonadherent after 2 or more doses are missed within 2 weeks. The primary care physician and case manager must be informed of any DOT nonadherence within the week of occurrence.

Patients who cannot be located by chest center staff must be referred to field staff for further RTS follow-up.

Prioritizing Patients for Further Return to Supervision

Several factors must be considered when deciding how to prioritize finding patients lost to follow-up. (See Box on p. 144). The first consideration is whether the patient has enough medication. Patients who are estimated to have sufficient medication and who report by telephone that they are taking the medication should be a lower priority than those who have run out of medication. In general, patients recently diagnosed with TB are a higher priority than older cases.

Cohort Review

Quarterly cohort review meetings were established by the BTBC in 1992 as a quality assurance tool for improving case management. This was one of several initiatives established at that time to help control the TB epidemic.

The cohort review consists of quarterly meetings for all staff responsible for patient care. This includes all case managers and their supervisors in BTBC chest clinics and in the field, all treating physicians and nurses, and any epidemiologists involved in case management. The cohort review is the BTBC's most important method of program evaluation as it provides a multi-disciplinary forum to review the management of each case and ensures accountability at all levels. It allows clinicians, managers and public health advisors to consult on difficult cases, especially nonadherent patients, those with MDRTB or cases with numerous contacts in several settings.

Cohort reviews take place 5 to 8 months after the patient is diagnosed with TB, allowing for

Prioritization for Locating Nonadherent Patients

1. Any patient with multidrug-resistant TB (MDRTB) with current positive bacteriology (smear or culture), regardless of the site of their disease
2. Newly diagnosed patients, or reactivated patients, who have had AFB-positive sputum smears with no documentation of conversion to negative within the last 9 months
3. Any child younger than 18 years of age with less than 6 months of treatment, regardless of site of disease
4. Any patient who is HIV-positive with current sputum AFB-negative smears, but whose culture has not converted to negative
5. MDRTB patients with negative bacteriology (smear and culture) who have received less than 18 months of therapy
6. HIV-positive contacts of MDRTB patients (if they are known)
7. Patients with single drug-resistant TB who remain culture positive
8. Patients with drug-sensitive TB who have negative smears but remain culture positive
9. Patients with drug-sensitive TB who have negative smears and cultures but who have received less than 6 months of treatment
10. Patients with only drug-sensitive extra-pulmonary TB

most patients to complete treatment. During these meetings, all confirmed cases of TB diagnosed during a particular quarter are presented in a standardized format to the Bureau Director by the case manager responsible for them. The Bureau Director reviews each case, verifying details such as the patient's clinical status, appropriateness of the treatment regimen, treatment adherence, treatment completion and outcome of the contact investigation. As each case is presented, the cohort epidemiologist enters the information into a spreadsheet, while another epidemiologist systematically documents the issues or problems identified for each patient during the meeting. Individual staff is required to follow up on all issues identified.

Objectives of the cohort review process are to:

- Ensure the implementation of comprehensive case management procedures for all TB patients in NYC

- Improve promptness of appropriate interventions
- Maintain reliability of data on the TB registry
- Provide immediate analysis of treatment outcomes and contact investigation efforts, measured against previous cohorts
- Assess NYC's efforts compared to local and national TB control targets
- Identify, track and follow up on important case management issues
- Provide ongoing training and education for staff
- Provide staff with a forum for open discussion with BTBC management

These objectives provide the technical rigor needed to comprehensively assess program experience, provide feedback to staff and continually improve the TB control program.

Nonadherent Patients Who Should Be Referred for Detention

- The patient has missed chest center appointments for 2 or more months and has refused voluntary center or field DOT.
- The patient is nonadherent to, or considered inappropriate for, self-administered treatment by the treating physician and is unwilling or unable to start or continue BTBC chest center or field DOT.
- The patient has exhibited adherence to self-administered therapy monitored with a MEMS cap of less than 80%.
- Pharmacy checks show insufficient medications being picked up by the patient.
- The barriers to treatment adherence were addressed to the extent feasible and possible, but the patient continues to be nonadherent.
- A range of DOT options (e.g., including DOT at a worksite or methadone maintenance program) were offered to the patient; however, the patient continues to fail to maintain more than 80% adherence to DOT.
- Appropriate referrals to address chemical dependency issues were provided and patient remains non-adherent.
- Appropriate referrals to address mental health problems were provided and patient remains non-adherent to treatment.
- The patient was referred to a social worker for assistance because unstable housing arrangements interfered with adherence to TB treatment. However, the patient refuses placement and/or continues to fail treatment even following housing placement.

Regulatory Intervention Options

Nonadherent patients who have, or are suspected of having, TB must be referred to the Regulatory Affairs Unit for evaluation for regulatory actions. This should be done when customary interventions fail to result in patient evaluation and adherence to an anti-TB regimen. All efforts and interventions made to facilitate adherence to prescribed TB treatment regimens must be documented in detail in TB control records and forms. For nonadherent patients referred to Regulatory Affairs, field efforts to return patients to medical supervision must continue until a decision is made and executed. Legal intervention should be considered when all reasonable efforts to assist the patient in completing the entire course of TB treatment regimens have failed (see Box above).

The purpose of regulatory intervention is to:

- Ensure that nonadherent TB patients complete an adequate course of TB treatment
- Ensure that patients suspected of having TB undergo appropriate evaluation
- Ensure that the public is protected from infectious TB patients who have refused to voluntarily agree to isolation
- Prevent the development of an epidemic of acquired drug resistance among TB patients who are unwilling or unable to adhere to an interrupted course of treatment

Commissioner's Orders

Section 11.47 of the NYC Health Code authorizes the Commissioner of Health to exercise a range of compulsory options to control TB (i.e., to issue "any orders he or she deems necessary to

protect the public health”) from someone who is a danger to the public health, including, but not limited to sections (d) (1) through (d) (5) orders in the current Health Code (see Box on p. 147).

The Commissioner has long been empowered to detain patients with TB whose presence in the community constitutes a danger to the public health. As amended, §11.47 of the Health Code expanded that authority and mandated constitutional due process safeguards for detainees. Section 11.47 emphasizes that involuntary detention should generally be considered a measure of last resort.

The Commissioner continues to have general authority to issue any orders deemed necessary to protect the public (or an individual’s) health [Health Code §11.47 (d)] and is given specific authority to detain nonadherent TB patients who represent a public health threat.

Less restrictive orders may also be requested by providers treating patients for whom adherence to anti-TB medication is an issue. The provider may request, and the Commissioner may order, that a person with TB complete an appropriate prescribed course of medication [11.47 (d) (2)] and/or that a patient’s ingestion of medication be monitored through DOT [11.47 (d) (3)].

1. The Department conducts an intensive evaluation of the medical and TB treatment histories of patients referred for detention, which includes:
 - Analysis of all relevant Department and hospital records to verify past TB-related behavior
 - Documentation of providers’ efforts to promote adherence to treatment
 - Description of the patient’s present circumstances
2. All applicable clinical and social service records are reviewed in detail, both to determine whether the patient can reliably maintain pertinent contagion precautions and whether he/she can comply with voluntary treatment. The Department must be able to demonstrate that less restrictive treatment alternatives were identified, attempted and failed, or were considered and ruled out.
3. Patients detained pursuant to Commissioner’s orders may request release at any time after

an order is served. They are entitled to representation by a private or city-appointed attorney. When the detainee requests release, the city has 3 business days to file an application in Supreme Court seeking a court order authorizing continued detention also known as an order to show cause.

The order to show cause requests the court to schedule an expedited hearing at the facility where the patient is being detained.

Patients who do not request release may be held for up to 60 days by Commissioner’s order. If longer detention is anticipated, the Department must apply for a court order authorizing continued detention. All court orders must be reviewed by the court issuing the order every 90 days thereafter.

The burden of proof supporting the detention of an individual with TB rests with the Health Department, which must provide clear and convincing evidence that the continued presence in the community of the individual with active TB presents a danger to the public health and that there is no measure short of detention that can be reasonably applied.

Documentation in the form of hospital, clinic and other clinical records constitutes the Department’s evidence that detention is necessary. Certified copies of hospital and other records are required. The records include, but are not limited to:

- All TB-related admissions and clinic visits
- Incident reports for elopement (leaving the hospital without notice)
- Leaving the hospital against medical advice
- Records of visiting nurse and other-provider home visits for DOT
- Notes or memoranda from psychiatric, medical, nursing, social worker or other provider staff

The records require documented observations of a patient’s past TB compliance history and other factors that appear to rule out reliance on voluntary completion of prescribed TB therapy. The Department’s access to such records is authorized by applicable city, state and federal law, and a Department representative will request them in writing.

Tuberculosis-Related Regulatory Interventions Sections of the Current Health Code

Health Code 11.47 d (1) authorizes removal and/or detention in a hospital of individuals who have or are suspected of having active TB and who are unable or unwilling to submit to voluntary examination. An additional order pursuant to 11.47 d (4) or d (5) must be issued if circumstances warrant continued detention after examination confirms active TB disease.

Criteria for issuing:

- Diagnosis of TB likely, based on the clinical picture, a chest radiograph consistent with TB and /or sputum smear results positive for acid-fast bacilli (AFB).
- Individual persistently refuses medical evaluation for active TB.
- Individual is in close physical contact with others.

Health Code 11.47 d (2) authorizes the Commissioner to require that persons having or suspected of having active TB complete an appropriate prescribed course of medication for TB.

Criteria for issuing:

- Patient leaves the hospital against medical advice (AMA), refuses anti-TB treatment or fails to attend TB-related clinic appointments.
- Sputum cultures pending or awaiting confirmation

Health Code 11.47 d (3) or “CoDot” authorizes the Commissioner to require that persons with active TB who are unable or unwilling to complete an appropriate prescribed course of medication for TB follow a course of DOT.

Criteria for issuing:

- Sputum culture was positive for *M. tb* during the past year.
- Individual has not completed treatment and is unreliable to self-medicate.
- Individual is consistently < 80% adherent despite voluntary clinic, home or field DOT.

In some cases:

- History of violation of isolation precautions and/or being impossible to locate.
- Individual refused anti-TB medications or stopped treatment without valid reason.

Health Code 11.47 d (4) authorizes removal and/or detention in a hospital or other health care facility of persons having or suspected of having active infectious TB who are considered substantially likely to transmit the disease to others because they are unable or unwilling to observe appropriate anticontagion precautions. The detention order may be lifted if circumstances change indicating that the patient is either no longer infectious and/or is able or willing to comply with respiratory isolation or other necessary contagion precautions.

Criteria for issuing:

- Individual refuses hospitalization or threatens to leave the hospital AMA.
- Despite education, individual cannot or will not be separated from other persons who are at risk of becoming infected with TB.

Health Code 11.47 d (5) authorizes the Commissioner to remove and/or detain in a hospital or other health care facility individuals with active TB (infectious or noninfectious) that, based on past or present nonadherent behavior, cannot be relied upon to complete the appropriate TB treatment regimen and/or to maintain anticontagion precautions. This section allows long-term detention for patients who require it.

Criteria for issuing:

- Sputum culture was positive for *M. tb* during the past year.
- There is no evidence of treatment completion.
- History and/or risk of individual being impossible to locate.
- All reasonable DOT options, including CoDOT (d3), have failed or are failing.
- In some cases, individual refuses to accept the diagnosis of active TB.

Procedures for Infectious or Potentially Infectious Patients Who Want to Leave the Hospital

Once a provider has grounds to believe that a patient may leave the hospital without authorization, the BTBC should be contacted immediately. Patients deemed infectious and who do not meet discharge criteria should not be allowed to leave by signing out against medical advice.

As it can take some hours to gather and review all pertinent records to issue a Notice of Obligation to Isolate, once the Bureau is notified, the hospital is obligated to hold the patient, with a guard if necessary, and prevent him or her from leaving until the actual Notice is sent to the facility. (10NYCRR2.27)

Upon receiving the Notice, the hospital must monitor the patient's activity and take all necessary measures to prevent him or her from leaving the hospital. A signed Commissioner's order for detention [a d(1) or d(4) order] will be faxed to the hospital within 24 business hours of the issuance of a Notice of Obligation to Isolate.

Upon receiving a request for a detention order, BTBC staff will conduct an assessment of the patient's risk to the public health. Based

on hospital and other clinical records, the patient's TB treatment-related behaviors will be evaluated. Additionally, the Bureau will assess documentation pertaining to case management efforts to identify and address barriers to patient compliance. This assessment determines whether a Commissioner's detention order should be issued (see Box on p. 147).

The patient who is to be detained is personally served with the Detention Order by BTBC or hospital staff. When the patient is served, he or she is informed of the legal authority for the order and his/her rights, which include the right to request release at any time and the right to an attorney. The Order includes the BTBC and other Health Department telephone numbers that the patient may call to request legal representation and/or release. The City of New York will assign a lawyer to the patient upon request by the patient.

To facilitate the Commissioner's Order, DOHMH must provide clear, convincing evidence of nonadherence. The evidence must sustain the need of a regulatory action for detention of an individual with active TB who is unable or unwilling to adhere to treatment and DOT.

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Section IX.

Contact Evaluation and
Public Health Management

Tuberculosis

Section IX.

Contact Evaluation and Public Health Management

Importance of Contact Evaluation

Contact investigations (CIs) are a key part of any tuberculosis control program; they encompass all aspects of TB control, including surveillance, case containment and prevention.

Reasons for conducting contact investigations include:

- Identifying persons who have been exposed to the presenting case, which puts them at greater risk of developing both latent TB infection (LTBI) and active TB than the general population
- Identifying persons who are infected with *M. tuberculosis* (*M. tb*) through appropriate screening
- Ensuring that individuals with LTBI have access to medical evaluation and appropriate treatment to prevent disease from occurring
- Identifying, when possible, the source of TB transmission for the presenting case. This is particularly important for children with active TB since, given their age, transmission is likely to have been recent.
- Identifying, when possible, environmental factors that may contribute to the transmission of TB
- Ensuring medical evaluation, treatment and follow-up for any additional cases of active TB that are identified in the course of contact tracing

Successful contact investigation requires skills in patient assessment, interviewing, counseling and evaluation, in addition to basic epidemiologic methodology.

Definitions

The following terms are used in this section:

- **Associate:** Close associate to an index patient when the index case has a clinical presentation consistent with recently acquired disease/infection (e.g., children). Associates are tested as part of source case investigations.
- **Concentric Circle:** A method of classifying and screening contacts in order of intensity of exposure and risk of being infected. Contacts with the most exposure or highest risk of infection are screened first.
- **Contact:** An individual who is at risk for TB infection or disease due to exposure to someone with infectious TB disease.
 - **Close Contact:** A person who has had prolonged, intense or frequent contact (on average 8 or more hours per week) with the TB patient during the infectious period. The extent of exposure also depends on environmental conditions.
 - **Other-Than-Close Contact:** A person who has had less prolonged, intense or frequent contact with the TB patient during the infectious period (less than 8 hours per week).
- **Contact Investigation:** A process that involves identifying, evaluating and, if appropriate, placing persons exposed to the TB patient on treatment for either LTBI or TB disease. These individuals are managed until completion of therapy.
- **Contact Investigator:** Field staff, chest center staff or other DOHMH staff member who conducts a contact investigation. In most cases, a Contact Investigator would be a Public Health Adviser or Nurse Case Manager.

- **Exposed:** Person(s) who shared air with the individual who has active TB disease during the infectious period (see *Contact*).
- **High-Priority Contacts:** Contacts who are to be evaluated without delay, including:
 - Those most likely to be infected (e.g., close contacts to highly infectious cases), and
 - Those with risk factors for progression to disease once infected (this applies to close and other-than-close contacts)
- **Index Case, Index Patient:** The individual with confirmed or suspected TB disease reported to the health department. The index patient is not always the source patient.
- **Infectious Period:** The time during which a person with active TB disease is able to transmit *M. tb* to others.
 - **Beginning of Infectious Period:** The infectious period usually begins 12 weeks before the start of anti-TB treatment. This date can be readjusted on a case-by-case basis according to epidemiological and medical considerations.
 - **End of Infectious Period:** The infectious period ends when the person with active TB disease is either isolated or separated from the exposed contacts, or when appropriate treatment starts.
- **Infection Rate:** The percentage of all identified contacts who are newly found to have a positive test for TB infection (TTBI). Contacts who have prior positive test results for TB are not included in this calculation. The calculation is:
 - Contacts with a newly positive TTBI divided by the total number of contacts without prior positive TTBI, multiplied by 100.
- **Noncounted Case:** A case that is determined not to be TB after having been initially classified as a *suspected case*.
- **Positive Skin Test Reaction:** For contacts, a tuberculin skin test (TST) reaction with an induration of 5mm or more.
- **Post-Window Skin Testing:** Testing contacts after the window period—8 weeks after the date of last known experience.
- **Relapse:** A new episode of active TB disease in a person who has previously completed treatment for TB disease.
- **Skin Test Conversion:** A documented increase in reaction size of 10 mm or more within a period of 2 years. This is indicative of recent infection with *M. tb*.
- **Smear or Culture Reversion:** A positive AFB smear or culture, after preceding smears and/or cultures were negative. Smear or culture reversion is a sign that the patient may once again be infectious.
- **Source Case, Source Patient:** A person with confirmed infectious pulmonary or laryngeal TB who is responsible for transmitting *M.tb* to others. The source patient is not necessarily the index patient.
- **Source Case Investigation:** A process to identify the source of transmission of TB when recent transmission is likely. It is used to determine who transmitted *M.tb* to an index patient, infected child or persons in a cluster of TTBI conversions. Source case investigations are routinely performed for all pediatric (younger than 18 years) patients with active TB in any anatomical site.
- **Transmission Determination:** A determination of the probability that TB was transmitted to others by the patient.
 - **Transmission Unlikely:** When the proportion of persons with a positive TTBI in the exposure group is not significantly different from a comparison group, and when there were no documented TTBI conversions or secondary cases.
 - **Transmission Possible:** When the proportion of persons with a positive TTBI among the exposed is greater than expected. However, the number or proportion of contacts tested was not sufficient to assess transmission.
 - **Transmission Probable:** When a higher than expected proportion of exposed persons had a positive TTBI; or a documented TTBI conversion was observed; or secondary case(s) were linked through epidemiological findings to the index case.
- **Treatment Failure:** When the patient's cultures remain persistently positive, despite appropriate treatment for more than 4 months.

- **Unexposed:** Person(s) who did not share airspace with the TB patient during the infectious period.
- **Window Period:** The 8-week period during which the immune system may not yet have developed a response to infection by the TB bacillus. The window period begins on the date of last known exposure. The start date may vary for different contacts of the same patient.
- **Window Period Treatment:** Treatment given to high-risk contacts (children less than 5 years of age and immunosuppressed individuals) who have a negative result on a TTBI during the window period.

Confidentiality

During the contact investigation process, it is imperative to protect the patient's and their contacts' right to confidentiality. New York State and City Health Codes provide guidelines for maintaining confidentiality and sharing personal health information. See p. 16 for information regarding confidentiality in contact investigations.

Epidemiological Assessment of Transmission

Transmission of TB from an infectious patient to contacts depends on many factors, including: infectiousness of the TB index patient; duration of infectiousness; characteristics of the shared environment; and duration of contact and proximity of contact. For the purpose of most CIs, the infectious period is defined as the 3 months prior to start of therapy in the index patient. Evaluation of contacts to TB patients is conducted based on the concentric circle approach to contact investigations. The first concentric circle includes testing of close contacts (individuals who spent 8 hours or more per week with the index patient during the infectious period). If transmission is probable among close contacts, testing is expanded to include the second concentric circle, other-than-close contacts.

Transmission from the index case to contacts is defined as unlikely, possible, or probable. See Definitions in this section (p. 154).

Priorities for Contact Investigation

Contacts of individuals who have smear- and culture-positive pulmonary or laryngeal TB are much more likely to become infected with *M. tb* than are contacts of individuals who have smear-negative or culture-negative pulmonary TB. The policy of the Bureau of Tuberculosis Control (BTBC) is to assign priority to contact evaluation, based on both the characteristics of the known or suspected TB index patient and the characteristics of the contact.

A CI is initiated for suspected or confirmed cases of respiratory (pulmonary and/or laryngeal) TB that have any of the following:

- Smear result of respiratory specimen positive for acid-fast bacilli (AFB)
- Nucleic acid amplification (NAA) test result of respiratory specimen positive for *M. tb*
- Culture result of respiratory specimen positive for *M. tb*
- Cavitory disease with high clinical suspicion of TB, regardless of smear, NAA and/or culture results

When a smear result of a respiratory specimen is positive but NAA-negative, CI will be suspended until the culture result is obtained. The CI should not be delayed while awaiting NAA result.

Evaluation of contacts is prioritized based both on the characteristics of the TB patient and on the contact's risk of progression to disease.

High priority contacts include those who are most likely to be infected (i.e., close contacts of highly infectious cases) as well as all contacts (close and other-than-close) who have other risk factors for progression to disease once infected. CIs are initiated immediately for all respiratory cases with a sputum or pathology smear positive for AFB, pending results of NAA or culture. A CI can be suspended under certain circumstances. (See p. 156, Table IX-1 and p. 160, Table IX-2.)

The concentric circle approach is used to organize, prioritize and test contacts. (See p. 157, Figure IX-1.) The concentric circle is

Table IX-1

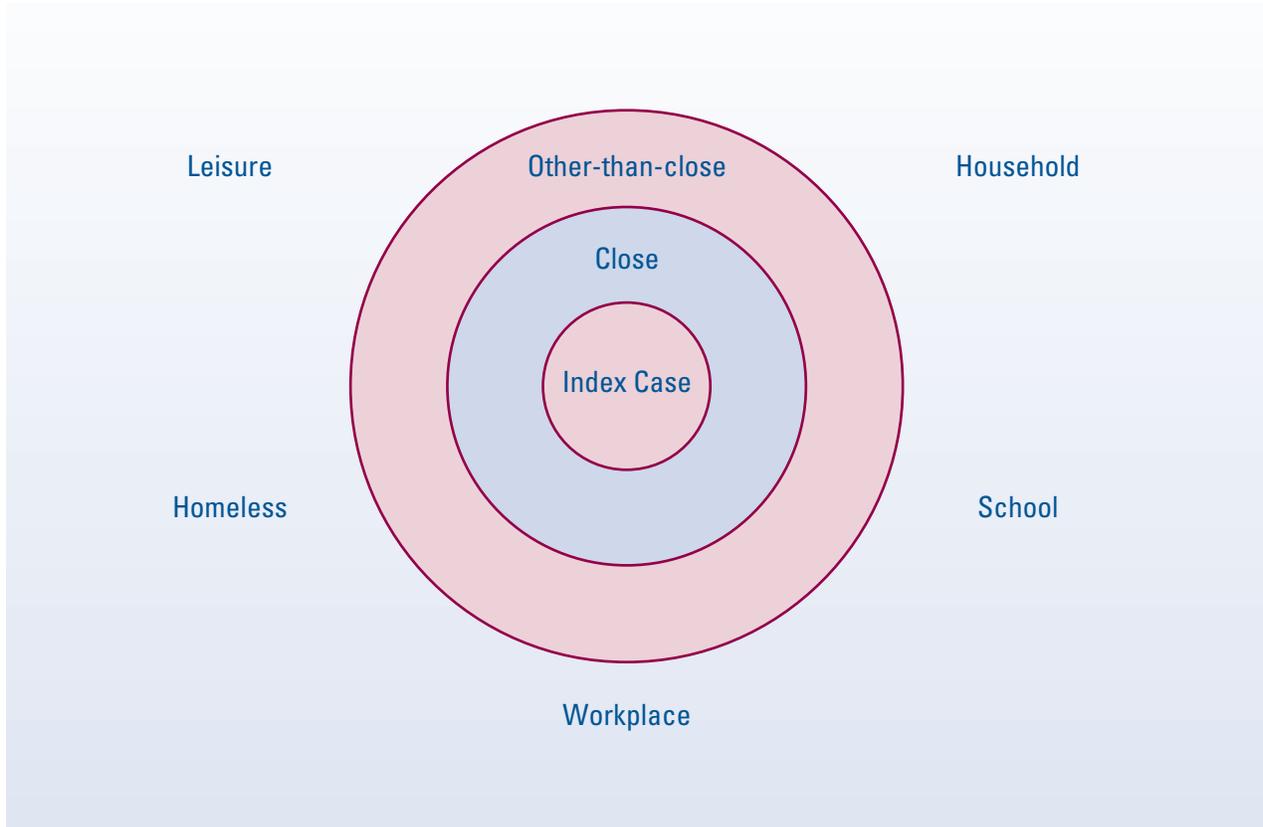
Decision to Conduct or Continue Contact Investigation by Bacteriological Status and Clinical Suspicion of Respiratory Tuberculosis

Smears <u>Positive</u> for Acid-Fast Bacilli						
Respiratory Smear Result	Nucleic Acid Amplification Result	Culture Result	Clinical Suspicion	Contact Investigation		
				Start (elicit contacts)	Continue (test high priority contacts)	Complete
Positive for AFB	Positive for <i>M. tb</i> Or Not done	Pending		Yes	Yes	Yes, if verified
		Positive		Yes	Yes	Yes
		Negative		Yes	Yes	Yes, if verified
		Not Done		Yes	Yes	Yes
	Negative for <i>M. tb</i>	Pending		Yes	Delay	Yes, if verified
		Positive		Yes	Yes	Yes
		Negative	High	Yes	Continue, particularly if cavitory CXR	Yes, if verified
			Low	Yes	Delay	No, unless verified
		Not Done	High	Yes	Continue, particularly if cavitory CXR	Yes, if verified
			Low	Yes	Delay	No, unless verified
Smears <u>Negative</u> for Acid-Fast Bacilli						
Respiratory Smear Result	Nucleic Acid Amplification Result	Culture Result	Clinical Suspicion	Contact Investigation		
				Start (elicit contacts)	Continue (test high priority contacts)	Complete
Negative for AFB	Positive for <i>M. tb</i>	Pending	High (cavitory CXR)	Yes	Yes	Yes, if verified
		Positive		Yes, after NAA	Yes	Yes
		Negative	High (cavitory CXR)	Yes, after NAA	Yes, if medical/epi review determines need	Yes, if verified
		Not Done		Yes, after NAA	Yes	Yes, if verified
	Negative for <i>M. tb</i> Or Not done	Pending	High (cavitory CXR)	Yes	Delay	No, unless verified
		Positive		Yes, after culture	Yes	Yes
		Negative	High (cavitory CXR)	Yes	Delay	Yes, if verified
			Low	No	No	No
		Not Done	High (cavitory CXR)	Yes	Delay	Yes, if verified
			Low	No	No	No

Abbreviations: AFB = Acid-fast bacilli; CXR = Chest X-ray; NAA = Nucleic Acid Amplification result

Figure IX-1

Concentric Circle for Evaluating Tuberculosis Contacts



divided into 5 settings in which the exposure may have occurred:

- Household
- School
- Workplace
- Leisure
- Homeless

Each setting is further divided according to the extent of exposure. The inner circle refers to close contacts and the outer circle refers to other-than-close contacts. The first concentric circle includes testing of close contacts (individuals who spent more than 8 hours per week with the index patient during the infectious period). If transmission is probable among close contacts, testing is expanded to include the second concentric circle, other-than-close contacts.

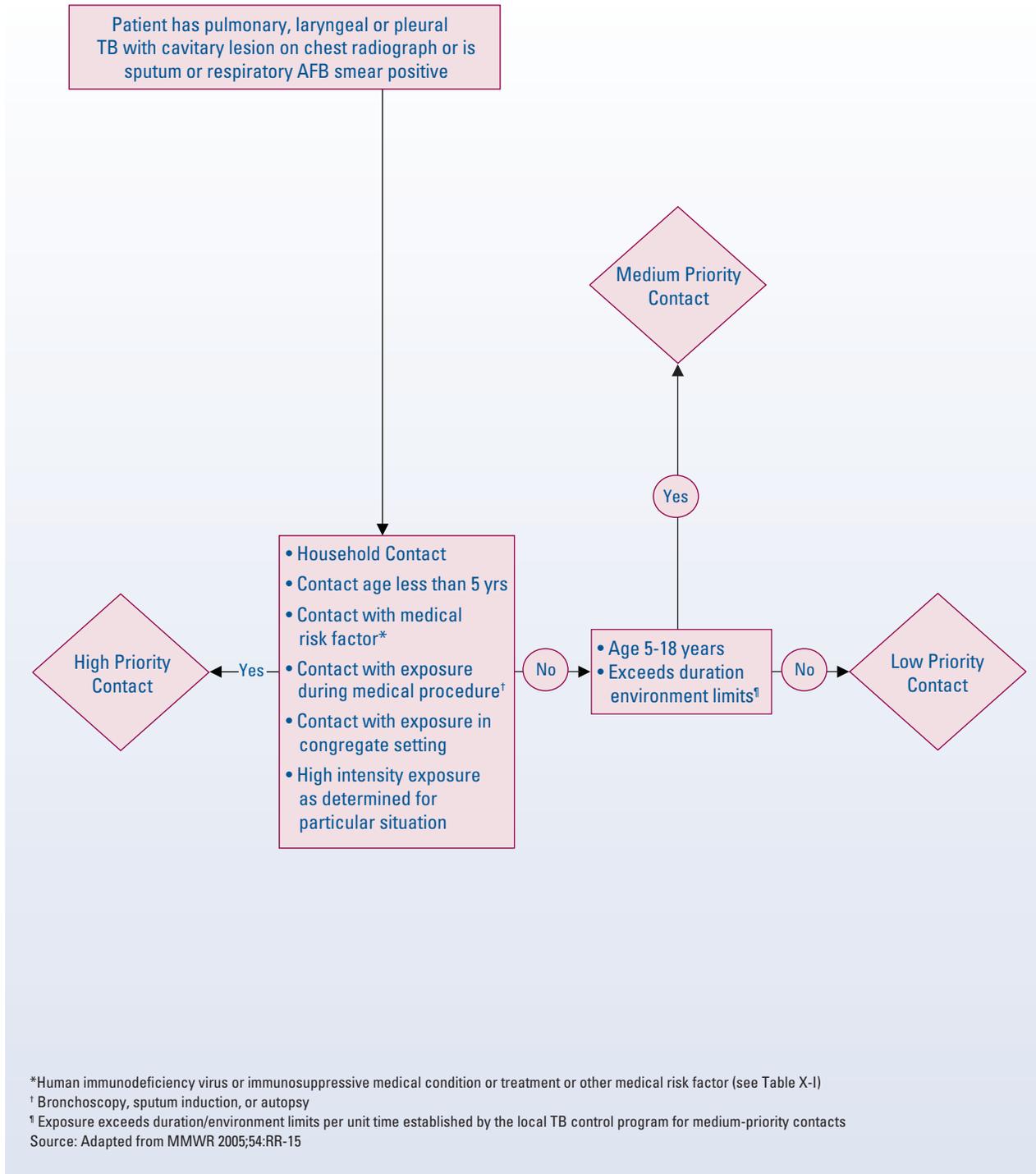
In addition to high-risk contacts that must be tested without delay (e.g., HIV- infected or medical-risk contacts and children under 5 years of age), contacts with the highest level of exposure (close contacts) in each of the settings are tested first. See pp. 158 and 159, Figures IX-2 and IX-3 for the prioritization of contacts for evaluation in different clinical situations.

In addition, a source case investigation should be performed, at least in the household, if an individual younger than 18 years old (i.e., up to the day of the 18th birthday) is found to have TB disease. (See p. 167.) The purpose of the source case investigation is to seek the infectious source patient who infected this individual.

Contacts of patients with extrapulmonary TB should be evaluated only if the patient has concurrent pulmonary or laryngeal TB. Contact evaluation is not necessary for patients with extrapulmonary TB alone, or for patients with culture-negative, non-cavitary pulmonary disease.

Figure IX-2

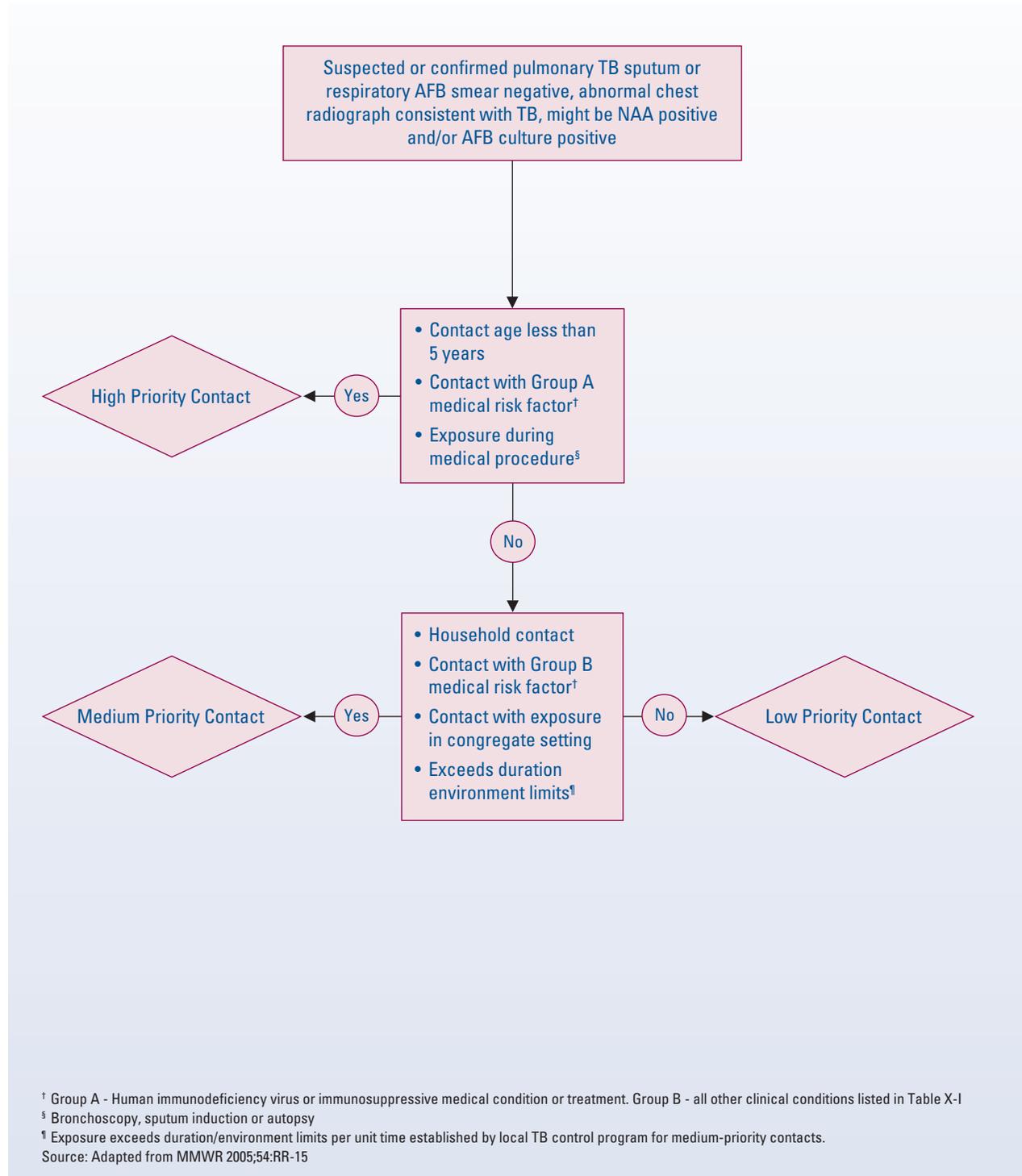
Prioritization for Evaluation of Contacts Exposed to Persons with Sputum or Respiratory Acid-Fast Bacilli Smear Positive or Cavitory Tuberculosis Cases



Abbreviations: AFB: = acid-fast bacilli; TB= tuberculosis

Figure IX-3

Prioritization for Evaluation of Contacts Exposed to Persons with Sputum or Respiratory Acid-Fast Bacilli Smear Negative Tuberculosis Cases



Abbreviations: AFB = acid-fast bacilli; NAA = Nucleic acid amplification test; TB = tuberculosis

Table IX-2

Rationale for Prioritization of Contacts to Tuberculosis Cases

Contacts Most Likely to be Infected (Close Contacts)	Contacts at High Risk of Developing Tuberculosis Once Infected
<ul style="list-style-type: none"> • Contacts exposed to patients with a high degree of infectiousness based on the following factors: <ul style="list-style-type: none"> ◦ Laryngeal or pulmonary TB ◦ AFB sputum smear positive ◦ Cavitory disease on CXR ◦ Cough • Contacts exposed to patients in: <ul style="list-style-type: none"> ◦ Congregate settings (e.g., prison, shelter, nursing home, single-room-occupancy hotels, health care facilities) ◦ Small or crowded rooms ◦ Areas that are poorly ventilated ◦ Areas without air-cleaning systems • Contacts who: <ul style="list-style-type: none"> ◦ Have prolonged exposure (longer than 8 hours per week during infectious period) ◦ Have been physically close to the patient 	<ul style="list-style-type: none"> • Contacts who are young children less than 5 years of age • Contacts with any of these conditions: <ul style="list-style-type: none"> ◦ HIV infection/AIDS or high risk for HIV infection and refuse HIV testing ◦ Injection of drugs ◦ Diabetes mellitus ◦ Silicosis ◦ Prolonged corticosteroid therapy ◦ Immunosuppressive therapy ◦ Chemotherapy ◦ Certain types of cancer (e.g., carcinoma of head, neck or lung) or hematological disorders, such as leukemia and lymphoma ◦ Chronic renal failure ◦ Gastrectomy or jejunioileal bypass ◦ Low body weight (10% or more below ideal) ◦ Fibrotic lesions on CXR consistent with old TB

Abbreviations: AFB = Acid-fast bacilli; CXR = Chest X-ray; TB = tuberculosis

A CI follows these steps:

- Identification of a case of active TB requiring a CI
- Review of the medical record of the case (interview should not be delayed if medical record is not available)
- Interview with the patient to elicit contacts
- Determination of the infectious period
- Assessment of transmission risk
- Prioritization of contacts
- Field investigation

- Evaluation of contacts
- Transmission determination
- Expansion of contact investigation, if necessary
- Medical evaluation of contacts who have a positive TTBI, and/or have specific medical risk factors
- Start of LTBI treatment
- Monitoring of contacts on LTBI treatment
- Ensuring completion of LTBI treatment

Calculating the Infectious Period

The infectious period is calculated to identify the period during which exposure is most likely to have occurred, and thus to reduce the number of individuals evaluated during a contact investigation. The calculation of the infectious period depends upon the patient's clinical characteristics.

The infectious period usually starts 12 weeks prior to the beginning of treatment for TB, and ends either on the day that the patient is removed from interaction with the contacts, or on the date appropriate treatment starts. In case of multidrug-resistant TB (MDRTB), a determination of the end of the infectious period should be made in consultation with a BTBC supervising physician.

The infectious period may be recalculated, based on the results of the contact evaluations and on changes in the clinical condition of the TB patient. If transmission was found in contacts who had been clearly exposed at the beginning of the infectious period, the patient is re-interviewed to obtain further information regarding the start of symptoms. It may be necessary to add 1 to 2 additional months to the start of the infectious period and to identify additional contacts exposed to the patient during that time.

If the TB patient had a culture conversion and smear and/or culture status has reverted from negative to positive, a new infectious period must be determined. The decision to extend the infectious period—in either direction—is based on medical and/or epidemiological consultation.

Assessing Risk of Transmission

The risk of transmission is based on the characteristics of the TB case, the environment in which potential exposure may have occurred and the extent of the potential exposure (see Box). The test results of the contacts will determine if transmission was probable, possible or unlikely (see p. 154).

Source case characteristics that increase the risk of transmission include:

- Sputum AFB smear positive (the higher the smear grade, the greater the risk)
- Site of disease—pulmonary or laryngeal TB
- Length of time the potential index patient has been infectious (longer time = greater risk)
- Cavitory disease
- Cough or hoarseness (possible sign of laryngeal disease)

Environmental characteristics associated with increased risk of transmission include:

- Small room size
- Poor ventilation (lack of windows)

Extent of exposure associated with increased risk of transmission include:

- Prolonged exposure—more than 8 hours/week
- Frequent exposure
- Close physical proximity (e.g., sleeping in the same room)

Evaluation and Management of Contacts

Symptom Review

All close contacts should be evaluated for symptoms of TB. Contacts who exhibit TB symptoms have the highest priority.

- Individuals who have symptoms consistent with TB and who have been in close contact with a person who has either a positive *M. tb* culture or an AFB-positive sputum smear, should be evaluated promptly for TB disease with a TTBI, a chest X-ray (CXR), sputum smears and cultures and drug susceptibility testing. (See p. 26.) If appropriate, there should also be a search for extrapulmonary sites of TB.
- For contacts with definite TB symptoms (e.g., weight loss, a cough of at least 2 weeks duration, fever, night sweats) with or without an abnormal CXR, treatment for active TB disease should be initiated while TB culture results are pending, unless there is another likely cause for such symptoms.

- For contacts with vague symptoms, treatment for active TB disease or treatment for LTBI should be withheld until the diagnostic evaluation is complete. Treatment for LTBI should not be initiated until active TB disease has been ruled out.
- Contacts with TB symptoms should be classified as TB Class V (High), regardless of the CXR findings and TTBI results.

HIV Screening and Testing

All contacts should be evaluated for HIV infection, since it greatly increases the risk of disease progression for persons with LTBI. In the field, an HIV risk-behavior screening tool should be used to assess a contact's risk for HIV infection. HIV counseling and testing should be offered to all contacts, especially close contacts and those other-than-close contacts with HIV risk factors. All contacts should be referred to a chest center or to their private physician for HIV counseling and testing. Rapid HIV testing is currently available at BTBC chest centers.

Initial Test for Tuberculosis Infection and Follow-Up

All close contacts of an individual who has a positive *M. tb* culture or an AFB-positive sputum smear should be screened for LTBI with a TTBI unless they have documentation of a previous positive TTBI.

If the reaction to the initial TTBI is negative, the contact should be classified as TB Class I, and a repeat TTBI should be given 8 weeks after the contact's last exposure to the index patient during the period of time that the index case was infectious. During the window period between the 2 tests for TB infection, the following contacts should receive a clinical evaluation and CXR to rule out active TB disease, and should start treatment for presumed LTBI, even if the TTBI is negative:

- Contacts younger than 5 years of age (i.e., up to the day of the fifth birthday)
- Contacts between 5 and 15 years of age, at the physician's discretion

Table IX-3

Individuals Who Need Medical Evaluation and Chest Radiograph

Status		
New Positive Test for TB Infection	Prior Positive Test for TB Infection	Regardless of Test for TB Infection Result (+ or - TTBI)
<ul style="list-style-type: none"> • Contacts (close and other than close) • Persons being evaluated in source case investigation 	<ul style="list-style-type: none"> • Symptomatic • Persons being evaluated in source case investigation • Additional persons with heavy exposure 	<ul style="list-style-type: none"> • Contacts with HIV infection or other medical risk factors • Children younger than 5 years of age identified during window period • Anyone with symptoms suggestive of tuberculosis, regardless of TTBI result or age • Sexual contacts of HIV-infected index patients • All associates in a source case investigation

TTBI = test for TB infection (TST or blood-based assay)

- Contacts who are HIV positive or otherwise immunosuppressed.
- Contacts with behavioral risk factors for HIV infection who decline HIV testing

If the reaction to the initial TTBI is positive, the contact should undergo a CXR.

- If the CXR and physical are normal, the contact should be classified as TB Class II and started on treatment for LTBI, as indicated (see p. 192.)
- If the CXR is abnormal, or if there is clinical evidence of TB disease, the contact should be classified as TB Class V and evaluated for TB disease (see p. 26).

In some instances, an individual may present at a BTBC chest center and report a positive or negative TTBI. If it is not possible to verify this information, 2 options are available: (1) Perform a CXR if the person reports both a positive TTBI and contact with a person who has TB disease; or (2) Repeat the TTBI, unless the person describes a “very large” reaction (size of a quarter or bigger) to a previous TST or residual evidence (e.g., scar or pigmentation) is seen. In general, the safest option is to perform the CXR if a possible contact reports a prior TTBI infection, even when the history cannot be verified.

Medical Evaluation and Chest Radiograph

The following persons should receive a medical evaluation, including a CXR, after the index patient is diagnosed (see p. 162, Table IX-3):

- All contacts (close and other-than close) with a positive TTBI
- Persons being evaluated as part of a source case investigation, who have either a positive TTBI result or have documentation of a prior positive TTBI result
- Persons with history of TB disease
- Contacts infected with HIV or other immunosuppressive conditions, regardless of TTBI result
- Children less than 5 years of age who are contacts identified during the window period, regardless of TTBI result
- All persons with symptoms, regardless of TTBI results

- Sexual contacts of HIV-infected index patients who decline HIV counseling and testing

Close contacts with a documented previous positive TTBI should have a CXR if they have symptoms that suggest TB, if they are HIV positive or if they are sexual contacts of an HIV-infected index case and refuse HIV testing.

A CXR should also be considered for the following individuals who have a previous positive TTBI, but who have subsequently been in close contact with a person who has AFB smear-positive pulmonary or laryngeal TB:

- Persons with medical risk factors for TB other than HIV infection
- Children younger than 18 years of age
- Asymptomatic, HIV-negative persons who have had heavy exposure to a person with highly infectious pulmonary or laryngeal TB (i.e., the presence of secondary cases or documented conversions in other contacts).

See p. 193 for guidelines on treatment for LTBI in these situations.

Repeat Test for Tuberculosis Infection and Follow-Up

If the reaction to the initial TTBI is negative and was given before the end of the 8-week window period, contacts should have a repeat test 8 weeks after their last exposure to the index patient.

If the reaction to the repeat TTBI is negative and the individual is no longer in close contact with an infectious index patient:

- No follow-up is necessary for immunocompetent contacts (including immunocompetent children). Treatment for LTBI, if started, should be discontinued. These contacts should be classified as TB Class I.
- A full course of treatment for LTBI is still indicated for most close contacts who are HIV positive or otherwise immunosuppressed, or who have behavioral risk factors for HIV infection but decline HIV testing, regardless of the TTBI reaction. These contacts should remain classified as TB Class I.

If the reaction to the repeat TTBI is negative, but the individual remains in close contact with an infectious index patient, the person should continue treatment for LTBI if:

- Less than 5 years of age
- Between the ages of 5 and 15, at the physician's discretion
- HIV-positive or otherwise immunosuppressed
- Has behavioral risk factors for HIV infection but declines HIV testing

Contacts whose TTBI is negative but who remain in close contact with an infectious index patient should have a repeat test and, if necessary, a CXR, every 3 months. If the reaction to a repeat TTBI is positive, the contact should be re-evaluated:

- If the CXR is normal, the contact should be classified as TB Class II and started on treatment for LTBI (see p. 192).
- If the CXR is abnormal, the contact should be classified as TB Class V and evaluated for TB disease (see p. 26).

Contact Evaluation for Patients Whose Cultures Convert Back to Positive

In some instances, a TB patient's cultures may convert to negative and then become positive again. This may happen if a patient is lost to follow-up and discontinues medication before completing treatment, or if treatment was not adequate because of multidrug resistance.

If the patient is located after a treatment lapse of 3 months or longer, and if the patient's cultures have become positive again, or if the patient relapses while on treatment after becoming culture negative, a second window period should be defined and the patient should be re-interviewed. Contacts identified during the initial investigation should be reevaluated if they were exposed again. If new contacts are identified, they should be tested and evaluated.

Special Considerations for Infant and Child Contacts

Infants (i.e., babies less than 1 year of age) and children younger than 5 years of age (i.e., up to the day of the fifth birthday) who live in the same household as an infectious TB patient should be kept out of the home setting until one of the following conditions is met:

- The infectious patient is taking anti-TB treatment and has demonstrated an adequate clinical response to treatment (i.e., negative AFB smears and a decrease in symptoms).
- The child has started treatment for LTBI (including window prophylaxis).
- The infant is given Bacille Calmette-Guèrin (BCG) vaccine (see p. 227, Appendix I-G). This is the least desirable option.

Initial Test for Tuberculosis Infection and Chest X-ray for Infants and Children

All infant contacts should receive an initial TTBI, medical evaluation and both a posterior-anterior and lateral CXR, regardless of the results of the TTBI result.

If the CXRs are normal, the infant should start treatment for LTBI, even if the TTBI is negative. Isoniazid should be used for infant contacts of patients with isoniazid-susceptible TB; rifampin should be used for contacts of patients with isoniazid-resistant but rifampin-susceptible TB. Multidrug treatment of LTBI with medications other than isoniazid and rifampin should be considered for infant contacts of patients with isoniazid- and rifampin-resistant TB (see p. 201, Table XI-4).

If the reaction to the initial TTBI was positive, the infant should complete a full course of treatment for LTBI.

If the CXR shows hilar adenopathy with or without a pulmonary infiltrate, the child should be treated with a 6-month regimen similar to the one used for pulmonary TB. If TB diagnosis is in doubt, consultation with a pediatric pulmonologist may be indicated for diagnostic investigation of the cause of lymphadenopathy. (See p. 37.)

Repeat Test for Tuberculosis Infection and Chest X-ray for Infants and Children

All infant contacts with a negative reaction to the initial TTBI should have a repeat test and posterior-anterior and lateral CXRs (regardless of the TTBI result) when they are at least 6 months of age, and when at least 8 weeks have passed since their last exposure to the infectious index patient. (Infants younger than 6 months of age may be anergic.)

- If the reaction to the repeat TTBI is positive and CXRs are normal, a full course of treatment for LTBI should be administered.
- If the CXRs show evidence of active TB, the child should be treated with a 6-month regimen similar to the one used for pulmonary TB.
- If the reaction to the repeat TTBI is negative and the CXRs are normal, LTBI treatment should be discontinued.
- If the child cannot be separated from the source patient who remains infectious due to unresponsive MDRTB, BCG should be considered if the TTBI is still negative. (See p. 227, Appendix I-G.)

Contact Investigation for Smear-Negative, Culture-Pending Cases

The BTBC does not routinely evaluate contacts of suspected TB patients (1) whose smears are negative for AFB and whose culture results are pending, or (2) whose smear and culture results are pending.

However, contacts with symptoms of TB, and HIV-positive contacts of suspected TB patients, should be evaluated for LTBI and TB disease, even if the patient is smear negative.

All contacts should be offered HIV counseling and testing, as HIV-positive patients are at increased risk of developing active tuberculosis.

The contact evaluation must be completed if the suspected TB case (TB Class V) is reclassified as a TB Class III on the basis of a positive *M. tb* culture.

If the suspected TB case is reclassified as a culture-negative TB Class III, transmission

from this index patient is less likely. If a contact is found to have LTBI, a physician should review the individual's risk of TB and the need for treatment of LTBI, as the contact may not have been infected from this source case. Some adult contacts whose TTBI is positive may actually have been infected before their exposure to the index patient. In this group of contacts, treatment for LTBI may be less imperative.

Expanding a Contact Investigation

If transmission has occurred among the closest contacts, based on the criteria indicated on p. 154, the CI should be expanded to include the next level of exposure and/or site.

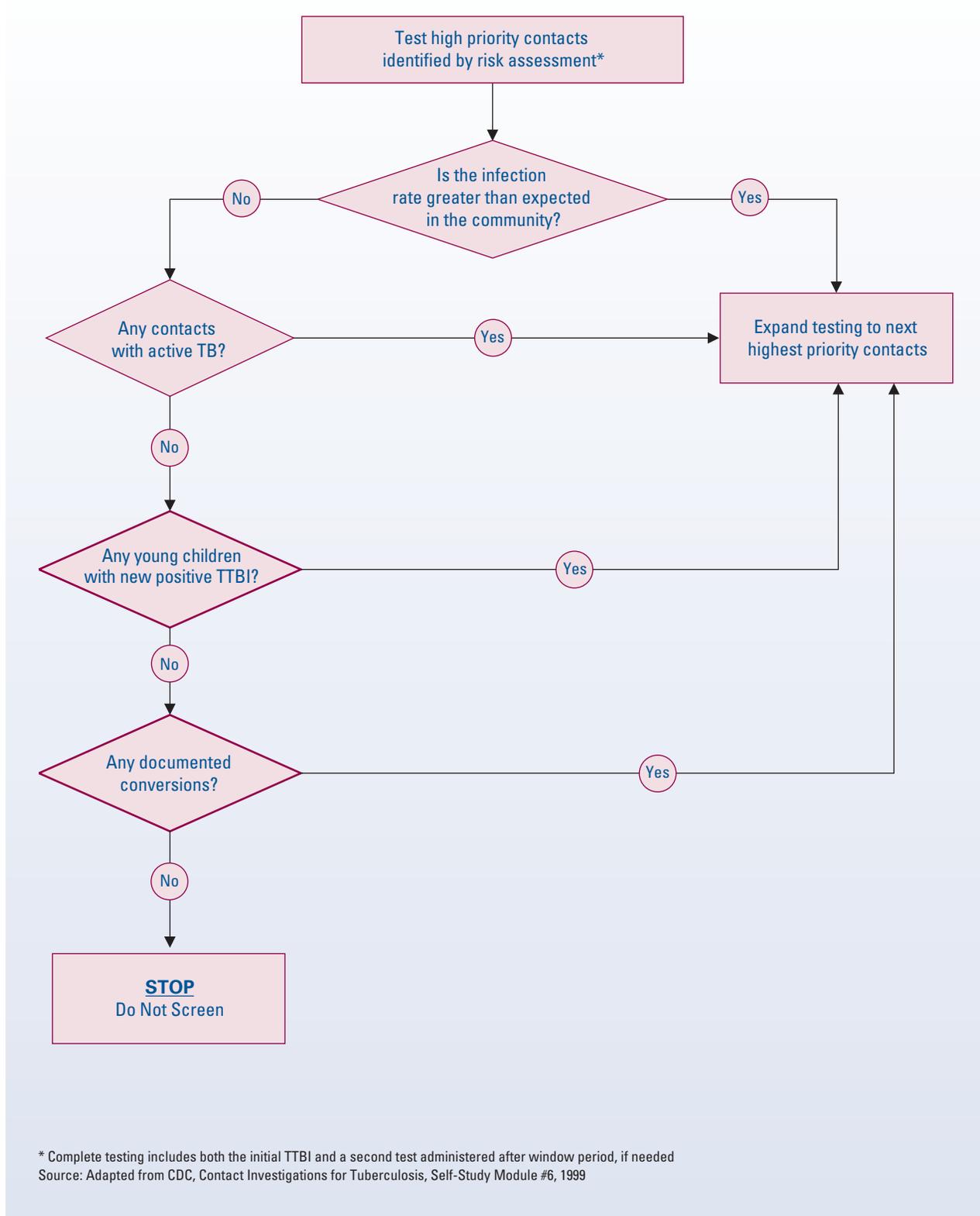
The concentric circle approach should be used to guide the expansion of a CI (see p. 166, Figure IX-4). If transmission is found within the inner circle (i.e., close contacts) of the concentric circle, the investigation should be expanded to the outer circle of that setting (i.e., to include the other-than-close contacts). If there is evidence of transmission in the outer circle in any exposure setting(s), then an additional interview with the index case is conducted to elicit additional contacts and exposure settings (see p. 166, Figure IX-4).

An expanded contact investigation may be needed if the index patient fits one or more of the following criteria:

- Is homeless or currently living in a congregate setting, shelter or single-room-occupancy hotel
- Works in or attends a school or daycare facility
- Works in a potentially politically sensitive worksite
- Works in a setting where coworkers are aware of the TB diagnosis
- Works, studies or lives in a setting with 15 or more individuals
- Is a health care worker
- Arrives in New York City during the infectious period and travel involved 8 hours or more exposure on airplane, train, ship or bus
- Attends a place of worship regularly during the infectious period

Figure IX-4

Expanding Contact Investigation Tuberculosis Testing



* Complete testing includes both the initial TTBI and a second test administered after window period, if needed
Source: Adapted from CDC, Contact Investigations for Tuberculosis, Self-Study Module #6, 1999

TTBI = test for TB Infection

- Attends an after-school program or other extracurricular program during the infectious period.
- Frequently attends a health care setting (e.g., infectious patient was not isolated appropriately during hospitalization or index patient had frequent outpatient visits during the infectious period).

Airline Exposures

All commercial jets built after the 1980s and a few retrofitted aircraft recirculate cabin air, (filtered air from within the cabin and conditioned air from the outside). Depending on the type of aircraft, air may be recirculated throughout the entire cabin or only within limited zones. All large commercial jet aircraft provide approximately 20 air exchanges per hour during cruising, and lower amounts during descent and when on the ground. There is no evidence that recirculation of cabin air facilitates transmission of infectious disease agents on board. When cabin air is recirculated, it passes through a set of filters before it is mixed with outside conditioned air, which is virtually free of organisms. Filtration of the air removes large particles and particles such as *M.tb* organisms, thus eliminating the risk of exposure for passengers and crew from this source.

In the case of a potential exposure to a patient with active tuberculosis, the airline must cooperate with the public health authorities responsible for informing passengers and/or crew of their potential exposure to *M. tb*. See p. 168, Figure IX-5 for the steps the CDC/DGMQ takes when deciding whether a contact investigation is needed. The CDC/DGMQ must evaluate the risk of TB transmission and decide whether it is necessary to inform selected passengers and crew of the potential exposure. The following criteria are used:

- Infectiousness of the person with TB
- Duration of the exposure
- Time elapsed between the flight(s) and the notification of the case
- Proximity of other passengers and crew to the index patient

The infectiousness of the person with TB is determined based on several criteria. With respect to duration of exposure, informing close contacts is indicated if the total flight duration exceeded 8 hours. Tuberculosis transmission on airlines has been found *only* when exposure to the person exceeded 8 hours. It is difficult to determine retrospectively if the person with TB was symptomatic at the time of the flight. Passenger-to-passenger transmission of *M. tb*, however, has been documented among close contacts seated in the same section of the airplane as the person with infectious TB (i.e., seated in the same row or 2 rows ahead or behind, and cabin crew members working in the same cabin section as the person with TB). Notification therefore, should be made to passengers and crew that were on flights within the 3 months before notification of the case to the health authorities.

If one of the flight crew (i.e., pilot, copilot or flight engineer) is infectious, passengers are not considered to be at risk, as there is no contact between the flight crew and the passengers. Cabin crew members, however, should be notified of the exposure and evaluation should be recommended.

Source Case Investigation for Pediatric Tuberculosis Cases

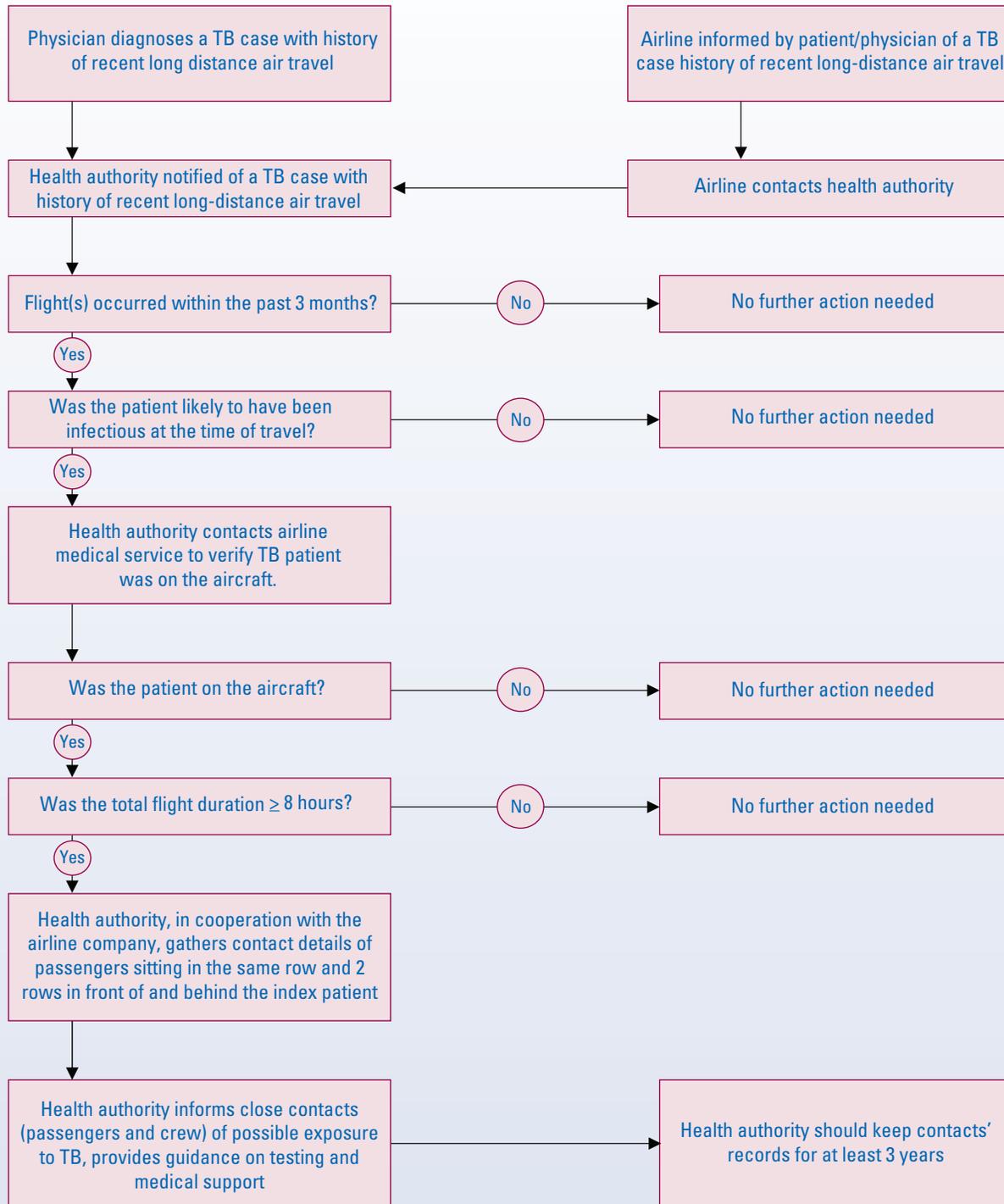
When a child less than 18 years of age is diagnosed with active TB disease, an investigation (source case and/or contact) should be completed based on the specific circumstances of the child's illness.

The investigation evaluates all persons (adults and children) who have had close or household contact with the pediatric index case during the relevant time period. All possible associates in the 1 year prior to the time that the pediatric case was diagnosed should be located.

If the pediatric index patient is deemed to be infectious (i.e., a child older than 10 years of age, with positive respiratory cultures), a contact investigation is also initiated for the pediatric TB case. The source case investigation aims to identify, test and evaluate the following:

Figure IX-5

Determining if a Contact Investigation is Needed for Potential Air Travel Exposure to Tuberculosis*



*Adapted from World Health Organization: Tuberculosis and Travel WHO/HTM/TB/2006.363. Geneva, Switzerland, 2006

Abbreviations: TB = tuberculosis

- The source case—the individual with active TB disease who may have infected the child. (The possible source patient is usually an adult in the home, a frequent visitor or an adult with whom the child spends significant periods of time—e.g., babysitters, daycare personnel, relatives.)
- Secondary cases
- Other high-risk close associates, that is, children and adults who may have been infected in the same setting.

Any possible source patient should be evaluated for TB (see p. 26), with a TTBI. Regardless of the result, source patients should also receive CXR and medical evaluation. Associates with a previously positive TTBI only need CXR (taken after the child was diagnosed) and medical evaluation.

Case Management and Treatment of Contacts with Latent Tuberculosis Infection

Every contact started on treatment for LTBI should be case managed throughout the duration of treatment. A case manager is assigned to a contact based on where the contact is receiving treatment, not on the location of the index case. Contacts treated at a BTBC chest center are case managed by a nurse case manager (or clinic Public Health Advisor [PHA], based on staffing levels) at the BTBC chest center. Contacts treated at a non-DOHMH facility are case managed by a Field-Based Unit PHA in the borough where the non-DOHMH facility is based.

Responsibilities of the Case Manager

The contact's case manager is responsible for the following:

- Ensuring monthly follow-up
- Reminder phone calls
- Referrals to other chest center units
- Updating the DOHMH TB registry
- Providing treatment information and outcomes to the case manager of the index case

The index patient's case manager is responsible for the following:

- Knowing the status of all the contacts of the index patient, regardless of who is case managing the contacts
- Providing information as requested to the network epidemiologist
- Reporting the outcome of the contact investigation at the DOHMH Cohort Review

Return to Supervision Procedures for Contacts Being Treated for Latent Tuberculosis Infection

Contacts who miss their appointments should be located. A phone call should be made within 1 working day of the first missed appointment. If unsuccessful, within 3 working days, a letter should be sent to follow up with their provider. If the contact is being managed at a BTBC chest center, a new appointment time should be sent with a notice to call the chest center if the appointment time is not convenient. If the patient does not contact the case manager and/or chest center by phone or visit, a home visit will be made within 5 working days of the missed appointment. To prevent chronic non-compliance, a reminder card (a phone call for a non-DOHMH patient) should be sent to the client routinely 1 week prior to each appointment.

Key Sources

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Section X.
Testing for Latent
Tuberculosis Infection

Tuberculosis

Section X.

Testing for Latent Tuberculosis Infection

Note: The term “tuberculin skin testing” (TST) is no longer used, as it does not reflect the availability of blood-based tests for TB infection. A more general term, test for TB infection (TTBI), is used except in specific instances that reference the TST.

Despite the dramatic decline in the number of reported cases of TB in New York City (NYC), many New Yorkers remain at high risk for developing active TB disease once they have been infected with *M. tuberculosis* (*M. tb*) (i.e., have latent TB infection [LTBI]). Groups at especially high risk are those who have had contact with persons who have active TB, persons who are HIV infected, individuals with certain predisposing medical conditions and recent immigrants from countries with high rates of TB.

Candidates for Testing for Latent Tuberculosis Infection

TB screening should be focused on populations that are most at risk for recent infection, or, if already infected, are at increased risk for developing TB due to medical conditions. In general, populations at low risk for LTBI should not be tested since false positive reactions are common.

Currently, the tuberculin skin test (TST) performed by the Mantoux method using purified protein derivative (PPD) is the most commonly used test to diagnose LTBI. A TST is not necessary for individuals with a reliable history of, or a previously documented positive TST result.

Blood-based tests are increasingly becoming an alternative to the TST for identifying TB infection. The same target populations as listed above should be tested. See p. 183 for more detail.

Priorities for Testing

The following individuals should be screened for LTBI (see p.174 and 175, Tables XI-1 and XI-2):

- Contacts of persons who have pulmonary or laryngeal TB. (see p. 160, Table IX-2).
- Persons who have HIV infection.
- Persons who have immigrated to the United States within the past 5 years and who come from an area where TB rates are high (see p. 175, Table X-2).
- Injection drug users, whether or not they are HIV positive.
- Persons who have medical risk factors for TB disease, such as:
 - Diabetes mellitus
 - Silicosis
 - Cancers of the head, neck or lung
 - Hematologic and reticuloendothelial malignancies (e.g., leukemia and Hodgkin’s disease)
 - End-stage renal disease
 - Intestinal bypass or gastrectomy
 - Chronic malabsorption syndromes
 - Low body weight (10% or more below ideal)
 - Transplant recipient or currently on transplant lists
 - Receiving prolonged corticosteroid therapy (e.g., receiving the equivalent of more than 15 mg of prednisone for more than 1 month)
 - Receiving other immunosuppressive agents (e.g., chemotherapy, TNF-blockers)
- Persons with radiographic evidence of old, healed TB lesions.

- Employees or residents of congregate settings where TB exposure may be likely, such as:
 - Hospitals
 - Correctional facilities
 - Homeless shelters
 - Nursing homes
 - Drug treatment centers
- Children/adolescents exposed to adults in high-risk categories.
- Persons with a prolonged stay (more than 1 month) in areas with high TB rates (see p. 175, Table X-2).

In addition, the TTBI is valuable as a diagnostic tool in patients who have symptoms and/or clinical evidence, radiographic evidence or acid-fast bacilli smears suggestive of TB disease. In these patients, a positive TTBI reaction indicates TB infection and supports a diagnosis of active TB disease. A negative reaction usually, but not always, excludes TB as a cause. However, immunosuppression and other medical conditions, including severe TB disease itself, can cause a false-negative reaction to the TTBI.

TTBIs are not contraindicated for persons who have been vaccinated with Bacille Calmette-Guérin (BCG). A history of BCG vaccination should not be considered, either when deciding

Table X-1

Individuals Who Should be Tested for Latent Tuberculosis Infection

Individuals Who May Have Been Recently Infected	Individuals with Clinical Conditions Associated with Progression from LTBI to Active TB
<ul style="list-style-type: none"> • Persons who have had close contact with individuals with active TB. Retesting may be necessary 8 weeks after original test. • Persons who have immigrated to the United States within the past 5 years from areas with high TB rates* should be tested the first time they enter the health care system in the States. • Persons who have made prolonged stays (longer than 1 month) in areas with high TB rates.* • Persons who live or work in clinical or institutional settings where TB exposure may be likely (e.g., hospitals, prisons, homeless shelters, nursing homes, mycobacteriology labs); most CDC and local guidelines recommend testing annually. • Children/adolescents exposed to adults in high-risk categories. 	<ul style="list-style-type: none"> • Persons with HIV infection should be tested as soon as possible after diagnosis of HIV infection, and at least once a year afterward. • Injection drug users • Persons with evidence of old, healed TB lesions on chest X-ray • Underweight persons ($\geq 10\%$ under ideal body weight) • Persons with any of the following medical conditions or risk factors for TB disease: <ul style="list-style-type: none"> ◦ Diabetes mellitus ◦ Silicosis ◦ Cancer of the head, neck or lung ◦ Hematologic and reticuloendothelial malignancies (e.g., leukemia and Hodgkin's disease) ◦ End-stage renal disease ◦ Gastrectomy or jejunioileal bypass ◦ Chronic malabsorption syndromes ◦ Organ transplants or on transplant lists ◦ Receiving prolonged corticosteroid therapy or other immunosuppressive therapy (e.g., the equivalent of $\geq 15\text{mg}$ of prednisone for ≥ 1 month, TNF-α blockers or chemotherapy)

*See p. 175, Table X-2

Table X-2
Countries and Areas with an Estimated or Reported High Incidence of Tuberculosis, 2005¹

<p>Africa All countries except Seychelles</p> <p>Eastern Mediterranean Afghanistan Bahrain Djibouti Egypt Iraq Morocco Pakistan Qatar Somalia Sudan Yemen</p> <p>Europe Armenia Azerbaijan Belarus Bosnia and Herzegovina Estonia Georgia Kazakhstan Kyrgyzstan Latvia Lithuania Moldova (Republic of) Romania Russian Federation Tajikistan Turkmenistan Ukraine Uzbekistan</p>	<p>North, Central and South America Belize Bolivia Brazil Columbia Dominican Republic Ecuador El Salvador Guatemala Guyana Haiti Honduras Mexico² Nicaragua Panama Paraguay Peru Suriname</p> <p>Southeast Asia Bangladesh Bhutan India Indonesia North Korea (DPRK) Maldives Myanmar Nepal Sri Lanka Thailand Timor-Leste</p>	<p>Western Pacific Brunei Darussalam Cambodia China China (Hong Kong SAR) Guam Kiribati Lao PDR Macao (China) Malaysia Marshall Islands Micronesia Mongolia New Caledonia Northern Mariana Islands Palau Papua New Guinea Philippines Solomon Islands South Korea (ROK) Vanuatu Viet Nam</p>
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¹ Source: World Health Organization *Global Tuberculosis Control—Surveillance, Planning, Financing: WHO Report 2007* Geneva, World Health Organization (WHO/HTM/TB/2007.376) (www.who.int/tb/publications/global_report/2007/pdf/full_report.pdf). “High-incidence areas” are defined by the New York City Tuberculosis Control Program as areas with reported or estimated ≥ 20 new smear-positive cases per 100,000 persons.

² Has an estimated incidence of < 20 smear-positive cases per 100,000 persons; however, the Mexican community in NYC has a high burden of disease.

whether to test and/or when determining whether the test result is positive in high-risk individuals.

Although BCG vaccination can cause a false-positive cross-reaction to the TST (especially within the first 12 months after vaccination), sensitivity to tuberculin is highly variable and tends to decrease over time. There is no way to distinguish between a positive reaction due to

BCG-induced sensitivity and a positive reaction due to true LTBI. Therefore, a positive reaction to the TST in BCG-vaccinated persons should be interpreted as indicating infection with *M. tb* when the person tested is at increased risk of recent infection or when the person has a medical condition that increases the risk of progression to active TB disease.

Since the QuantiFERON®-TB Gold (QFT-G) blood-based test does not cross-react with BCG, this test is particularly useful for testing individuals with a history of BCG vaccination. (See p. 183.)

Testing for Pregnant Women

The TST is safe and reliable for pregnant women. No teratogenic effects have been documented. Routine TST screening for pregnant women is not indicated since pregnancy does not increase the risk for LTBI. However, pregnant women at high risk for LTBI or active TB disease should be tested. Specifically, pregnant women should be screened for LTBI if they have any of the high-risk conditions noted on p. 174, Table X-1.

Guidelines for Testing Specific High-Risk Groups

Close contacts of persons with active TB disease should receive a baseline TTBI immediately after exposure. Retesting is sometimes necessary, however, to determine whether or not infection resulted from the exposure. Since it can take up to 8 weeks after *M. tb* infection for the immune system to respond to a TTBI, tests may be falsely negative. Close contacts tested during the window period who had a negative result on the initial TTBI, should be retested 8 weeks from the contact's most recent exposure to active TB. (See p. 161.)

All individuals who are HIV-positive should receive a TTBI as soon as HIV infection is diagnosed. The test should be repeated at least every 12 months thereafter.

Recent immigrants (i.e., those who have been in the United States for less than 5 years), who have come from countries with high rates of TB should be tested for TB infection when they enter the medical care system in the States. They should also be tested any time after they return to their native country or after a prolonged (more than 1 month) stay abroad (see p. 175, Table X-2).

Individuals who have had a prolonged stay (more than 1 month) abroad in areas where TB rates are high should be evaluated immediately after return or at their next medical examination. (See p. 175, Table X-2.)

Individuals who live or work in institutional settings (e.g., prisons, hospitals, nursing homes, shelters) are under testing recommendations that vary according to risk of transmission based on local and Centers for Disease Control and Prevention guidelines (CDC). Most guidelines recommend annual testing. Individuals who will undergo serial testing should have either a 2-step TST or a single blood-based TTBI as part of their baseline evaluation.

Individuals with immunosuppressive conditions or who are being treated with immunosuppressive agents should be evaluated and treated for LTBI, either at the time that the condition is diagnosed or before starting treatment with immunosuppressive therapies such as prolonged corticosteroids and TNF-alpha antagonists (infliximab, etanercept and adalimumab). Patients awaiting transplant should be evaluated for LTBI and a TST result of greater than 5 mm should be considered indicative of TB infection in all such individuals. TST results in immunosuppressed individuals may be falsely negative, either due to the drug therapy or to the underlying medical condition causing anergy. The individual may still be infected with *M. tb* and some experts recommend 2-step testing as this may increase the yield of positive TSTs (blood-based tests have not yet been studied adequately in such cases).

Testing and treatment recommendations for children and adolescents were published in October 2004 by the Pediatric Tuberculosis Collaborative Group (for more information, visit: <http://pediatrics.aappublications.org/cgi/content/extract/114/4/S2/v>).

Targeted testing in children and adolescents should focus on pediatric populations at high risk for LTBI, and those at risk of progression to TB. Groups of children and adolescents who should be tested are high risk cases such as those who have had contact with an infected person, recent immigrants from high-TB-incidence countries and those at high risk of progression due to underlying conditions (See p. 174 and p. 175, Tables X-1 and X-2.) A risk-assessment questionnaire should be used to screen children and adolescents for risk factors for TB disease and LTBI. (See p. 177, Table X-3 for a sample questionnaire.)

Children should be tested only if one or more risk factor is present. Administrative or mandated tests for TB infection for entry to day care, school,

Table X-3

Sample Risk Assessment Questionnaire for Children*

Ask the following questions:

1. Was your child born outside the United States?

If yes, and the child was born in Africa, Asia, Latin America or Eastern Europe, a test for TB infection should be administered.

2. Has your child traveled outside the United States?

If yes, and the child stayed with friends or family members in Africa, Asia, Latin America or Eastern Europe for > 1 month cumulatively, a test for TB infection should be administered.

3. Has your child been exposed to anyone with TB disease?

If yes, and it has been confirmed that the child has been exposed to someone with suspected or known TB disease, a test for TB infection should be administered, and the Health Department should be notified.

4. Does your child have close contact with a person who had a positive test for TB infection?

If yes, proceed as in question 3 (above).

Risk assessment questionnaires can include the following questions, based on local epidemiology and priorities:

1. Does your child spend time with anyone who has been in jail (or prison), who is in a shelter, who uses illegal drugs or who has HIV?

2. Has your child consumed dairy products obtained from abroad such as raw milk or fresh cheese?

3. Does your child have a household member or caregiver who was born outside the United States?

4. Does your child have a household member or caregiver who has traveled outside the United States?

* Adapted from The Pediatric Tuberculosis Collaborative Group: Targeted tuberculin skin testing and treatment of latent tuberculosis infection in children and adolescents. *Pediatrics*, 2004;114(4):1175-1201

summer camp or college are discouraged in the absence of risk factors. However, in NYC, many children and adolescents will still need to be

tested for LTBI because of requirements based on the NYC Health Code and NY State regulations.

Administering the Tuberculin Skin Test

The TST should be administered by the Mantoux technique, in which PPD tuberculin is injected intradermally with a needle and syringe. Multiple-puncture tests (e.g., the Tine test) should not be used, even in infants and children, as this type of test is much less accurate than a properly administered Mantoux test.

TST by the Mantoux technique should be administered in the following manner:

Preparation

- Wash hands and put on gloves. If no water is available, use an appropriate skin-cleaning product (e.g., an antibacterial towelette).
- Check PPD vial's expiration/opening date.
- Place patient's arm on a flat surface, exposing the volar (inside) surface of the forearm.
- Locate site for the injection (2-4 inches below elbow, where no scars, bumps or veins are located).
- Clean the injection site with an alcohol swab.
- Wipe the top of the PPD vial with a second alcohol swab and place the vial on a flat surface.
- Use a short, disposable 26-gauge syringe needle.
- Prepare the syringe by inserting it into the vial. Inject 0.1 ml of air into the airspace in the vial. Do not inject air into the PPD solution.
- Invert the vial, keeping the needle tip below fluid level.
- Pull back on the plunger of the syringe and draw slightly more than 0.1 ml of PPD solution.
- Remove the syringe from the vial and tap the syringe lightly to dispel air bubbles. Hold the syringe point up and expel air and/or excess fluid, leaving exactly 0.1 ml of PPD solution in the syringe.
- Return the PPD vial to the refrigerator when not in use and place on a cooling pad when in use.

Injection

- Stretch the skin of the injection site with the thumb of the non-dominant hand (e.g., left hand for right-handed persons).
- Hold the syringe between the thumb and forefinger of the dominant hand, (e.g., right hand for right-handed persons) with the bevel of the needle pointing upward. Insert the needle intradermally (just under the top layer of skin) at a 5°-15° angle.
- Inject the PPD solution slowly. A firm resistance should be felt as the tuberculin solution enters the skin. Ensure that the entire needle bevel lies just under the skin.
- Release the stretched skin and remove the needle from the injection site (**DO NOT RECAP**). Discard the syringe immediately in a sharps container.
- Ensure that a discrete skin elevation (wheal), 6 to 10 mm in diameter, has been formed (measure wheal using a TST ruler). If the injection angle was too deep, no wheal will appear. If the angle was too shallow, fluid may leak. Be sure to check for leakage at the insertion site.
- Repeat injection 2 inches (5 cm) from site, or on opposite arm, if wheal is smaller than 6 mm or if less than 0.1 ml was injected (both tests need to be documented; [see below]). If, after a second injection, the wheal is still less than 6 mm or not enough fluid is injected, chest center staff should speak with a supervisor.

Post-Injection

- Educate the patient on the possible reactions to the TST, (e.g., mild itching, swelling, irritation).
- Instruct patient not to rub, scratch or put an adhesive bandage or lotion on the test site. The area may be washed and patted dry.
- Document the test in the patient's chart (including second test if done).
- Schedule reading date and explain the importance of the patient returning for reading in 48 to 72 hours.

Note: Vaccination with live attenuated viral vaccines such as measles, mumps and/or rubella (MMR) can cause a false-negative reaction to the TST. The TST can be administered on the same day as the live vaccine, because immunosuppression does not appear until after the first 48 hours post-vaccination. If a skin test is needed, and was not given in conjunction with the vaccination, wait 4-6 weeks before administering it.

Reading the Tuberculin Skin Test Reaction

The test result should be read only by a trained health care worker. Patients should never be allowed to read their own reaction. The following procedure should be used to read the reaction:

- Read the result 48 to 72 hours after administering the test.
- Inspect the injection site for raised areas.
- Palpate the arm for a hard, raised area known as an induration. Feel the edges of the induration with the index finger.
- Mark the 2 edges of the induration with a dot, using a black, watermark pen, if available.
- Measure the induration (not redness) at its widest point transversely, from 1 marked edge to the other, using a flexible TST ruler. If the reading is between 2 points, the lower value should be used. Swollen areas, if they feel hard, (but not red areas) should be palpated and included in the measurement.
- Record the size in millimeters and not simply as “positive” or “negative.” If there is no induration, record the result as “00 mm.”
- Interpret the reaction as positive or negative based on both the size of the induration and the individual’s risk factors (see p. 180, Table X-4).
- Explain the meaning of a positive or negative reaction to the individual and refer for follow-up evaluation, if needed. Provide appropriate literature.

If the patient fails to return for the scheduled reading but returns up to a week after the test, examine the test site and measure any induration present; if it is large enough to be classified as positive, record the result. No further testing is needed. If there is no reaction, or the induration is too small to be classified as positive, repeat the test. A repeat test can be given immediately.

Interpretation of the Tuberculin Skin Test Reaction

Whether a reaction to the TST is classified as positive depends on both the size of the induration and the person’s medical and epidemiologic risk factors for TB. (See p. 180, Table X-4.)

Patients who have a positive TST reaction should undergo clinical evaluation, including a chest X-ray (CXR) to rule out TB. (See p. 189.) If the initial CXR is normal, repeated ones are not indicated unless the individual develops signs or symptoms of TB. TST-positive individuals should be started on treatment for LTBI according to the guidelines in Section XI. (See also p. 181, Table X-5, for false-negative and false-positive reactions.)

An individual with either TB symptoms or an abnormal CXR should be appropriately evaluated using sputa and other tests as indicated. Active pulmonary or extra-pulmonary TB should be ruled out before treatment for LTBI is started.

Documentation of the results should be provided to the individual as repeat testing in the future is not necessary once a TST or blood-based test is determined to be positive.

Interpretation of the Tuberculin Skin Test in Bacille Calmette-Guérin-Vaccinated Individuals

BCG vaccine is used in many countries to protect children against some forms of TB disease. However, its efficacy in preventing TB in adults is variable and controversial. TST-positive persons from countries where TB is common are likely to be infected with TB and are at risk of developing active TB disease, even if they have been vaccinated with BCG.

Table X-4

Determination of a Positive Tuberculin Skin Test

The reaction to a TST is classified as positive based on the individual’s risk factor(s) and the following measurements of induration:

Test Result	Considered Positive In:
≥ 5 mm	<ul style="list-style-type: none"> • Persons with HIV infection • Recent contacts of persons with active tuberculosis (TB) • Persons with evidence of old, healed TB lesions on chest X-rays • Persons with organ transplants and other immunosuppressed persons, such as patients receiving prolonged corticosteroid therapy (the equivalent of more than 15 mg/d of prednisone for 1 month or more), TNF-α blockers and chemotherapy
≥ 10 mm	<ul style="list-style-type: none"> • Persons who have immigrated within the past 5 years from areas with high TB rates (see Table X-2). • Injection drug users • Persons who live or work in institutional settings where exposure to TB may be likely (e.g., hospitals, prisons, homeless shelters, single room occupancy units, nursing homes) • Mycobacteriology laboratory personnel • Persons with clinical conditions associated with increased risk of progression to active TB, including: <ul style="list-style-type: none"> • Silicosis • Chronic renal failure • Diabetes mellitus • Gastrectomy/jejunioileal bypass • Certain hematologic disorders, such as leukemias or lymphomas • Specific malignancies, such as carcinoma of the head, neck or lung • Body weight equal to or greater than 10% below ideal or BMI lower than 18.5 • Children less than 5 years of age or children/adolescents exposed to adults in high-risk categories • Persons with a prolonged stay (more than 1 month) in areas with high TB rates (see Table X-2)
≥ 15 mm	<ul style="list-style-type: none"> • Persons at low risk for TB disease, for whom testing is not generally indicated

Table X-5

Factors Associated with False-Negative or False-Positive Tuberculin Skin Test Reactions*

Factors	False-negative Reactions	False-positive Reactions
Infections	<ul style="list-style-type: none"> • Viral illnesses (HIV, measles, varicella) • Bacterial illnesses (typhoid fever, pertussis, brucellosis, typhus, leprosy) • Early TB infection (< 12 wks.) • Severe TB disease (meningitis, miliary) • Fungal disease 	Exposure to nontuberculous mycobacteria (e.g., <i>M. marinum</i> , <i>M. kansasii</i>)
Live virus vaccines	<ul style="list-style-type: none"> • Measles • Polio • Varicella • Smallpox 	Bacille Calmette-Guérin vaccine
Concomitant medical conditions	<ul style="list-style-type: none"> • Metabolic abnormalities • Chronic renal failure • Primary immunodeficiencies • Malignancies (e.g., Hodgkin's disease, lymphoma, leukemia) • Sarcoidosis • Poor nutrition • Newborns and children < 2 years of age • Low protein states 	Transfusion with whole blood from donors with known positive tuberculin skin test
Drugs and technical factors	<ul style="list-style-type: none"> • Corticosteroids or other immunosuppressive medications • Chemotherapy • Material—poor quality, inadequate dose (1 TU), improper storage (exposure to heat/light), expired • Administration—not injected intradermally; too long in syringe • Reading—inexperienced or biased reader; recording error, read too early/late 	Inexperienced or biased reader
Interpretative	Decreasing mm induration	Increasing mm induration

* Adapted from: The Pediatric Tuberculosis Collaborative Group: Targeted Tuberculin Skin Testing and Treatment of Latent Tuberculosis Infection in Children and Adolescents *Pediatrics*, 2004;114(4):1175-1201

BCG vaccination complicates the interpretation of TST results because it can produce a false-positive reaction to the TST, especially if BCG was given after age 1 year. There is no way to distinguish between a positive reaction due to BCG vaccination and a positive reaction due to LTBI. In BCG-vaccinated persons, however, sensitivity to tuberculin is highly variable, but the effect of BCG wanes with time. (BCG given only at birth does not appear to be a significant cause of false-positive TST reactions, especially after the age of 5 years.)

In general, a history of vaccination with BCG should not influence the need for tuberculin skin testing, the interpretation of the TST reaction or clinical decisions regarding the management of individuals who are TST positive. (Exceptions include cases where BCG was given within the last 12 months and where the patient is from a low-incidence country. [See p. 175, Table X-2.]

In BCG-vaccinated persons who did not receive the vaccine within the last 12 months, the TST reaction should be classified according to the guidelines described on p. 180, Table X-4. In particular:

- Patients who are close contacts of an individual with pulmonary or laryngeal TB disease are considered TST positive if they have a reaction greater than or equal to 5 mm, regardless of their BCG status. TST-positive contacts are candidates for treatment for LTBI (see p. 192).
- Patients who are from a high-incidence country (see p. 175, Table X-2) and who have no other risk factors are considered TST positive if they have a reaction of greater than or equal to 10 mm, regardless of their BCG status. (This is true even if the BCG was given within the last 12 months.)

Patients who are not from a high-incidence country (see p. 175, Table X-2) and who have no other risk factors are considered TST-positive if they have a reaction of greater than or equal to 15 mm, regardless of their BCG status.

Patients who were given BCG within the last 12 months and who are from countries where there is a low prevalence of TB should not be given a TST. If such a person is at risk for TB disease (e.g., a close contact), he/she should undergo a CXR and clinical examination to rule out active TB disease.

There may be patients who were given BCG within the last 12 months and who are from a low-prevalence country, but present at the center with a recent, documented TST reaction. If the induration is less than 15 mm, it should be considered negative if, after a clinical evaluation, it is determined the person has no medical or epidemiological risk factors for TB as listed in Table X-1 (see p. 174). If the TST is greater than or equal to 15 mm, the person should receive a CXR and medical evaluation. If both are normal, treatment is not indicated unless the person is either a recent contact of an active TB case or is infected with HIV.

Role of Anergy Testing

Anergy is the inability to mount a delayed-type, cutaneous, cellular immune response. Patients who are anergic may have a negative TST reaction, even if they have LTBI.

In the United States, anergy testing is no longer recommended as part of routine screening for TB infection among individuals infected with HIV. It also has no role in the evaluation of contacts. In general, TST-negative, HIV-infected close contacts of a person with pulmonary or laryngeal TB should receive treatment for LTBI, whether or not they are TST-negative. HIV-infected individuals who are not known to be contacts should be evaluated for treatment for LTBI according to their risk for TB exposure and infection.

Two-Step Tuberculin Skin Testing

Background

In some TB-infected individuals, the ability to react to a TST diminishes over time. Thus, infected individuals who are skin tested many years after infection may have a negative TST reaction. However, if they are retested within the next year, they may have a positive reaction. This phenomenon, called the “booster phenomenon,” occurs because the first TST “boosted” the immune response that had diminished over the years. Boosting is most common in persons age 55 and older and can also occur in BCG-vaccinated persons.

The booster phenomenon can complicate the interpretation of TST results in settings where testing is done repeatedly since a boosted reaction to a second TST may be mistaken for a recent conversion. Consequently, an infection acquired years ago may be interpreted as recent infection.

To eliminate boosted reactions as a cause of confusion, individuals who will be tuberculin skin tested repeatedly should undergo 2-step testing the first time that they are tested. With this type of testing, an initial TST is done. If the result is negative, a second TST is given 1 to 3 weeks later. The result of the second test is then used as the baseline. If it is positive, the patient is considered infected. If it is negative, the patient is considered uninfected.

Candidates and Procedure for 2-Step Testing

Two-step testing should be offered to individuals who cannot document a history of a negative TST reaction within the past year and who will be tested repeatedly. This would include health care workers and employees or residents of congregate settings. The procedure is as follows:

- If the reaction to the initial TST is negative, repeat the TST in 1 to 3 weeks using the same dose and strength of tuberculin. Inject the tuberculin on the other forearm or at least 5 cm away from the original test site.
- If the reaction to the second TST is negative (see p. 179), classify the individual as uninfected (TB Class 0 or TB Class I).
- If the reaction to the second TST is positive (see p. 179), obtain a CXR; if it is abnormal, classify the individual as Class V and evaluate for TB disease (see p. 26) or for another pulmonary disorder. If the CXR is normal, classify the individual as Class II and evaluate for treatment for LTBI (see p. 189).

Individuals who can provide documentation of a negative reaction to a TST given within the preceding year should be given an initial TST and should be classified on the basis of that result. A second TST is not necessary because the earlier test is, in effect, the first step of a 2-step test.

Blood-Based Tests for Tuberculosis Infection: The QuantiFERON®-Gold Test

QuantiFERON®-TB Gold (QFT-G) is a new FDA-approved blood test for detection of TB infection. As a modern alternative to the 100-year-old tuberculin skin test (TST), QFT-G may offer clinicians a simpler, more accurate, reliable and convenient TB diagnostic tool. QFT-G is highly specific, and a positive test result is strongly predictive of true infection with *M. tb*. The test is approved as an aid for diagnosing both active TB disease and LTBI; however, it cannot differentiate between them.

The QFT-G test is an indirect test for *M. tb* infection, based on measurement of a cell-mediated immune response in infected individuals. The

Like the TST, the QFT is a useful, but imperfect, diagnostic aide. It should not replace clinical judgment.

T lymphocytes of these individuals are sensitized to *M. tb*. When whole blood is incubated with *M. tb*-specific antigens used in the test, the T lymphocytes secrete interferon-gamma (IFN- γ), which is measured via a sensitive enzyme-linked immunosorbent assay (ELISA).

Advantages of the QFT-G Test

QFT-G specifically detects responses to 2 proteins, Early Secretory Antigenic Target-6 (ESAT-6), and Culture Filtrate Protein-10 (CFP-10), which are made by *M. tb*. These proteins are absent from all BCG vaccine preparations and from all environmental, i.e., nontuberculous mycobacteria (NTM), with the exception of *M.kansasii*, *M.marinum* and *M.szulgai*. As a result, the QFT-G test is completely unaffected both by the tested individual's BCG vaccination status and by the individual's sensitization to the majority of NTMs, thus providing a more accurate test of TB infection.

QFT-G	vs.	TST
<ul style="list-style-type: none"> • <i>In vitro</i>, controlled laboratory test with minimal inter-reader variability • <i>M. tb</i>-specific antigens used • No boosting; 2-step testing not needed • One patient visit possible • Unaffected by BCG or most environmental mycobacteria • Simple positive/negative result • Ability to predict the risk of LTBI progression to TB disease has not yet been determined in high-risk patients 		<ul style="list-style-type: none"> • <i>In vivo</i>, subject to errors during implantation and interpretation • Less specific PPD used • Boosting, with repeated testing • Two patient visits minimum • False-positive tests can occur after BCG and environmental mycobacteria exposure • Interpretation based on patient's risk of TB or development of disease

Abbreviations: LTBI = latent tuberculosis infection, PPD = purified protein derivative, QFT-G = QuantiFERON®-TB Gold test, TB = tuberculosis, TST = tuberculin skin test

Limitations of the QFT-G Test

At present, the major drawback to this test is that blood samples must be processed within 12 hours of the blood draw. In addition, the test has not been studied in many groups, including children, those with impaired immune function and with those with contacts to active TB cases. The ability of QFT-G to predict risk of LTBI progression to TB disease has not yet been determined. The risk of TB may be different from the risk in individuals with a positive TST.

Eligibility and Interpretation of the Results of the QFT-G Test

The QFT-G can be used to assess any patient for LTBI who is a candidate for a TST. It can also be used to aid in the diagnosis of active TB. However, it should **not** be used for patients

currently receiving anti-TB drugs for active TB, or for patients receiving treatment for LTBI. The test is reported as positive, negative and indeterminate, and the actual concentration level of IFN- γ is also reported.

Negative: A test is considered negative if the IFN- γ concentration is less than 0.35 IU/mL. A negative QFT-G result should be interpreted as a negative TST result: no further TB evaluation is needed unless indicated by clinical judgment.

Positive: A test is considered positive if the IFN- γ concentration is greater than 0.35 IU/mL. A positive QFT-G result should be interpreted as a positive TST result: medical evaluation and CXRs are still needed to exclude TB disease and to confirm LTBI.

Indeterminate: A test is considered indeterminate if the QFT-G results cannot be interpreted due to a response by the control groups. Repeat QFT-G or administer TST as diagnostic aide for TB or LTBI. QFT-G results may be indeterminate due to laboratory error or patient anergy. If 2 different specimens from a patient yield indeterminate results, do not repeat QFT-G for that person.

Costs and Benefits of the QFT-G Test

QFT-G can yield cost savings in terms of medical staff time—both by elimination of a second patient visit for test interpretation and by the elimination of common false-positive results, which typically involve both unnecessary follow-up testing and treatment for LTBI.

QFT-G can eliminate the need for the repeat 2-step testing that is required when TST is used for screening health care workers. That, in turn, may lower the administrative cost of maintaining testing compliance in health care facilities, which may offset the slightly higher cost of QFT-G, compared to TST.

Future Blood-Based Assays

Newer versions of the QuantiFERON® tests, which may address some of the limitations of the QFT-G, may be available in the near future. In addition, other blood-based tests are in development or under FDA review. TB diagnosis is a rapidly evolving field, and these guidelines may change as more data becomes available.

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Tuberculosis

Section XI.

Latent Tuberculosis Infection:
Evaluation, Treatment,
Monitoring and Follow-Up

Section XI.

Latent Tuberculosis Infection: Evaluation, Treatment, Monitoring and Follow-Up

Note: The term “tuberculin skin testing” (TST) is no longer used as it does not reflect the availability of blood-based tests for tuberculosis infection. A more general term, test for TB infection (TTBI), is used except in specific instances that reference the TST.

When a patient has been found to have latent TB infection (LTBI), based on the criteria detailed in Section X, the physician must make a treatment decision. Not everyone with latent infection is a candidate for treatment. However, all high-risk individuals who test positive for TB infection (see p. 174, Table X-1 and p. 180, Table X-4) should receive treatment for LTBI as soon as active TB has been ruled out.

Clinical Evaluation

Every patient who tests positive for TB infection should be examined by a physician, both to rule out TB disease and to be evaluated for treatment of LTBI. The clinical evaluation should include the elements listed below:

Medical History and Physical Examination

All patients should be asked about risk factors for the development of TB disease, including recent close contact with a person who has TB. Some patients, however, are not aware that they are contacts. For that reason, the TB Registry should also be checked to determine if the patient has been reported as a contact.

All patients should be asked about previous treatment for LTBI (the patient may refer to it as “preventive treatment”). Those who have completed a course of treatment for LTBI in the past should be asked about recent close contact with a person who has TB. In some situations, a chest X-ray (CXR) and a repeat course of treatment for LTBI may be indicated. (see p. 193).

All patients 18 years of age or older, including those without behavioral risk factors for HIV, should be counseled and offered HIV testing unless they have documentation of (1) a positive HIV antibody test or (2) a negative HIV antibody test obtained within the last 6 months.

Those younger than 18 years should be counseled and offered testing if they have behavioral risk factors for HIV and have no documented history of a positive HIV test. Parental consent for HIV testing is advised for patients younger than 18 years of age (see p. 26).

All patients should be evaluated for, and asked about, their history of alcohol ingestion, liver disease and hepatitis. See p. 190 for specific tests that should be ordered.

All patients should be assessed for contraindications to treatment for LTBI.

Chest X-ray

Everyone considered for LTBI treatment should undergo a CXR to rule out pulmonary TB disease. Children younger than 5 years of age (i.e., up to the day of their 5th birthday) should have both a posterior-anterior and a lateral CXR. All others should undergo a posterior-anterior CXR only. Additional X-rays should be done at the physician’s discretion. In general, if a CXR is done within 3 months of the medical evaluation and is documented as normal, a repeat CXR is not necessary unless the patient is currently symptomatic, immunosuppressed or a child younger than 5 years of age. In these cases the CXR should be taken within 1 month.

Patient Chest X-ray Classifications

A patient who has:

- A normal CXR, a positive test for TTBI and no signs or symptoms of TB disease should be classified as Class II.

- An abnormal CXR consistent with active TB disease should be classified as Class V (High), and should be managed according to Sections II and III of this manual.
- A CXR showing noncalcified fibrotic lesions, suggestive of old, healed TB, should be evaluated for current symptoms of TB. Physicians should take a complete blood count, chemistry panel, hepatitis screen and 3 consecutive sputum samples for smear, culture and susceptibility testing.
 - If there are no symptoms, classify the individual as Class V (Low), and follow the guidelines for treatment outlined on page 200.
 - If sputum cultures are negative for *M. tuberculosis* (*M. tb*) and the follow-up CXR at 2 months shows no change, reclassify the individual as Class IV.
 - If there are symptoms, classify the individual as Class V (High) and evaluate and treat for TB disease according to Sections II and III of this manual. If sputum cultures are positive for *M. tb*, if the follow-up CXR shows improvement, or if the patient responds clinically, reclassify the individual as Class III.

Some individuals appear at a Bureau of Tuberculosis Control (BTBC) chest center, with a report of a positive TTBI and a normal CXR, and request treatment for LTBI. In this case, the CXR report should be given to a center physician, who should decide whether a repeat CXR is indicated. In general, a repeat CXR should be obtained if:

- The original CXR was taken more than 3 months ago.
- The language in the CXR report is ambiguous, regardless of the date the CXR was taken.
- The individual currently has symptoms consistent with TB.

A CXR should be obtained immediately, even during the first trimester, for pregnant women:

- Who have symptoms that are highly suggestive of TB disease (e.g., prolonged cough, fever, night sweats, chest pain)

- Who are HIV-positive and (1) have a positive TTBI or (2) have a negative TTBI, but have been in close contact with a person who has pulmonary or laryngeal TB disease.

Other pregnant women who have a positive TTBI should be advised to obtain a CXR after the end of the first trimester.

A lead shield should be used for all pregnant women receiving CXR. Many are hesitant to receive CXR, because they fear exposing the fetus to unnecessary radiation. It should be stressed that the amount of radiation is minimal. (Explain that the patient would get the same amount of radiation by flying cross country in an airplane.) Also, the risk of untreated TB in a pregnant woman and the subsequent possibility of congenital TB in her infant far outweighs the risk from the small amount of radiation exposure.

Laboratory Tests for Individuals Being Considered for Latent Tuberculosis Infection Treatment

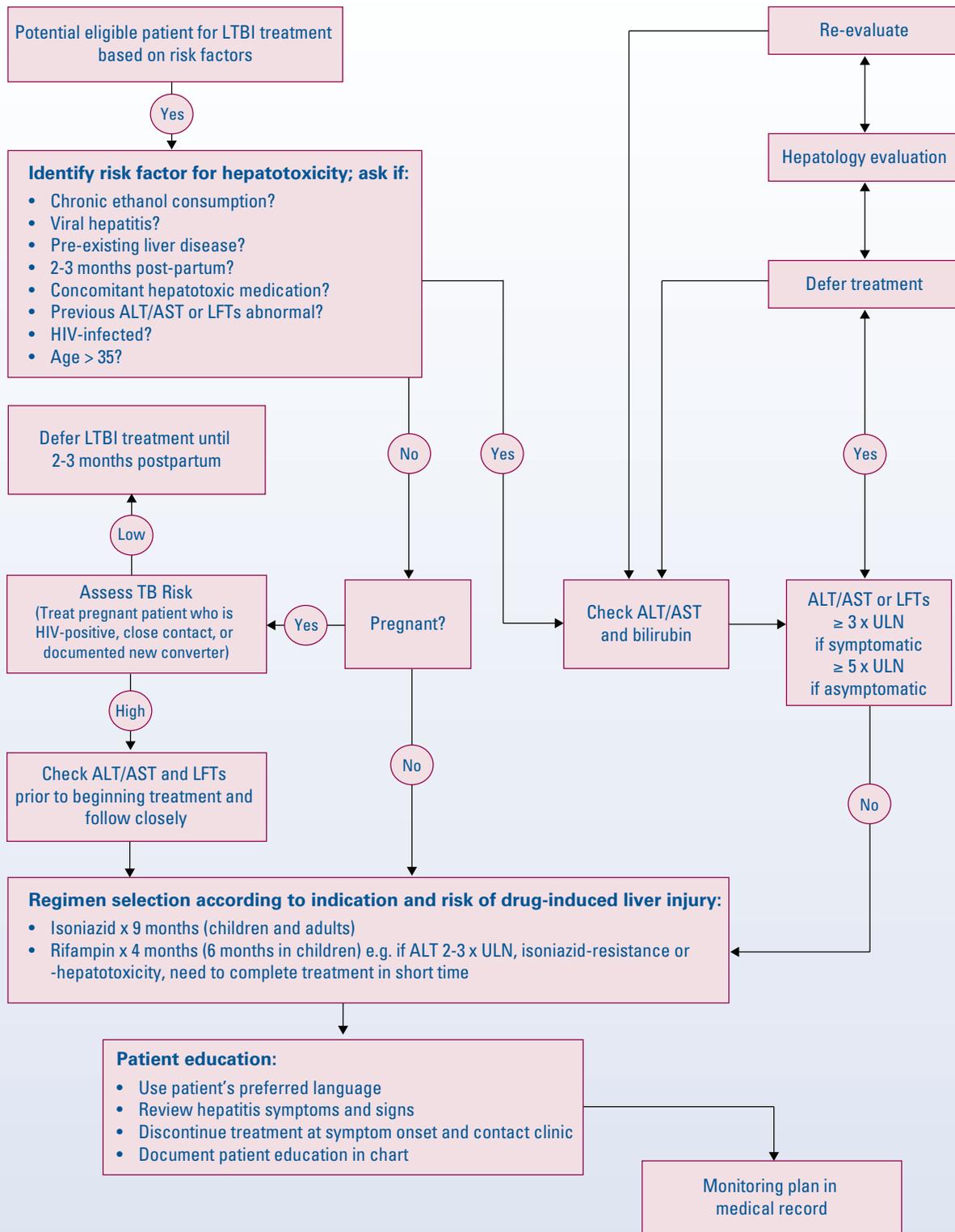
A complete blood cell count (CBC) and baseline liver function tests (LFTs) (AST/SGOT, ALT/SGPT, alkaline phosphatase, and total bilirubin), as well as a viral hepatitis screening profile, should be obtained for patients who:

- Are HIV-positive
- Have a history of heavy alcohol ingestion, liver disease or chronic hepatitis
- Are pregnant or are postpartum (up to 2-3 months after delivery)
- Have a history of drug injection
- Are older than 35 years
- Are starting treatment for LTBI with 2 or more anti-TB drugs
- Are already taking hepatotoxic drugs for other medical conditions

All abnormal test results should be evaluated by a physician as soon as possible and in all cases within 2 days of starting LTBI treatment. The physician should document follow-up in the medical record. See p. 191, Figure XI-1 for pretreatment clinical evaluation and counseling for LTBI.

Figure XI-1

Latent Tuberculosis Infection Pretreatment Clinical Evaluation and Counseling



Adapted from ATS Hepatotoxicity Statement (see Key Sources at end of section for full citation).

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, LFT = liver function test, LTBI = latent tuberculosis infection, TB = tuberculosis, ULN = upper limit of normal

XI. LATENT TB INFECTION (LTBI): EVALUATION, TREATMENT, MONITORING AND FOLLOW-UP

Candidates for Treatment For Latent Tuberculosis Infection

High-risk individuals fall into 2 categories (1) people presumed to have been recently infected, and (2) people whose underlying medical conditions substantially increase their risk of developing active TB disease. (See p. 174, Table X-1.) Routine testing of individuals at low risk for developing TB is *not* recommended.

Individuals Who May Have Been Recently Infected

- All close contacts of a person who has pulmonary or laryngeal TB (who have newly tested positive for TB infection) should be treated. See p. 163 for how to manage contacts with previously positive TTBI.
- Recent tuberculin skin test (TST) converters (who show an increase greater than or equal to 10 mm within a 2-year period) may have recent infection. When a TST-positive patient claims to have had a negative reaction to a Mantoux (not Tine) TST given in the past 2 years but cannot document it, accept the statement if the patient's history is reliable *and* if he or she is considered a recent converter. This protocol does *not* apply if the previous test was a Tine test.
- People who test positive for TB infection, or who have emigrated to the U.S. within the past 5 years from areas with high TB rates, or who have been abroad for more than 1 month in areas with high TB rates should be treated (see p. 175, Table X-2).

Patients with Clinical Conditions Associated with Progression From Latent Tuberculosis Infection to Active Tuberculosis

People who:

- Are HIV positive and those with behavioral risk factors for HIV infection who decline HIV testing
- Inject drugs, particularly those who also have HIV infection
- Show evidence of old, healed TB lesions on CXR. (See p. 200.)
- Are $\geq 10\%$ under ideal body weight

- Have clinical conditions that lead to a stressed or incompetent immune system, such as diabetes mellitus; silicosis; cancer of the head, neck or lung; hematologic and reticuloendothelial malignancies (e.g., leukemia or Hodgkin's disease); end-stage renal disease; intestinal bypass or gastrectomy; and chronic malabsorption syndromes
- Are receiving immunosuppressive therapy (i.e., prolonged corticosteroid therapy [the equivalent of greater than 15 mg/d of prednisone for 1 month or more], chemotherapy and tumor necrosis factor-alpha antagonists).
- Have diabetes mellitus and thus have an increased risk of progressing from latent infection to active TB. This is particularly true for insulin-dependent diabetics and for those with poorly controlled disease. If such individuals test positive for TB infection, they should be treated for LTBI regardless of age. Those whose diabetes is well controlled on oral agents or through diet, who do not have additional clinical conditions associated with increased risk of progression to active TB, or who do not have factors associated with recent infection should not be considered for treatment.

For guidelines on when to give a repeat course of treatment for LTBI in contacts that have already completed such treatment, see p. 193.

Persons with Immunosuppressive Conditions or Who Are Being Treated with Immunosuppressive Agents

- Evaluation and treatment for LTBI is recommended at the time the immunosuppressive condition is diagnosed or before starting treatment with immunosuppressive therapies such as prolonged corticosteroids; tumor necrosis factor-alpha antagonists (infliximab, etanercept, adalimumab) and chemotherapy.
- Patients awaiting transplant should be evaluated for LTBI.
- A TST result of greater than 5 mm should be considered indicative of TB infection in all these individuals. (See p. 180, Table X-4.) TST results in immunosuppressed individuals may be falsely negative due to drug therapy or to an underlying medical condition causing anergy. The individual may still be infected with *M. tb*. Two-step testing in these individuals

is recommended by some experts, as this may increase the yield of positive TSTs. Blood-based tests have not been studied in these individuals.

Contacts Who Should Start Treatment Regardless of Their Tuberculin Skin Test Reaction

People who have recently been exposed to TB may have a false-negative reaction to the test for TB infection. This may occur if they are tested within 8 weeks of their last exposure, even if they are truly infected. These patients should be retested 8 weeks after their last exposure. During the 8-week window between the 2 tests, the following individuals should start treatment for LTBI, even if the test is negative.

Contacts who are:

- Less than 5 years of age
- Between 5 and 15 years of age, at the physician's discretion
- HIV infected or otherwise immunosuppressed
- At behavioral risk for HIV infection who decline HIV testing

These contacts should undergo a CXR to rule out TB disease before starting treatment for LTBI.

If the second test for TB infection is negative, and the contact is not immunosuppressed, treatment may be discontinued. For most close contacts who are immunosuppressed or known to have HIV infection or who are at risk for HIV infection, a full course of treatment for LTBI is recommended—regardless of age or history of previous treatment (see p. 163.)

Pregnant Women as Candidates for Latent Tuberculosis Infection Treatment

Pregnant women should receive a TTBI only if they are in a high risk category. (See p. 174, Table X-1.) The need to treat active TB during pregnancy is unquestioned. Treatment of LTBI in pregnant women is more controversial, since the possible risk of hepatotoxicity must be weighed against the risk of developing active TB. However, for women who are HIV-positive, or have been recently infected (such as contacts of active TB cases or known recent conversions), start of therapy should not be delayed on the basis of pregnancy alone, even during the first trimester.

- Treatment should be started during the first trimester of pregnancy for:
 - TST-positive (≥ 5 mm) pregnant women who are HIV-positive or who have behavioral risk factors for HIV infection but decline HIV testing.
 - TST-positive (≥ 5 mm) pregnant women who have been in close contact with a smear-positive pulmonary TB patient. (At the physician's discretion, start of treatment can be delayed until after the second trimester but the patient should be under close observation for development of TB symptoms.)
- Treatment should be started promptly after the first trimester for pregnant women who have had a documented TST conversion in the past 2 years.
- Treatment, if indicated, should be started 2 to 3 months after delivery for all other pregnant women, including those with radiographic evidence of old, healed TB.

In pregnant women known or suspected to be infected with a TB strain resistant to at least isoniazid and rifampin, treatment for LTBI should be delayed until after delivery. This will avoid possible adverse effects of the medications on the developing fetus. A CXR should be obtained initially and again if the woman develops symptoms suggestive of TB disease. A lead shield should be used for CXRs in pregnant women. See p. 194, Figure XI-2 for evaluation of the pregnant woman at risk for TB.

See p. 196, Table XI-I for further information on LTBI treatment regimens for pregnant women.

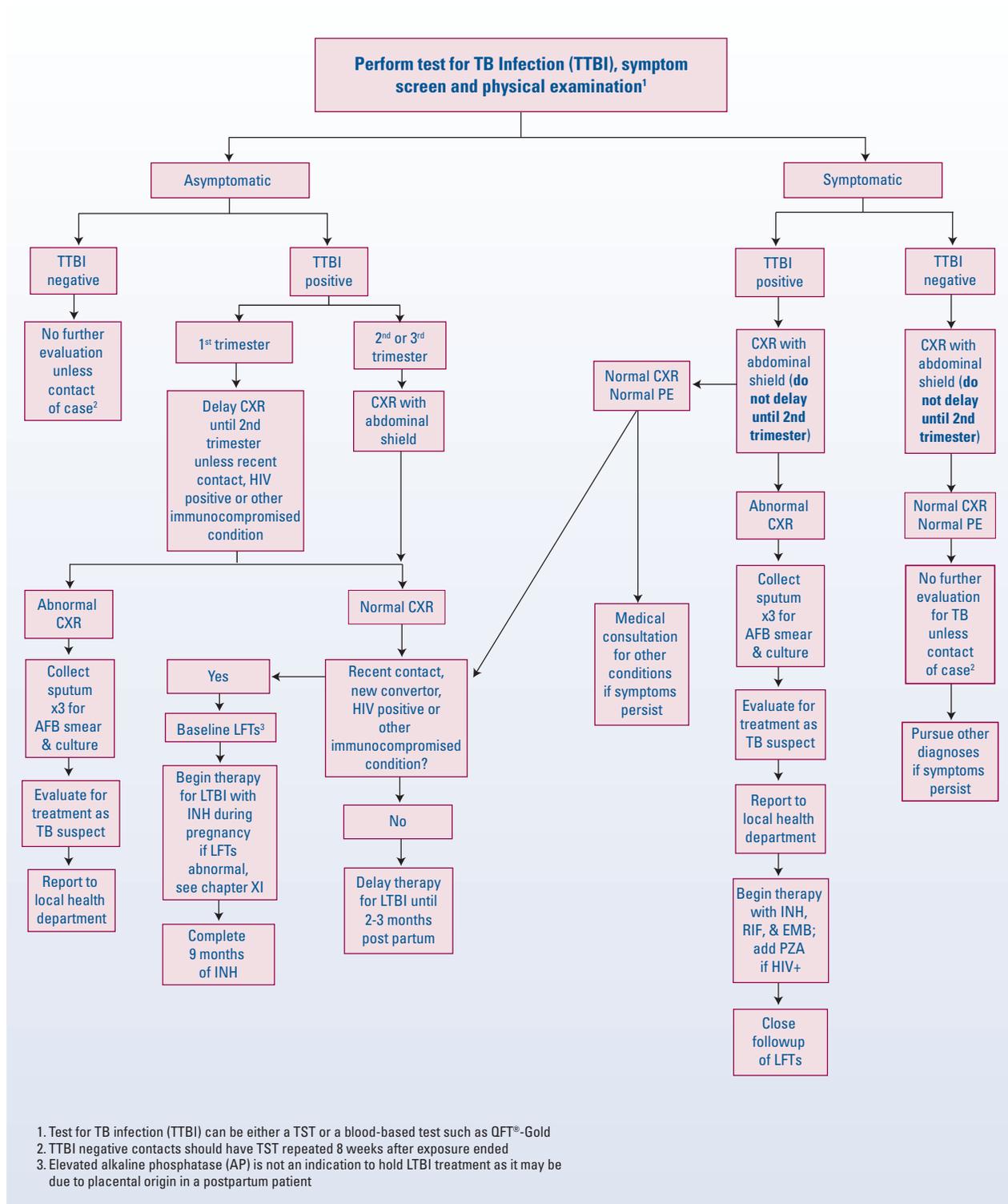
Children as Candidates for Latent Tuberculosis Infection Treatment

Children younger than 5 years old with LTBI have by definition been infected recently and are at high risk for progression to active TB. However, treatment is recommended for all children and adolescents diagnosed with LTBI because:

- The drugs used are safe in the pediatric population.
- Infection with *M. tb* is more likely to have been recent.
- Young children are at higher risk for progression to TB disease.

Figure XI-2

Evaluation of Pregnant Patients at Risk for Tuberculosis



Abbreviations: AFB = acid-fast bacilli, CXR = chest X-ray, EMB = ethambutol, INH = isoniazid, LFT = liver function test, LTBI = latent tuberculosis infection, PE = physical examination, PZA = pyrazinamide, RIF = rifampin, TTBI = test for tuberculosis infection

- Children have more years to potentially develop TB disease.

The recommended regimen for children (with or without HIV infection) is 9 months of isoniazid. The risk for isoniazid-related hepatitis is minimal in infants and children, who generally tolerate the drug better than adults. Vitamin B₆ should be given to undernourished or HIV-infected children treated with isoniazid. Children (with or without HIV infection) who have been exposed to a person with isoniazid-resistant, rifampin-susceptible TB, or who are intolerant to isoniazid, should be treated with at least 6 months of rifampin. (See p. 196, Table XI-1.)

Latent Tuberculosis Infection Treatment Regimens

Standard Regimen: Isoniazid

The optimal regimen for treatment for LTBI for all individuals is isoniazid, given daily or twice weekly for 9 months (see p. 196, Table XI-1). For adults who are HIV negative, 6 months of isoniazid is an acceptable alternative if the 9-month regimen cannot be given. However, 6 months of isoniazid is not recommended for HIV-positive persons, children younger than 18 years of age and individuals with fibrotic lesions consistent with TB on CXR. The 9-month regimen may be administered concurrently with any antiretroviral regimen used to treat HIV infection (see p. 196, Table XI-1).

Contraindications to treatment for LTBI with isoniazid are:

- A history of an isoniazid-induced reaction, including hepatic, skin or allergic reactions, or neuropathy
- Close contact with a person who has isoniazid-resistant TB
- Severe chronic liver disease
- Pregnancy, unless the woman is HIV infected, a recent TST converter or a close contact (see p. 193).

The risk of isoniazid toxicity has been shown to increase with age, in particular in persons older than 55 years of age. Those who are contacts, or who have clinical conditions associated

with increased risk of progression to active TB, should be treated regardless of age. However, the risk-benefit ratio from isoniazid may not favor treatment of patients older than 55 years whose only risk factor is recent immigration. This group should be closely monitored for isoniazid toxicity and should even possibly be excluded from treatment.

Directly Observed Therapy (DOT) for LTBI is an excellent method for promoting adherence to treatment. Because of limited resources, however, DOT cannot be offered to all patients receiving LTBI treatment through the BTBC. Currently, the principal candidates for Bureau-provided LTBI DOT are household contacts of patients with TB disease who are receiving home-based DOT. Patients receiving DOT treatment for LTBI may be candidates for intermittent therapy.

Alternative Regimen: Rifampin

An alternative regimen to isoniazid is to give adult patients (with or without HIV infection) 4 months of rifampin for treatment of LTBI (see p. 196, Table XI-1). This course is especially recommended if there are adverse reactions or resistance to isoniazid, but not to rifampin; or if the individual will not be available for more than 4 to 6 months and is thus unlikely to complete a 9-month isoniazid regimen.

If a rifampin-containing regimen is chosen for HIV-infected patients with LTBI, the drug-drug interactions and dose adjustments for antiretroviral drugs and rifamycin apply as indicated on p. 54, Figure III-2; p. 55, Table III-3; and p. 196, Table XI-1.

Children (with or without HIV infection) who have been exposed to isoniazid-resistant, rifampin-susceptible TB should be treated with at least 6 months of rifampin. Although isoniazid is the only drug that has been studied on a large scale for treatment for LTBI, rifampin is probably equally effective.

In many cases, rifabutin can be substituted for rifampin. Rifabutin may be used with regimens containing: (1) the non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz and nevirapine, or (2) many protease inhibitors (PIs). See p. 54, Figure III-2 and p. 55, Table III-3 for the recommended dosages of rifabutin, when it

Table XI-I

Treatment for Latent Tuberculosis Infection

Drug and Duration	Dosage		Major Adverse Reactions	Comments
	Daily	Twice Weekly	Recommended Monthly Monitoring ¹	
Isoniazid Children: 9 months Adults: 9 months	Children: 5-10 mg/kg (max 300 mg) Adults: 5 mg/kg (max 300 mg) Completion Criteria 270 doses within 12 months	Children: 20-30 mg/kg (max 900 mg) Adults: 15 mg/kg (max 900 mg) Completion Criteria 76 doses within 12 months	Symptoms: Unexplained anorexia, nausea, vomiting, dark urine, jaundice, persistent fatigue, weakness, abdominal tenderness (especially right upper quadrant discomfort), easy bruising or bleeding, rash, persistent paresthesias of the hands and feet, arthralgia Signs: Elevated LFTs, hepatitis, icterus, rash, peripheral neuropathy, increased phenytoin levels and possible interaction with disulfiram (Antabuse®) Clinical evaluation: LFTs (if baseline is abnormal or patient has risk factors for toxicity) ²	Preferred regimen for all individuals Vitamin B ₆ (25 mg/day) or pyridoxine may decrease peripheral and CNS effects, and should be used in patients who are: <ul style="list-style-type: none"> • Abusing alcohol • Pregnant • Breastfeeding infants on isoniazid • Malnourished Or who have: <ul style="list-style-type: none"> • HIV • Cancer • Chronic renal or liver disease • Diabetes • Pre-existing peripheral neuropathy <i>Note: aluminum-containing antacids reduce absorption.</i>
Rifampin Children: 6 months Adults: 4 months	Children: 10-20 mg/kg (max 600 mg) Completion Criteria 182 doses within 9 months Adults: 600 mg [range, 8-12 mg/kg] (max 600 mg) Completion Criteria 120 doses within 6 months	Children: Not recommended Adults ³ : 600 mg [range 8-12 mg/kg] (max 600 mg) Completion Criteria 34 doses within 6 months	Symptoms: Nausea, vomiting, loss of appetite, rash, fever or flu-like symptoms, easy bruising. Sign: Elevated LFTs, hepatitis, rash, thrombocytopenia Reduced levels of many drugs, including methadone, warfarin, hormonal contraception, oral hypoglycemic agents, theophylline, dapson, ketoconazole, PIs and NNRTIs Clinical evaluation: LFTs (if baseline is abnormal or patient has risk factors for toxicity) ² CBC, including platelets as needed	May be used to treat persons who have been exposed to isoniazid-resistant, rifampin-susceptible TB, or who have severe toxicity to isoniazid, or who are unlikely to be available for more than 4-6 months. Be aware that: <ul style="list-style-type: none"> • There will be orange discoloration of secretions, urine, tears and contact lenses. • Patients receiving methadone will need their methadone dosage increased by an average of 50% to avoid opioid withdrawal. • Interactions with many drugs can lead to decreased levels of either or both. • Rifampin may make glucose control more difficult in diabetics. • Rifampin is contraindicated for patients taking most PIs and NNRTIs.⁴ • Patients should be advised to use barrier contraceptives while on rifampin.

Abbreviations: CBC = complete blood count, CNS = central nervous system, LFTs = liver function tests, NNRTI = non-nucleoside reverse transcriptase inhibitors, PI = protease inhibitor, TB = tuberculosis

(Table XI-I cont.)

Drug and Duration	Dosage		Major Adverse Reactions	Comments
	Daily	Twice Weekly	Recommended Monthly Monitoring ¹	
Rifabutin Children: 6 months Adults: 4 months	Children: 5 mg/kg (max 300 mg) (Little data) Completion Criteria 182 doses within 9 months Adults: 5 mg/kg (max 300 mg) Completion Criteria 120 doses within 6 months	Children: Not recommended Adults ³ : 5 mg/kg (max 300 mg) Completion Criteria 34 doses within 6 months	Symptoms include: Stomach upset, chest pain, nausea, vomiting, headache, rash, muscle aches, redness and pain of the eye. Signs include: LFTs elevation, hepatitis, neutropenia, thrombocytopenia Reduced levels of many drugs including PIs, NNRTIs, dapsone, ketoconazole and hormonal contraception. However, some drugs, including PIs and some NNRTIs do increase levels of rifabutin. Clinical evaluation: LFTs (if baseline is abnormal or patient has risk factors for toxicity) ² . CBC, including platelets as needed	May be used to treat LTBI in HIV-infected patients who fit the criteria for rifampin treatment, but for whom rifampin is contraindicated, or for others who need a rifamycin but are not able to tolerate rifampin. Be aware that: <ul style="list-style-type: none"> • There will be orange discoloration of secretions, urine, tears and contact lenses. • Interaction occurs with many drugs. • For HIV-infected persons, it is necessary to adjust the daily or intermittent dose of rifabutin and monitor for decreased antiretroviral activity and for rifabutin toxicity, if taken concurrently with PIs and NNRTIs.⁴ • Methadone dosage generally does not need to be increased. • Patients should be advised to use barrier contraceptives.

Abbreviations: CBC = complete blood count, CNS = central nervous system, LFTs = liver function tests, NNRTI = non-nucleoside reverse transcriptase inhibitors, PI = protease inhibitor

1. Baseline LFTs should be done for everyone over the age of 35, all HIV-infected persons, pregnant and postpartum women (up to 2-3 months postpartum), those with history of hepatitis, liver disease or alcohol abuse, injection drug users and those on treatment with other potential hepatotoxic agents. A baseline CBC with platelets should be done on anyone prescribed a rifamycin-containing regimen.
2. Monthly LFTs should be conducted for all HIV-infected persons, pregnant and postpartum women (up to 2-3 months postpartum), those with history of hepatitis, liver disease or alcohol abuse, injection drug users and those on treatment with other potential hepatotoxic agents. Those whose baseline LFTs were abnormal should be monitored monthly, regardless of other conditions.
3. There is very little data or clinical experience on the use of intermittent treatment of latent TB infection with rifampin or rifabutin. These regimens should be used with caution.
4. Please see the NYC BTBC's HIV/TB treatment guidelines. (www.nyc.gov/html/doh/downloads/pdf/tb/tbanti.pdf).

is co-administered with these agents. There is insufficient data on the use of rifabutin in anti-retroviral regimens containing combinations of NNRTIs and PIs, or other multiple PI combinations.

Contraindications to use of rifampin for treating LTBI are:

- A history of rifampin-induced reactions, including skin and other allergic reactions, hepatitis or thrombocytopenia
- Severe chronic liver disease
- Pregnancy, unless the woman is HIV-infected, a recent TST converter, a close contact of an isoniazid-resistant case or is intolerant to isoniazid and needs to be treated (see p. 193).
- Current treatment with a PI or certain NNRTIs (an alternative is to use selected antiretroviral drugs with rifabutin, see above)

Rifampin and Pyrazinamide

The 2-month regimen containing rifampin and pyrazinamide as an option for LTBI treatment is no longer recommended due to high rates of hospitalization and death from liver injury associated with the use of a daily or twice-weekly 2-month regimen of rifampin plus pyrazinamide. As a result, this regimen should generally not be offered to HIV-negative or HIV-positive persons with LTBI.

Alternative Regimens for Contacts of Persons with Isoniazid- and Rifampin-Resistant Tuberculosis (Multidrug Resistant Contacts)

There have been no controlled trials of treatment for LTBI with drugs other than isoniazid and rifampin. Therefore, treatment protocols for contacts of patients with isoniazid- and rifampin-resistant TB (multidrug resistant TB or MDRTB) are largely empirical, and all regimens must be individualized. (See p.199, Table X1-2.) TB disease must be excluded before any therapy regimens for LTBI are initiated.

The following factors should be considered in decision-making:

- **HIV infection.** HIV infection is one of the most important risk factors for developing TB disease, and all contacts should be

strongly encouraged to undergo voluntary HIV counseling and testing.

- **The drug susceptibility pattern of the source patient.** The treatment regimen should be able to include 2 anti-TB medications that will treat the source patient's strain of TB.
- **Contact's risk factors for multidrug resistant TB (MDRTB) infection and disease.** Contacts who are not likely to be infected with MDRTB or who are at low risk of developing TB disease may not be candidates for an alternative treatment regimen.

In designing treatment, consider the following questions:

1. How likely is it that the individual is newly TB infected?

An individual with a documented prior positive test for TB infection is less likely to be newly infected and is probably not a candidate for alternative treatment for LTBI. By contrast, for example, an HIV-infected spouse of an individual with MDRTB whose 3 children have TST conversions is highly likely to be newly TB infected, even if the spouse's test for TB infection is negative.

2. How likely is it that the individual is infected with a strain of MDRTB?

- **Infectiousness of the source patient.** A source patient who is sputum acid-fast bacilli (AFB) smear positive, has cavitory disease and is coughing is much more infectious than one who is smear negative and not coughing. Also, a source patient whose contacts had TST conversions is more infectious than a source patient whose contacts did not have TST conversions.
- **Closeness and intensity of the MDRTB exposure.** Contacts are at higher risk for infection if they have (1) spent a prolonged period of time sharing air with a person who has MDRTB, (2) if they were exposed in a small, poorly ventilated area, or (3) if they were exposed during cough-inducing procedures (e.g., bronchoscopy, sputum induction, endotracheal intubation).

- **Contact’s risk of exposure to drug-susceptible TB.** Individuals who have been exposed to several sources of TB (e.g., health care workers or recent immigrants from high TB incidence areas) may be less likely to have been infected with a MDRTB strain than individuals whose only known exposure to TB was to an infectious MDRTB patient (e.g., a TST-positive infant of a mother with MDRTB).

3. How likely is an individual to develop TB disease?

Contacts are at high risk of developing TB disease if they have been recently infected, they are infants, or if they are HIV-infected or otherwise immunosuppressed (see p. 160).

4. What should be considered in making a final decision?

- **Low likelihood of infection with MDRTB.** If an individual is thought to be newly infected with non-MDRTB, contacts should be evaluated for treatment with isoniazid.
- **Intermediate or high likelihood of infection with MDRTB.** If an individual is thought to be newly infected, contacts should be evaluated for an alternative regimen for

treatment for LTBI, according to their age and immune status; specifically:

- o Those who are HIV-positive, otherwise immunosuppressed and younger than 5 years of age should be given multidrug treatment for LTBI with drugs other than isoniazid and rifampin (see p. 200, Table XI-3 for regimens).
- o Those who are HIV-negative, immunocompetent and younger than 5 years of age, should be managed according to 1 of the following 2 options:
 - Consider multidrug treatment for LTBI with anti-TB medications other than isoniazid or rifampin (see p. 200, Table XI-3 for regimens). This option is important for contacts who convert their TTBI.
 - Do not administer any treatment. Educate the patient about the symptoms of TB and evaluate by CXR and symptom review at 4, 8, 12, 18 and 24 months.

All patients starting treatment for LTBI with 2 or more drugs should have baseline LFTs, a complete blood count (CBC) and a viral hepatitis screen. The drug options for managing MDRTB patients are summarized on p. 201, Table XI-4.

Table XI-2

Likelihood of Infection with Multidrug-Resistant Tuberculosis Among Contacts Thought to Be Newly Infected*

Infectiousness of the Source MDRTB Patient	Closeness and Intensity of MDRTB Exposure	Contact’s Risk of Exposure to Drug-Susceptible TB	Estimated Likelihood of Infection with MDRTB
+	+	-	High
+	-	-	High-intermediate
-	+	-	High-intermediate
-	-	-	Intermediate
+	+	+	Intermediate
+	-	+	Low-intermediate
-	+	+	Low-intermediate
-	-	+	Low

Key: (+) = high; (-) = low

*Adapted from Centers for Disease Control and Infection. Management of persons exposed to multidrug-resistant TB. *Morb Mortal Wkly Rep.* 1992; 41:507-509.

Physicians confronted with the complexities of providing LTBI treatment to contacts of patients with MDRTB may consult with the Director of Medical Affairs for the BTBC.

Regimens for Women Who Become Pregnant while Taking Treatment for Latent Tuberculosis Infection

In general, treatment for LTBI should be discontinued in women who become pregnant while taking either isoniazid or rifampin, unless they are HIV positive or have risk factors for HIV; were a new converter when LTBI treatment was started; or are a contact to an infectious case. To reduce the risk of peripartum hepatitis, treatment for LTBI should not be restarted until 2-3 months after delivery. When treatment is restarted, a full course should be given (previous doses ignored).

However, females with a positive TTBI, and with certain risk factors, should continue therapy during pregnancy. For example:

- Women who are HIV-positive, have behavioral risk factors for HIV infection but decline HIV testing, or have been in close contact with an AFB smear-positive TB patient should continue treatment for LTBI, even during the first trimester.

- For women who have had a TTBI conversion within the past 2 years, treatment for LTBI should be discontinued during the first trimester and resumed at the beginning of the second trimester. When treatment is restarted, a full course should be given with no regard for previous doses.

Isoniazid is the preferred regimen for treatment of LTBI in pregnant women (see p. 196, Table XI-1). Extensive use of isoniazid during pregnancy indicates that it is not teratogenic, even when given during the first trimester of pregnancy. Pregnant women taking isoniazid should receive vitamin B₆. Breastfeeding is not contraindicated when the mother is being treated for LTBI. Vitamin B₆ is not indicated in nursing infants unless the baby is also being given isoniazid.

Regimens for Individuals with Radiographic Evidence of Old, Healed Tuberculosis (Classes IV and V)

- For asymptomatic individuals who have a TST reaction equal to or greater than 5 mm or a positive blood test for TB infection and a CXR that shows noncalcified fibrotic lesions suggestive of old, healed TB, treatment decision is based on clinical suspicion, prior TB treatment history, sputum results

Table XI-3

Options for Managing Contacts Likely to Be Infected with Multidrug-Resistant Tuberculosis*

Contact's Age and Immune Status	
Immunosuppressed or < 5 Years Old	Not Immunosuppressed and ≥ 5 Years Old
12 months of 2 drugs (no isoniazid or rifampin) [†]	6-12 months of 2 drugs ^{†, ‡} (no isoniazid or rifampin) Or No treatment. Medical evaluation and CXR at 4, 8, 12, 18 and 24 months

* "Likely to be infected" means an intermediate, high-intermediate or high likelihood of infection with MDRTB. (See also Table IX-1)

[†] Isoniazid may be considered for the regimen, in addition to the 2 indicated drugs, if the source patient's isolate is resistant at low concentrations (0.2 µg/ml) but is susceptible at high concentrations (1.0 µg/ml) of isoniazid. If isoniazid is added to the regimen, it should be given twice weekly at a dosage of 15 mg/kg for adults, or 20 mg/kg for children (maximum 900 mg per dose).

[‡] Suggested option for (1) recent test for TB infection converters, (2) persons with a high likelihood of infection with TB resistant to isoniazid and rifampin and (3) children 10-14 years of age who have an intermediate to high likelihood of infection with TB resistant to isoniazid and rifampin.

Table XI-4

Alternative Regimens for Preventive Treatment for Contacts Likely To Be Infected with Multidrug-Resistant Tuberculosis*

	Medications	Notes
Adults	Option I Pyrazinamide and Ethambutol	The New York City Bureau of Tuberculosis Control recommends 6-12 months of treatment with this regimen, as these drugs are bacteriostatic, not bactericidal. However, the Center for Disease Control and Prevention (CDC) recommends a 6-month course of treatment.
	Option II Pyrazinamide and a Fluoroquinolone	Treatment should last 6-12 months. Levofloxacin is the fluoroquinolone of choice. Moxifloxacin may be used in special situations.
	Option III Ethionamide and Cycloserine	Recommended for contacts of a source patient whose isolate is resistant to pyrazinamide, ethambutol and a fluoroquinolone; it should last 12 months and pyridoxine should also be given (see p. 62, Table III-4).
Children**	Option IV Pyrazinamide and Ethambutol	The preferred regimen for children if the source patient's isolate is susceptible to these drugs and if the child's vision can be monitored. Treatment should last 12 months.
	Option V Pyrazinamide and a Fluoroquinolone	Treatment should last 6-12 months. Fluoroquinolones in children should only be used if absolutely necessary.
	Option VI Pyrazinamide and Ethionamide	May be used if the source patient's isolate is resistant to ethambutol or the child's vision cannot be monitored. Treatment should last 12 months.
	Option VII Ethionamide and Cycloserine	Use if the source patient's isolate is resistant to both pyrazinamide and ethambutol; it should last 12 months and pyridoxine should also be given (see p. 62, Table III-4).

* "Likely to be infected" means an intermediate, high-intermediate or high likelihood of infection with MDRTB. (See p. 156, Table IX-1).

** For children who are receiving treatment for LTBI and are contacts to a case of MDRTB, DOT should be strongly considered.

and repeat CXR. All such patients should be evaluated for active TB with physical exam, CXR and sputa.

- If sputa are AFB smear negative and there is no evidence of adequate prior treatment for TB, treatment should be started with isoniazid and rifampin (always use Rifamate®, a combination of isoniazid and rifampin), along with pyrazinamide and ethambutol for 2 months. Prescribe pyridoxine if the patient is malnourished, alcoholic, HIV-positive or pregnant (see p. 196, Table XI-1). Ensure that the patient is followed monthly by the physician and nurse.

- This regimen has several advantages: it can be used to treat patients who may have isoniazid-resistant organisms; it may promote better adherence than the 9-month treatment regimen for LTBI; and it allows patients to start treatment at the first medical visit, rather than waiting until sputum cultures are shown to be negative for *M. tb*.

- If all cultures are negative by 2 months, repeat CXR.
- If the CXR shows no change, the lesions were presumably inactive. Classify the patient as having old TB (class IV). In addition:

- If the patient has no prior TB treatment history, continue with 2 additional months of isoniazid and rifampin only.
 - If there is a history of prior TB treatment, continue all 4 drugs for an additional 2 months.
 - Other diagnoses should also be considered as warranted.
- If CXR shows improvement, the lesions presumably were active. Classify the person as having culture-negative active TB (class III).
- If the patient has no prior TB treatment history, continue with 2 additional months of isoniazid and rifampin only.
 - If there is a history of previous TB treatment, continue all 4 drugs for an additional 2 months.

After 4 months of therapy, the patient should receive an end-of-treatment CXR, which will serve as a baseline for future reference. Some patients classified as having old TB (Class IV or V) may show improvement on the 4-month CXR and should be reclassified as having culture-negative active TB (Class III).

Individuals who have culture-negative TB may need 6 months of therapy (i.e., for extensive fibrotic disease or HIV infection). Clinical judgment should be used to make this decision. There is little literature on the use of 4-month regimens for extrapulmonary TB.

If there is low clinical suspicion of active TB, and AFB smears are negative, there is an additional option not to treat until the cultures are finalized. If cultures are negative and a 2-month CXR shows no change, there are 2 possible regimens for LTBI therapy for individuals with evidence of old, healed TB and no history of treatment:

- 9 months of isoniazid **or**
- 4 months of rifampin (some authorities recommend using isoniazid as well)

If the 4-drug regimen cannot be used because of adverse reactions or other circumstances, isoniazid can be used alone for a total of 9 months. The physician should clearly document in the medical record the reason that a 4-drug regimen could not be used.

Treatment of Close Contacts with a Prior Positive Test for Tuberculosis Infection

Close contacts with a documented previous positive TTBI should be treated again for LTBI after active TB is ruled out, if they are HIV positive, or are sexual contacts of an HIV-infected index case, and refuse HIV testing.

Treatment should also be considered for the following individuals who have a previous positive TTBI, but who have subsequently been in close contact with a person who has AFB smear-positive pulmonary or laryngeal TB:

- Persons with immunosuppressive conditions and other medical risk factors for TB, other than HIV infection
- Children younger than 18 years of age
- Asymptomatic, HIV-negative persons who have had heavy exposure to a person with highly infectious pulmonary or laryngeal TB (i.e., the presence of secondary cases or documented conversions in the close contacts).

The regimen should depend on the susceptibility of the index case isolate. Contacts with prior positive TTBI exposed to an index case with MDRTB should be managed as per guidelines on p. 198.

Case Management of Latent Tuberculosis Infection Patients

Each patient treated for LTBI at the BTBC chest centers will be assigned a case manager (i.e., a Public Health Nurse [PHN] or Public Health Adviser [PHA]) within 1 month of the starting of therapy.

Contacts of active TB cases treated at the chest centers should preferably be case managed by a PHN. Contacts of active TB cases treated at sites other than BTBC chest centers should be case managed by a field PHA.

Monitoring Patients during Treatment

All patients receiving treatment for LTBI should be monitored on a monthly basis, with

directed clinical examinations and blood tests as needed. Patients also need to be educated about the signs and symptoms of adverse drug reactions and the need for prompt cessation of treatment and clinical evaluation should symptoms occur. Adverse effects may include unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paresthesias of the hands and feet, persistent fatigue, weakness or fever lasting 3 days or more, abdominal tenderness (especially right upper quadrant discomfort), easy bruising or bleeding and arthralgia. Appropriate educational materials in the patient's language should be provided.

Monthly LFTs should be administered to:

- All HIV-positive patients
- Patients with a history of alcohol abuse, liver disease, chronic hepatitis
- Pregnant and postpartum women (up to 2-3 months after delivery)
- Patients currently injecting drugs
- Patients on potentially hepatotoxic agents
- Patients with baseline abnormal LFTs not due to conditions above

See p. 204, Figure XI-3 for monitoring for hepatotoxicity during treatment for LTBI.

In addition, laboratory testing should be used to evaluate specific adverse events that may occur during treatment.

Ensuring Adherence During Treatment

Many people with LTBI do not complete treatment. Most are not sick and may not feel the urgency to complete the prolonged therapy. Patients receiving treatment for LTBI must be encouraged to return for follow-up every month. Providers must educate patients about the importance of adherence to treatment and about potential side effects. Barriers to adherence should be addressed and overcome. (See Box)

How Providers Can Assess and Promote Adherence:

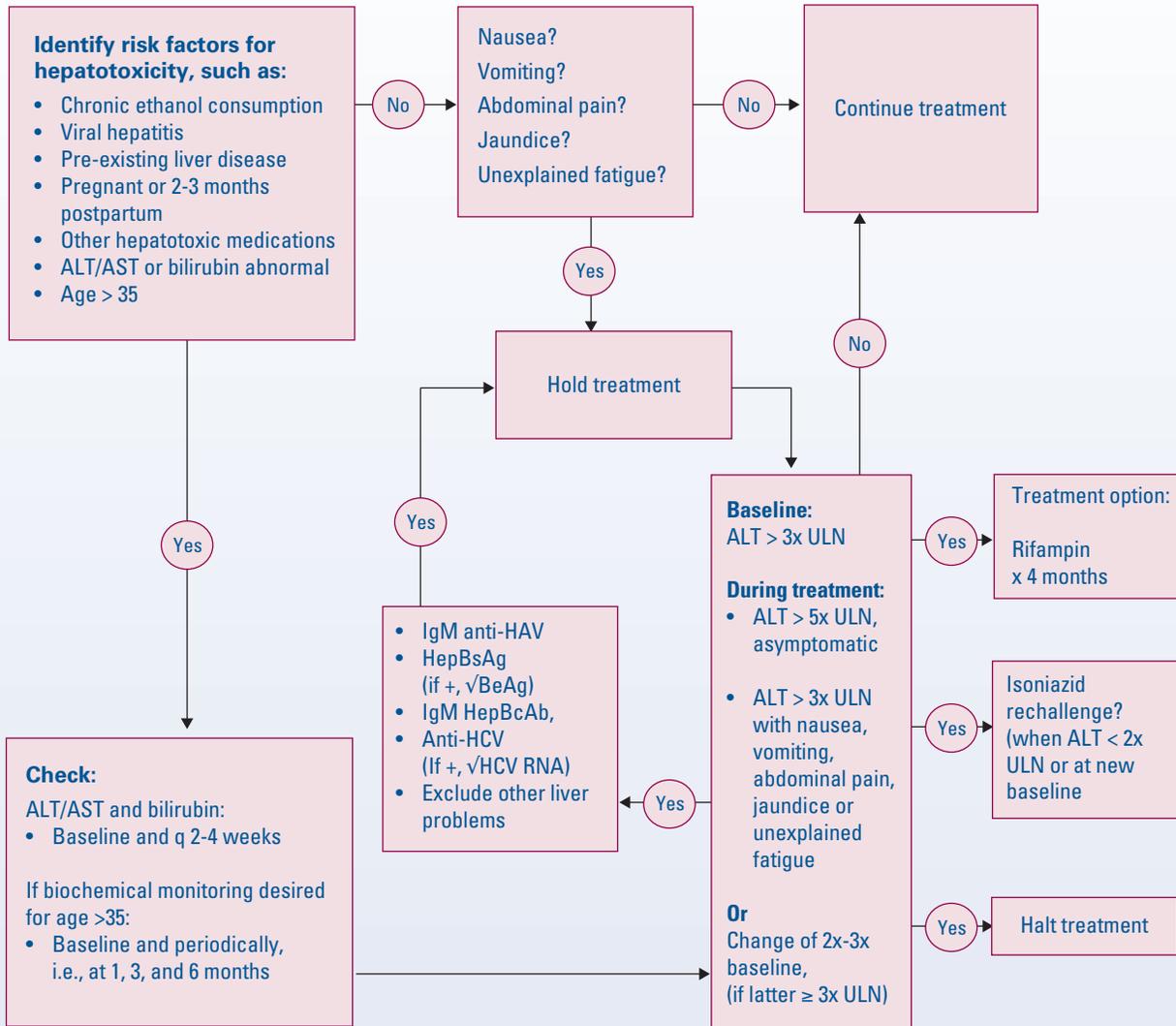
- Use DOT for LTBI when available, especially for children, contacts and HIV-infected persons. DOT can be performed at many locations such as clinics, schools, homes, work sites and day care programs.
- Provide written information about potential adverse effects of the medications at the start of treatment.
- Provide incentives such as MetroCards to help with transportation.
- Send reminder letters or call patients before appointments.
- Follow up promptly on missed appointments to prevent interruption or cessation of treatment.
- Minimize wait time at clinics.
- Ask patients at monthly visits about the number of missed pills in the past week.
- Remind patients to bring in their medication bottle(s); monitor pill counts (but not in their presence).
- During each monthly visit, stress the importance of adherence and educate patients about potential adverse effects of medication.

Managing Interruptions in Treatment

If there are interruptions in treatment, patients can be given 2 to 3 additional months to complete the regimen. The decision regarding completion of treatment should be based on the total number of medication doses administered, as well as on the duration of therapy (see p. 196, Table XI-1). For those on isoniazid, if there is a gap greater than 3 months, it may be necessary to restart treatment. However, adults with 6 or more months of treatment should be considered as having completed treatment.

Figure XI-3

Monitoring for Hepatotoxicity during Treatment for Latent Tuberculosis Infection*



*Adapted from ATS Hepatotoxicity Statement. See Key Sources at end of section for full citation.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit of normal

Completing Treatment

Patients receiving treatment for LTBI may be discharged from the chest center when they return for the final month's supply of medication (e.g., after the 8th month for patients taking a 9-month treatment regimen). The exception would be individuals being treated for LTBI as a contact to a MDRTB case.

The provider performing the monthly evaluation should note in the clinic medical record that the patient received enough medication for the last month of treatment for LTBI and was discharged from the chest center.

The patient should be advised to return to the center if either symptoms of TB or side effects to medication occur. Otherwise, further evaluation is not necessary.

The discharged patient should be informed that repeated CXRs and TTBI are not necessary. Documentation of the results of the TTBI and the LTBI treatment should be provided to the patient in writing, as repeat testing and treatment is generally not indicated except in specific circumstances as noted below.

Follow-up for Patients Who Have Completed Treatment

Follow-up care, including CXR and medical evaluations, is not necessary for patients who complete a course of treatment for LTBI unless 1) they develop symptoms of TB disease or 2) they were being treated for LTBI as a contact to an MDRTB case.

Repeat treatment for LTBI should be considered, however, for individuals who have been treated in the past, but who have subsequently been in close contact with someone who has AFB smear-positive pulmonary or laryngeal TB disease.

These individuals include:

- Persons who are HIV-positive or have another medical risk factor for developing TB disease
- Children who are younger than 18 years of age
- Persons who are HIV-negative, but have had heavy exposure to a patient with highly infectious TB (i.e., the presence of secondary cases or documented TTBI conversions in other contacts)

When treatment for LTBI is repeated, an entire course should be given (i.e., 9 months for adults, both HIV-positive and HIV-negative) on the assumption that exogenous reinfection may have occurred. This is more likely if there are TTBI conversions among other contacts who had similar exposure to the individual with TB.

Key Sources

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Appendices

Tuberculosis

Appendix I-A

Dosages for Primary Medications Used in the Treatment of Tuberculosis

Drug Route of Administration Mode of Action	Daily Dose [Max]	3 Times a Week Dose [Max]	2 Times a week Dose [Max]	Major Adverse Reactions*
Isoniazid ¹ Oral/Intramuscular Bactericidal	Children: 5-10 mg/kg ² Adults: 5 mg/kg [300mg]	Children: 20 mg/kg Adults: 10 mg/kg (range 8-12 mg/kg) [900mg]	Children: 20 mg/kg Adults: 15 mg/kg (range 13-17 mg/kg) [900mg]	Hepatic enzyme elevations, hepatitis, rash, peripheral neuropathy, CNS effects, increased phenytoin levels, possible interaction with disulfiram (Antabuse®)
Rifampin ¹ Oral/Intravenous Bactericidal	Children: 10-20 mg/kg ³ Adults: 600 mg (range 8-12 mg/kg) [600mg]	Children: 10-20 mg/kg Adults: 600 mg (range 8-12 mg/kg) [600mg]	Children: 10-20 mg/kg Adults: 600 mg (range 8-12 mg/kg) [600mg]	Hepatic enzyme elevations, hepatitis, rash, fever, thrombocytopenia, influenza-like syndrome, reduced levels of many drugs (including methadone), warfarin, hormonal forms of contraception, oral hypoglycemic agents, theophylline, dapsone, ketoconazole, PIs and NNRTIs.
Rifabutin ⁴ Oral Bactericidal	Children: 5 mg/kg Adults: 5 mg/kg [300mg]			Rash; hepatitis, fever, neutropenia, thrombocytopenia, reduced levels of many drugs, including PIs, NNRTIs, dapsone, ketoconazole and hormonal forms of contraception.
Rifapentine ⁵ Oral Bactericidal				Same as rifampin
Pyrazinamide ¹ Oral Bacteriostatic	Children: 25 mg/kg (range 20-30 mg/kg) Adults: 25 mg/kg (range 20-30 mg/kg) [2 g for C and A]	Children: 35 mg/kg (range 30-40 mg/kg) Adults: 35 mg/kg (range 30-40 mg/kg) [3 g for C and A]	Children: 50 mg/kg (range 40-60 mg/kg) Adults: 50 mg/kg (range 40-60 mg/kg) [3.5 g for C and A]	Gastrointestinal (GI) upset, hepatotoxicity, hyperuricemia, gout (rarely), arthralgias, rash
Ethambutol Oral Bacteriostatic	Children: 20 mg/kg (range 15-25 mg/kg) [1.5 g] Adults: 15-25 mg/kg [2.0 g]	Children: 30 mg/kg (range 25-35 mg/kg) Adults: 30 mg/kg (range 25-35 mg/kg) [2.8 g]	Children: 40-50 mg/kg [2.5 g] Adults: 45 mg/kg (range 40-50 mg/kg) [3.6 g]	Decreased red-green color discrimination, decreased visual acuity, skin rash
Streptomycin Intramuscular/ Intravenous Bactericidal	Children: 15-30 mg/kg Adults: 15 mg/kg [1,000 mg]	Children: 15 mg/kg Adults: 15 mg/kg [1,000 mg]	Children: 15 mg/kg Adults: 15 mg/kg [1,000 mg]	Auditory toxicity, renal toxicity, hypokalemia, hypomagnesemia

Abbreviations: HAART = highly active antiretroviral therapy, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor

* All toxicities are not listed here. Full prescribing information should be checked in the package insert or pharmacology texts.

Use of brand names is for informational purposes only and does not imply endorsement by the NYC Department of Health and Mental Hygiene.

¹ An isoniazid/rifampin combination tablet (Rifamate®)* containing 150 mg of isoniazid and 300 mg of rifampin, and an isoniazid/rifampin/pyrazinamide combination (Rifater®)* containing 50 mg of isoniazid, 120 mg of rifampin, and 300 mg of pyrazinamide are available and should be used whenever patients are NOT on directly observed therapy.

Recommended Regular Monitoring	Comments
<ul style="list-style-type: none"> • Monthly clinical evaluation • Liver function tests⁶ 	<ul style="list-style-type: none"> • Vitamin B₆ (pyridoxine) 25 mg/day may decrease peripheral neuritis and central nervous system effects and should be used in patients who are abusing alcohol, pregnant, breastfeeding infants on isoniazid, malnourished, or who have HIV infection, cancer, chronic renal or liver disease, diabetes, or pre-existing peripheral neuropathy. • Aluminum-containing antacids reduce absorption. • Drug interactions with several agents
<ul style="list-style-type: none"> • Monthly clinical evaluation • Complete blood cell count including platelets and liver function tests as indicated⁶ 	<ul style="list-style-type: none"> • Orange discoloration may occur in contact lenses and body secretions such as tears and urine. • Patients receiving methadone will need their methadone dosage increased, by an average of 50%, to avoid opioid withdrawal. • Interaction with many drugs leads to decreased levels of the co-administered drug. • May make glucose control more difficult in people with diabetes. • Contraindicated for patients taking most PIs and NNRTIs. • Patients should be advised to use barrier contraceptives while on rifampin.
<ul style="list-style-type: none"> • Monthly clinical evaluation • Complete blood cell count including platelets and liver function tests as indicated⁶ 	<ul style="list-style-type: none"> • Orange discoloration may occur in contact lenses and body secretions, urine, tears and contact lenses. • Can be used daily, or in 2 or 3 times per week dosing schedule. [See Table III-3, p. 55 for treatment of HIV-infected persons.] • If taken concurrently with PIs or NNRTIs, adjust dose of rifabutin and monitor for decreased antiretroviral activity and for rifabutin toxicity. • Contraindicated for patients taking single PI, ritonavir/saquinavir or delavirdine based HAART regimen. • Methadone dosage generally does not need to be increased. • Patients should be advised to use barrier contraceptives while on rifabutin.
<ul style="list-style-type: none"> • Monthly clinical evaluation • Complete blood cell count including platelets and liver function tests as indicated⁶ 	<ul style="list-style-type: none"> • Same as rifampin. • Rifapentine 600 mg should be administered with isoniazid 900 mg once a week only in the continuation phase of treatment of non-cavitary drug-susceptible pulmonary TB in HIV-negative patients 12 years of age and older, who are not pregnant.
<ul style="list-style-type: none"> • Monthly clinical evaluation • Liver function test as indicated⁶ 	<ul style="list-style-type: none"> • May complicate management of diabetes mellitus. • Hyperuricemia can be used as indicator of compliance. • Treat increased uric acid only if symptomatic. • Allopurinol increases level of pyrazinamide by inhibiting xanthine oxidase resulting in failure of allopurinol to lower serum uric acid.
<ul style="list-style-type: none"> • Monthly clinical evaluation • Check color vision and visual acuity monthly 	<ul style="list-style-type: none"> • Optic neuritis may be unilateral; check each eye separately. If possible, avoid in children too young to undergo vision testing. • If patient develops visual complaints, refer for prompt ophthalmologic evaluation. May need to discontinue ethambutol while awaiting evaluation.
<ul style="list-style-type: none"> • Monthly clinical evaluation • Audiometry, renal function, electrolytes, including magnesium 	<ul style="list-style-type: none"> • Ultrasound and warm compresses to injection site may reduce pain and induration.

² World Health Organization (WHO), International Union Against TB and Lung Disease (IUATLD), and British Thoracic Society (BTS) recommend 5 mg/kg in children; Centers for Disease Control and Prevention (CDC)/American Thoracic Society (ATS), Infectious Disease Society of America (IDSA) and the American Academy of Pediatrics (AAP) recommend 10-20 mg/kg.

³ WHO, IUATLD, and BTS recommend 10 mg/kg in children; CDC/ATS and the AAP recommend 10-20 mg/kg.

⁴ Not FDA-approved for the treatment of TB

⁵ Rifapentine should not be used in patients who are HIV-infected.

⁶ Liver function tests are indicated if baseline is abnormal or patient has risk factors for toxicity.

Appendix I-B

Dosages for Reserve Medications Used in the Treatment of Tuberculosis*

Drug Route of Administration Mode of Action	Daily Dose [Max]	Major Adverse Reactions*	Recommended Regular Monitoring	Comments
Capreomycin Intramuscular/Intravenous Bactericidal	Children: 15–30 mg/kg Adults: 15 mg/kg [1000 mg]	Auditory, vestibular, and renal toxicity, eosinophilia, hypokalemia, hypomagnesemia	<ul style="list-style-type: none"> Monthly clinical evaluation Audiometry, renal function, electrolytes, including magnesium 	<ul style="list-style-type: none"> Ultrasound and warm compresses to injection site may reduce pain and induration.
Cycloserine Oral Bacteriostatic	Children: 10–20 mg/kg Adults: 500–1000 mg, divided doses [1000 mg]	Psychosis, seizures, headache, depression, suicide, other CNS effects, rash, increased phenytoin levels	<ul style="list-style-type: none"> Monthly clinical evaluation Assess and monitor mental status 	<ul style="list-style-type: none"> Increase gradually, checking serum levels. Pyridoxine hydrochloride (vitamin B₆) may decrease CNS effects (use 50 mg for each 250 mg of cycloserine).
Ethionamide Oral Bacteriostatic	Children: 15–20 mg/kg Adults: 500–1000 mg, divided doses [1000 mg]	Nausea, vomiting, diarrhea, abdominal pain, bloating, hepatotoxicity, hypothyroidism (especially when administered with PAS), metallic taste	<ul style="list-style-type: none"> Monthly clinical evaluation Liver function tests (if baseline abnormal) Thyroid function periodically especially if also on para-aminosalicylic acid 	<ul style="list-style-type: none"> Antacids/anti-emetics and lying supine for 20 minutes after dose may help tolerance. Start with 250 mg daily and increase as tolerated.
Kanamycin Amikacin Intramuscular/Intravenous Bactericidal	Children: 15–30 mg/kg Adults: 15–22.5 mg/kg [1000 mg]	Auditory toxicity, renal toxicity, vestibular toxicity (rare), hypokalemia, hypomagnesemia	<ul style="list-style-type: none"> Monthly clinical evaluation Audiometry, renal function, electrolytes, including magnesium 	<ul style="list-style-type: none"> Ultrasound and warm compresses to injection site may reduce pain and induration.
Levofloxacin** Oral/Intravenous Bacteriostatic, possibly bactericidal	Children: 6 months to under 5 years old: 10 mg/kg bid 5 years and older: 10 mg/kg qd. Adults: 500–1000 mg in one dose	Nausea, vomiting, diarrhea, abdominal pain, tremulousness, insomnia, headache, dizziness, lightheadedness, photosensitivity, tendonitis, tendon rupture, possible hypo- and hyperglycemia hypersensitivity	<ul style="list-style-type: none"> Monthly clinical evaluation Monitor blood sugar 	<ul style="list-style-type: none"> Most active of the fluoroquinolones commonly used for TB (ciprofloxacin, levofloxacin, ofloxacin) Preferred fluoroquinolone Our clinical experience shows safety with long term use.
Moxifloxacin** Oral/Intravenous Bactericidal	Children: Dose unknown Adults: 400 mg	Similar to levofloxacin	<ul style="list-style-type: none"> Monthly clinical evaluation Monitor blood sugar 	<ul style="list-style-type: none"> More active than levofloxacin against <i>M. tb</i>. There is little experience with the use of this drug for longer than 14 days. Therefore, data on adverse effects with prolonged use for TB are limited. Avoid in patients with prolonged QT interval and those receiving class Ia or III antiarrhythmic agents.
Para-aminosalicylic Acid Oral Bacteriostatic	Children: 150 mg/kg Adults: 4 g every 12 h [12g]	Nausea, vomiting, diarrhea, abdominal pain, hypersensitivity, hepatotoxicity, hypothyroidism (especially when administered with ethionamide), decreased digoxin levels, increased phenytoin levels, PAS levels decreased by diphenhydramine	<ul style="list-style-type: none"> Monthly clinical evaluation Thyroid function periodically especially if also on ethionamide 	<ul style="list-style-type: none"> Begin gradually and increase dosage as tolerated. May cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (G-6-PD) deficiency.

Abbreviation: PAS = para-aminosalicylic acid

* All toxicities are not listed here. Full prescribing information should be checked in the package insert or pharmacology texts. Use of brand names is for informational purposes only and does not imply endorsement by the New York City Department of Health and Mental Hygiene.

** Although fluoroquinolones are not approved for use in children in most countries, the benefit of treating children with MDRTB with a fluoroquinolone may outweigh the risk in many instances.

Appendix I-C

The Use of Antituberculosis Drugs during Pregnancy, Breastfeeding, Tuberculosis Meningitis, and Renal and Hepatic Failure¹

Drug	Safety in Pregnancy ²	Safety in Breastfeeding	Central Nervous System Penetration ³	Dosage in Renal Insufficiency ⁴	Dosage in Hepatic Insufficiency
Isoniazid	Has been used safely ⁵	Moderately safe	Good (20%-100%)	No change	No change, but use with caution
Rifampin	Has been used safely (isolated reports of malformations)	Safe	Fair (inflamed meninges) (10%-20%)	No change	No change, but use with caution
Rifapentine	Safety not established	No data	Not established	Not established Use with caution	No change, but use with caution
Rifabutin	Use with caution (limited data on safety)	No data	Good (30%-70%)	No change	No change, but use with caution
Pyrazinamide	Recommended by WHO ⁶ (not by US FDA ⁷)	Moderately safe	Good (75%-100%) (use with caution)	Decrease dosage/ increase interval (use with caution)	No change, but use with caution
Ethambutol	Has been used safely	Safe	Inflamed meninges only (4%-64%)	Decrease dosage/ increase interval ⁴	No change
Aminoglycosides (streptomycin, kanamycin, amikacin)	Avoid ⁸ (associated with ototoxicity in fetus)	Safe	Poor ⁹	Decrease dosage/ increase interval ^{4,10}	No change
Capreomycin	Avoid ⁸ (limited data on safety)	No data	Poor	Decrease dosage/ increase interval ¹⁰	No change
Levofloxacin	Do not use (teratogenic in laboratory animals)	Moderately safe	Fair (16%-20%)	Increase interval	No change, but use with caution
Moxifloxacin	Do not use (teratogenic in laboratory animals)	Moderately safe	Fair (5%-10%) Inflamed meninges (50%-90%)	No change, but use with caution	No change, but use with caution, especially with severe hepatic insufficiency
Cycloserine	Use with caution (limited data on safety)	Moderately safe	Good (50%-100%)	Decrease dosage/ increase interval ⁴	No change
Ethionamide	Do not use (premature labor, congenital malformations)	No data	Good (100%)	No change, but use with caution	No change, but use with caution
Para-aminosalicylic acid	Has been used safely	Moderately safe	Inflamed meninges only	No change, but use with caution	No change, but use with caution

¹ This table presents a consensus of published data and recommendations.

² As with all medications given during pregnancy, anti-TB medications should be used with extreme caution. The risk of TB to the fetus far outweighs the risk of most medications. Data are limited on the safety of anti-TB medications during pregnancy.

³ Steroid treatment appears to improve outcome in TB meningitis, particularly in patients with altered mental status.

⁴ If possible, monitor serum drug levels of patients with renal insufficiency.

⁵ Supplement with pyridoxine hydrochloride (vitamin B₆), 25 mg per day

⁶ World Health Organization

⁷ Food and Drug Administration

⁸ If an injectable medication must be used during pregnancy, streptomycin is the preferred agent if the organism is susceptible.

⁹ Has been used intrathecally; efficacy not documented

¹⁰ If possible, avoid aminoglycosides and capreomycin in patients with reversible renal damage.

Appendix I-D

Late Complications of Treated Pulmonary Tuberculosis

Some patients who have been successfully treated for pulmonary tuberculosis (TB) in the past develop symptoms or have abnormalities on a chest X-ray (CXR) that raise the possibility of a recurrence of active TB. However, a few other late complications should be considered in the differential diagnosis in such patients.

Hemoptysis

Bleeding from ruptured bronchial veins. Some individuals with fibrotic residuals of pulmonary TB, such as contracted lobes or segments, residual “open healed” cavities, or localized fibrosis, develop hemoptysis due to bleeding from the old, inactive post-tuberculous lesion. In most cases, the origin of the blood is a ruptured bronchial vein that occurs in rich plexuses in the endobronchial mucosa in such lesions. Hemoptysis often begins during an acute viral respiratory infection. It is usually self-limited, but may be so severe as to require emergency surgical resection.

This cause of hemoptysis can be diagnosed only by ruling out the other causes outlined here, as well as active TB (by obtaining multiple sputum cultures). If sputum cultures are negative, and no other criteria prove active TB, patients with hemoptysis should not be retreated for active TB.

Mycetoma. Healed TB cavities can be colonized by fungi, usually *Aspergillus species*, and evolve into a mass of matted mycelia—a movable, intracavitary “fungus ball.” This process is accompanied by the development of vascular granulation tissue in the internal wall of the cavity, which appears on serial CXRs as a progressive thickening of the cavity wall. In some cases, this thickening is evident even before a mycetoma can be visualized. The granulation tissue is the site of bleeding in some individuals with *Aspergillus*-colonized cavities, usually with mycetoma. Some patients experience massive hemoptysis and require an emergency surgical resection of involved tissue or radiological intervention. Others experience chronic or recurrent hemoptysis of lesser amounts.

The diagnosis can be suspected on the basis of characteristic radiological signs, cultural isolation *Aspergillus* from sputum and the presence of serum antibodies, usually against *Aspergillus fumigatus*.

Other causes of hemoptysis. Many conditions unrelated to TB may lead to hemoptysis in patients who were treated for TB in the past. Among these are pneumonia, pulmonary emboli, bronchiectasis, lung abscess and tumors.

Patients with hemoptysis may need further evaluation such as computed tomography (CT) scan of the chest, and pulmonary/ surgical consultation.

Chest Pain

Some patients with successfully treated tuberculous pleural effusions experience chest pain over a period of months or years. Some describe pleuritic pain; others, chronic aching or a burning sensation. Often the cause is not clear. Unless there is a demonstrable recurrence of a pleural effusion on the CXR, treatment for active TB is not indicated. Infrequently, chest pain may be due to a spontaneous pneumothorax caused by the rupture of a bleb, which can evolve in an area of pulmonary scarring related to TB.

Dyspnea

Patients with extensive pulmonary or pleural fibrosis due to healed TB may experience exertional dyspnea. Pulmonary function tests demonstrate a restrictive defect. Except for this cause, the development of dyspnea after successful therapy for TB usually reflects the presence of another, unrelated cause (e.g., chronic obstructive pulmonary disease, asthma, heart disease, anemia).

Recurrence of Cough, Sputum, Fever or Weight Loss

Such symptoms are nonspecific and may occur from a wide variety of respiratory diseases other than TB. Among these are viral, mycoplasmal, bacterial, fungal and other respiratory infections; exacerbations of bronchiectasis or chronic bronchitis; and tumors. In such cases, the reinstatement of anti-TB treatment is not indicated unless cultures are positive for *Mycobacterium tuberculosis* or the CXR suggests recurrent TB.

Clubbed Fingers

Clubbed fingers may be found in individuals with very advanced pulmonary TB and chronic respiratory insufficiency. However, if a patient who has been previously treated for pulmonary TB subsequently develops clubbed fingers, another cause — especially a tumor — should be strongly suspected, even if the CXR has not changed.

Changes in the Appearance of the Chest X-ray

In an individual who has been treated for TB, these changes may reflect a recurrence of active TB, even in the absence of symptoms. However, they could be due to completely different causes, including the following:

Mycetoma. A mycetoma is usually characterized by a thickening of the cavity wall or the presence of an intracavitary mass, often manifesting a “crescent” sign.

Tumor. “Scar” cancer may develop at the site of post-tuberculous fibrosis, or even on the wall of a healed TB cavity. The former usually presents as a new solitary spherical lesion in the lung parenchyma; the latter, as a localized thickening of the cavity wall or as a nonmovable intracavitary mass that can closely resemble a mycetoma.

Endobronchial lesions. Endobronchial lesions that obstruct lobar or segmental bronchi usually lead to an airless, “collapsed” lobe or segment or to chronic organizing pneumonia in the parenchyma distal to the obstruction. Such lobar or segmental lesions should be suspected to be due to a tumor, malignant or benign, or to a foreign body. Appropriate diagnostic investigation should be undertaken.

Fluid level in an emphysematous bleb. Although “open healed” TB cavities are rarely secondarily infected, or the site of fluid levels, emphysematous bullae in the area of healed TB may develop fluid levels, especially after lower respiratory infections. These rarely represent reactivated TB.

Pleural effusion. Recurrent TB infection may present as a pleural effusion in a previously treated patient, but many nontuberculous causes must be considered as well. Among these are pneumonia, pulmonary emboli, trauma, tumor, pleurodynia, connective tissue disease and others.

Appendix I-E

Procedures for Therapeutic Drug Monitoring of Patients

Therapeutic drug monitoring (TDM) should be done when there is a clear indication for it. Routine monitoring of antituberculosis drug levels is not recommended in clinical practice. The significance of low serum levels of antituberculosis drugs in relation to clinical response has not been demonstrated. Studies have shown that as many as 60% of TB patients had low serum levels of isoniazid or rifampin. However, the clinical response to TB therapy did not differ in those with low drug levels when compared to those with normal levels.

Nonetheless, some patients will fail to respond to antituberculosis treatment despite documented adherence to the medications and absence of drug resistance. Some of these patients may have malabsorption syndromes that prevent them from achieving therapeutic levels of these drugs. Diseases such as HIV infection, cystic fibrosis, diabetes and sprue have been implicated in malabsorption of antituberculosis drugs.

A select number of patients with drug susceptible TB will therefore require drug level testing at some point during their treatment for tuberculosis. Patients with drug-resistant TB are more likely to require drug level testing.

In order to optimize the treatment of patients with TB while maintaining the highest levels of sound medical practice the Bureau of Tuberculosis Control (BTBC) recommends that TDM be used in the following circumstances:

- Lack of clinical response (i.e., culture conversion) while on appropriate drugs and doses, on directly observed therapy (DOT) for at least 2 months and in the absence of drug resistance;
- Lack of clinical response from 2nd-line drugs with a narrow therapeutic window, such as cycloserine, when alternative drugs are limited, and when plans are in place to increase the dose of the drug should levels be low;
- Patients with few effective drugs in their regimen, in order to optimize the effect of available drugs;
- Lack of clinical response (i.e., lack of culture conversion at 2 months) in a patient with known or suspected malabsorption syndrome;
- Patients with renal insufficiency and who have multidrug resistant tuberculosis (MDRTB) or are on certain drugs such as ethambutol;
- Patients who relapse with active TB despite appropriate therapy.

If drug levels are low and doses are increased, clinical monitoring should be used to judge the response; TDM should only be done when there is no clinical response after a reasonable amount of time.

Patients with pansensitive, cavitary, or otherwise very extensive disease tend to have a delayed clinical response to treatment even when adherence is documented (under DOT). In most cases these patients will respond if given enough time, usually in the third month of therapy. All patients with a delayed response (i.e., lack of culture conversion at 2 months) should be treated for 9 months instead of 6 months.

In order to obtain accurate results BTBC staff must adhere strictly to the guidelines on specimen procurement and handling. Failure to do so will lead to inaccurate results, which may ultimately harm the patient. The following sections delineate procedures for obtaining and handling specimens for TDM.

Physicians

1. Order blood drawing for approximately 2 hours after an observed dose of antituberculosis medications (for para-aminosalicylic acid [PAS], the blood must be drawn 5 hours after ingestion of PAS granules). Since the serum must be frozen immediately after being centrifuged, do not schedule a blood drawing if the freezer is not functional or not available.
2. For most assays, continue all other antituberculosis medication as usually given. However, if kanamycin is to be assayed, withhold all other antibiotics and antituberculosis medications for 24 hours prior to dosing. After giving kanamycin, draw a 2-hour post dose blood sample. It is no longer necessary to withhold other medications if capreomycin is being monitored. The assay process for this drug has changed. If you are requesting TDM for streptomycin inquire if patient is taking ampicillin and record this on requisition form.

Phlebotomists

1. Draw blood 2 hours after an observed dose of anti-tuberculosis medication(s). One plain 10 ml red-top tube provides enough serum for 2 drugs to be assayed. Serum separator tubes (SST) may be used, but plain red-top tubes are preferred.
2. Approximately 30–60 minutes after drawing blood, centrifuge the specimen until the serum is fully separated and place the specimen in a 2 ml cryovial.
3. After placing the serum in a cryovial, label the cryovial with the patient's name, the center's name, the date and time the blood was drawn, and the name of the drug(s) to be assayed. Complete a National Jewish Medical and Research Center's Infectious Disease Pharmacokinetics Laboratory (IDPL) Requisition Form to accompany the sample. Available at www.njc.org/pdf/Infectious_Disease_Pharm_Lab.pdf
4. Place the cryovial with the label in the freezer compartment in the chest center for a minimum of 8 hours or until the sample is frozen solid, whichever is longer.
5. On the day after blood drawing, when the serum is frozen solid, arrange to have the frozen sample and ice packs picked up and transported directly to the Bureau of Public Health Laboratories (PHL) in a cooler with ice packs. Send a requisition form with the serum sample. Call the Mycobacteriology Laboratory (Room 259) at (212) 447-6745 to alert the laboratory to expect specimens. At PHL the specimen will be inspected and placed immediately in a -70°C refrigerator.

Bureau of Public Health Laboratory

1. At PHL, the sample will be frozen overnight at minus 70°C ; the next day it will be packed in dry ice and labeled as specified in full compliance with the shipper and guidelines on handling of dry ice and potentially infectious materials. The requisition form sent with the specimen will be included in the shipping package.
2. PHL staff will call the shipper to pick up and deliver the samples.
3. PHL will alert National Jewish about the arrival of the specimen at 303-398-1974.
4. PHL staff will return ice packs and coolers to the appropriate center. All packs and coolers should be marked with the name and address of the center that sent them.

National Jewish Medical and Research Center

1. Results will be sent from National Jewish to the center directly.
2. National Jewish will bill the BTBC and the bill will go directly to Internal Accounting. Packaging slips and/or any other accompanying slips should be sent to the BTBC Office of Operations.

Appendix I-F

Potential Drug Interactions with Antituberculosis Medications*

Antituberculosis Medication	Drug or Drug Type** (most common brand names)	Potential Interaction
Aminoglycosides		
	ACE inhibitors	↑ Nephrotoxicity
	Antifungal, Amphotericin B (Amphotec®)	↑ Nephrotoxicity (synergistic)
	Aminoglutethimide (Cytadren®)	↑ Nephro- and ototoxicity
	Botulinum toxin type A	Possible ↑ effect of the toxin
	Bumetanide (Bumex®)	↑ Ototoxicity (additive)
	Capreomycin (Capastat®)	↑ Oto- and nephrotoxicity (additive)
	Carmustine (BiCNU®)	↑ Nephrotoxicity
	Cephalosporins	↑ Nephrotoxicity
	Chloroquine (Aralen®)	↑ Ototoxicity
	Cisplatin (Platinol®)	↑ Nephrotoxicity
	Colistine Sulfate (Coly-Mycin®)	↑ Nephrotoxicity
	Cyclosporine (Neoral®)	↑ Nephrotoxicity (possible additive or synergistic)
	Deferoxamine (Desferal®)	↑ Nephro- and ototoxicity
	Diuretics	↑ Ototoxicity (synergistic)
	Enflurane (Ethrane®)	Possible nephrotoxicity
	Ethacrynic acid (Edecrin®)	Ototoxicity (additive)
	Furosemide (Lasix®)	↑ Oto- and nephrotoxicity
	Gallium (Ganite®)	Nephrotoxicity (additive)
	Gold salts	Possible ↑ nephrotoxicity
	Hydroxychloroquine (Plaquenil®)	Possible ↑ nephrotoxicity
	Lithium (Lithobid®, Lithotabs®)	↑ Oto- and nephrotoxicity
	Magnesium sulfate	↑ Neuromuscular blockade (additive)
	Malathion (Ovide®)	Possible respiratory depression (additive)
	Methotrexate (Rheumatrex®)	Possible ↑ methotrexate toxicity
	Neostigmine (Prostigmin®)	Decreased effects of neostigmine
	Neuromuscular blocking agents (Pavulon®, Norcuron®)	↑ Neuromuscular blockade (additive)
	Nonsteroidal anti-inflammatory	Acute renal failure with ibuprofen
	Penicillins	↓ Aminoglycoside effect with high concentrations of carbenicillin, ticarcillin, or piperacillin (inactivation)
	Polymyxins (Aerosporin®)	Nephrotoxicity, ↑ neuromuscular blockade (additive)
	Vancomycin (Vancocin®)	Possible ↑ oto- and nephrotoxicity (additive)

Antituberculosis Medication	Drug or Drug Type** (most common brand names)	Potential Interaction
Aminoglycosides	Vincristine (Oncovin®)	Possible ↑ oto- and nephrotoxicity (additive)
	Zalcitabine (Hivid®)	Possible ↑ risk of peripheral neuropathy (additive)
Cycloserine	Alcohol	↑ Alcohol effect or convulsions
	Ethionamide	↑ CNS effect of cycloserine
	Isoniazid (Nydravid®)	↑ CNS effect, dizziness, drowsiness
Ethionamide	Cycloserine (Seromycin®)	↑ CNS effect of cycloserine
	Efavirenz (Sustiva®)	↓ Levels of ethionamide
	Excess ethanol	Possible psychotic reaction
	Isoniazid (Nydravid®)	↑ Serum concentrations of INH, toxic psychosis and peripheral neuritis (case report)
	Nevaripine (Viramune®)	↓ Levels of ethionamide
	Non-nucleoside reverse transcriptase inhibitors	↑ Levels of ethionamide
	Protease inhibitors	↑ Levels of ethionamide
Fluoroquinolones	Amiodarone (Cordarone®)	Possible QT prolongation & arrhythmia with levofloxacin & probably moxifloxacin
	Antacid with metal cations	↓ Fluoroquinolones effect with aluminum, magnesium, or calcium
	Anticoagulants, oral	↑ Anticoagulant effect
	Antifungal, imidazole & triazoles	Possible QT prolongation & torsades de pointes with fluconazole & levofloxacin
	Antidepressants, tricyclic (TCA)	Possible QT prolongation (levofloxacin)
	Arsenic trioxide (Trisenox®)	Possible QT prolongation with levofloxacin or moxifloxacin (additive)
	Benzodiazepines (Valium®)	Possible diazepam toxicity with ciprofloxacin
	Bepiridil (Vascor®)	Possible QT prolongation with levofloxacin or moxifloxacin (additive)
	Beta-adrenergic blockers	Possible metoprolol toxicity with ciprofloxacin, possible QT prolongation with sotalol and moxifloxacin
	Caffeine	Possible caffeine toxicity with ciprofloxacin
	Calcium	↓ Fluoroquinolone effect
	Calcium polycarbophil	↓ Ciprofloxacin effect
	Cisapride (Propulsid®)	Possible QT prolongation with levofloxacin or moxifloxacin (additive)
	Clozapine (Clozaril®)	Possible clozapine toxicity with ciprofloxacin
	Corticosteroids	Possible ↑ risk of Achilles tendon disorders
	Cyclosporine (Neoral®)	Possible cyclosporine toxicity with ciprofloxacin

Abbreviation: CNS = central nervous system

* This is not an exhaustive list of drug interactions. Readers should refer to drug information texts and sources and manufacturer package inserts for the latest and complete information. BTBC has a subscription to The Medical Letter's Drug Interaction Program.

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Appendix I-F (continued)

Potential Drug Interactions with Antituberculosis Medications*

Antituberculosis Medication	Drug or Drug Type** (most common brand names)	Potential Interaction
Fluoroquinolones	Didanosine (Videx®)	↓ Fluoroquinolone effect
	Digoxin (Lanoxin®)	Possible digoxin toxicity with gatifloxacin
	Disopyramide (Disopyramide®)	Possible QT prolongation with levofloxacin or moxifloxacin (additive)
	Dofetilide (Tikosyn®)	Possible QT prolongation with levofloxacin or moxifloxacin (additive)
	Domperidone (Motilium®)	Possible QT prolongation with levofloxacin or moxifloxacin (additive)
	Droperidol (Inapsine®)	Possible QT prolongation with levofloxacin or moxifloxacin (additive)
	Duloxetine (Cymbalta®)	Possible duloxetine toxicity with ciprofloxacin
	Foscarnet (Foscavir®)	Seizures with ciprofloxacin
	Hypoglycemics, sulfonylurea	Possible ↑ risk of hypoglycemia
	Halofantrine (Halfan®)	Possible QT prolongation with levofloxacin or moxifloxacin (additive)
	Haloperidol (Haldol®)	Possible QT prolongation with levofloxacin or moxifloxacin (additive)
	Ibutilide	Possible QT prolongation with levofloxacin or moxifloxacin (additive)
	Iron (Ferosol®)	↓ Fluoroquinolone effect
	Lithium (Lithobid®)	Possible lithium toxicity with levofloxacin
	Macrolide	Possible QT prolongation with levofloxacin or moxifloxacin (additive)
	Magnesium citrate (Citroma®)	↓ Fluoroquinolone effect
	Methotrexate (Rheumatex®)	Possible methotrexate toxicity with ciprofloxacin
	Mexiletine (Mexitil®)	Possible mexiletine toxicity
	Narcotics: methadone & congeners	Possible methadone toxicity with ciprofloxacin
	Olanzapine (Zyprexa®)	Possible olanzapine toxicity with ciprofloxacin
	Penicillins	Possible ciprofloxacin toxicity with azlocillin
	Pentamidine (Pentam 300®)	Possible QT prolongation with levofloxacin or moxifloxacin (additive)
	Pentoxifylline (Trental®)	Headache due to pentoxifylline toxicity with ciprofloxacin
Phenothiazines (Compazine®, Mellaril®)	Possible QT prolongation with levofloxacin or moxifloxacin and chlorpromazine, mesoridazine or thioridazine (additive)	

Antituberculosis Medication	Drug or Drug Type** (most common brand names)	Potential Interaction
Fluoroquinolones	Phenytoin (Dilantin®)	Altered phenytoin effect with ciprofloxacin
	Pimozide (Orap®)	Possible QT prolongation with levofloxacin or moxifloxacin (additive)
	Pioglitazone (Actos®)	Possible hypoglycemia
	Probenecid (Probalan®)	↑ Serum levels of fluoroquinolones
	Procainamide (Pronestyl®)	Possible procainamide toxicity
	Pyrazinamide	Possible in ↑ adverse effects with levofloxacin and ciprofloxacin
	Quinidine (Quinaglute®)	Possible QT prolongation with levofloxacin or moxifloxacin (additive)
	Ramelton (Rozerem®)	↑ Ramelton toxicity with ciprofloxacin
	Ranolazine (Ranexa®)	↑ Ranolazine effect with ciprofloxacin
	Rasagiline (Azilect®)	↑ Rasagiline toxicity with ciprofloxacin
	Repaglinide (Prandin®)	Possible hypoglycemia
	Ropinirole (Requip®)	↑ Ropinirole effect with ciprofloxacin
	Ropivacaine (Naropin®)	Possible ↑ risk of ropivacaine toxicity with ciprofloxacin
	Sevelamer (Renegel®)	↓ Effects of oral fluoroquinolones
	Sucralfate (Carafate®)	↓ Fluoroquinolone effect
	Theophyllines	↑ Theophylline toxicity with ciprofloxacin, ↑ Toxicity with concurrent cimetidine
	Thyroid hormones	Possible ↓ levothyroxine effect
	Tizidine (Zanaflex®)	↑ Tizidine toxicity
	Ursodiol (Urso®)	↓ Ciprofloxacin effect
	Zinc (Calcet®)	↓ Fluoroquinolone effect
Ziprasidone (Geodon®)	Prolonged QT interval and possible fatal arrhythmias with moxifloxacin (additive)	
Isoniazid	Acetaminophen (Tylenol®)	Acetaminophen toxicity (↑ toxic metabolites)
	Alfentanil (Alfenta®)	↓ Plasma clearance, ↑ Duration of action of alfentanil
	Alcohol	↑ Incidence of hepatitis, possible decreased isoniazid effect
	Aminosalicic acid (Paser®)	Hepatotoxicity (↑ toxic metabolites)
	Antacids (Maalox®, Mylanta®)	↓ Isoniazid absorption

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Appendix I-F (continued)

Potential Drug Interactions with Antituberculosis Medications*

Antituberculosis Medication	Drug or Drug Type** (most common brand names)	Potential Interaction
Isoniazid		
	Anticoagulants, oral (Coumadin®)	↑ Anticoagulant effect
	Benzodiazepines	Potential ↑ benzodiazepine toxicity
	Carbamazepines (Tegretol®)	↑ Toxicity of both drugs,
	Cycloserine (Seromycin®)	↑ CNS effects, dizziness, drowsiness
	Disulfiram (Antabuse®)	Psychotic episodes, ataxia (avoid concurrent use)
	Enflurane (Ethrane®)	↑ Nephrotoxicity (avoid concurrent use)
	Ethionamide	Toxic psychosis, peripheral neuritis
	Haloperidol (Haldol®)	↑ Haloperidol toxicity
	Ketoconazole (Nizoral®)	↓ Ketoconazole effect (isoniazid and rifampin)
	Meperidine (Demerol®)	↑ Meperidine effect
	Mephenytoin (Mesantoin®)	↑ Mephenytoin effect
	Niacin (Niaspan®)	↓ Niacin effect
	Phenytoin (Dilantin®)	↑ Phenytoin effect
	Rifampin (Rifadin®, Rimactane®)	Hepatotoxicity (possibly ↑ toxic metabolites)
	Stavudine (Zerit®)	↑ Risk of peripheral neuropathy
	Theophyllines (Theodur®, Theolair®)	↑ Theophylline toxicity
	Tyramine-rich foods and beverages	Palpitations, tachypnea, sweating, urticaria, headache, vomiting
	Valproate (Depakene®)	↑ Hepatic and CNS toxicity
	Vincristine (Oncovin®)	Neurotoxicity
Zalcitabine (Hivid®)	↑ Risk of peripheral neuropathy	
Linezolid		
	Citalopram (Celexa®)	↑ Risk serotonin syndrome (additive)
	Diphenhydramine (Benadryl®)	Possible ↑ risk delirium
	Duloxetine (Cymbalta®)	Possible ↑ risk serotonin syndrome (additive)
	Fluoxetine (Prozac®)	↑ Risk serotonin syndrome (additive)
	Fluvoxamine (Luvox®)	↑ Risk serotonin syndrome (additive)
	Monoamine Oxidase Inhibitors	Severe hypertension and possible crisis (additive)
	Paroxetine (Paxil®)	Possible ↑ risk serotonin syndrome (additive)
	Rasagiline (Azilect®)	Severe hypertension and possible crisis (additive)
Sertraline (Zoloft®)	Possible ↑ risk serotonin syndrome (additive)	

Antituberculosis Medication	Drug or Drug Type** (most common brand names)	Potential Interaction
Linezolid (continued)		
	Sympathomimetic amines (phenylpropanolamine, pseudoephedrine, dextromethorphan)	Hypertension
	Tyramine-rich foods and beverages	Hypertension due to ↓ metabolism of MAO
	Venlafaxine (Effexor®)	↑ Risk serotonin syndrome (additive)
Para-aminosalicylic acid		
	Digoxin (Lanoxin®)	Possible ↓ digoxin effect
	Probenecid (Probalan®)	Possible aminosalicylic acid toxicity
	Rifampin (Rifadin®, Rimactane®)	↓ Rifampin effect
Pyrazinamide		
	Allopurinol (Zyloprim®)	↑ Pyrazinamide level by inhibiting xanthine oxidase. Failure of allopurinol to ↓ serum uric acid
	Cyclosporine (Neoral®)	↓ Cyclosporine effect, acute myopathy
	Fluoroquinolones	Possible ↑ in adverse effects with levofloxacin
	Isoniazid (Nydrazid®)	↓ Serum isoniazid levels
	Probenecid (Probalan®)	Antagonizes effects of probenecid
	Rifampin (Rifadin®, Rimactane®)	↑ Risk of severe hepatic toxicity and death (additive)
	Sulfapyrazone (Anturane®)	Antagonizes effects of sulfapyrazone
Pyridoxine		
	Barbiturates	↓ Barbiturate effect
	Levodopa	↓ Levodopa effect, but not if taking carbidopa
	Phenytoin (Dilantin®)	↓ Phenytoin effect
Rifampin, Rifabutin and Rifapentine		
	Aminosalicylic acid (Paser®)	↓ Rifampin absorption
	Amiodarone (Cordarone®)	↓ Amiodarone effect
	Amprenavir (Agenerase®)	↓ Amprenavir effect (rifampin), possible ↑ Rifabutin toxicity
	Anticoagulants, oral (Coumadin®)	↓ Anticoagulant effect
	Antidepressants, tricyclic (TCA)	↓ TCA effect
	Antifungals (imidazoles, triazoles)	↓ Fluconazole, itraconazole and ketoconazole effect (rifampin), uveitis with fluconazole and itraconazole (rifabutin)
	Antifungals (terbinafine)	↓ Effect terbinafine
	Aprepitant (Emend®)	↓ Aprepitant effect

* This is not an exhaustive list of drug interactions. Readers should refer to drug information texts and sources and manufacturer package inserts for the latest and complete information. BTBC has a subscription to The Medical Letter's Drug Interaction Program.

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Appendix I-F (continued)

Potential Drug Interactions with Antituberculosis Medications*

Antituberculosis Medication	Drug or Drug Type** (most common brand names)	Potential Interaction
Rifampin, Rifabutin and Rifapentine		
(continued)	Atazanavir (Reyataz®)	↓ Atazanavir effect, ↑ rifabutin toxicity
	Atovaquone (Malarone®)	↓ Atovaquone effect, ↑ rifampin effect
	Barbiturates	↓ Barbiturate effect
	Benzodiazepines	↓ Benzodiazepine effect that undergo oxidative oxidation such diazepam, alprazolam, midazolam, and triazolam
	Beta-adrenergic blockers	↓ Beta blockade with atenolol, carvedilol, propranolol, or metoprolol (rifampin >> rifabutin)
	Buspiron (BuSpar®)	↓ Buspiron effect
	Carbamazepine (Tegretol®)	↓ Carbamazepine effect
	Caspofungin	↓ Caspofungin effect
	Chloramphenicol (Chloromycetin®)	↓ Chloramphenicol effect
	Chlorpropamide (Diabinese®)	↓ Chlorpropamide effect
	Cimetidine (Tagamet®)	↓ Cimetidine effect
	Citalopram (Celexa®)	↓ Citalopram effect
	Clarithromycin (Biaxin®)	↓ Clarithromycin effect
	Clofazimine (Lamprene®)	Possible ↓ rifampin effect
	Clofibrate (Atromid-S®)	Possible ↓ clofibrate effect
	Clozapine (Clozaril®)	↓ Clozapine effect
	Contraceptives, combination, hormonal	↓ Contraceptive effect (↓ ethinyl estradiol and norethindrone) (rifampin > rifabutin)
	Corticosteroids	Marked ↓ corticosteroid effect
	COX-2 inhibitors (Vioxx®, Celebrex®)	↓ Rofecoxib and celecoxib effect
	Cyclosporine (Neoral®)	↓ Cyclosporine effect
	Dapsone (Dapson®)	Possible ↓ dapsone effect (rifabutin > rifampin)
	Delavirdine (Rescriptor®)	Marked ↓ delavirdine effect (rifampin and rifabutin), ↑ rifabutin effect
	Digitoxin (Crystodigin®)	↓ Digitoxin effect
	Digoxin (Lanoxin®)	↓ Digoxin effect
	Diltiazem (Cardizem®)	↓ Diltiazem effect
	Disopyramide (Norpace®)	↓ Disopyramide effect
	Dolasetron (Anzemet®)	Possible ↓ dolasetron effect

Antituberculosis Medication	Drug or Drug Type** (most common brand names)	Potential Interaction
Rifampin, Rifabutin and Rifapentine		
(continued)	Domperidone (Motilium®)	Possible ↓ domperidone effect (rifampin and rifabutin)
	Doxycycline (Vibramycin®)	↓ Doxycycline effect
	Efavirenz (Sustiva®)	↓ Efavirenz effect (rifampin), possible ↓ rifabutin effect
	Enalapril (Vasotec®)	↓ Enalapril effect
	Erlotinib (Tarceva®)	Possible ↓ erlotinib effect
	Erythromycin (Ery-Tab®)	↓ Erythromycin effect
	Estrogens	↓ Estrogen effect
	Eszopiclone (Lunesta®)	Possible ↓ eszopiclone effect
	Etravirine (TMC-125)	Possible ↓ etravirine effect (rifampin)
	Fexofenadine (Allegra®)	Possible ↓ fexofenadine effect
	Fluconazole	↓ Fluconazole effect
	Folic Acid	↓ Microbiological assay of serum folate
	Fos-amprenavir (Lexiva®)	↓ Fos-amprenavir effect (rifampin), possible ↑ rifabutin toxicity
	Gefitinib (Iressa®)	↓ Gefitinib effect
	Glimepiride (Amaryl®)	↓ Glimepiride effect
	Glyburide (DiaBeta®, Micronase®)	↓ Glyburide effect
	Haloperidol (Haldol®)	↓ Haloperidol effect
	Halothane	Possible ↑ hepatotoxicity
	HMG-CoA reductase inhibitors (Lipitor®, Lescol®, Zocor®)	↓ Fluvastatin and simvastatin effect possible ↑ hepatotoxicity
	Hydroxychloroquine (Plaquenil®)	↓ Hydroxychloroquine effect
	Hypoglycemics, sulfonylurea	↓ Hypoglycemic effect of glyburide, tolbutamide and possibly glipizide
	Indinavir (Crixivan®)	Marked ↓ indinavir effect (rifampin), possible ↑ Rifabutin toxicity
	Isoniazid (Nydrazid®)	↑ Hepatotoxicity (↑ toxic metabolites)
	Itraconazole (Sporanox®)	↓ Itraconazole effect
	Ketoconazole	↓ Ketoconazole and rifampin effect
	Lamotrigine (Lamictal®)	↓ Lamotrigine effect
	Leflunomide (Arava®)	Possible leflunomide toxicity
	Levothyroxine (Levoxyl®)	↓ Levothyroxine effect

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Appendix I-F (continued)

Potential Drug Interactions with Antituberculosis Medications*

Antituberculosis Medication	Drug or Drug Type** (most common brand names)	Potential Interaction
Rifampin, Rifabutin and Rifapentine		
(continued)	Lopinavir/ritonavir (Kaletra®/ Norvir®)	↓ Lopinavir/ritonavir effect (rifampin), possible ↑ rifabutin toxicity
	Losartan (Cosaar®)	Possible ↓ losartan effect
	Macrolide antibiotics	↓ Macrolide effect, ↑ rifabutin toxicity (clarithromycin)
	Maraviroc (Selzentry®)	↓ Maraviroc effect (rifampin)
	Mefloquine (Lariam®)	↓ Mefloquine effect
	Mephenytoin (Mesantoin)	↓ Mephenytoin effect (rifampin)
	Metoprolol	Possible ↓ beta blockade
	Metronidazole (Flagyl®)	↓ Metronidazole effect
	Mexiletine (Mexitil®)	↓ Antiarrhythmic effect
	Morphine (Avinza®)	↓ Morphine effect
	Moxifloxacin (Avelox®)	↓ Moxifloxacin effect (with intermittently dosed rifampin)
	Narcotics/opiates	Cross-reactivity & false positive urine screening tests
	Narcotics: Methadone, Congeners	↓ Methadone effect (rifampin, rifabutin) withdrawal symptoms
	Narcotics: Morphine-like	Possible ↓ codeine or morphine response
	Nateglinide (Starlix®)	↓ Nateglinide effect
	Nelfinavir (Viracept®)	Marked ↓ nelfinavir effect, possible ↑ rifabutin toxicity
	Nevirapine (Viramune®)	↓ Nevirapine effect (rifampin) possible ↑ Rifabutin toxicity
	Nifedipine (Adalat®)	↓ Antihypertensive effect
	Nisoldipine (Sular®)	↓ Antihypertensive effect
	Ondansetron (Zofran®)	↓ Ondansetron effect
	Phenytoin (Dilantin®)	↓ Phenytoin effect
	Pioglitazone (Actos®)	Possible ↓ pioglitazone effect
	Pravastatin (Pravachol®)	Possible ↓ pravastatin effect
	Praziquantel (Biltricide®)	↓ Praziquantel effect
	Probenecid (Probalan®)	Possible ↑ rifampin effect
	Progestin	↓ Progestin (norethindrone) effect
	Propafenone (Rythmol®)	↓ Propafenone effect

Antituberculosis Medication	Drug or Drug Type** (most common brand names)	Potential Interaction
Rifampin, Rifabutin and Rifapentine (continued)		
	Pyrazinamide	Possible ↑ hepatotoxicity and death (additive)
	Quetiapine (Seroquel®)	↓ Quetiapine effect
	Quinidine (Quinaglute®)	↓ Quinidine effect
	Quinine (Quindan®)	↓ Quinine effect
	Radiocontrast media	↓ Biliary excretion of contrast media
	Raltegravir (Isentress™, MK0518)	Possible ↓ raltegravir effect (rifampin)
	Ramelteon (Rozerem®)	Possible ↓ ramelteon effect
	Ranolazine (Ranexa®)	↓ Ranolazine effect
	Repaglinide (Prandin®)	Possible ↓ repaglinide effect
	Ritonavir	Possible ↓ ritonavir effect (rifampin), ↑ Rifabutin toxicity
	Ropivacaine (Naropin®)	Possible ↓ ropivacaine effect
	Rosiglitazone (Avandia®)	↓ Rosiglitazone effect
	Saquinavir (Fortovase®)	↓ Saquinavir effect (rifampin rifabutin) Possible ↑ rifabutin toxicity
	Sertraline (Zoloft®)	↓ Sertraline effect
	Sirolimus (Rapamune®)	↓ Sirolimus effect
	Sulfonamides	Possible ↓ sulfamethoxazole effect (rifampin), ↑ Risk sulfamethoxazole toxicity (rifabutin)
	Tacrolimus (Prograf®)	↓ Tacrolimus effect
	Tadalafil (Cialis®)	↓ Tadalafil effect
	Tamoxifen (Nolvadex®)	Possible ↓ tamoxifen effect
	Telithromycin (Ketex®)	Possible ↓ telithromycin effect Possible ↑ hepatotoxicity
	Tetracyclines (Sumicin®)	↓ Tetracycline effect
	Theophyllines (Uni-Dur®)	↓ Theophylline effect
	Thyroid hormones	↓ Thyroid hormone effect
	Tinidazole (Tindamax®)	Possible ↓ tinidazole effect (rifampin)
	Tocainide (Tonocard®)	Possible ↑ tocinide effect
	Toremifene (Fareston®)	Possible ↓ toremifene effect
	Trazadone	Possible ↓ trazadone effect
	Trimethoprim	↓ Trimethoprim effect

* This is not an exhaustive list of drug interactions. Readers should refer to drug information texts and sources and manufacturer package inserts for the latest and complete information. BTBC has a subscription to The Medical Letter's Drug Interaction Program.

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Appendix I-F (continued)

Potential Drug Interactions with Antituberculosis Medications*

Antituberculosis Medication	Drug or Drug Type** (most common brand names)	Potential Interaction
Rifampin, Rifabutin and Rifapentine (continued)		
	Trimethoprim-sulfamethoxazole (Bactrim®)	Possible ↑ rifampin toxicity, possible ↓ Trimethoprim-sulfamethoxazole effect (rifampin and rifabutin)
	Sulfobromophthalein	↓ Hepatic uptake of sulfobromophthalein sodium
	Verapamil (Isoptin®)	↓ Verapamil effect
	Vitamin B ₁₂	Inhibits microbiological assays for vitamin B ₁₂
	Voriconazole (Vfend®)	↓ Voriconazole effect, possible ↑ rifabutin toxicity
	Zaleplon (Sonata®)	↓ Zaleplon effect
	Zidovudine (Retrovir®, AZT)	Possible ↓ zidovudine effect
	Zolpidem (Ambien®)	↓ Zolpidem effect

* This is not an exhaustive list of drug interactions. Readers should refer to drug information texts and sources and manufacturer package inserts for the latest and complete information. BTBC has a subscription to The Medical Letter's Drug Interaction Program.

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Appendix I-G

The Use of Bacille Calmette-Guérin Vaccine

Bacille Calmette-Guérin (BCG) vaccine¹ is a live, attenuated strain of *Mycobacterium bovis*. In most parts of the world, BCG vaccine is used routinely to prevent serious complications of TB, such as miliary TB and central nervous system (CNS) TB, in infants and children and in health care workers with frequent exposure to individuals with infectious TB.

Although the evidence is conflicting, a large body of research indicates that BCG vaccination does not completely prevent latent TB infection (LTBI) or pulmonary TB. Some studies suggest that BCG vaccination lessens the likelihood of disseminated TB and TB meningitis, especially in infants.

In the United States, BCG vaccine is not recommended routinely for children or used as a control strategy against TB. Specifically, it is not recommended as a general preventive strategy for health care workers because it complicates the interpretation of tuberculin skin test (TST) reactions and because it has not been proven effective in preventing LTBI. Health care workers who work primarily with patients who have multidrug-resistant TB (MDRTB) should be counseled on the risks and benefits of BCG vaccine.

BCG is not recommended for HIV-infected children or adults, and HIV testing must be performed before BCG is administered. Similarly, active TB must be ruled out before BCG can be given.

Nonetheless, BCG vaccine may be considered in very specific circumstances. These circumstances include instances in which infants and children are close household contacts of an individual with persistently untreated or ineffectively treated smear-positive TB, especially MDRTB.

On occasion, it may make clinical sense to give BCG to a young child who is going to live in a TB-endemic area for a prolonged period.

As of February 2007, Organon Pharmaceuticals (800) 631-1253 has vaccine available through a wholesale distributor. In addition, the TICE BCG vaccine is available from the manufacturer IVES.

All requests for BCG must be approved by the Director, Bureau of Tuberculosis Control, or a designee. BCG vaccine can be obtained from the principal pharmacist, STD/TB Pharmacy, New York City Department of Health and Mental Hygiene, 455 First Avenue, Room 147, NY, NY 10016. Telephone: (212) 447-2209.

1. Indications and Contraindications for Bacille Calmette-Guérin Vaccine

Before deciding to give BCG vaccine to a contact of an individual with persistently untreated or ineffectively treated smear-positive TB, every effort should be made to (1) ensure that the inadequately treated individual with infectious TB is treated properly, and to (2) separate the individual with TB and the exposed contact(s).

If this is not possible, giving BCG vaccine may be considered if the contact meets **all** of the following criteria:

- The contact has a negative test for TB infection (TTBI).
- The contact is repeatedly exposed to an individual with persistently untreated or ineffectively treated smear-positive MDRTB (TB resistant to isoniazid and rifampin).
- The contact is HIV-negative. (In some situations, however, BCG vaccine may be given to infants who have a positive HIV antibody as below.)

Notes:

1. Product names are provided for identification purposes only; their use does not imply endorsement by the New York City Department of Health and Mental Hygiene.

BCG vaccine should not be given to the following individuals:

- Persons with a documented history of a positive reaction to a TTBI
- Persons who are HIV-positive or otherwise immunosuppressed
- Persons with behavioral risk factors for HIV infection who decline HIV testing

There have been no reports of harmful effects of BCG vaccine on the fetus. Nevertheless, giving BCG vaccine should be avoided in pregnant women, unless there is an unusual risk of unavoidable exposure to infectious MDRTB.

2. Special Considerations for Infants

At least 2 other factors must be weighed before a decision is made to give BCG vaccination to a newborn or infant younger than 9 months old:

- Because an infant may not be able to mount a cellular immune response to infection with *M. tb*, a TST may not be a reliable indicator of infection. Thus, there may be instances where an infant with a negative TST may receive BCG vaccine even though he or she may be infected with *M. tb*.
- The blood of some infants born to mothers who are HIV infected may show the presence of placentally transferred HIV antibodies for a number of months after birth, even if the infant is not infected with HIV. Because HIV infection cannot be excluded in this situation, BCG vaccine could be considered if the infant is otherwise healthy, especially if the evaluation of other close contacts reveals a high rate of documented TST conversions and if all other efforts to prevent transmission have failed. Such an infant needs to be followed by a specialist until HIV infection is ruled out based on the most current recommendations.

3. Evaluation and Follow-up

- An individual who is being considered for BCG vaccination who cannot document a history of a previous positive TST reaction should have a TST, using 5 tuberculin units of purified protein derivative (PPD). A blood based test is not recommended in this setting.
- An individual who is being considered for BCG vaccination should be offered HIV counseling and testing if he or she has risk factor(s) for HIV infection.
- If the individual being considered for BCG vaccination is an infant or child, the parent or legal guardian must be interviewed and must agree. This must be documented in the chart.
- Eight weeks after the administration of BCG vaccine, the individual should have a repeat TST performed to document any reaction. If the contact's TST is < 5 mm, the BCG vaccination should be repeated.
- There is no evidence that revaccination with BCG affords any additional protection and therefore revaccination is not recommended.

4. New Blood-based Test for Tuberculosis Infection

- The new blood-based tests will differentiate between infection with BCG and *M. tb*. In this case, a blood-based test may be a reliable indicator of TB infection as the test can differentiate between *M. tb* complex and most other atypical mycobacteria.

Appendix II-A

Reporting Requirements for Suspected or Confirmed Tuberculosis

Medical providers and infection control practitioners are required by the New York City Health Code Article 11, in particular, Sections 11.03, 11.05 and 11.47(a), to report all patients suspected and confirmed with tuberculosis (TB) to the New York City Department of Health and Mental Hygiene (DOHMH), Bureau of Tuberculosis Control (BTBC) within 24 hours of the time the diagnosis is first suspected. Medical providers must report these patients even though microbiologists and pathologists are also required to report findings consistent with TB. Note that the reports have to be received by the DOHMH within 24 hours, whether by express or overnight mail, fax, telephone or electronically.

It is **mandatory** to report patients who meet **any** of the following criteria:

- Smear (from any anatomic site) positive for acid-fast bacilli (AFB)
- Rapid diagnostic tests, such as nucleic acid amplification test (NAA) (e.g., Roche's AMPLICOR®, Genprobe's MTD™)¹ result suggests *Mycobacterium tuberculosis* (*M. tb.*) complex
- Culture positive for *M. tb* complex including: *M. tb.*, *M. africanum*, *M. bovis-BCG*, *M. caprae*, *M. canettii*, *M. microti*, *M. pinnipedii*, *M. bovis*
- Biopsy, pathology or autopsy findings consistent with active tuberculosis disease, including but not limited to caseating granulomas in biopsy of lung, lymph nodes or other specimen
- Treatment with 2 or more anti-TB medications for suspected or confirmed active TB
- Clinical suspicion of pulmonary or extrapulmonary tuberculosis such that the physician or other health care provider has initiated or intends to initiate isolation or treatment for TB
- Continuation, discontinuation, completion, or other outcomes of treatment for TB
- Contact of an active TB case receiving treatment for TB infection
- Any child younger than five years old (up to the day of the fifth birthday) who has a positive result on a tuberculin skin test or a positive U.S. Food and Drug Administration (FDA) approved blood-based test for TB infection (such as Quantiferon)²
- In addition, Section 47.21 requires that Day Care staff report those with LTBI to the Bureau of Day Care

When an individual has an AFB-positive smear or has started treatment for TB, reporting should never be delayed pending identification of *M. tb.* with rapid diagnostic tests (e.g., NAA tests). Patients should be reported whenever TB is suspected, even if bacteriologic evidence of disease is lacking or treatment has not been initiated.

Microbiology and Pathology Laboratories

The New York City Health Code also requires laboratories to report as per Articles 11 and 13, Sections 11.03, 11.05 and 13.03, all of the following to the New York City DOHMH, BTBC:

- AFB-positive smears (regardless of anatomic site)
- Cultures positive for *M. tb.* complex
- Any culture or NAA result associated with an AFB-positive smear (even if negative for *M. tb.* complex)
- Rapid diagnostic test results that identify *M. tb.* complex (e.g., AMPLICOR®, MTD™)
- Results of susceptibility tests performed on *M. tb.* complex cultures
- Pathology findings consistent with TB, including the presence of AFB and granulomas

Reporting by Telephone and on the Universal Reporting Form

All suspected and confirmed TB patients may be reported by telephone to the TB Hotline, (212) 788-4162, but a completed Universal Reporting Form (URF) must follow within 48 hours.² The URF should be faxed to the BTBC at (212) 788-4179 and the original mailed to DOHMH at 125 Worth Street, Room 315, CN-6 NY, NY 10013. The URF can also be completed online, by first creating an account on NYC-MED at www.nyc.gov/health/nycmed. Assistance is available by calling (888) NYC-MED9 or (212) 442-3384.

Information reported on the URF should be as complete as possible. The following essential information must be included when the report is submitted to the New York City DOHMH:

- Information needed to identify and locate the individual (i.e., name, telephone number, address, and date of birth)
- Provider information (i.e., physician's name and telephone number, reporting facility)
- Results of smear for AFB (including the date the specimen was obtained and the accession number, if available)
- Results of chest radiographs

Laboratories can report via the Electronic Clinical Laboratory Reporting System (ECLRS). As of July 1, 2006, ECLRS will be the mandatory method of laboratory reporting in New York City. Assistance with ECLRS is available by calling (212) 442-3380. In addition, within 24 hours of observing growth of *M. tb.* complex in a culture from any specimen, the New York City Health Code Section 13.05(a) requires that a portion of the initial culture be sent to the NYC DOHMH Public Health Laboratory, 455 First Avenue, Room 236, New York, NY 10016, for DNA analysis. Laboratories outside of New York City will submit isolates directly to the New York State Wadsworth Center Mycobacteriology Laboratory in Albany, NY for genotyping.

Patient Follow-up

Treating physicians should also report whether the patient completed treatment and the outcome of the patient (cured, failed, relapsed, lost, moved) or whether treatment was discontinued if the patient was found not to have TB. Physicians must assist the DOHMH in its efforts to evaluate persons suspected of having TB and in patient follow-up. Case managers will be in contact with the treating physicians to request updates and ensure that appropriate treatment and monitoring is being conducted. A Report of Patient Services Form (TB 65) may need to be completed.

Reporting Tuberculosis-Related Evaluation and Treatment of Contacts

Medical providers are required, under Section 11.47(b) of the New York City Health Code, to report to the DOHMH, when requested, all information on the evaluation, testing, and treatment of individuals who have been in contact with a person with active TB disease.

Inquiries and Forms

To inquire further about reporting procedures, please call the BTBC Surveillance Office at (212) 788-4162. To order copies of the Report of Patients Services Form (TB 65) call (212) 442-5100. Obtain the URF by calling toll free (866) NYC-DOH1 (866 692-3641) or at www.nyc.gov/html/hcp/hcp-urf2.shtml.

Notes:

2. For guidelines for interpreting skin test results, see City Health Information: Testing and Treating for Latent TB Infection, April 2006, www.nyc.gov/html/doh/downloads/pdf/chi.chi25-4.pdf.

Appendix II-B

Procedures for Follow-Up of Centers for Disease Control Tuberculosis-Classified Immigrants and Refugees by the Bureau of Tuberculosis Control/Immigration and Refugee Unit

A medical examination that includes chest X-ray (CXR) for tuberculosis (TB) evaluation is mandatory for all refugees coming to the U.S. and all applicants outside the U.S. applying for an immigrant visa, and those who are applying for immigration status while already in the U.S., in accordance with the Immigration and Nationality Act and the Public Health Service Act.

Outside the U.S., medical examinations are performed by panel physicians selected by the Department of State (DOS) consular officials. The Division of Global Migration and Quarantine (DGMQ) at the Centers for Disease Control and Prevention (CDC) provide the DOS and the U.S. Citizenship and Immigration Services (USCIS) with medical screening guidelines for all examining physicians, which outline in detail the scope of the medical examination. DGMQ also provides the Technical Instructions for Medical Examination of Aliens (TI) and guidance to panel physicians conducting the medical examination including the CXR and any necessary laboratory procedures for tuberculosis evaluation for migration. (The TI is currently under revision.) The panel physicians are required to complete Medical Examination for Immigrant and Refugee Form DS-2053 and the CXR and Classification Worksheet Form DS-3024, DS-3026 with a classification of the patient into one of the following categories:

Class A: Non-Communicable for Travel Purposes

- Abnormal chest radiograph(s) suggestive of current pulmonary TB
- History of one or more sputum smear exams positive for acid-fast bacilli
- Currently on recommended TB treatment **AND**
- Sputum smears negative for AFB on 3 consecutive days while on treatment

A waiver is required for such applicants to travel to the U.S.

Class B1: Tuberculosis Pulmonary, Clinically Active, Noninfectious

- Abnormal chest X-ray (CXR) suggestive of current pulmonary TB
- Sputum smears negative for AFB on 3 consecutive days

Class B1: Tuberculosis Extrapulmonary, Clinically Active, Noninfectious

- Radiographic or other evidence of extrapulmonary TB

Class B2: Tuberculosis, Inactive, Noninfectious

All immigrants and refugees with a CDC TB classification are given the CXR films along with DS-forms (overseas medical evaluation forms) to bring to the United States. The medical evaluation forms are collected at the U.S. ports of entry by the Homeland Security Inspectors and passed on to the local CDC DGMQ office. The overseas CXR films are not collected at the ports of entry. The regional DGMQ offices issue a letter from the CDC to migrants indicating their tuberculosis status asking them to contact the Health Department in their resettlement jurisdiction.

The regional DGMQ offices transmit all DS-forms and other overseas medical documents collected from immigrants and refugees at the U.S. ports of entry to the CDC-DGMQ central office in Atlanta via Electronic Disease Notification (EDN), a CDC initiated web-based notification system via Secure Data Network (SDN). The DGMQ central office inputs all alien data, DS-forms and medical documents into EDN, and generates a Follow-Up Worksheet for TB classified aliens and transmits them to designated health jurisdictions via EDN. The DGMQ then sends email notifications to receiving jurisdictional EDN

TB coordinators. The DGMQ transmits notifications to NYC BTBC/IRU of TB classified aliens who have indicated New York City as their destination in the U.S.

Bureau of Tuberculosis Control/Immigration and Refugee Unit Procedures

Upon receipt of CDC email notifications, the BTBC/IRU accesses EDN to view, download and print all alien documents and TB Follow-up Worksheets entered in EDN and processes domestic evaluation and follow-up of all notified aliens.

The IRU public health advisers (PHAs) immediately contact above notified immigrants and refugees, interview them and collect their overseas CXR films. The IRU case managers create individual charts for each TB classified alien consisting of all documents downloaded and printed from the EDN system, overseas CXR, IRU Evaluation form and BTBC Universal Referral Form. The charts are given to the BTBC assigned medical consultant for re-reading of CXR and review of medical examination documents. The medical consultant records his reading of chest radiographs and documents instructions for necessary follow-up as follows:

1. Refer immediately to chest center/clinic-highly suspicious of TB;
2. Refer to chest clinic-rule out TB;
3. Refer for TTBI-normal CXR;
4. Non-TB condition-referral to medical clinic recommended;
5. No follow-up-no follow-up necessary;

In general, the CXR abnormalities can be grouped as follows:

1. Changes that suggest active TB, such as cavities, "soft" infiltrates, etc. (Class V [High]). These individuals are promptly notified of their clinical situation, and an appointment is made as soon as possible at a nearby New York City Bureau of Tuberculosis Control (BTBC) chest center. The BTBC/IRU follows subsequent events to ensure that these individuals keep their appointment and receive an evaluation. This group accounts for about 5% of all individuals with an abnormal CXR.
2. Changes that suggest inactive TB, such as non-calcified nodules, linear densities, etc., but thought to be sufficient to warrant treatment for active tuberculosis or latent TB infection (LTBI) (Class V [Low]). These individuals are also given appointments in a chest center for medical evaluation and treatment. This group accounts for about 40% of all individuals with an abnormal CXR.
3. Changes that were reported as abnormal but on review have an indication for treatment of LTBI. Among these are calcified Ghon complex, calcified granuloma, apical "caps," pleural thickening, bullae, etc. Individuals with this type of CXR are given an appointment in the BTBC/IRU for a tuberculin skin test (TST). Those with a positive result are referred to a chest center to be evaluated for treatment of LTBI (Class II). This group represents approximately 55% of those with an abnormal CXR.
4. Changes that suggest serious nontuberculous disease include primary or metastatic lung tumor, bronchial obstruction, mediastinal masses, aortic aneurysm, etc. These individuals are contacted and assisted in arranging appointments with a general chest or medical center for appropriate diagnostic investigation and treatment as indicated. These individuals represent 1%-2% of the total.
5. If CXR findings are either normal or findings require no medical follow-up, the alien is notified of such.

The aliens are referred as per medical consultant's recommendations to DOHMH chest centers and non-DOHMH providers for appropriate follow-up and treatment. The IRU case managers contact the referral facilities, obtain clinic appointments for the migrants and notify them of their appointments via phone calls and letters. The PHAs also send referral packages consisting of IRU-created charts to the chest centers/clinics before the scheduled appointment.

In addition, some aliens are referred to DOHMH chest centers for CXRs because they report to have lost their overseas chest radiograph or did not bring it with them from overseas. Some aliens walk in to DOHMH and non-DOHMH chest centers/clinics on their own without any referral from IRU.

The examining physician has to complete the CDC-TB Follow-up Worksheets with diagnostic, follow-up, treatment and outcome data and return them to IRU. The IRU PHAs visit DOHMH chest centers and non-DOHMH facilities and work closely with them to obtain all follow-up data and update the IRU database. IRU users complete Follow-up Worksheets and transmit them to CDC-DGMQ via EDN.

Appendix II-C

Surveillance for Tuberculosis by Health Systems Examination

In New York City, applicants for disability or welfare assistance must have a health examination that is provided by Health Systems Inc., a medical group under contract with New York City. Individuals judged to have a greater-than-average risk of tuberculosis (TB) also receive a chest X-ray (CXR). These include persons with symptoms suggestive of chronic respiratory disease, present or past history of TB, a positive tuberculin skin test or other conditions that increase TB risk. The CXRs are read by a certified radiologist at Health Systems.

CXRs with abnormalities possibly related to TB are referred to the New York City Bureau of Tuberculosis Control (BTBC) for a review and assessment of the need for follow-up. Needed follow-up is provided by the Immigrant and Refugee Health Unit (IRU), organized to conduct this type of surveillance. The CXRs reviewed in the IRU show a variety of abnormalities, ranging from far-advanced cavitory lesions typical of TB (Class V [High]) to those with linear densities or non-calcified nodules, typical of inactive TB (Class V [Low]).

In every case, the next step is a computer search of the TB Registry. Most, but not all, of those with advanced active disease are being treated in a center in New York City. If the registry shows an acceptable level of compliance, no further follow-up is requested. If there is no evidence of TB diagnosis or treatment, or if the patient has been receiving therapy but is delinquent, the IRU locates the individual and attempts to refer the patient to a center for reevaluation and treatment if indicated. At least 27 new cases of culture-positive TB have been identified since this program began in July 1996.

Some individuals have evidence of old, healed TB on the CXR (Class V [Low] or Class IV). If the registry indicates prior therapy and discharge at completion of treatment, no further follow-up is requested in most cases. Otherwise, the individual is referred to a BTBC chest center to be evaluated for treatment of latent TB infection.

A few CXRs show abnormalities consistent with nontuberculous disease, such as bronchial obstruction, mediastinal mass, pleural effusion or other conditions that suggest the need for invasive diagnostic procedures. In this situation, the individual is referred by the IRU to a general chest or medical clinic for appropriate diagnostic investigation and treatment.

Appendix III-A and Appendix III-B

In 2006, the “*International Standards for Tuberculosis Care*”^{*} were published to describe a widely accepted level of care that all practitioners, public and private, should seek to achieve in managing patients who have, or are suspected of having, tuberculosis. The same group has also developed the “*Patients’ Charter for Tuberculosis Care*.” The two documents were developed in tandem and serve as a companion to and support each other.

Appendix III-A International Standards for Tuberculosis Care

The *Standards* are intended to facilitate the effective engagement of all care providers in delivering high-quality care for patients of all ages, including those with sputum smear positive, sputum smear negative, and extra-pulmonary tuberculosis, tuberculosis caused by drug-resistant *Mycobacterium tuberculosis* complex (*M. tuberculosis*) organisms, and tuberculosis combined with human immunodeficiency virus (HIV) infection.

These *Standards* are reproduced here from the above document to serve as a reference for all TB care providers. BTBC guidelines generally adhere to all these *Standards*; however there are some differences but usually BTBC guidelines are more stringent.

Standards for Diagnosis

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

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

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 and, where facilities and resources are available, for culture and histopathological examination.

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

Standard 5. The diagnosis of sputum smear-negative pulmonary tuberculosis should be based on the following criteria: at least three negative sputum smears (including at least one early morning specimen); chest radiography findings consistent with tuberculosis; and lack of response to a trial of broad spectrum antimicrobial agents. (NOTE: Because the fluoroquinolones are active against *M. tuberculosis* complex and, thus, may cause transient improvement in persons with tuberculosis, they should be avoided.) For such patients, if facilities for culture are available, sputum cultures should be obtained. In persons with known or suspected HIV infection, the diagnostic evaluation should be expedited.

Standard 6. The diagnosis of intrathoracic (i.e., pulmonary, pleural, and mediastinal or hilar lymph node) tuberculosis in symptomatic children with negative sputum smears should be based on the finding of chest radiographic abnormalities consistent with tuberculosis and either a history of exposure to an infectious case or evidence of tuberculosis infection (positive tuberculin skin test or interferon gamma release assay). For such patients, if facilities for culture are available, sputum specimens should be obtained (by expectoration, gastric washings, or induced sputum) for culture.

^{*} From “Tuberculosis Coalition for Technical Assistance. *International Standards for Tuberculosis Care (ISTC)*. The Hague: Tuberculosis Coalition for Technical Assistance, 2006.”

Standards for Treatment

Standard 7. Any practitioner treating a patient for tuberculosis is assuming an important public health responsibility. To fulfill this responsibility the practitioner must not only prescribe an appropriate regimen but, also, be capable of assessing the adherence of the patient to the regimen and addressing poor adherence when it occurs. By so doing, the provider will be able to ensure adherence to the regimen until treatment is completed.

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 preferred continuation phase consists of isoniazid and rifampicin given for four months. Isoniazid and ethambutol given for six months is an alternative continuation phase regimen that may be used when adherence cannot be assessed, but it is associated with a higher rate of failure and relapse, especially in patients with HIV infection.

The doses of antituberculosis 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, especially when medication ingestion is not observed.

Standard 9. To foster and assess 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 gender-sensitive and age-specific 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) by a treatment supporter who is acceptable and accountable to the patient and to the health system.

Standard 10. All patients should be monitored for response to therapy, best judged in patients with pulmonary tuberculosis by follow-up sputum microscopy (two specimens) at least at the time of completion of the initial phase of treatment (two months), at five months, and at the end of treatment. Patients who have positive smears during the fifth month of treatment should be considered as treatment failures and have therapy modified appropriately. (See Standards 14 and 15.) In patients with extrapulmonary tuberculosis and in children, the response to treatment is best assessed clinically. Follow-up radiographic examinations are usually unnecessary and may be misleading.

Standard 11. A written record of all medications given, bacteriologic response, and adverse reactions should be maintained for all patients.

Standard 12. In areas with a high prevalence of HIV infection in the general population and where tuberculosis and HIV infection are likely to co-exist, HIV counseling and testing is indicated for all tuberculosis patients as part of their routine management. In areas with lower prevalence rates of HIV, HIV counseling and testing is indicated for tuberculosis patients with symptoms and/or signs of HIV-related conditions and in tuberculosis patients having a history suggestive of high risk of HIV exposure.

Standard 13. All patients with tuberculosis and HIV infection should be evaluated to determine if antiretroviral therapy is indicated during the course of treatment for tuberculosis. Appropriate arrangements for access to antiretroviral drugs should be made for patients who meet indications for treatment. Given the complexity of co-administration of antituberculosis treatment and antiretroviral therapy, consultation with a physician who is expert in this area is recommended before initiation of concurrent treatment for tuberculosis and HIV infection, regardless of which disease appeared first. However, initiation of treatment for tuberculosis should not be delayed. Patients with tuberculosis and HIV infection should also receive cotrimoxazole as prophylaxis for other infections.

Standard 14. 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. Patients who fail treatment and chronic cases should always be assessed for possible drug resistance. For patients in whom drug resistance is considered to be likely, culture and drug susceptibility testing for isoniazid, rifampicin, and ethambutol should be performed promptly.

Standard 15. Patients with tuberculosis caused by drug-resistant (especially multiple drug resistant [MDR]) organisms should be treated with specialized regimens containing second-line antituberculosis drugs. At least four drugs to which the organisms are known or presumed to be susceptible should be used, and treatment should be given for at least 18 months. Patient centered measures are required to ensure adherence. Consultation with a provider experienced in treatment of patients with MDR tuberculosis should be obtained.

Standards for Public Health Responsibilities

Standard 16. All providers of care for patients with tuberculosis should ensure that persons (especially children under 5 years of age and persons with HIV infection) who are in close contact with patients who have infectious tuberculosis are evaluated and managed in line with international recommendations. Children under 5 years of age and persons with HIV infection who have been in contact with an infectious case should be evaluated for both latent infection with *M. tuberculosis* and for active tuberculosis.

Standard 17. All providers must report both new and retreatment tuberculosis cases and their treatment outcomes to local public health authorities, in conformance with applicable legal requirements and policies.

Appendix III-B Patients' Charter for Tuberculosis Care

The *Charter* specifies patients' rights and responsibilities and is meant to serve as a set of standards from the point of view of the patient, defining what the patient should expect from the provider and what the provider should expect from the patient. These standards are meant to empower patients to evaluate the quality of care they are being provided. Good care for individuals with tuberculosis is also in the best interest of the community. These are being reproduced in full in this manual to serve as reference. (See p. 238.)

The Patients' Charter for Tuberculosis Care

Patients' Rights

Patients have the right to:

Care

- The right to free and equitable access to tuberculosis care, from diagnosis through treatment completion, regardless of resources, race, gender, age, language, legal status, religious beliefs, sexual orientation, culture, or having another illness
- The right to receive medical advice and treatment which fully meets the new *International Standards for Tuberculosis Care*, centering on patient needs, including those with multidrug-resistant tuberculosis (MDR-TB) or tuberculosis-human immunodeficiency virus (HIV) coinfections and preventative treatment for young children and others considered to be at high risk
- The right to benefit from proactive health sector community outreach, education, and prevention campaigns as part of comprehensive care programs

Dignity

- The right to be treated with respect and dignity, including the delivery of services without stigma, prejudice, or discrimination by health providers and authorities
- The right to quality healthcare in a dignified environment, with moral support from family, friends, and the community

Information

- The right to information about what healthcare services are available for tuberculosis and what responsibilities, engagements, and direct or indirect costs are involved
- The right to receive a timely, concise, and clear description of the medical condition, with diagnosis, prognosis (an opinion as to the likely future course of the illness), and treatment proposed, with communication of common risks and appropriate alternatives
- The right to know the names and dosages of any medication or intervention to be prescribed, its normal actions and potential side-effects, and its possible impact on other conditions or treatments
- The right of access to medical information which relates to the patient's condition and treatment and to a copy of the medical record if requested by the patient or a person authorized by the patient
- The right to meet, share experiences with peers and other patients, and to voluntary counseling at any time from diagnosis through treatment completion

Choice

- The right to a second medical opinion, with access to previous medical records
- The right to accept or refuse surgical interventions if chemotherapy is possible and to be informed of the likely medical and statutory consequences within the context of a communicable disease
- The right to choose whether or not to take part in research programs without compromising care

Confidence

- The right to have personal privacy, dignity, religious beliefs and culture respected
- The right to have information relating to the medical condition kept confidential and released to other authorities contingent upon the patient's consent

Justice

- The right to make a complaint through channels provided for this purpose by the health authority and to have any complaint dealt with promptly and fairly
- The right to appeal to a higher authority if the above is not respected and to be informed in writing of the outcome

Organization

- The right to join, or to establish, organizations of people with or affected by tuberculosis and to seek support for the development of these clubs and community-based associations through the health providers, authorities, and civil society
- The right to participate as “stakeholders” in the development, implementation, monitoring, and evaluation of tuberculosis policies and programs with local, national, and international health authorities

Security

- The right to job security after diagnosis or appropriate rehabilitation upon completion of treatment
- The right to nutritional security or food supplements if needed to meet treatment requirements

Patients’ Responsibilities

Patients have the responsibility to:

Share Information

- The responsibility to provide the health care giver as much information as possible about present health, past illnesses, any allergies and any other relevant details
- The responsibility to provide information to the health provider about contacts with immediate family, friends and others who may be vulnerable to tuberculosis or may have been infected by contact

Follow Treatment

- The responsibility to follow the prescribed and agreed treatment plan and to conscientiously comply with the instructions given to protect the patient’s health, and that of others
- The responsibility to inform the health provider of any difficulties or problems with following treatment or if any part of the treatment is not clearly understood

Contribute to Community Health

- The responsibility to contribute to community well-being by encouraging others to seek medical advice if they exhibit the symptoms of tuberculosis
- The responsibility to show consideration for the rights of other patients and healthcare providers, understanding that this is the dignified basis and respectful foundation of the tuberculosis community

Show Solidarity

- The moral responsibility of showing solidarity with other patients, marching together towards cure
- The moral responsibility to share information and knowledge gained during treatment and to pass this expertise to others in the community, making empowerment contagious
- The moral responsibility to join in efforts to make the community tuberculosis free

Appendix III-C

NEW YORK CITY DEPARTMENT OF HEALTH AND MENTAL HYGIENE BUREAU OF TUBERCULOSIS CONTROL

AGREEMENT FOR DOT IN THE FIELD

Date: _____

Between _____ and _____
Network Patient/Guardian

PATIENT SECTION

It has been explained to me that the most effective way to treat tuberculosis is by providing medication to the patient and having a trained health care worker observe the ingestion of all oral medication and verify the administering of injectables. Therefore, I _____, agree to the following:
Patient

1. I will take my treatment under direct observation (DOT) and will keep all my DOT appointments.
2. I will attend all scheduled appointments on time at my doctor's office until my physician tells me that my treatment is complete.

_____ MD Name _____ Address _____ Phone # _____

- 2a. It has been determined by my physician that I will initially be taking medication _____ times a week. It has been explained to me that only my physician can change my medication and that all changes will be sent in writing to the _____.
Field Office
3. If, for any reason, I cannot go to a scheduled physician appointment, I will **notify my DOT observer** and try to reschedule my visit.
- 3a. I will inform my DOT observer in advance of planned vacations and other appointments, and also if my address or telephone number changes.
4. I agree to comply with DOT visits at the mutually agreed upon place _____ and time frame _____.
- 4a. If I cannot meet the DOT observer at the above agreed upon place and time frame, I will contact DOT at:
_____ Central Phone
_____ DOT Observer Pager
5. If I have any questions, concerns, suggestions or complaints about any aspect of my care, I will tell

_____ Name/Title _____ Phone # _____

STAFF SECTION

I, _____, agree to the following:
DOT Assignee

1. I will assist the patient in maintaining his/her appointments.
2. I will respond to all questions and concerns raised by the patient and assist with referral for social services, to the best of my capacity.
3. I will ensure patient confidentiality to the best of my ability.
4. Occasionally, DOT observer and schedule may change and if so, the patient will be notified as quickly as possible.
5. I will ensure that your treating physician will receive a copy of this Agreement.

Signature of Patient

Signature of DOT Observer

Signature of Supervisor

Appendix III-D

NEW YORK CITY DEPARTMENT OF HEALTH AND MENTAL HYGIENE BUREAU OF TUBERCULOSIS CONTROL

AGREEMENT FOR DOT IN THE CHEST CENTER

Between _____ Chest Center and
Name of Center

Name of Patient on this date _____
Today's Date

PATIENT SECTION

It has been explained to me that the most effective way to treat tuberculosis is by providing medication to the patient and having a trained health care worker observe the ingestion of all oral medication and verify the administering of injectables.

Therefore, I _____, agree to the following:
Name of Patient

1. I agree to have my treatment given under direct observation (DOT) and keep all my DOT appointments.
2. I will attend all scheduled appointments on time at the _____
Name of Center
Chest Center until my physician tells me that my treatment is complete.
3. If, for any reason, I cannot go to a scheduled appointment, I will call
_____ at (_____) _____ to reschedule.
Name of Person to call Telephone Number
- 3a. I will inform DOT staff in advance of planned vacations and other appointments and if my address or telephone number changes.
4. If I have any questions, concerns, suggestions or complaints about any aspect of my care, I will tell
_____ or _____.
Name of Person to Notify Name of Person to Notify

CHEST CENTER STAFF SECTION

Therefore, I _____ , agree to the following:
Name of Case Manager/DOT Observer

1. I will observe all the treatment and ask questions about how the patient is doing.
2. I will ensure that the patient is given free medications and reimbursed for all transportation to and from every center visit,
3. I will respond to all questions and concerns raised by the patient and assist with referral for social services, to the best of my capacity.
4. I will assist the patient in maintaining his/her appointments.

Therefore, I _____ , agree to the following:
Name of Treating Physician

1. I will ensure that the patient is being treated with the most advanced and effective therapy known to the medical profession.
2. I will inform and respond to questions from both the patient and case manager of all relevant medical information concerning the patient's progress, as permitted by the patient.

Signature of Patient

Signature of Case Manager/DOT Observer

Signature of Treating Physician

Appendix III-E



THE CITY OF NEW YORK

DEPARTMENT OF HEALTH AND MENTAL HYGIENE

Michael R. Bloomberg
Mayor

Thomas R. Frieden, M.D., M.P.H.
Commissioner

nyc.gov/health

Instructions for patients with potentially infectious TB

You are being discharged from the hospital although your sputum tests indicate that you may still infect other people with TB or you are advised to be evaluated as an outpatient while you may have infectious TB.

You are being discharged because you said that either you live alone or will be going back to a living arrangement where the other people living there are healthy and wish to have you home. We are required by law to notify them that they have been exposed to TB and to evaluate them.

You may have been placed on medication to treat TB already or are waiting to start medications after you have been evaluated as an outpatient.

The following instructions will help reduce the spread of TB germs to other people and you should follow them carefully:

- If you return to a home that has other people, you should always:
 - Limit the time spent in common household areas (such as bathroom or kitchen) and keep your bedroom door closed
 - Wear a surgical mask when spending time in a space that is also used by others to reduce the number of TB germs that you put in the air when you cough or talk.
- You should always cover your mouth when coughing or sneezing
- You should not be around infants, young children or, to the best of your knowledge, persons who have weakened immunity such as people with HIV/AIDS. (If there are young children at home, you may still be discharged to the home if the children have been evaluated for latent TB infection and are on “preventive” medication, as determined by their physician)
- You should participate in a program of directly observed therapy (DOT), about which you have been educated by an employee of the NYC health department
- You should avoid going to public places or return to work or school until your doctor, working with the health department, says it is OK for you to do so
- You should keep your doctor’s or clinic appointments to ensure that treatment for TB is not interrupted
- Some of these restrictions will be removed once your physician, along with the health department, determines that you are no longer infectious
- Your TB treatment and DOT will continue even after these restrictions are removed.

Following these instructions will help in limiting the spread of TB germs to your family and others. If you have questions about your treatment please call your physician or health department at 311.

You can also find more information about TB on our website at nyc.gov/health/tb.

Appendix III-F



THE CITY OF NEW YORK

DEPARTMENT OF HEALTH AND MENTAL HYGIENE

Michael R. Bloomberg
Mayor

Thomas R. Frieden, M.D., M.P.H.
Commissioner

nyc.gov/health

Information for persons who live with patients with TB

*A family member or someone in your household was recently diagnosed with or is suspected of having active TB. TB is a preventable and treatable disease. TB is transmitted through the air when a patient with the disease coughs or sneezes without covering his or her mouth. People with the active form of the disease must take their medication and must follow certain rules to prevent the spread of TB germs to people they live or work with. **We are required by state law to inform you of this information.***

If there are children in your home they should be evaluated by their doctor and they should be placed on “preventive” therapy if appropriate. They can also be evaluated and treated at the health department’s chest centers.

If a family member or someone in your household has been diagnosed with TB:

- You should get tested to see if you have already been infected with the germs that cause TB
- If you have been infected with the germs that cause TB, you should have a medical evaluation and a chest x-ray to make sure that you have not progressed to active TB
- If you have TB infection, you should take medicine to prevent the development of active TB.
- **The member of your household with TB should stay at home until his or her physician and the health department says he/she can go out.**
- He/she should not go to work or school during this time period and should avoid going to any public areas during this time period.
- Please assist the TB patient by doing their errands, such as grocery shopping.
- Your household member with TB should cover his/her mouth with a tissue whenever he/she coughs or sneezes; he/she should put the used tissue in the regular garbage.
- When around other people, the patient should wear a surgical mask that covers the nose and mouth.
- While at home, limit your contact with the TB patient as much as possible; the patient should sleep in a separate room until advised by their physician.
- It is OK to share eating utensils (spoons, forks, cups or glasses) and other household items.

Following these instructions will help in limiting the spread of TB germs to your family and others.

If you have questions about your treatment please call your physician or health department at 311.

You can also find more information about TB on our website at nyc.gov/health/tb.

Appendix III-G



THE CITY OF NEW YORK

DEPARTMENT OF HEALTH AND MENTAL HYGIENE

Michael R. Bloomberg
Mayor

Thomas R. Frieden, M.D., M.P.H.
Commissioner

nyc.gov/health

HOME ISOLATION PATIENT AGREEMENT

I _____, acknowledge that I have active infectious tuberculosis,
(Patient's full name)
and that I must separate myself from others in order to prevent other from being exposed to my tuberculosis disease.
I have discussed this agreement with _____
(Full name of DOHMH employee)

a _____ at the Department of Health and Mental Hygiene
(Job title)

(DOHMH), who has answered my questions about home isolation fully to my satisfaction. I further acknowledge that if I am unable or unwilling to observe any of the conditions of this agreement, while my tuberculosis remains infectious, I represent a danger to the health of others and I am subject to removal to a hospital for respiratory isolation either voluntarily or by order of the Commissioner of Health.

In return for being allowed to remain in my home while my tuberculosis is infectious, I agree to all of the following conditions.

- I will take all my prescribed anti-tuberculosis medications in a program of daily directly observed therapy (DOT) as directed by my physician or the Commissioner of Health.
- I will entertain no visitors in my home and will not visit other persons' home.
- I will cover my mouth and nose whenever I cough, sneeze, or hack while indoors or outdoors in the presence of other people.
- I will not use any public (bus, train, taxi, subway, airplane) or private (automobile) transportation unless absolutely necessary to obtain medical attention, and then only using the mask which my physician has prescribed for me.
- I will not visit enclosed public spaces such as theaters, shopping malls, department, supermarket or other stores; but I may spend time in open spaces such as parks, backyards or public streets which are not crowded.
- I will not care for or spend time with children of any age or work outside my home without permission from my physician and the DOHMH.
- I will not leave New York City for any reason without the DOHMH and my physician's permission and under such conditions as are prescribed.
- I have received a copy of the instructions entitled "Instructions for Patients with Potentially Infectious TB"
- Any additional conditions:

If I have any further questions about how to comply with this agreement, I will telephone

_____ at _____
(Full name and title of contact person at DOHMH) (Telephone number with area code)

Date: _____ (Patient's signature)

Date: _____ (Staff signature)

Revised: July 2006

International Classification of Tuberculosis

Class	Type	Description
0	No TB exposure Not infected	No history of exposure Negative test for TB infection ^{1,2}
I	TB exposure No evidence of infection	History of exposure Negative test for TB infection ^{1,2}
II	TB infection No disease	Positive test for TB infection ^{1,2} No clinical or radiographic evidence of TB Negative bacteriologic studies (if done)
III	Current TB disease	Positive culture for <i>M. tuberculosis</i> and/or Clinical or radiographic evidence of current TB disease, with or without a positive test for TB infection ^{1,2}
IV	Previous TB disease	History of episode(s) of TB or Abnormal but stable radiographic findings, positive test for TB infection ^{1,2} , no clinical or radiographic evidence of current TB disease and negative bacteriologic studies (if done)
V (High) ³	Current TB disease suspected	Diagnosis pending, but expected to evolve as Class III
V (Low) ³	Previous TB disease suspected	Diagnosis pending, but expected to evolve as Class IV or as an abnormality not related to TB

Adapted from CDC. *Core Curriculum on Tuberculosis, Third Ed.* Atlanta: Centers for Disease Control and Prevention; 1994

¹ Whether a tuberculin skin test reaction is classified as positive or negative depends on the TB risk factors of the person being tested. For guidelines on classifying the skin test reaction, see p.179 of this manual.

² Tests for TB infection are either a tuberculin skin test or a blood-based assay.

³ The division of Class V into "high" and "low," intended to improve case management, is specific to the New York City Department of Health and Mental Hygiene; it is not part of the International Classification.

Product names are listed in this publication for identification purposes only; their use does not imply endorsement by the New York City Department of Health and Mental Hygiene

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ERRATA AND ADDITIONS
TUBERCULOSIS
CLINICAL POLICIES AND PROCEDURES, 4TH EDITION MARCH 2008

Section II, Initial Evaluation of Suspected Tuberculosis

Page 33, Table II-2, replace superscript *c* in MGIT column with 3

Section IV, Evaluation and Treatment of Extrapulmonary Tuberculosis

Page 72, addition in left column, end of first full paragraph. *In several forms of TB, corticosteroids have been shown to be useful (see Table IV-2).*

Page 73, replace (*Meningeal*), *Tuberculoma* with *Central Nervous System Tuberculosis*

Section VII, Infection Control

Page 127, left column, paragraph 9, replace *smear* with *culture*

Page 129, left column, third bullet point, replace *Hospitals* with *Patient care areas*

Section IX, Contact Evaluation and Public Health Management

Page 156, Table IX-1, upper half of table, under second column (Nucleic Acid Amplification Result move *Or/Not done* ” from under “Negative for M.tb” to under “Positive for M.tb”

Table IX-1, upper half of table, under last column entitled “complete,” in the first box, *add if verified* so that the cell reads, *Yes, if verified.*

Page 167, left column, under Airline Exposures, second paragraph, change *BTBC* to *CDC/DGM* in sixth and eighth lines.

Section XI, Latent TB Infection (LTBI): Evaluation, Treatment, Monitoring and Follow-up

Page. 192, right column, after the first three bullets add, *For guidelines on when to give a repeat course of treatment for LTBI in contacts that have already completed such treatment, see pages 163 and 193.*

Page 199, right column, first bullet, second line, change *older* to *younger*

Replace *flouroquinolones* with *fluoroquinolones* on:

Page 92, left column, third paragraph

Page 210 in the second footnote (twice)

Replace *para-aminosalicyclic* with *para-aminosalicylic* on:

Page 210 (2 times)

Page 211

Page 215, first bullet



*Michael R. Bloomberg,
Mayor*

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Health & Mental
Hygiene**

*Thomas R. Frieden, M.D., M.P.H.
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