

INTERNATIONAL STANDARDS FOR

# Tuberculosis Care

DIAGNOSIS TREATMENT PUBLIC HEALTH



3RD EDITION, 2014

Developed by TB CARE I with funding by the United States Agency for International Development (USAID)

**TB CARE I**



---

#### TB CARE I Organizations



TUBERCULOSIS FOUNDATION



International Union Against  
Tuberculosis and Lung Disease  
*Health solutions for the poor*



---

#### Disclaimer:

The Global Health Bureau, Office of Health, Infectious Disease and Nutrition (HIDN), US Agency for International Development, financially supports this publication through TB CARE I under the terms of Agreement No. AID-OAA-A-10-00020. This publication is made possible by the generous support of the American people through the United States Agency for International Development (USAID). The contents are the responsibility of TB CARE I and do not necessarily reflect the views of USAID or the United States Government.

#### Suggested citation:

TB CARE I. *International Standards for Tuberculosis Care*, Edition 3. TB CARE I, The Hague, 2014.

#### Contact information:

Philip C. Hopewell, MD  
Curry International Tuberculosis Center  
University of California, San Francisco  
San Francisco General Hospital  
San Francisco, CA 94110, USA  
Email: [phopewell@medsfgh.ucsf.edu](mailto:phopewell@medsfgh.ucsf.edu)

#### Available at the following web sites:

<http://www.tbcare1.org/publications>

<http://istcweb.org>

<http://www.currytbcenter.ucsf.edu/international>

<http://www.who.int/tb/publications>

To access a mobile version of ISTC, go to [www.walimu.org/istc](http://www.walimu.org/istc)

INTERNATIONAL STANDARDS FOR

# Tuberculosis Care

---

DIAGNOSIS   TREATMENT   PUBLIC HEALTH

3RD EDITION, 2014

# Table of Contents

Acknowledgments.....	1
List of Abbreviations.....	2
Preface.....	4
Summary.....	8
Introduction.....	14
Standards for Diagnosis.....	20
Standards for Treatment.....	34
Standards for Addressing HIV Infection and Other Co-morbid Conditions ..	50
Standards for Public Health and Prevention.....	57
References.....	64
Annexes.....	77

# Acknowledgments

Development of the third edition of the *International Standards for Tuberculosis Care* was guided by a steering committee of World Health Organization Global Tuberculosis Programme staff and by an expert committee whose members were chosen to represent perspectives and areas of expertise relevant to tuberculosis care and control. Both committees are listed below. The expert committees for editions 1 and 2 are in Annex 1.

## Steering Committee (WHO)

- Haileyesus Getahun
- Chris Gilpin
- Malgosia Grzemska
- Ernesto Jaramillo
- Knut Lönnroth
- Mario Raviglione
- Mukund Uplekar
- Diana Weil

## Expert Committee

- |                                   |                                  |
|-----------------------------------|----------------------------------|
| • RV Asokan, India                | • Ernesto Jaramillo, WHO         |
| • Erlina Burhan, Indonesia        | • Aamir Khan, Pakistan           |
| • J.M. Chakaya, Kenya             | • Knut Lönnroth, WHO             |
| • Gavin Churchyard, South Africa  | • G. B. Migliori, Italy          |
| • Marcus Conde, Brazil            | • Dyah Mustikawati, Indonesia    |
| • Charles Daley, USA              | • Madhukar Pai, Canada           |
| • Saidi Egwaga, Tanzania          | • Rose Pray, USA                 |
| • Elizabeth Fair, USA             | • Mario Raviglione, WHO          |
| • Paula Fujiwara, USA             | • Elizabeth Soares, Brazil       |
| • Haileyesus Getahun, WHO         | • Mukund Uplekar, WHO (Co-Chair) |
| • Chris Gilpin, WHO               | • Dalene Von Delft, South Africa |
| • Steve Graham, Australia         | • Jan Voskens, Netherlands       |
| • Malgosia Grzemska, WHO          | • Diana Weil, WHO                |
| • Philip Hopewell, USA (Co-chair) | • Gini Williams, UK              |

**Elizabeth Fair** (University of California, San Francisco) in addition to being a member of the expert committee, provided scientific staffing and coordination.

**Fran Du Melle** (American Thoracic Society) provided administrative coordination as well as guidance on dissemination and implementation.

**Cecily Miller** and **Baby Djojonegoro** (University of California, San Francisco) provided assistance in organizing and preparing the document.

In addition to the committees, many individuals have provided valuable input. All comments received were given serious consideration by the co-chairs, although not all were incorporated into the document.



# List of Abbreviations

<b>AFB</b>	Acid-fast bacilli
<b>AIDS</b>	Acquired immunodeficiency syndrome
<b>ART</b>	Antiretroviral therapy
<b>ATS</b>	American Thoracic Society
<b>BCG</b>	Bacille Calmette-Guérin
<b>CDC</b>	Centers for Disease Control and Prevention
<b>CI</b>	Confidence interval
<b>COPD</b>	Chronic obstructive pulmonary disease
<b>CPT</b>	Cotrimoxazole
<b>CRI</b>	Colorimetric redox-indicator
<b>DOT</b>	Directly observed treatment
<b>DOTS</b>	The internationally recommended strategy for tuberculosis control
<b>DR</b>	Drug-resistant
<b>DST</b>	Drug susceptibility testing
<b>EMB</b>	Ethambutol
<b>FDA</b>	Food and Drug Administration (US)
<b>FDC</b>	Fixed-dose combination
<b>FHI 360</b>	Formerly Family Health International
<b>FM</b>	Fluorescence microscopy
<b>HAART</b>	Highly active antiretroviral therapy
<b>HIV</b>	Human immunodeficiency virus
<b>IDSA</b>	Infectious Diseases Society of America
<b>IGRA</b>	Interferon-gamma release assay
<b>INH</b>	Isoniazid
<b>IMAAI</b>	Integrated Management of Adolescent and Adult Illness
<b>IMCI</b>	Integrated Management of Childhood Illness
<b>IPT</b>	Isoniazid preventive therapy
<b>IRIS</b>	Immune reconstitution inflammatory syndrome
<b>ISTC</b>	International Standards for Tuberculosis Care
<b>IUATLD</b>	International Union Against Tuberculosis and Lung Disease (The Union)
<b>JATA</b>	Japan Anti-tuberculosis Association
<b>KNCV</b>	KNCV Tuberculosis Foundation
<b>LED</b>	Light emitting diode
<b>LPA</b>	Line probe assay
<b>LTBI</b>	Latent tuberculosis infection
<b>M&amp;E</b>	Monitoring and Evaluation
<b>MDR</b>	Multidrug-resistant
<b>MIC</b>	Minimal inhibitory concentration

<b>MODS</b>	Microscopic observation drug susceptibility
<b>MSH</b>	Management Sciences for Health
<b>NAAT</b>	Nucleic acid amplification test
<b>NALC</b>	N-acetyl L-cysteine
<b>NaOH</b>	Sodium hydroxide
<b>NIOSH</b>	National Institute for Occupational Services and Health
<b>NNRTI</b>	Non-nucleoside reverse transcriptase inhibitors
<b>NRA</b>	Nitrate reductase assay
<b>NTM</b>	Non-tuberculous mycobacteria
<b>NTP</b>	National tuberculosis control program
<b>PCTC</b>	Patients' Charter for Tuberculosis Care
<b>PI</b>	Protease inhibitor
<b>PLHIV</b>	People living with HIV
<b>PPM</b>	Public-private mix
<b>PZA</b>	Pyrazinamide
<b>RIF</b>	Rifampicin
<b>RR</b>	Risk ratio
<b>STI</b>	Sexually transmitted infection
<b>TB</b>	Tuberculosis
<b>TBCTA</b>	Tuberculosis Coalition for Technical Assistance
<b>TNF</b>	Tumor necrosis factor
<b>TST</b>	Tuberculin skin test (Mantoux)
<b>USAID</b>	United States Agency for International Development
<b>WHO</b>	World Health Organization
<b>XDR</b>	Extensively drug-resistant
<b>ZN</b>	Ziehl-Neelsen staining



# Preface to Edition 3

*The standards in the ISTC are all supported by existing WHO guidelines and policy statements, many of which had recently been developed using rigorous methodology.*

## Development Process

Development of the first edition of the *International Standards for Tuberculosis Care (ISTC)* was funded by the United States Agency for International Development (USAID) via the Tuberculosis Coalition for Technical Assistance (TBCTA) and was guided by an expert committee of 28 members from 14 countries representing relevant perspectives and areas of expertise. The committee was co-chaired by Mario Raviglione of the World Health Organization (WHO) and Philip Hopewell of the American Thoracic Society (ATS). The group first agreed on a content outline and then identified areas in which systematic reviews were needed. Six reviews, largely related to approaches to diagnosis, were conducted and subsequently published in peer-reviewed publications.

Development of Edition 2 of the *ISTC* was also funded by USAID via its TB Control Assistance Program (TBCAP). A new expert committee of 56 persons from 15 countries, plus WHO, chaired by Drs. Raviglione and Hopewell guided the process. Only one systematic review, related to contact investigation (subsequently published), was identified.

Edition 3 was again funded by USAID via TB CARE I and was developed using essentially the same process. Development was led by Mukund Uplekar (WHO) and Philip Hopewell (ATS). A steering committee from the staff of the Global TB Programme at the WHO identified areas in which revisions were needed. It was felt that no new systematic reviews were needed for this edition. The standards in the *ISTC* are all supported by existing WHO guidelines and policy statements, many of which had recently been developed using rigorous methodology, including systematic reviews. The draft document was then reviewed by an expert committee of 27 members from 13 countries, co-chaired by Drs. Uplekar and Hopewell. Subsequent drafts were also reviewed and approved by the expert committee. The final draft was reviewed and approved by the TB CARE I member organizations (ATS, FHI 360, the Japan Antituberculosis Association [JATA], KNCV Tuberculosis Foundation [KNCV], Management Sciences for Health [MSH], the International Union against Tuberculosis and Lung Disease [The Union], and WHO).



## Key differences between *ISTC* Edition 2 and Edition 3

Edition 1 of the *ISTC* stated, “The *Standards* should be viewed as a living document that will be revised as technology, resources, and circumstances change.” It has now been five years since Edition 2 of the *ISTC* was published (2009); new information has emerged; new approaches are now feasible; and new guidelines have been written. These changes warrant an updating of the *ISTC* to be consistent with the concept of a “living document.”

It was also stated in Edition 1 that, “As written, the *Standards* are presented within a context of what is generally considered to be feasible now or in the near future.” There is continued recognition that not all of the standards in this edition can be met in all places at this time. However, given the rapidity of technical advances and deployment of new technologies and approaches, it is anticipated that compliance with the standards will be possible in most places in the near future. It is hoped that having standards that are higher than the minimum necessary will serve to stimulate more rapid improvements in tuberculosis care worldwide.

It must be emphasized that the basic principles that underlie the *ISTC* have not changed. Case detection and curative treatment remain the cornerstones of tuberculosis care and control and the fundamental responsibility of providers to ensure completion of treatment is unchanged. Within these basic principles, however, there have been changes that are of sufficient importance to be incorporated into the *ISTC*. The areas of change that are addressed are summarized in Table 1.

An important companion document of which the reader should be aware is *The Handbook for Utilizing the International Standards for Tuberculosis Care*. The *Handbook* is based mainly on experiences in countries that began utilizing the *ISTC* soon after it was developed and provided documentation of these experiences. The findings from these pilot countries are summarized briefly in the Introduction. The *Handbook* is available at [www.istcweb.org](http://www.istcweb.org). A set of training modules based on the third edition of the *ISTC* is also available on the same website. Summaries of the utilization handbook and the training materials are in Annexes 2 and 3, respectively. Revisions of the *Handbook* and training modules will be available online in October 2014.

A second companion document, the *Patients' Charter for Tuberculosis Care (PCTC)*, was developed in tandem with the first edition of the *ISTC* and describes patient rights and responsibilities. The *ISTC* and the *PCTC* are mutually reinforcing documents, serving to define expectations from both the provider and the patient perspective. The *PCTC* is also available at [www.istcweb.org](http://www.istcweb.org).

TABLE 1.

**Key differences between the 2009 and 2014 editions of the *ISTC***

Section	Key Differences
<b>Overall</b>	<ul style="list-style-type: none"> <li>• Relevant WHO guidelines published since 2008 have been included.</li> <li>• References have been reviewed and, where necessary, replaced with new references to reflect current information.</li> <li>• The wording has been tightened and made more concise throughout.</li> </ul>
<b>Introduction</b>	<ul style="list-style-type: none"> <li>• Language has been added indicating that an additional purpose of the <i>ISTC</i> is to provide support to the integrated, patient-centered care and prevention component of WHO's global strategy for tuberculosis prevention, care, and control after 2015. Engagement of all providers is a critical component of the updated strategy and the <i>ISTC</i> will serve as a means of facilitating implementation of the strategy, especially among private providers.</li> <li>• Also noted is the importance of identifying individuals or groups at increased risk of tuberculosis and utilizing appropriate screening methods and preventive interventions in these persons or groups.</li> </ul>
<b>Standards for Diagnosis</b>	
<b>Standard 1</b>	<ul style="list-style-type: none"> <li>• This is a new standard emphasizing the responsibility of providers to be aware of individual and population risk factors for tuberculosis and to reduce diagnostic delay.</li> </ul>
<b>Standard 2</b>	<ul style="list-style-type: none"> <li>• Formerly Standard 1. The wording has been changed to include radiographic abnormalities as an indication for evaluation for tuberculosis.</li> <li>• The discussion of the standard emphasizes the importance of including not only cough, but also fever, night sweats, and weight loss as indications for evaluation for tuberculosis.</li> </ul>
<b>Standard 3</b>	<ul style="list-style-type: none"> <li>• Formerly Standard 2. The current WHO recommendations for use of rapid molecular testing as the initial microbiologic test in specified patients are now included.</li> <li>• The WHO recommendation against using serologic assays for diagnosing tuberculosis is emphasized.</li> </ul>
<b>Standard 4</b>	<ul style="list-style-type: none"> <li>• Previous Standard 4 now combined with Standard 1.</li> <li>• The importance of microbiological diagnosis of extrapulmonary tuberculosis is emphasized.</li> <li>• WHO recommendations for the use of rapid molecular testing for samples from extrapulmonary sites are included.</li> </ul>
<b>Standard 5</b>	<ul style="list-style-type: none"> <li>• The WHO recommendations for use of rapid molecular testing for diagnosis of tuberculosis among persons who are suspected of having the disease but have negative sputum smear microscopy are presented.</li> </ul>
<b>Standard 6</b>	<ul style="list-style-type: none"> <li>• The WHO recommendations for the use of rapid molecular testing for the diagnosis of tuberculosis in children are presented.</li> </ul>

TABLE 1.

**Key differences between the 2009 and 2014 editions of the *ISTC***

Section	Key Differences
<b>Standards for Treatment</b>	
<b>Standard 7</b>	• No change
<b>Standard 8</b>	• No change
<b>Standard 9</b>	• No change
<b>Standard 10</b>	• The role of microscopy in monitoring response in patients who had the diagnosis established by a rapid molecular test is described.
<b>Standard 11</b>	• This standard describes the use of Xpert® MTB/RIF in assessing for rifampicin resistance and line probe assay for detecting resistance to both isoniazid and rifampicin.
<b>Standard 12</b>	• The standard has been changed to reflect the revised WHO recommendations for programmatic management of drug-resistant tuberculosis.
<b>Standard 13</b>	• No change
<b>Standards for Addressing HIV Infection and other Co-morbid Conditions</b>	
<b>Standard 14</b>	• No change
<b>Standard 15</b>	• The standard has been modified to reflect the current WHO recommendations for treating HIV in PLHIV who have tuberculosis .
<b>Standard 16</b>	• No change
<b>Standard 17</b>	• No change
<b>Standards for Public Health and Prevention</b>	
<b>Standard 18</b>	• No change
<b>Standard 19</b>	• No change
<b>Standard 20</b>	• No change
<b>Standard 21</b>	• No change



# Summary

*All providers who undertake evaluation and treatment of patients with tuberculosis must recognize that, not only are they delivering care to an individual, they are assuming an important public health function.*

The purpose of the *International Standards for Tuberculosis Care (ISTC)* is to describe a widely accepted level of care that all practitioners, public and private, should seek to achieve in managing patients who have, are suspected of having, or are at increased risk of developing tuberculosis. The standards are intended to promote the effective engagement of all providers in delivering high quality care for patients of all ages, including those with sputum smear-positive and sputum smear-negative pulmonary tuberculosis, extrapulmonary tuberculosis, tuberculosis caused by drug-resistant *Mycobacterium tuberculosis* complex (*M. tuberculosis*) organisms, and tuberculosis combined with HIV infection and other co-morbidities. Moreover, there is increasing recognition of the importance for providers to employ proven approaches to screening and prevention of tuberculosis in persons at increased risk of developing the disease.

The basic principles of care for persons with, or suspected of having, tuberculosis are the same worldwide: a diagnosis should be established promptly and accurately; standardized treatment regimens of proven efficacy should be used, together with appropriate treatment support and supervision; the response to treatment should be monitored; and the essential public health responsibilities must be carried out. Prompt, accurate diagnosis and appropriate treatment are the most effective means of interrupting transmission of *M. tuberculosis*. As well as being essential for good patient care, they are the foundation of the public health response to tuberculosis. **Thus, all providers who undertake evaluation and treatment of patients with tuberculosis must recognize that, not only are they delivering care to an individual, they are assuming an important public health function that entails a high level of responsibility to the community and to the individual patient.**

Many national and international guidelines are directed toward and accessible to providers working for government tuberculosis control programs. Moreover, these providers are subject to regular monitoring and evaluation. However, private providers are generally not considered to be the main target for guidelines and recommendations and don't undergo assessments of the care they provide. Consequently, the *ISTC* is focused mainly on private and non-program public sector providers. It should be emphasized, however, that national and local tuberculosis control programs may need to develop policies and procedures that enable non-program providers to adhere to the *ISTC*. Such accommodations may be necessary, for example, to facilitate treatment supervision and contact investigations, as described in the *ISTC*.

In addition to private sector health care providers and government tuberculosis programs, both patients and communities are part of the intended audience. Patients are increasingly aware of and expect that their care will measure up to a high standard. Having generally agreed upon standards will 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.

The standards in the *ISTC* are intended to be complementary to local and national tuberculosis control policies that are consistent with WHO recommendations. They are not intended to replace local guidelines and were written to accommodate local differences in practice. They focus on the contribution that good clinical care of individual patients with or suspected of having tuberculosis makes to population-based tuberculosis control. A balanced approach emphasizing both individual patient care and public health principles of disease control is essential to reduce the suffering and economic losses from tuberculosis.

The *ISTC* is also intended to serve as a companion to and support for the *Patients' Charter for Tuberculosis Care*. The *Charter* specifies patients' rights and responsibilities and will 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.

The *ISTC* should be viewed as a living document that will be revised as technology, resources, and circumstances change. As written, the standards in the *ISTC* are presented within a context of what is generally considered to be feasible now or in the near future.

The standards are as follows:

## Standards for Diagnosis

- Standard 1.** To ensure early diagnosis, providers must be aware of individual and group risk factors for tuberculosis and perform prompt clinical evaluations and appropriate diagnostic testing for persons with symptoms and findings consistent with tuberculosis.
- Standard 2.** All patients, including children, with unexplained cough lasting two or more weeks or with unexplained findings suggestive of tuberculosis on chest radiographs should be evaluated for tuberculosis.
- Standard 3.** All patients, including children, who are suspected of having pulmonary tuberculosis and are capable of producing sputum should have at least two sputum specimens submitted for smear microscopy or a single sputum specimen for Xpert® MTB/RIF\* testing in a quality-assured laboratory. Patients at risk for drug resistance, who have HIV risks, or who are seriously ill, should have Xpert MTB/RIF performed as the initial diagnostic test. Blood-based serologic tests and interferon-gamma release assays should not be used for diagnosis of active tuberculosis.

\*As of this writing, Xpert®MTB/RIF (Cepheid Corp. Sunnyvale, California, USA) is the only rapid molecular test approved by WHO for initial use in diagnosing tuberculosis, thus, it is specifically referred to by its trade name throughout this document.



- Standard 4.** For all patients, including children, suspected of having extrapulmonary tuberculosis, appropriate specimens from the suspected sites of involvement should be obtained for microbiological and histological examination. An Xpert MTB/RIF test is recommended as the preferred initial microbiological test for suspected tuberculous meningitis because of the need for a rapid diagnosis.
- Standard 5.** In patients suspected of having pulmonary tuberculosis whose sputum smears are negative, Xpert MTB/RIF and/or sputum cultures should be performed. Among smear- and Xpert MTB/RIF negative persons with clinical evidence strongly suggestive of tuberculosis, antituberculosis treatment should be initiated after collection of specimens for culture examination.
- Standard 6.** For all children suspected of having intrathoracic (i.e., pulmonary, pleural, and mediastinal or hilar lymph node) tuberculosis, bacteriological confirmation should be sought through examination of respiratory secretions (expectorated sputum, induced sputum, gastric lavage) for smear microscopy, an Xpert MTB/RIF test, and/or culture.

## Standards for Treatment

- Standard 7.** To fulfill her/his public health responsibility, as well as responsibility to the individual patient, the provider must prescribe an appropriate treatment regimen, monitor adherence to the regimen, and, when necessary, address factors leading to interruption or discontinuation of treatment. Fulfilling these responsibilities will likely require coordination with local public health services and/or other agencies.
- Standard 8.** All patients who have not been treated previously and do not have other risk factors for drug resistance should receive a WHO-approved first-line treatment regimen using quality assured drugs. The initial phase should consist of two months of isoniazid, rifampicin, pyrazinamide, and ethambutol.\* The continuation phase should consist of isoniazid and rifampicin given for 4 months. The doses of antituberculosis drugs used should conform to WHO recommendations. Fixed-dose combination drugs may provide a more convenient form of drug administration.
- \*Ethambutol may be omitted in children who are HIV-negative and who have non-cavitary tuberculosis.
- Standard 9.** A patient-centered approach to treatment should be developed for all patients in order to promote adherence, improve quality of life, and relieve suffering. This approach should be based on the patient's needs and mutual respect between the patient and the provider.
- Standard 10.** Response to treatment in patients with pulmonary tuberculosis (including those with tuberculosis diagnosed by a rapid molecular test) should be monitored by follow up sputum smear microscopy at the time of completion of the initial phase of treatment (two months). If the sputum smear is positive at completion of the initial phase, sputum microscopy should be

performed again at 3 months and, if positive, rapid molecular drug sensitivity testing (line probe assays or Xpert MTB/RIF) or culture with drug susceptibility testing should be performed. In patients with extrapulmonary tuberculosis and in children, the response to treatment is best assessed clinically.

**Standard 11.** An assessment of the likelihood of drug resistance, based on history of prior treatment, exposure to a possible source case having drug-resistant organisms, and the community prevalence of drug resistance (if known), should be undertaken for all patients. Drug susceptibility testing should be performed at the start of therapy for all patients at a risk of drug resistance. Patients who remain sputum smear-positive at completion of 3 months of treatment, patients in whom treatment has failed, and patients who have been lost to follow up or relapsed following one or more courses of treatment should always be assessed for drug resistance. For patients in whom drug resistance is considered to be likely an Xpert MTB/RIF test should be the initial diagnostic test. If rifampicin resistance is detected, culture and testing for susceptibility to isoniazid, fluoroquinolones, and second-line injectable drugs should be performed promptly. Patient counseling and education, as well as treatment with an empirical second-line regimen, should begin immediately to minimize the potential for transmission. Infection control measures appropriate to the setting should be applied.

**Standard 12.** Patients with or highly likely to have tuberculosis caused by drug-resistant (especially MDR/XDR) organisms should be treated with specialized regimens containing quality-assured second-line antituberculosis drugs. The doses of antituberculosis drugs should conform to WHO recommendations. The regimen chosen may be standardized or based on presumed or confirmed drug susceptibility patterns. At least five drugs, pyrazinamide and four drugs to which the organisms are known or presumed to be susceptible, including an injectable agent, should be used in a 6–8 month intensive phase, and at least 3 drugs to which the organisms are known or presumed to be susceptible, should be used in the continuation phase. Treatment should be given for at least 18–24 months beyond culture conversion. Patient-centered measures, including observation of treatment, are required to ensure adherence. Consultation with a specialist experienced in treatment of patients with MDR/XDR tuberculosis should be obtained.

**Standard 13.** An accessible, systematically maintained record of all medications given, bacteriologic response, outcomes, and adverse reactions should be maintained for all patients.

# Standards for Addressing HIV Infection and other Co-morbid Conditions

**Standard 14.** HIV testing and counseling should be conducted for all patients with, or suspected of having, tuberculosis unless there is a confirmed negative test within the previous two months. Because of the close relationship of tuberculosis and HIV infection, integrated approaches to prevention, diagnosis, and treatment of both tuberculosis and HIV infection are recommended in areas with high HIV prevalence. HIV testing is of special importance as part of routine management of all patients in areas with a high prevalence of HIV infection in the general population, in patients with symptoms and/or signs of HIV-related conditions, and in patients having a history suggestive of high risk of HIV exposure.

**Standard 15.** In persons with HIV infection and tuberculosis who have profound immunosuppression (CD4 counts less than 50 cells/mm<sup>3</sup>), ART should be initiated within 2 weeks of beginning treatment for tuberculosis unless tuberculous meningitis is present. For all other patients with HIV and tuberculosis, regardless of CD4 counts, antiretroviral therapy should be initiated within 8 weeks of beginning treatment for tuberculosis. Patients with tuberculosis and HIV infection should also receive cotrimoxazole as prophylaxis for other infections.

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

**Standard 17.** All providers should conduct a thorough assessment for co-morbid conditions and other factors that could affect tuberculosis treatment response or outcome and identify additional services that would support an optimal outcome for each patient. These services should be incorporated into an individualized plan of care that includes assessment of and referrals for treatment of other illnesses. Particular attention should be paid to diseases or conditions known to affect treatment outcome, for example, diabetes mellitus, drug and alcohol abuse, undernutrition, and tobacco smoking. Referrals to other psychosocial support services or to such services as antenatal or well-baby care should also be provided.

## Standards for Public Health and Prevention

**Standard 18.** All providers should ensure that persons in close contact with patients who have infectious tuberculosis are evaluated and managed in line with international recommendations. The highest priority contacts for evaluation are:

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

**Standard 19.** Children <5 years of age and persons of any age with HIV infection who are close contacts of a person with infectious tuberculosis, and who, after careful evaluation, do not have active tuberculosis, should be treated for presumed latent tuberculosis infection with isoniazid for at least six months.

**Standard 20.** Each health care facility caring for patients who have, or are suspected of having, infectious tuberculosis should develop and implement an appropriate tuberculosis infection control plan to minimize possible transmission of *M. tuberculosis* to patients and health care workers.

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



# Introduction

*The ISTC is intended to facilitate the effective engagement of all care providers in delivering high quality care utilizing established best practices for patients of all ages with all forms of tuberculosis.*

## Purpose

The fundamental purpose of the *International Standards for Tuberculosis Care (ISTC)* is 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, or are at increased risk of developing the disease. The *ISTC* is intended to facilitate the effective engagement of all care providers in delivering high quality care utilizing established best practices for patients of all ages with all forms of tuberculosis. In addition, providers must be aware of conditions and epidemiologic circumstances that impose an increased risk of tuberculosis and of approaches to screening for tuberculosis and applying preventive therapies in these situations.<sup>1</sup>

The *ISTC* is also intended to provide support to the integrated, patient-centered tuberculosis care and prevention component of WHO's proposed *Global Strategy and Targets for Tuberculosis Prevention, Care and Control after 2015*.<sup>2</sup> Engagement of all providers is a critical component of the updated strategy and the *ISTC* will serve as a means of facilitating implementation of the strategy especially among non-program providers.<sup>3,4</sup> The updated strategy presents the framework necessary for effective tuberculosis care and control and, when fully implemented, provides the elements essential for delivery of good tuberculosis care and prevention.

Much of the information presented in the *ISTC* is derived from existing WHO documents. Thus, the *ISTC* serves as a compendium of recommendations and guidelines developed by a rigorous, evidence-based process required by WHO.<sup>5</sup> Taken together these documents provide comprehensive guidance for best practices in tuberculosis care and control.

In addition to the fundamental purpose of the *ISTC*, an important goal is to promote unified approaches to the diagnosis, management, and prevention of tuberculosis among all care providers offering services for tuberculosis and to facilitate coordination of activities and collaboration between tuberculosis control programs and non-program providers. Given that public health authorities are responsible for normative functions, surveillance, monitoring, evaluation, and reporting, it is crucial that there is coordination between control programs and non-program providers, especially in dealing with complicated issues such as diagnosis and management of patients with drug-resistant tuberculosis. The



*ISTC* provides a common ground of understanding on which to build collaborations at national, regional, or local levels, or even within individual institutions.

The basic principles of care for persons with, or suspected of having, tuberculosis are the same worldwide: a diagnosis should be established promptly and accurately; standardized treatment regimens of proven efficacy should be used, together with appropriate treatment support and supervision; the response to treatment should be monitored; and the essential public health responsibilities must be carried out. Additionally, persons at increased risk of tuberculosis should be identified, evaluated, and preventive measures applied when appropriate.<sup>1</sup> The ways in which these principles are applied vary depending on available technology and resources. However, prompt, accurate diagnosis and effective timely treatment are not only essential for good patient care; they are the key elements in the public health response to tuberculosis and are the cornerstone of tuberculosis control. Thus, all providers who undertake evaluation and treatment of patients with tuberculosis must recognize that, not only are they delivering care to an individual, they are also assuming an important public health function that entails a high level of responsibility to the community, as well as to the individual patient.

## Audience

The *ISTC* is addressed to all health care providers, private and public, who care for persons with proven tuberculosis, with symptoms and signs suggestive of tuberculosis, or with factors that place them at increased risk of developing the disease. In many instances clinicians (both private and public) who are not part of a government-coordinated tuberculosis control program lack the guidance and systematic evaluation of outcomes provided by programs and, commonly, are not in compliance with the *ISTC*. Although government program providers are not exempt from adherence to the *ISTC*, non-program providers are the main target audience. It should be emphasized, however, that public tuberculosis control programs may need to develop policies and procedures that enable non-program providers to adhere to the *ISTC*. Such accommodations may be necessary, for example, to facilitate treatment supervision and contact investigations.<sup>6-8</sup> In addition to health care providers and government tuberculosis programs, both patients and communities are part of the intended audience. Patients are increasingly aware of and have the right to care that measures up to a high standard, as described in the *Patients' Charter for Tuberculosis Care* (available at <http://www.istcweb.org> and at [http://www.who.int/tb/publications/2006/istc\\_charter.pdf](http://www.who.int/tb/publications/2006/istc_charter.pdf)). Having generally agreed upon standards will 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. Community contributions to tuberculosis care and control are increasingly important in raising public awareness of the disease, providing treatment support, encouraging adherence, reducing the stigma associated with having tuberculosis, and demanding that health care providers in the community adhere to a high standard of tuberculosis care.<sup>9</sup> The community should expect that care for tuberculosis will be up to the accepted standard and, thus, create a demand for high quality services.

*The standards focus on the contribution that good clinical care of individual patients with or suspected of having tuberculosis makes to population-based tuberculosis control.*

## Scope

The *ISTC* draws from a number of existing WHO guidelines and recommendations developed using modern rigorous methodology to provide its evidence base. In addition, generally we have cited summaries, meta-analyses, and systematic reviews of evidence that have examined and synthesized primary data, rather than referring to the primary data themselves. Throughout the document we have used the terminology recommended in the *Definitions and Reporting Framework for Tuberculosis, 2013 Revision*.<sup>10</sup>

The *ISTC* is intended to be complementary to and provide support for local and national tuberculosis control policies that are consistent with WHO recommendations. They are not intended to replace local guidelines and were written to accommodate local differences in practice while at the same time fostering a high standard of care. They focus on the contribution that good clinical care of individual patients with or suspected of having tuberculosis makes to population-based tuberculosis control. A balanced approach emphasizing both individual patient care and public health principles of disease control is essential to reduce the suffering and individual and community economic losses from tuberculosis.

To meet the requirements of the *ISTC*, approaches and strategies determined by local circumstances and practices and developed in collaboration with local and national public health authorities will be necessary. There are many situations in which local conditions, practices, and resources will support a level of care beyond what is described in the *ISTC*.

The *ISTC* should be viewed as a living document that will be revised as technology, resources, and circumstances change. As written, the standards are presented within a context of what is generally considered to be feasible now or in the near future. Within the standards priorities may be set that will foster appropriate incremental changes, such as moving in a stepwise from no, or very limited, drug susceptibility testing to universal testing.

The *ISTC* is also intended to serve as a companion to and support for the *Patients' Charter for Tuberculosis Care*. The *Charter* specifies patients' rights and responsibilities and serves 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.

An additional use of the *ISTC* has been to serve as a model framework for adaptation (see below) by countries or regions as has been done, for example, for the European Union and India.<sup>11,12</sup>

There are several critical areas that are beyond the scope of the document. The *ISTC* does not address the issue of access to care. Obviously, if there is no care available, the quality of care is not relevant. Additionally, there are many factors that impede access even when care is available: poverty, gender, stigma, and geography are prominent among the factors that interfere with persons seeking or receiving care. Also, if the residents of a given area perceive that the quality of care provided by the local facilities is substandard, they will not seek care there. This perception of quality is a component of access that adherence to these standards will address.<sup>3</sup>

Also not addressed by the *ISTC* is the necessity of having a sound, effective tuberculosis control program based on established public health principles. The level of care described

in the *ISTC* cannot be achieved without there being an enabling environment, generally provided by an effective public health program supported by appropriate legal and regulatory framework and financial resources. The requirements of such programs are described in publications from the WHO, the US Centers for Disease Control and Prevention (CDC), and The International Union Against Tuberculosis and Lung Disease (The Union).<sup>13-16</sup> Having an effective control program at the national or local level with linkages to non-program providers enables bidirectional communication of information including case notification, consultation, patient referral, provision of drugs or services such as treatment supervision/support for private patients, and contact evaluation. In addition, the program may be the only source of quality-assured laboratory services for the private sector.

In providing care for patients with or suspected of having tuberculosis, or at risk of the disease, clinicians and persons responsible for health care facilities should take measures that reduce the potential for transmission of *M. tuberculosis* to health care workers and to other patients by following local, national, or international guidelines for infection control.<sup>17-19</sup> This is especially true in areas or specific populations with a high prevalence of HIV infection. Detailed recommendations are contained in the WHO document, *WHO Policy on TB Infection Control in Health-care Facilities, Congregate Settings and Households*.<sup>18</sup>

## Rationale

Although in the past decade there has been substantial progress in the development and implementation of the strategies necessary for effective tuberculosis control, the disease remains an enormous global health problem.<sup>20,21</sup> It is estimated that one-third of the world's population is infected with *M. tuberculosis*, mostly in developing countries where 95% of cases occur. In 2012, there were an estimated 8.6 million new cases of tuberculosis. The number of tuberculosis cases that occur in the world each year has been declining slightly for the past few years, and the global incidence per 100,000 population is decreasing at slightly more than 2%/year.<sup>21</sup> Incidence, prevalence, and mortality are now decreasing in all six of the WHO regions. In Africa, the case rate has only recently begun to decrease but remains very high both because of the epidemic of HIV infection in sub-Saharan countries and the poor health systems and primary care services throughout the region. In Eastern Europe, after a decade of increases, case rates reached a plateau in the early 2000's and now have begun to decrease slightly. The increases in the 1990's are attributable to the collapse of the public health infrastructure, increased poverty, and other socio-economic factors complicated further by the high prevalence of drug-resistant tuberculosis.<sup>22</sup> In many countries, because of incomplete application of effective care and control measures, tuberculosis case rates are either stagnant or decreasing more slowly than should be expected. This is especially true in high-risk groups such as persons with HIV infection, the homeless, and recent immigrants. The failure to bring about a more rapid reduction in tuberculosis incidence, at least in part, relates to a failure to fully engage non-tuberculosis control program providers in the provision of high quality care, in coordination with local and national control programs. Fostering such engagement is an important purpose of the *ISTC*.<sup>6</sup>

It is widely recognized that many providers are involved in the diagnosis and treatment of tuberculosis.<sup>23</sup> Traditional healers, general and specialist physicians in private practice,

*The failure to bring about a more rapid reduction in tuberculosis incidence relates to a failure to fully engage non-tuberculosis control program providers in the provision of high quality care, in coordination with local and national control programs.*

nurses, clinical officers, academic physicians, unlicensed practitioners, and community organizations, among others, all play roles in tuberculosis care and, therefore, in tuberculosis control. In addition, other public providers, such as those working in prisons, army hospitals, or public hospitals and facilities, regularly evaluate persons suspected of having tuberculosis and treat patients who have the disease.

Little is known about the adequacy of care delivered by non-program providers, but evidence from studies conducted in many different parts of the world show great variability in the quality of tuberculosis care, and poor quality care continues to plague global tuberculosis control efforts even in low-prevalence, high-income settings.<sup>24,25</sup> A global situation assessment reported by WHO suggested that delays in diagnosis were common.<sup>26,27</sup> The delay was more often in receiving a diagnosis rather than in seeking care, although both elements have been shown to be important.<sup>27,28</sup> Even after a patient is found to have a positive sputum smear, delays are common.<sup>29</sup> The WHO survey and other studies also show that clinicians, in particular those who work in the private health care sector, often deviate from standard, internationally recommended, tuberculosis management practices. These deviations include under-utilization of sputum smear microscopy for diagnosis, generally associated with over-reliance on radiography; use of non-recommended drug regimens with incorrect combinations of drugs and mistakes in both drug dosage and duration of treatment; and failure to supervise and assure adherence to treatment.<sup>25,26,30-36</sup> Recent evidence also suggests over-reliance on poorly validated or inappropriate diagnostic tests such as serologic assays, often in preference to conventional bacteriological evaluations.<sup>37</sup> Because of the unreliability of these tests the WHO has taken the unusual step of specifically recommending against their use.<sup>38</sup>

Together, these findings highlight flaws in health care practices that lead to substandard tuberculosis care for populations that, sadly, are most vulnerable to the disease and are least able to bear the consequences of such systemic failures. Any person anywhere in the world who is unable to access quality health care should be considered vulnerable to tuberculosis and its consequences.<sup>3</sup> Likewise, any community with no or inadequate access to appropriate diagnostic and treatment services for tuberculosis is a vulnerable community. The *ISTC* is intended to reduce vulnerability of individuals and communities to tuberculosis by promoting high quality care for persons with, or suspected of having, tuberculosis.

There is also an ethical imperative, which applies equally to program and non-program providers, to the provision of effective, appropriate tuberculosis care.<sup>39</sup> Tuberculosis care (including prevention) is a public good. The disease not only threatens the health of individuals, the health of the community is also at risk. It is generally agreed that universal access to health care is a human right and governments have the ethical responsibility to ensure access, a responsibility that includes access to quality-assured tuberculosis services. In particular, tuberculosis disproportionately affects poor and marginalized people, groups that governments and health care systems have an ethical obligation to protect. Tuberculosis not only thrives on poverty, it breeds poverty by consuming often very limited personal and family resources. Poor care compounds the costs that already impoverished individuals and families cannot afford and commonly results in persons being unable to work for long periods while at the same time incurring catastrophic costs.<sup>40,41</sup> Substandard care, be it on the part of program or non-program providers, is unethical. The care and

control measures in the *ISTC* describe approaches to tuberculosis care, control, and prevention that are consistent with the ethical standards articulated by the *Guidance on Ethics of Tuberculosis Prevention, Care, and Control* developed by the WHO.<sup>39</sup>

## Utilization of the *ISTC*

The *ISTC* is potentially a very powerful tool to improve the quality of tuberculosis care. Because of the way in which the *ISTC* was developed and the international endorsements it has received through the two previous editions, the document is authoritative and broadly credible across categories of practitioners. This credibility is a major strength of the *ISTC* and should be capitalized upon in its utilization. A variety of possible ways in which the *ISTC* can be utilized is summarized in Annex 2.

Ideally, the *ISTC* should be used in conjunction with a set of tools developed by WHO, *Public-Private Mix for TB Care and Control: A Toolkit*.<sup>6</sup> The tools included in the *Toolkit* present a framework for analyzing the role of all sectors in providing tuberculosis care and control and a variety of tools to facilitate engagement of all providers. In addition, the *ISTC* should be used in conjunction with the *Patients' Charter for Tuberculosis Care*, which was developed in tandem with the *ISTC* and specifies the rights and responsibilities of patients. A third document developed by The Union, *Management of Tuberculosis: A Guide to the Essentials of Good Practice*<sup>16</sup>, focuses on the critical roles of nurses and other health workers in providing tuberculosis services and in managing tuberculosis control programs. Taken together these documents provide a framework and guidance that can be used to develop a tailored, comprehensive multi-sectoral approach to tuberculosis care and control at the local or national level, with each component having a set of defined roles and responsibilities.

## Adaptation of the *ISTC*

The *ISTC* has been developed for a global audience and it is expected and desirable that regions and countries adapt and operationalize the document to suit their own circumstances. These circumstances include consideration of the epidemiology of tuberculosis and the facilities and resources available in both the public and private sectors. The ultimate goal of these adaptations should be to improve the quality of services for tuberculosis within a more limited setting. Ideally, a consultative process involving all relevant stakeholders should be undertaken to ensure that the adaptation of the *ISTC* is appropriate for the environment and provides appropriate guidance for implementation of the practices described in the document. Moreover, broad input is necessary to ensure that the document reflects the perspectives of all sectors of the health care system and creates a sense of ownership of and commitment to the principles and practices described in the *ISTC*.

As with any set of guidelines, there should be establishment of an effective and standardized monitoring and evaluation (M&E) system. To enable global M&E it is strongly suggested that adaptations retain the title *International Standards for Tuberculosis Care* as part of the adapted document's title.





# Standards for Diagnosis

*Providers must recognize that in evaluating persons who may have tuberculosis they are assuming an essential public health function that entails a high level of responsibility to the community as well as to the individual patient.*

**STANDARD 1.** To ensure early diagnosis, providers must be aware of individual and group risk factors for tuberculosis and perform prompt clinical evaluations and appropriate diagnostic testing for persons with symptoms and findings consistent with tuberculosis.

## Rationale and Evidence Summary

Providers must recognize that in evaluating persons who may have tuberculosis they are assuming an essential public health function that entails a high level of responsibility to the community as well as to the individual patient. Early and accurate diagnosis is critical to tuberculosis care and control.<sup>42</sup> Despite dramatically improved access to high quality tuberculosis services during the past two decades<sup>21</sup>, there is substantial evidence that failure to identify cases early is a major weakness in efforts to ensure optimal outcomes for the patient and to control the disease. Diagnostic delays result in ongoing transmission in the community and more severe, progressive disease in the affected person.

There are three main reasons for delays in diagnosing tuberculosis: the affected person either not seeking or not having access to care; the provider not suspecting the disease; and the lack of sensitivity of the most commonly available diagnostic test, sputum (or other specimen) smear microscopy.<sup>27,28,42</sup> Approaches to reducing these delays are, obviously, quite different. Reducing delays on the part of the affected person entails providing accessible health care facilities, enhancing community and individual awareness, and active case-finding in high risk populations—all of which are largely beyond the scope of this document.<sup>9</sup> Reducing provider delay is best approached by increasing provider awareness of the risks for and symptoms of tuberculosis and of the appropriate and available WHO-approved diagnostic tests in their communities. Rapid molecular tests that increase both the speed and the sensitivity for identifying *Mycobacterium tuberculosis* are increasingly available and, in some situations as described in Standards 3, 5, and 6, are the recommended initial diagnostic test.

Providers commonly fail to initiate appropriate investigations when persons with symptoms suggestive of tuberculosis, especially respiratory symptoms, seek care.<sup>29</sup> Of particular note, in at least one study women were less likely to receive an appropriate diagnostic evaluation than men.<sup>43</sup> There must be a clinical suspicion of tuberculosis before proper

diagnostic tests are ordered. Clinical suspicion is prompted largely by the presence of clinical symptoms, suggestive radiographic findings, and by awareness of co-morbidities and epidemiological circumstances that increase the risk of tuberculosis in an individual patient. These risks are summarized in the WHO guidelines for screening for tuberculosis.<sup>1</sup> Vulnerable groups such as persons living with HIV and other co-morbidities, children, and populations at increased risk such as prisoners and persons living in high-incidence urban areas require special attention, even in the absence of typical symptoms, as noted subsequently.

---

**STANDARD 2. All patients, including children, with unexplained cough lasting two or more weeks or with unexplained findings suggestive of tuberculosis on chest radiographs should be evaluated for tuberculosis.**

### **Rationale and Evidence Summary**

The most commonly reported symptom of pulmonary tuberculosis is persistent cough that generally, but not always, is productive of mucus and sometimes blood (hemoptysis). In persons with tuberculosis the cough is often accompanied by systemic symptoms such as fever, night sweats, and weight loss. In addition, findings such as lymphadenopathy consistent with concurrent extrapulmonary tuberculosis, may be noted, especially in patients with HIV infection. However, chronic cough with sputum production is not always present, even among persons having sputum smears showing acid-fast bacilli. Data from several tuberculosis prevalence surveys show that an important proportion of persons with active tuberculosis do not have cough of 2 or more weeks that conventionally has been used to define suspected tuberculosis.<sup>44-46</sup> In these studies 10–25% of patients with bacteriologically-confirmed tuberculosis do not report cough. These data suggest that evaluation for tuberculosis, using a symptom review that includes, in addition to cough of 2 weeks or more, cough of any duration, fever, night sweats, or weight loss, may be indicated in select risk groups, especially in areas where there is a high prevalence of the disease and in high risk populations and individuals with increased susceptibility, such as persons with HIV infection.<sup>1</sup> Use of this broadened set of questions in a population of PLHIV was found to have a negative predictive value of 97.7% for tuberculosis.<sup>47</sup>

Although many patients with pulmonary tuberculosis have cough, the symptom is not specific to tuberculosis; it can occur in a wide range of respiratory conditions, including acute respiratory tract infections, asthma, and chronic obstructive pulmonary disease.<sup>48</sup> Having cough of 2 weeks or more in duration serves as the criterion for defining suspected tuberculosis and is used in most national and international guidelines, particularly in areas of moderate to high prevalence of tuberculosis, as an indication to initiate an evaluation for the disease.<sup>16,49,50</sup> In a survey conducted in primary health care services of 9 low- and middle-income countries with a low prevalence of HIV infection, respiratory complaints, including cough, constituted on average 18.4% of symptoms that prompted a visit to a health center for persons older than 5 years of age.<sup>51</sup> Of this group, 5% of patients overall were categorized as possibly having tuberculosis because of the presence of an unexplained cough for more than 2–3 weeks. This percentage varies somewhat depending on whether there is pro-active questioning concerning the presence of



*Missed opportunities for earlier detection of tuberculosis lead to increased disease severity for the patients and a greater likelihood of transmission of *M. tuberculosis* to family members and others in the community.*

cough. Respiratory conditions, therefore, constitute a substantial proportion of the burden of diseases in patients presenting to primary health care services.

Even in patients with cough of less than 2 weeks there may be an appreciable prevalence of tuberculosis. An assessment from India demonstrated that by using a threshold of  $\geq 2$  weeks to prompt collection of sputum specimens, the number of patients with suspected tuberculosis increased by 61% but, more importantly, the number of tuberculosis cases identified increased by 46% compared with a threshold of  $> 3$  weeks.<sup>52</sup> The results also suggested that actively inquiring as to the presence of cough in all adult clinic attendees may increase the yield of cases; 15% of patients who, without prompting, volunteered that they had cough, had positive smears. In addition, 7% of patients who did not volunteer that they had cough but, on questioning, admitted to having cough  $\geq 2$  weeks had positive smears.

In countries with a low prevalence of tuberculosis, it is likely that chronic cough will be due to conditions other than tuberculosis. Conversely, in high prevalence countries, tuberculosis will be one of the leading diagnoses to consider, together with other conditions, such as asthma, bronchitis, and bronchiectasis that are common in many areas. Tuberculosis should also be considered in the differential diagnosis of community acquired pneumonia, especially if the pneumonia fails to resolve with appropriate antimicrobial treatment.<sup>53,54</sup> Several features have been identified that suggest tuberculosis in patients hospitalized for community acquired pneumonia. These are age less than 65 years, night sweats, hemoptysis, weight loss, exposure to tuberculosis, and upper lobe opacities on chest radiograph.<sup>54</sup>

Unfortunately, several studies suggest that not all patients with respiratory symptoms receive an adequate evaluation for tuberculosis.<sup>26-30,32-35,43,55-58</sup> These failures result in missed opportunities for earlier detection of tuberculosis and lead to increased disease severity for the patients and a greater likelihood of transmission of *M. tuberculosis* to family members and others in the community.

Although sputum (or other specimen) smear microscopy remains the most widely available test to establish a microbiological diagnosis, other more sensitive means of identifying *M. tuberculosis*, particularly rapid molecular tests, are rapidly gaining acceptance as their performance and applicability are increasingly understood.<sup>59,60</sup> Table 2 presents a succinct summary of the performance and evidence base for the various diagnostic tests for tuberculosis.

In many settings chest radiographic examination is the initial test used for persons with cough since it is a useful tool to identify persons who require further evaluation to determine the cause of radiographic abnormalities, including tuberculosis.<sup>1</sup> Thus, radiographic examination (film, digital imaging, or fluoroscopy) of the thorax or other suspected sites of involvement may serve as the entry point for a tuberculosis diagnostic evaluation. Also, chest radiography is useful to evaluate persons who are suspected of having tuberculosis but have negative sputum smears and/or negative Xpert MTB/RIF. The radiograph is useful to find evidence of pulmonary tuberculosis and to identify other abnormalities that may be responsible for the symptoms. However, a diagnosis of tuberculosis cannot be established by radiography alone. Although the sensitivity of chest radiography for the pres-

ence of tuberculosis is high, the specificity is low, as shown in Table 2. Reliance on the chest radiograph as the sole test for the diagnosis of tuberculosis will result in both over-diagnosis of tuberculosis and missed diagnoses of tuberculosis and other diseases. Thus, the use of radiographic examinations alone to diagnose tuberculosis is unacceptable.

Scoring systems in which the likelihood of tuberculosis is estimated based on specific radiographic criteria, each of which is given a preset value, have similar sensitivity and specificity as radiographic assessment not using a scoring system.<sup>61</sup> Such systems are useful in ruling-out pulmonary tuberculosis, particularly for infection control purposes in hospitals, but their low specificity precludes ruling-in tuberculosis.

TABLE 2.

### WHO-approved microbiologic tests for tuberculosis

Test	Site	Major Findings/results of Systematic Reviews
<b>Diagnosis of Active Tuberculosis</b>		
<b>Sputum smear microscopy</b>	<b>Pulmonary</b>	<ul style="list-style-type: none"> <li>Fluorescence microscopy is on average 10% more sensitive than conventional microscopy. Specificity of both fluorescence and conventional microscopy is similar. Fluorescence microscopy is associated with improved time efficiency.<sup>62</sup></li> <li>Same-day sputum smear microscopy is as accurate as standard smear microscopy. Compared with the standard approach of examination of two smears with light microscopy over 2 days, examination of two smears taken on the same day had much the same sensitivity (64% for standard microscopy vs 63% for same-day microscopy) and specificity (98% vs 98%)<sup>63-65</sup></li> </ul>
<b>Nucleic acid amplification tests (NAATs)</b> [other than Xpert MTB/RIF]	<b>Pulmonary and extra-pulmonary TB</b>	<ul style="list-style-type: none"> <li>Commercial, standardized NAATs have high specificity and positive predictive value, however, they have relatively lower (and highly variable) sensitivity and negative predictive value for all forms of TB, especially in smear-negative and extrapulmonary disease.<sup>66-73</sup></li> </ul>
<b>Xpert MTB/RIF</b>	<b>Pulmonary TB and extrapulmonary TB and RIF resistance</b>	<ul style="list-style-type: none"> <li>Xpert MTB/RIF used as an initial diagnostic test for detection of <i>M. tuberculosis</i> and rifampicin is sensitive and specific. Xpert MTB/RIF is also valuable as an add-on test following microscopy for patients who are smear-negative. An Xpert MTB/RIF result that is positive for rifampicin resistance should be carefully interpreted and take into consideration the risk of MDR TB in a given patient and the expected prevalence of MDR TB in a given setting.<sup>73</sup></li> <li>When used as an initial test replacing smear microscopy Xpert MTB/RIF achieved a pooled sensitivity of 88% and pooled specificity of 98%. The pooled sensitivity was 98% for smear-positive, culture-positive cases and 68% for smear-negative cases; the pooled sensitivity was 80% in people living with HIV.<sup>73</sup></li> <li>For detection of rifampicin resistance Xpert MTB/RIF achieved a pooled sensitivity of 94% and pooled specificity of 98%.<sup>73</sup></li> </ul>
<b>Automated liquid cultures and rapid MPT64-based species identification tests</b>	<b>Pulmonary TB and extrapulmonary TB; speciation</b>	<ul style="list-style-type: none"> <li>Automated liquid cultures are more sensitive than solid cultures; time to detection is more rapid than solid cultures.<sup>72,74</sup></li> <li>MPT64-based rapid immunochromatographic tests (ICT) for species identification has high sensitivity and specificity.<sup>75</sup></li> </ul>



TABLE 3.

**Performance of chest radiography as a diagnostic test for tuberculosis**

Radiographic Finding (modified from Ref 1)		
	Pooled Sensitivity (%)	Pooled Specificity (%)
Any abnormality compatible with TB (active or inactive)	98 (95–100)	75 (72–79)
Abnormalities suggestive of active TB	87 (79–95)	89 (87–92)
After positive screening for symptoms (one study)	90 (81–96)	56 (54–58)
Chest radiography scoring systems <sup>61</sup>	96 (93–98)	46 (35–50)

**STANDARD 3.** All patients, including children, who are suspected of having pulmonary tuberculosis and are capable of producing sputum should have at least two sputum specimens submitted for smear microscopy or a single sputum specimen for Xpert® MTB/RIF\* testing in a quality-assured laboratory. Patients at risk for drug resistance, who have HIV risks, or who are seriously ill, should have Xpert MTB/RIF performed as the initial diagnostic test. Blood-based serologic tests and interferon-gamma release assays should not be used for diagnosis of active tuberculosis.

\* As of this writing, Xpert® MTB/RIF (Cepheid Corp. Sunnyvale, California, USA) is the only rapid molecular test approved by WHO for initial use in diagnosing tuberculosis, thus, it is specifically referred to by its trade name throughout this document.

### Rationale and Evidence Summary

To establish a diagnosis of tuberculosis every effort must be made to identify the causative agent of the disease.<sup>76</sup> A microbiological diagnosis can only be confirmed by culturing *M. tuberculosis* complex or identifying specific nucleic acid sequences in a specimen from any site of disease. Because the recommended initial microbiological approach to diagnosis varies depending on risks for drug resistance, the likelihood of HIV infection and the severity of illness, clinical assessment must address these factors. Currently, WHO recommends that the Xpert MTB/RIF assay should be used rather than conventional microscopy, culture, and DST as the initial diagnostic test in adults and children suspected of having MDR TB or HIV-associated tuberculosis.<sup>77</sup> Although availability of rapid molecular tests is rapidly increasing, in practice there are many resource-limited settings in which rapid molecular tests or culture are not available currently. Microscopic examination of stained sputum is feasible in nearly all settings and, in high-prevalence areas, finding acid-fast bacilli in stained sputum is the equivalent of a confirmed diagnosis. It should be noted that in persons with HIV infection sputum microscopy is less sensitive than in persons without HIV infection; however, mortality rates are greater in persons with HIV infection with clinically-diagnosed tuberculosis who have negative sputum smears than among HIV-infected patients who have positive sputum smears.<sup>78,79</sup>



Data suggest that a combination of sputum smear microscopy and Xpert MTB/RIF can substantially increase the diagnostic yield. Xpert MTB/RIF as an add-on test following a negative smear microscopy result has a sensitivity of 68% and specificity of 99% compared with culture. WHO recommendations also indicate that Xpert MTB/RIF may be used as the initial test in all patients if resources are available.



More rapid methods of identifying growth of *M. tuberculosis* such as micro culture techniques (MODS) and thin layer agar have variable performance characteristics and are not approved for general use by WHO at this time.<sup>76</sup>

Generally, it is the responsibility of government health systems (national tuberculosis programs [NTPs] or others) to ensure that providers and patients have convenient access to quality-assured diagnostic microbiology laboratories. As with any laboratory test it is critical that tuberculosis microbiological examinations be performed in a quality-assured laboratory.

Failure to perform a proper diagnostic evaluation before initiating treatment for tuberculosis potentially exposes the patient to the risks of unnecessary or wrong treatment with no benefit. Moreover, such an approach may delay accurate diagnosis and proper treatment. This standard applies to adults, adolescents, and children. With proper instruction and supervision many children five years of age and older can generate a specimen. Thus, age alone is not sufficient justification for failing to attempt to obtain a sputum specimen from a child or adolescent.

The optimum number of sputum specimens to establish a diagnosis has been examined in a number of studies that have served to support recommendations to decrease the minimum number of sputum specimens examined from 3 to 2, assuming they are examined in a quality-assured laboratory. In a systematic review of 37 studies on the yield of sputum smear microscopy, it was found that, on average, the initial specimen was positive in 85.8% of all patients ultimately found to have acid-fast bacilli detected, in an additional 11.9% with the second specimen, and a further 2.3% on the third specimen. In studies that used culture as the reference standard, the mean incremental yield in sensitivity of the second specimen was 11.1% and that of the third was 3.1%.<sup>64</sup>

A re-analysis of data from a study involving 42 laboratories in four high-burden countries showed that the incremental yield from a third sequential specimen ranged from 0.7% to 7.2%.<sup>80</sup> Thus, it appears that in a diagnostic evaluation for tuberculosis, at least two specimens should be obtained. In some settings, because of practicality and logistics, a third specimen may be useful, but examination of more than two specimens adds minimally to the number of positive specimens obtained.<sup>64</sup> Ideally, the results of sputum microscopy should be returned to the clinician within no more than one working day from submission of the specimen. Early detection of patients with infectious tuberculosis is an important component of infection control in health care facilities, thus, sputum specimens should be collected promptly from patients suspected of having the disease and laboratories should quickly return the results.

A variety of methods have been used to improve the performance of sputum smear microscopy.<sup>63,64,81</sup> However, a comprehensive systematic review of 83 studies describing

*During the past few years Xpert MTB/RIF has been validated under field conditions and, in a systematic review, shown to have excellent performance characteristics for detecting M. tuberculosis and rifampicin resistance.*

the effects of various physical and/or chemical methods for concentrating and processing sputum prior to microscopy found highly variable results.<sup>63</sup> Moreover, processing increases complexity and may be associated with increased infection risk to laboratory personnel. For these reasons these methods are not recommended by WHO for regular use in low-resource settings.

Fluorescence microscopy (FM), in which auramine-based staining causes the acid-fast bacilli to fluoresce against a dark background, is widely used in many parts of the world. A comprehensive systematic review of 45 studies, in which the performance of direct sputum smear microscopy using fluorescence staining was compared with Ziehl-Neelsen (ZN) staining using culture as the gold standard, indicates that FM is the more sensitive method.<sup>62</sup> This review showed that FM is on average 10% more sensitive than conventional light microscopy. The specificity of FM was comparable to ZN microscopy. The combination of increased sensitivity with little or no loss of specificity makes FM a more accurate test, although the increased cost and complexity has restricted its use in many areas. For this reason conventional FM has best been used in centers with specifically trained and proficient microscopists, in which a large number of specimens are processed daily, and in which there is an appropriate quality control program. However, lower cost, light emitting diode (LED) fluorescence microscopes with performance characteristics superior to conventional microscopes are now endorsed by WHO and are widely available.<sup>62</sup>

During the past few years Xpert MTB/RIF has been validated under field conditions and, in a systematic review, shown to have excellent performance characteristics for detecting *M. tuberculosis* and rifampicin resistance. The pooled sensitivity estimate was 98% for specimens that were smear positive and 68% for smear-negative specimens.<sup>73</sup> The overall sensitivity when used as an initial test in place of smear microscopy was found to be 89% with a specificity of 99%. Among persons with HIV infection the overall sensitivity was 79% (61% for persons with smear-negative culture positive tuberculosis and 97% for smear-positive specimens) and the specificity 98%. For detecting rifampicin resistance the sensitivity was 95% and the specificity 99%. The obvious advantage of Xpert MTB/RIF, in addition to its performance characteristics, is the rapidity with which an answer can be obtained—about two hours if the specimen is tested upon receipt in the laboratory—and its adaptability for use in more peripheral laboratories. It must be emphasized, however, that optimum benefit from any rapid molecular test can only be realized if the response to the result is also rapid.

Assessment of the performance characteristics and the practicalities of implementation (including costs) led WHO to issue recommendations for the use of Xpert MTB/RIF.<sup>83</sup> The WHO evidence synthesis process confirmed a solid evidence base to support widespread use of Xpert MTB/RIF for detection of *M. tuberculosis* and rifampicin resistance.<sup>22, 59, 73, 83</sup> Based on the evidence WHO recommended that Xpert MTB/RIF:

- **should** be used rather than conventional microscopy, culture, and drug susceptibility testing as the initial diagnostic test in individuals presumed to have MDR or HIV-associated tuberculosis;
- **may** be used as a follow-on test to microscopy in adults where MDR and HIV is of lesser concern, especially in further testing of smear-negative specimens;

- **may** be used rather than conventional microscopy and culture as the initial diagnostic test in all adults presumed to have tuberculosis;
- **should** be used rather than conventional microscopy, culture, and drug susceptibility testing as the initial diagnostic test in children presumed to have MDR or HIV-associated tuberculosis;
- **may** be used rather than conventional microscopy and culture as the initial diagnostic test in all children presumed to have tuberculosis.

Detection of rifampicin resistance in groups with a low prevalence of MDR TB should be an uncommon finding and a second Xpert MTB/RIF test on a different sample from the patient should be performed to exclude errors in performing the test. In patients with repeated rifampicin resistance, a WHO recommended MDR TB regimen that includes isoniazid should be initiated. Patients with discordant rifampicin resistance results by Xpert MTB/RIF should be assumed to have susceptible organisms and be given a first-line regimen. Discrepancies in the determination of rifampicin resistance by Xpert MTB/RIF may require resolution by DNA sequencing.<sup>83-85</sup>

Using Xpert MTB/RIF does not eliminate the need for conventional microscopy, culture, and drug susceptibility testing that are required to monitor treatment and to detect resistance to drugs other than rifampicin.

Commercial line probe assay performance characteristics have been adequately validated in direct testing of sputum smear-positive specimens and on isolates of *M. tuberculosis* complex grown from smear-negative and smear-positive specimens. Direct use of line probe assays on smear-negative clinical specimens is not recommended at present.<sup>86</sup>

Neither the tuberculin skin test nor Interferon-gamma release assays (IGRAs) have value for diagnosing active tuberculosis in adults although the result may serve to increase or decrease the diagnostic suspicion.<sup>38,87</sup> Both sensitivity and specificity are generally low and variable, especially among persons living with HIV.<sup>87</sup> Commercial serological antibody detection tests produce inconsistent and imprecise estimates of sensitivity and specificity.<sup>88</sup> For this reason WHO recommends against the use of these tests and the governments of India and Cambodia have banned their use.<sup>38</sup>

---

**STANDARD 4.** For all patients, including children, suspected of having extrapulmonary tuberculosis, appropriate specimens from the suspected sites of involvement should be obtained for microbiological and histological examination. An Xpert MTB/RIF test on cerebrospinal fluid is recommended as the preferred initial microbiological test in persons suspected of having tuberculous meningitis because of the need for a rapid diagnosis.

#### Rationale and Evidence Summary

Extrapulmonary tuberculosis (without associated lung involvement) accounts for at least 15–20% of tuberculosis in populations with a low prevalence of HIV infection.<sup>21,89</sup> In populations with a high prevalence of HIV infection, the proportion of cases with extrapulmonary tuberculosis is higher. Because appropriate specimens may be difficult to obtain from some of these sites, bacteriological confirmation of extrapulmonary tuberculosis is often



more difficult than for pulmonary tuberculosis. In spite of the difficulties, however, the basic principle that bacteriological confirmation of the diagnosis should be sought still holds.

Generally, there are fewer *M. tuberculosis* organisms present in extrapulmonary sites so identification of acid-fast bacilli by microscopy in specimens from these sites is less frequent and rapid molecular tests and/or culture are more important. Microscopic examination of pleural fluid in tuberculous pleuritis detects acid-fast bacilli in only about 5–10% of cases, and the diagnostic yield is similarly low in tuberculous meningitis although some studies have reported a higher sensitivity.<sup>90,91</sup> Given the low yield of microscopy, both microbiological and histological or cytological examination of tissue specimens, such as may be obtained by open or closed pleural biopsy or needle biopsy of lymph nodes, are important diagnostic tests. A systematic review showed the pooled sensitivity of Xpert MTB/RIF for the detection of TB in cerebro-spinal fluid (compared with culture) was 79.5%. Although the sensitivity is not optimal, the speed with which a result is returned makes the test highly useful and, thus, is the preferred initial test (although culture should be concurrently performed if sufficient specimen is available). For lymph node tissue and aspirates the sensitivity of Xpert MTB/RIF was 84.9% compared with culture. In pleural fluid the sensitivity was only 43.7%, much greater than the sensitivity of pleural fluid microscopy, but still not sufficiently sensitive to be used as the sole test in the evaluation of pleural effusions.<sup>77</sup>

In view of these findings it is recommended that Xpert MTB/RIF may be used as a replacement test for conventional microscopy, culture, and/or histopathology for testing of gastric lavage fluid and specific non-respiratory specimens.<sup>77</sup> However, patients suspected of having extrapulmonary tuberculosis but with a single Xpert MTB/RIF-negative result should undergo further diagnostic testing, and those with high clinical suspicion for TB (especially children) should be treated even if an Xpert MTB/RIF result is negative or if the test is not available. In patients who have an illness compatible with tuberculosis (pulmonary and/or extrapulmonary) that is severe or progressing rapidly, initiation of treatment should not be delayed pending the results of microbiological examinations. Even the best test may not detect tuberculosis when there is a low bacillary load such as occurs in tuberculous meningitis, in patients with HIV infection, and in young children. In these situations, or in critically ill patients where tuberculosis is suspected, clinical judgment may justify empirical treatment while waiting for final test results, or even when test results are negative.

In addition to the collection of specimens from the sites of suspected tuberculosis, examination of sputum and a chest radiograph may also be useful, especially in patients with HIV infection, in whom asymptomatic or minimally symptomatic pulmonary tuberculosis has been noted.<sup>92,93</sup>

*Ideally, Xpert MTB/RIF and, if negative, culture should be included in the evaluation of patients with negative sputum smears.*

**STANDARD 5.** In patients suspected of having pulmonary tuberculosis whose sputum smears are negative, Xpert MTB/RIF and/or sputum cultures should be performed. Among patients with sputum that is negative by smear and Xpert MTB/RIF who have clinical evidence strongly suggestive of tuberculosis, antituberculosis treatment should be initiated after collection of specimens for culture examination.

#### Rationale and Evidence Summary

The designation of “sputum smear-negative tuberculosis” (now broadened to include patients with a negative Xpert MTB/RIF test) presents a difficult diagnostic dilemma. In a systematic review the sensitivity of sputum smear microscopy ranged from 31% to 69%, thus, many cases may not be identified by smear microscopy alone.<sup>64</sup> However, given the nonspecific nature of the symptoms of tuberculosis and the multiplicity of other diseases that could be the cause of the patient’s illness, it is important that a rigorous approach be taken in diagnosing tuberculosis in a patient in whom at least two adequate sputum specimens are negative by microscopy or one specimen is negative by Xpert MTB/RIF. Because patients with HIV infection and tuberculosis frequently have negative sputum smears, and because of the broad differential diagnosis, including *Pneumocystis jirovecii* pneumonia and bacterial and fungal lower respiratory infections, a systematic approach to diagnosis is crucial. As indicated in Standard 3, persons who have HIV risks, or who are seriously ill, Xpert MTB/RIF should be performed as the initial diagnostic test.

It is important to balance the need for a systematic approach, in order to avoid both over- and under-diagnosis of tuberculosis, with the need for prompt treatment in a patient with an illness that is progressing rapidly. Over-diagnosis of tuberculosis when the illness has another cause will delay proper diagnosis and treatment of the true illness, whereas under-diagnosis will lead to more severe consequences of tuberculosis, including disability and possibly death, as well as ongoing transmission of *M. tuberculosis*. It should be noted that in making a diagnosis of smear-negative tuberculosis, a clinician who decides to treat with a full course of antituberculosis chemotherapy should report this as a case of sputum smear-negative pulmonary tuberculosis to local public health authorities (as described in Standard 21).

Algorithms, including a widely used approach developed by WHO,<sup>94</sup> may present a systematic approach to diagnosis. Performance of the WHO algorithm has been variable under field conditions, and there is little information or experience on which to base approaches to the diagnosis of smear-negative tuberculosis in persons with HIV infection when culture or Xpert MTB/RIF is not routinely available.<sup>95-97</sup>

There are several points of caution regarding the use of algorithms for the diagnosis of smear-negative tuberculosis. First, completion of all of the steps requires a substantial amount of time; thus, it may not be appropriate for patients with an illness that is progressing rapidly. This is especially true in patients with HIV infection in whom tuberculosis and other infections may be rapidly progressive. Second, several studies have shown that patients with tuberculosis may respond, at least transiently, to broad spectrum antimicrobial treatment.<sup>98,99</sup> Obviously such a response will lead one to delay a diagnosis of tuberculosis. Fluoroquinolones, in particular, are bactericidal for *M. tuberculosis* complex. Empiric fluoroquinolone monotherapy for respiratory tract infections has been associated with delays in initiation of appropriate antituberculosis therapy and acquired resistance to



the fluoroquinolones.<sup>100-102</sup> Third, applying all the steps in an algorithm may be costly and deter the patient from continuing with the diagnostic evaluation. Given all these concerns, application of a complex sequence of diagnostic steps in patients with at least two negative sputum specimen examinations and/or one negative Xpert MTB/RIF test must be done in a flexible manner. Ideally, the evaluation of smear-negative tuberculosis should be guided by locally-validated approaches, suited to local conditions, and the needs (financial or otherwise) of the patient.

Ideally, Xpert MTB/RIF and, if negative, culture should be included in the algorithm for evaluating patients with negative sputum smears. A positive Xpert MTB/RIF will greatly reduce the time to diagnosis and initiation of appropriate treatment, possibly saving money as well as staff time. Culture adds a significant layer of complexity and cost but also increases sensitivity, which should result in case detection earlier in the course of the disease.<sup>103,104</sup> While, commonly, the results of culture are not available until after a decision to begin treatment has to be made, treatment can be stopped subsequently if cultures from a reliable laboratory are negative, the patient has not responded clinically, and the clinician has sought other evidence in pursuing the differential diagnosis. It must be emphasized that, for seriously ill patients (particularly patients with HIV infection), a clinical decision to start treatment often must be made without waiting for the results of cultures. Such patients may die if appropriate treatment is not begun promptly. A rapid molecular test such as Xpert MTB/RIF, although less sensitive than culture on liquid media (but equal in sensitivity to culture on solid media), especially for smear-negative specimens, has the clear advantage of providing a result very quickly, thus, enabling appropriate treatment to be initiated promptly.<sup>85</sup>

The probability of finding acid-fast bacilli in sputum smears by microscopy is directly related to the concentration of bacilli in the sputum. Sputum microscopy is likely to be positive when there are at least 10,000 organisms per milliliter of sputum. At concentrations below 1,000 organisms per milliliter of sputum, the chance of observing acid-fast bacilli in a smear is less than 10%.<sup>105,106</sup> In contrast, a properly performed culture, especially if liquid media are used, can detect far lower numbers of acid-fast bacilli (detection limit is about 100 organisms per ml).<sup>104</sup> The culture, therefore, has a higher sensitivity than microscopy and, at least in theory, can increase case detection, although this potential has not been demonstrated in low-income, high-incidence areas. Further, culture makes it possible to identify the mycobacterial species and to perform full drug susceptibility testing in patients in whom there is reason to suspect drug-resistant tuberculosis.<sup>104</sup> The disadvantages of culture are its cost, technical complexity, infrastructure requirements, and the time required to obtain a result. In addition, ongoing quality assessment is essential for culture results to be credible.

In many countries, although culture facilities are not uniformly available, there is the capacity to perform culture or rapid molecular testing in some areas. Providers should be aware of the local capacity and use the resources appropriately, especially for the evaluation of persons suspected of having tuberculosis who have negative sputum smears and for persons with HIV infection or who are suspected of having tuberculosis caused by drug-resistant organisms.

Traditional culture methods use solid media such as Lowenstein-Jensen and Ogawa. Cultures on solid media are less technology-intensive and the media can be made locally. However, the time to identify growth is significantly longer than in liquid media systems such as the MGIT® system. Decisions to provide culture facilities for diagnosing tuberculosis depend on financial resources, infrastructure, trained personnel, and the ready availability of supplies and service for the equipment.



There is good evidence that liquid cultures are more sensitive and rapid than solid media cultures and is the gold standard reference method.<sup>107</sup> WHO has issued policy guidance on the use of liquid media for culture and drug susceptibility testing in low-resource settings.<sup>108</sup> This policy recommends phased implementation of liquid culture systems as a part of a country-specific comprehensive plan for laboratory capacity strengthening that addresses issues such as biosafety, training, maintenance of infrastructure, and reporting of results. However, development of the capacity to do cultures requires a well-functioning health care system, adequate laboratory infrastructure, and trained personnel.

In June 2008, WHO endorsed the use of molecular line-probe assays for rapid screening of patients at risk of MDR TB.<sup>86</sup> This policy statement was based in part on evidence summarized in systematic reviews,<sup>107</sup> expert opinion, and results of field demonstration projects. The recommended use of line probe assays is currently limited to culture isolates and direct testing of smear-positive sputum specimens. Line probe assays are not recommended as a complete replacement for conventional culture and drug susceptibility testing. Culture is still required for smear-negative specimens, and conventional drug susceptibility testing is still necessary to confirm resistance to drugs other than isoniazid and rifampicin.

Chest radiography may also play an important role in the evaluation of persons suspected of having tuberculosis but who have negative sputum smears. Cough is a nonspecific symptom; the chest radiograph can assist in determining the cause of the cough in persons with negative sputum smear microscopy. Commonly, in areas where adequate radiographic facilities are available the chest radiograph is obtained as the first test. Finding an abnormality consistent with tuberculosis should prompt the ordering of sputum specimens. Although the radiograph is a useful adjunct in diagnosing tuberculosis, as noted above, the radiograph alone cannot establish a diagnosis. However, in combination with clinical assessment, the radiograph may provide important circumstantial evidence as to the diagnosis.<sup>109</sup>

It is important to note that, just as with the microbiology laboratory, radiography requires quality control, both in terms of technical quality and interpretation. There are several resources that are useful both for assuring technical quality of the radiograph and for interpretation of the findings.<sup>109-111</sup>

**STANDARD 6.** For all children suspected of having intrathoracic (i.e., pulmonary, pleural, and mediastinal or hilar lymph node) tuberculosis, bacteriological confirmation should be sought through examination of respiratory secretions (expectorated sputum, induced sputum, gastric lavage) for smear microscopy, an Xpert MTB/RIF test, and/or culture.

#### **Rationale and Evidence Summary**

The diagnosis of tuberculosis in children relies on a thorough assessment of all the evidence derived from a careful history of exposure, clinical examination, and other relevant investigations. Although most children with tuberculosis have pulmonary involvement, they commonly have paucibacillary disease without evident lung cavitation but frequently with involvement of intrathoracic lymph nodes. Consequently, compared with adults, sputum smears from children are more likely to be negative. Although bacteriological confirmation of tuberculosis in children is not always feasible, it should be sought whenever possible by sputum (or other specimen) examination with Xpert MTB/RIF, smear microscopy, and culture.<sup>77,112-116</sup> Because many children less than five years of age do not cough and produce sputum effectively, culture of gastric lavage obtained by naso-gastric tube or induced sputum has a higher yield than spontaneous sputum.<sup>115,116</sup> A trial of treatment with antituberculosis medications is not recommended as a means of diagnosing tuberculosis in children. The decision to treat a child for tuberculosis should be carefully considered and once such a decision is made, the child should be treated with a full course of therapy. The approach to diagnosing tuberculosis in children recommended by WHO is summarized in Table 4.<sup>114</sup>

As a component of evaluating a child for tuberculosis, the social situation and nutritional status of the child must be taken into account and the need for support services assessed. The parent or responsible adult must be informed as to the importance of treatment in order to be an effective treatment supporter.

TABLE 4.

#### **Guidance on approach to diagnose TB in children**

1. Careful history (including history of TB contact and symptoms consistent with TB)
2. Clinical examination (including growth assessment)
3. Tuberculin skin testing
4. Chest X-ray if available
5. Bacteriological confirmation whenever possible
6. Investigations relevant for suspected pulmonary TB and suspected extrapulmonary TB
7. HIV testing



*As a component of evaluating a child for tuberculosis, the social situation and nutritional status of the child must be taken into account and the need for support services assessed.*

Several reviews have examined the effectiveness of various diagnostic tools, scoring systems, and algorithms to diagnose tuberculosis in children.<sup>112-115,117-119</sup> Many of these approaches lack standardization and validation, and, thus, are of limited applicability. Though scoring systems and diagnostic criteria remain widely used in the diagnosis of tuberculosis in children, validation has been difficult due to lack of an established and accessible gold standard.<sup>120</sup> Estimates of sensitivity and specificity vary widely, especially in populations with high HIV co-infection.<sup>120</sup>

In children the risk of tuberculosis is increased when there is an active case (infectious, smear-positive tuberculosis) in the same house, or when the child is malnourished, is HIV-infected, or has had measles in the past few months. WHO's Integrated Management of Childhood Illness (IMCI)<sup>121</sup> program, which is widely used in first-level facilities in low- and middle-income countries states that tuberculosis should be considered in any child with:

- Unexplained weight loss or failure to grow normally;
- Unexplained fever, especially when it continues for more than 2 weeks;
- Chronic cough;
- Exposure to an adult with probable or definite pulmonary infectious tuberculosis.

**Findings on examination that suggest tuberculosis include:**

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





# Standards for Treatment

*Failure of a provider to ensure adherence could be equated with, for example, failure to ensure that a child receives the full set of immunizations.*

**STANDARD 7.** To fulfill her/his public health responsibility, as well as responsibility to the individual patient, the provider must prescribe an appropriate treatment regimen, monitor adherence to the regimen and, when necessary, address factors leading to interruption or discontinuation of treatment. Fulfilling these responsibilities will likely require coordination with local public health services and/or other agencies.

## Rationale and Evidence Summary

Effective treatment of tuberculosis prevents ongoing transmission of the infection and the development of drug resistance and restores the health of the patient. As described in the Introduction, the main interventions to prevent the spread of tuberculosis in the community are the early detection of patients with tuberculosis and provision of effective treatment to ensure a rapid and lasting cure. Consequently, treatment for tuberculosis is not only a matter of individual health, as is the case with, for example, treatment of hypertension or asthma; it is also a matter of public health. Thus, all providers, public and private, who undertake to treat a patient with tuberculosis must have the knowledge to prescribe a recommended treatment regimen and the means to assess adherence to the regimen and to address poor adherence to ensure that treatment is completed.<sup>14,122</sup> National and local tuberculosis programs commonly possess approaches and tools, including incentives and enablers, as well as other means of support, to ensure adherence with treatment and, when properly organized, can offer these to non-program providers. Failure of a provider to ensure adherence could be equated with, for example, failure to ensure that a child receives the full set of immunizations. Communities and patients deserve to be assured that providers treating tuberculosis are doing so in accordance with this principle and are, thereby, meeting this standard.



---

**STANDARD 8.** All patients who have not been treated previously and do not have other risk factors for drug resistance should receive a WHO recommended first-line treatment regimen using quality assured drugs. The initial phase should consist of two months of isoniazid, rifampicin, pyrazinamide, and ethambutol.\* The continuation phase should consist of isoniazid and rifampicin given for 4 months. The doses of antituberculosis drugs used should conform to WHO recommendations. Fixed-dose combination drugs may provide a more convenient form of drug administration.

\*Ethambutol may be omitted in children who are HIV-negative and who have non-cavitary tuberculosis.

---

### Rationale and Evidence Summary

A large number of well-designed clinical trials have provided the evidence base for this standard and several sets of treatment recommendations based on these studies have been written in the past few years.<sup>14,16,122</sup> All these data indicate that with the current treatment options, a rifampicin-containing regimen is the backbone of antituberculosis chemotherapy and is highly effective in treating tuberculosis caused by drug-susceptible *M. tuberculosis*. It is also clear from these studies that the minimum duration of treatment for smear- and/or culture-positive tuberculosis is six months. Regimens of less than six months have an unacceptably high rate of relapse.<sup>123</sup> Thus, the current international standard duration of treatment for tuberculosis is a minimum of six months.<sup>14,16,122</sup> For the six-month treatment duration to be maximally effective, the regimen must include pyrazinamide during the initial two-month phase and rifampicin must be included throughout the full six months. Moreover, a systematic review of the outcome of treatment in the presence of single or poly-drug resistance (not multidrug resistance) demonstrated that failure, relapse, and acquisition of additional resistance were associated with shorter duration of rifampicin therapy.<sup>124</sup>

A retrospective review of the outcomes of treatment of tuberculosis in patients with HIV infection showed that relapse is minimized by the use of a regimen containing rifampicin throughout a six-month course of treatment.<sup>125</sup> This finding was confirmed in a more rigorous systematic review of treatment of tuberculosis in patients with HIV infection showing that better outcomes were associated with daily use of rifampicin in the initial phase of treatment and with rifampicin duration of  $\geq 8$  months. However, these effects of rifampicin duration were not seen in a small number of studies in which patients also received antiretroviral treatment.<sup>126</sup>

There are several variations in the frequency of drug administration that have been shown to produce acceptable results.<sup>14,16,122</sup> Intermittent administration of antituberculosis drugs enables supervision to be provided more efficiently and economically with no reduction in efficacy, although daily administration provides a greater margin of safety. The evidence on effectiveness of intermittent regimens has been reviewed.<sup>127-128</sup> These reviews, based on several trials, suggest that antituberculosis treatment may be given intermittently three times a week throughout the full course of therapy or twice weekly in the continuation phase without apparent loss of effectiveness except among individuals with advanced HIV infection.<sup>128-136</sup> However, the WHO does not recommend the use of twice-weekly intermittent regimens because of the potentially greater consequences of missing one of the two doses.

The evidence base for currently recommended antituberculosis drug dosages derives

from human clinical trials, animal models, and pharmacokinetic and toxicity studies. The evidence on drug dosages and safety and the biological basis for dosage recommendations have been extensively reviewed in publications by WHO, ATS, the United States Centers for Disease Control and Prevention (CDC), and the Infectious Diseases Society of America (IDSA), The Union, and others.<sup>14,16,122</sup> The recommended daily and thrice weekly doses are shown in Table 5.

TABLE 5.

### Doses of first-line antituberculosis drugs in adults and children

Drug*	Recommended Dose in mg/kg Body Weight (Range)	
	Daily	Three Times Weekly
<b>Isoniazid**</b>		
Children	10 (7–15), maximum 300 mg/day	—
Adults	5 (4–6), maximum 300 mg/day	10 (8–12), maximum 900 mg/dose
<b>Rifampicin</b>		
Children	15 (10–20), maximum 600 mg/day	—
Adults	10 (8–12), maximum 600 mg/day	10 (8–12), maximum 600 mg/dose
<b>Pyrazinamide</b>		
Children	35 (30–40), maximum 2,000 mg/day	—
Adults	25 (20–30), maximum 2,000 mg/day	35 (30–40), maximum 3,000 mg/dose
<b>Ethambutol</b>		
Children	20 (15–25), maximum 1,000 mg/day	—
Adults	15 (15–20), maximum 1,600 mg/day	30 (25–35), maximum 2,400 mg/dose

\* The recommended daily doses of all 4 antituberculosis medicines are higher in children who weigh less than 25 kg than in adults, because the pharmacokinetics are different (and to achieve the same plasma concentration as in adults, the doses need to be increased)

\*\*Same dosing for treatment of active disease and treatment of latent tuberculosis infection

Treatment of tuberculosis in special clinical situations such the presence of liver disease, renal disease, pregnancy, and HIV infection may require modification of the standard regimen or alterations in dosage or frequency of drug administration. For guidance in these situations see the WHO and ATS/CDC/IDSA treatment guidelines.<sup>14,122</sup>

In a clinical trial comparing a fixed-dose combination (FDC) of isoniazid, rifampicin, ethambutol, and pyrazinamide with a regimen of the same drugs given as separate pills, there was no difference in treatment outcome or adverse effects.<sup>137</sup> A systematic review came to the same conclusion.<sup>138</sup> However, because the FDC reduces the number of pills taken daily in the intensive phase of treatment from 9–16 to 3–4, patient convenience is increased and the potential for medication errors is decreased.<sup>137,139–141</sup>

**STANDARD 9.** A patient-centered approach to treatment should be developed for all patients in order to promote adherence, improve quality of life, and relieve suffering. This approach should be based on the patient's needs and mutual respect between the patient and the provider.

#### Rationale and Evidence Summary



*Interventions that target adherence must be tailored or customized to the particular situation and cultural context of a given patient.*

The approach described in the standard is designed to encourage and facilitate a positive partnership between providers and patients, working together to improve adherence. Adherence to treatment is the critical factor in determining treatment success.<sup>14,122</sup> A successful outcome of treatment for tuberculosis, assuming an appropriate drug regimen is prescribed, depends largely on patient adherence to the regimen. Achieving adherence is not an easy task, either for the patient or the provider. Anti-tuberculosis drug regimens, as described above, consist of multiple drugs given for a minimum of six months, often when the patient feels well (except, perhaps, for adverse effects of the medications). Commonly, treatments of this sort are inconsistent with the patient's cultural background, belief system, and living circumstances. Consequently, it is not surprising that, without appropriate treatment support, a significant proportion of patients with tuberculosis discontinues treatment before completion of the planned duration or is erratic in drug taking. Yet, failure to complete treatment for tuberculosis may lead to prolonged infectivity, poor outcomes, and drug resistance.

Adherence is a multi-dimensional phenomenon determined by the interplay of several sets of factors.<sup>13,142</sup> In a systematic review of qualitative research on patient adherence to tuberculosis treatment, eight major themes were identified across the studies reviewed (Table 6).<sup>142</sup> These themes were then further refined into four sets of interacting factors that influence adherence: structural factors including poverty and gender discrimination, the social context, health service factors, and personal factors. From this synthesis it was concluded that a group of factors was likely to improve patient adherence. These are listed in Table 7.

Despite evidence to the contrary, there is a widespread tendency to focus on patient-related factors as the main cause of poor adherence.<sup>13,142</sup> Sociological and behavioral research during the past 40 years has shown that patients need to be supported, not blamed.<sup>13</sup> Less attention is paid to provider and health system-related factors. Several studies have evaluated various interventions to improve adherence to tuberculosis therapy (Table 7). Among the interventions evaluated, DOT has generated the most debate and controversy.<sup>143,144</sup> The main advantage of DOT is that treatment is carried out entirely under close, direct supervision. This provides both an accurate assessment of the degree of adherence and greater assurance that the medications have actually been ingested. When a second individual directly observes a patient swallowing medications there is greater certainty that the patient is actually receiving the prescribed medications. Also, because there is a close contact between the patient and the treatment supporter, adverse drug effects and other complications can be recognized quickly and managed appropriately and the need for additional social support can be identified. Moreover, such case management can also serve to identify and assist in addressing the myriad other problems experienced by patients with tuberculosis such as under-nutrition, poor housing, and loss of income, to name a few.

TABLE 6.

## Primary themes identified in a systematic review of qualitative research on adherence to tuberculosis treatment

<b>Organization of treatment and care for TB patients</b> <ul style="list-style-type: none"> <li>• Access to services (urban ambulatory, distance, transport)</li> <li>• Health center problems (long waiting hours, queues, physical condition of clinic)</li> <li>• Treatment requirements (continuity, charging for drug, number of tablets, DOT, flexibility, and choice)</li> <li>• Relationship between treatment provider and patient (poor follow up, increased contact, maltreatment of patients)</li> </ul>		
<b>Interpretation of illness and wellness</b> <ul style="list-style-type: none"> <li>• Individual interpretations of recovery</li> <li>• Perceptions of TB</li> <li>• Recognition of TB as a disease</li> </ul>		
<b>Financial burden</b> <ul style="list-style-type: none"> <li>• Conflict between work and treatment; costs of treatment; expenses exceeding available resources</li> <li>• More pressing issues to attend to</li> <li>• Increased expenditure on food</li> </ul>		
<b>Knowledge, attitudes, and beliefs about treatment</b> <ul style="list-style-type: none"> <li>• Limited understanding of treatment, duration, and consequences of default</li> <li>• Beliefs about treatment efficacy</li> <li>• Denial and difficulty accepting diagnosis</li> <li>• Use of other medication, treatment requirements</li> </ul>		
<b>Law and immigration</b> <ul style="list-style-type: none"> <li>• Completion cards; impact on immigration status; fear of detention</li> </ul>		
<b>Personal characteristics and adherence behavior</b> <ul style="list-style-type: none"> <li>• Substance abuse</li> <li>• Mental illness</li> <li>• Ethnic characteristics</li> <li>• Residential mobility</li> <li>• Religion</li> <li>• Personal motivation</li> <li>• Gender</li> <li>• Structured environment</li> <li>• Personal agency</li> </ul>		
<b>Side effects</b> <ul style="list-style-type: none"> <li>• Real, anticipated, or culturally interpreted; insufficient information; insufficient communication; insufficient attention</li> </ul>		
<b>Family, community, and household influence</b> <ul style="list-style-type: none"> <li>• Peer influence</li> <li>• Stigma</li> <li>• Providing for family</li> <li>• Family support</li> <li>• Marriage</li> </ul>		

Source: Munro SA, Lewin S A, Smith H J, Engel M E, Fretjheim, A, Volmink J. Patient adherence to tuberculosis treatment: a systematic review of qualitative research. PLoS Med. 4: 2007; e238.

TABLE 7.

**Factors likely to improve TB treatment adherence**

- Increase the visibility of TB programs in the community, which may increase knowledge and improve attitudes towards TB
- Provide more information about the disease and treatment to patients and communities
- Increase support from family, peers, and social networks
- Minimize costs and unpleasantness related to clinic visits and increase flexibility and patient autonomy
- Increase flexibility in terms of patient choice of treatment plan and type of support
- Increase the patient-centeredness of interactions between providers and clients
- Address structural and personal factors, for example compensating high cost of treatment and income loss through cash transfers, travel vouchers, food assistance, micro-financing, and other empowerment initiatives and preventing loss of employment through addressing employment policies.
- Provide more information about the effects of medication to reduce the risk of patients becoming nonadherent when experiencing treatment side effects

Source: Modified from Munro SA, Lewin S A, Smith H J, Engel M E, Fretjheim, A, Volmink J. Patient adherence to tuberculosis treatment: a systematic review of qualitative research. PLoS Med. 4: 2007; e238.

The exclusive use of health facility-based DOT may be associated with disadvantages that must be taken into account in designing a patient-centered approach. For example, these disadvantages may include loss of income and time, stigma and discrimination, physical hardship, and travel difficulties, all factors that can have an important effect on adherence. Ideally a flexible mix of health facility- and community-based DOT, often with a family member serving as a treatment supporter, should be available.<sup>145</sup>

In a Cochrane systematic review that synthesized the evidence from six controlled trials comparing DOT with self-administered therapy,<sup>143,144</sup> the authors found that patients allocated to DOT and those allocated to self-administered therapy had similar cure rates and rates of cure plus treatment completion. They concluded that direct observation of medication ingestion did not improve outcomes. A more recent systematic review reached the same conclusion.<sup>146</sup> In contrast, programmatic assessments in several countries have found DOT to be associated with high cure and treatment completion rates.<sup>147-150</sup> It is likely that these inconsistencies are due to the fact that primary studies are often unable to separate the effect of DOT alone from the overall DOTS Strategy.<sup>13,144</sup> In a retrospective review of programmatic results, the highest rates of success were achieved with “enhanced DOT” which consisted of “supervised swallowing” plus social supports, incentives, and enablers as part of a larger program to encourage adherence to treatment.<sup>147</sup> Such complex interventions are not easily evaluated within the conventional randomized controlled trial framework.

Interventions other than DOT have also shown promise.<sup>147-150</sup> Incentives, peer assistance (for example, using cured patients), repeated motivation of patients, and staff training and motivation, all have been shown to improve adherence significantly.<sup>13,142,147</sup> In addition, adherence may be enhanced by provision of more comprehensive primary care (as described in the Integrated Management of Adolescent and Adult Illness),<sup>151,152</sup> as well as by provision of specialized services such as opiate substitution for injection drug users.



Providing every patient with a copy of the *PCTC* short version in their language may also serve to improve adherence.

Systematic reviews and extensive programmatic experience demonstrate that there is no single approach to case management that is effective for all patients, conditions, and settings. Consequently, interventions that target adherence must be tailored or customized to the particular situation and cultural context of a given patient.<sup>13,142</sup> Such an approach must be developed in concert with the patient to achieve optimum adherence. This patient-centered, individualized approach to treatment support is now a core element of all tuberculosis care and control efforts. It is important to note that treatment support measures, *and not the treatment regimen itself*, must be individualized to suit the unique needs of the patient.

Mobile technologies may provide a means of implementing a “remote DOT” form of supervision. Most health care workers and many patients in even the poorest countries are familiar with mobile phone technologies and many use them regularly in their daily lives. Voice messages, or possibly in the future video reminders, may serve both to support treatment and to monitor for adverse drug reactions.

In addition to one-on-one support for patients being treated for tuberculosis, community support is also of importance in creating a therapeutic milieu and reducing stigma.<sup>9,153</sup> Not only should the community expect that optimum treatment for tuberculosis is provided, but, also, the community should play a role in promoting conditions that facilitate and assist in ensuring that the patient will adhere to the prescribed regimen.

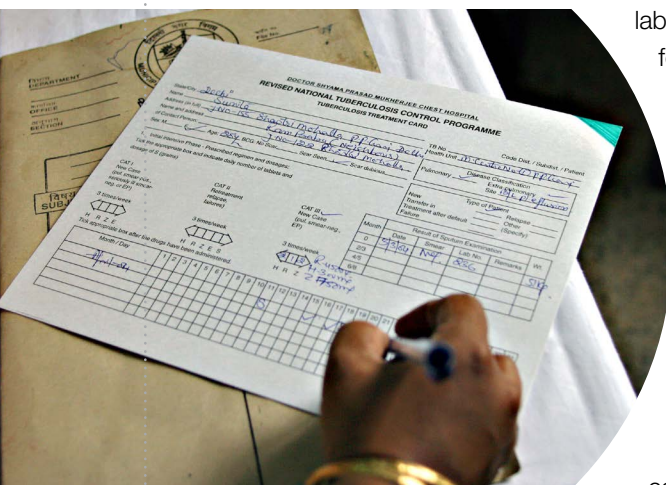
A number of studies have shown that persons with tuberculosis may incur catastrophic costs in seeking a diagnosis and appropriate treatment.<sup>40,41</sup> Sickness insurance, disability grants, and other social protection schemes are available in many countries, though they may not cover the entire population. Persons with tuberculosis may be eligible for financial support through such schemes, but may not be aware of them or have the capacity to access them. Health care providers should assist patients to access existing schemes, including help with administrative procedures, issuing sickness certificates, etc.

---

**STANDARD 10.** Response to treatment in patients with pulmonary tuberculosis (including those with tuberculosis diagnosed by a rapid molecular test) should be monitored by follow-up sputum smear microscopy at the time of completion of the initial phase of treatment (two months). If the sputum smear is positive at completion of the initial phase, sputum microscopy should be performed again at 3 months and, if positive, rapid molecular drug sensitivity testing (line probe assays or Xpert MTB/RIF) should be performed. In patients with extrapulmonary tuberculosis and in children, the response to treatment is best assessed clinically.

#### **Rationale and Evidence Summary**

Patient monitoring and treatment supervision are two separate functions. Patient monitoring is necessary to evaluate the response of the disease to treatment and to identify adverse drug reactions. To judge response of pulmonary tuberculosis to treatment, the most expeditious method is sputum smear microscopy. Ideally, where quality-assured



*A positive sputum smear at the end of the initial phase of treatment should trigger an assessment of the patient's adherence and a careful clinical re-evaluation.*

laboratories are available, sputum cultures, as well as smears, should be performed for monitoring.

Molecular tests, including Xpert MTB/RIF, are not suitable for patient monitoring because these tests detect residual DNA from non-viable bacilli.<sup>154</sup> However, Xpert MTB/RIF is useful for detecting rifampicin resistance in patients who remain sputum smear positive after 3 or more months of treatment. Patients whose diagnosis of tuberculosis is confirmed by Xpert MTB/RIF and who have rifampicin susceptible organisms should be monitored during treatment with sputum smear microscopy. For these patients, microscopy should be performed at completion of the intensive phase of treatment, five months into treatment and at the end of treatment as per current WHO guidelines.<sup>14</sup> Patients with TB and rifampicin resistance confirmed by Xpert MTB/RIF and placed on MDR TB treatment should be monitored by sputum smear and culture. If resources permit, monthly culture throughout treatment is recommended.<sup>155,156</sup>

Approximately 80% of patients with sputum smear-positive pulmonary tuberculosis should have negative sputum smears at the time of completion of the initial phase of treatment (2 months of therapy).<sup>128</sup> Patients who remain sputum smear-positive require particular attention. A positive sputum smear at the end of the initial phase of treatment should trigger an assessment of the patient's adherence and a careful re-evaluation to determine if co-morbid conditions, particularly HIV infection or other forms of immunosuppression and diabetes mellitus, are present that might interfere with response to treatment. However, a positive smear at the time of completion of the initial phase is not an indication to prolong this phase of treatment. If the sputum smear is positive at month two, sputum smear examination should be repeated at month three. Having a positive sputum smear after completion of three months of treatment raises the possibility of drug resistance and Xpert MTB/RIF, culture, and drug susceptibility testing should be performed in a quality-assured laboratory.<sup>14</sup>

Chest radiographs may be a useful adjunct in assessing response to treatment but are not a substitute for microbiologic evaluation. Similarly, clinical assessment can be unreliable and misleading in the monitoring of patients with pulmonary tuberculosis especially in the presence of co-morbid conditions that could confound the clinical assessment. However, in patients with extrapulmonary tuberculosis and in children, clinical evaluations may be the only available means of assessing the response to treatment.

**STANDARD 11.** An assessment of the likelihood of drug resistance, based on history of prior treatment, exposure to a possible source case having drug-resistant organisms, and the community prevalence of drug resistance (if known), should be undertaken for all patients. Drug susceptibility testing should be performed at the start of therapy for all patients at a risk of drug resistance. Patients who remain sputum smear-positive at completion of 3 months of treatment, patients in whom treatment has failed, and patients who have been lost to follow up or relapsed following one or more courses of treatment should always be assessed for drug resistance. For patients in whom drug resistance is considered to be likely, an Xpert MTB/RIF should be the initial diagnostic test. If rifampicin resistance is detected, culture and testing for susceptibility to isoniazid, fluoroquinolones, and second-line injectable drugs should be performed promptly. Patient counseling and education, as well as treatment with an empirical second-line regimen, should begin immediately to minimize the potential for transmission. Infection control measures appropriate to the setting should be applied.

Culture Identification  
Culture Identified as:

☒ Mycobacterium tuberculosis  
☐ Non tuberculous mycobacterium

Results of drug Sensitivity testing

Isoniazid	Rifampicin	Streptomycin	Ethambutol	NOT DONE
R	R	S	S	

S = Sensitive  
R = Resistant

Signature: S.B.

11 / 10 / 11

RECEIVED 13.0  
5 days

*Errors that lead to drug resistance include: failure to provide effective treatment support, inadequate drug regimens, adding a single new drug to a failing regimen, and failure to recognize existing drug resistance.*

### Rationale and Evidence Summary

Drug resistance is largely man-made and is a consequence of suboptimal regimens and treatment interruptions.<sup>25</sup> Clinical errors that commonly lead to the emergence of drug resistance include: failure to provide effective treatment support and assurance of adherence; inadequate drug regimens; adding a single new drug to a failing regimen; and failure to recognize existing drug resistance. In addition, co-morbid conditions associated with reduced serum levels of antituberculosis drugs (e.g., malabsorption, rapid transit diarrhea, use of antifungal agents) and interruptions caused by adverse drug reactions may also lead to the acquisition of drug resistance.<sup>157</sup> Programmatic causes of drug resistance include drug shortages and stock-outs, administration of poor-quality drugs and lack of appropriate supervision to prevent erratic drug intake.<sup>155-157</sup> Transmission of drug-resistant strains of *M. tuberculosis* has been well described in health care facilities, congregate settings, and in susceptible populations, notably HIV-infected persons.<sup>158-162</sup> However, multidrug-resistant (MDR) tuberculosis (tuberculosis caused by organisms that are resistant to at least isoniazid and rifampicin) may spread in the population at large as was shown in data from a number of countries, including China, the Baltic States, and countries of the former Soviet Union.<sup>163-166</sup>

Drug resistance surveillance data suggest that more cases of MDR tuberculosis occur among new cases of tuberculosis than among previously treated cases, although the proportion in the previously treated group is much higher.<sup>164</sup> In 2010, 30 countries with anti-tuberculosis drug resistance surveillance data were each estimated to have more than 700 multidrug-resistant tuberculosis cases among their notified cases each year. Patients who had not had previous treatment comprised a median of 54% of the MDR cases. The occurrence of MDR TB in a new patient is an indication that MDR organisms are spreading in a community. Although case-finding efforts for MDR tuberculosis should first prioritize previously treated patients for drug sensitivity testing, identification of all MDR TB cases will require screening for drug resistance in a much wider group of patients.<sup>164</sup>

The strongest factor associated with drug resistance is previous antituberculosis treat-

ment, as shown by the WHO/IUATLD Global Project on Anti-TB Drug Resistance Surveillance, started in 1994.<sup>22,166</sup> In previously treated patients, the odds of any resistance are at least 4-fold higher, and that of MDR TB at least 10-fold higher, than in new (untreated) patients.<sup>155</sup> Patients with chronic tuberculosis (sputum-positive after re-treatment) and those who fail treatment (sputum-positive after 5 months of treatment) are at highest risk of having MDR tuberculosis, especially if rifampicin was used throughout the course of treatment.<sup>155</sup> Persons who are in close contact with confirmed MDR tuberculosis patients, especially children and HIV-infected individuals, also are at high risk of being infected with MDR strains. In some closed settings prisoners, persons staying in homeless shelters and certain categories of immigrants and migrants are at increased risk of MDR tuberculosis.<sup>155,167</sup> These factors are summarized and presented in descending order of level of risk in Table 8.

By the mid-1990's, most countries participating in the global survey of antituberculosis drug resistance registered cases of MDR tuberculosis. Not surprisingly, in 2006, extensively drug-resistant (XDR) tuberculosis (defined as tuberculosis caused by *M. tuberculosis* resistant to at least isoniazid and rifampicin, as well as to any one of the fluoroquinolones and to at least one of three injectable second-line drugs [amikacin, capreomycin, or kanamycin]) was described and rapidly recognized as a serious emerging threat to global public health, as well as being deadly in the initial outbreak.<sup>168</sup> Subsequent reports have identified XDR tuberculosis in all regions of the world and, to date, treatment outcomes have been significantly worse than MDR tuberculosis outcomes.<sup>168-171</sup> In one cohort from KwaZulu-Natal, 98% of XDR tuberculosis patients co-infected with HIV died, with a median time of death of only 16 days from time of specimen collection.<sup>168</sup> The two strongest risk factors for XDR tuberculosis are:

1. Failure of a tuberculosis treatment which contains second-line drugs including an injectable agent and a fluoroquinolone.
2. Close contact with an individual with documented XDR tuberculosis or with an individual for whom treatment with a regimen including second-line drugs is failing or has failed.

More recently, strains of *M. tuberculosis* with resistance patterns beyond XDR tuberculosis have been described. The available evidence suggests that treatment outcomes are worse when resistance patterns become more complicated.<sup>172-174</sup>

TABLE 8.

**Assessing risk for drug resistance**

<b>Risk Factors for Resistance</b>	<b>Comments</b>
<b>Failure of re-treatment regimen</b> (a second course of treatment after failure, relapse, or default)	Patients who are still sputum smear-positive at the end of a re-treatment regimen have perhaps the highest MDR TB rates of any group, often exceeding 80%.
<b>Close contact with a known drug-resistant case</b>	Most studies have shown that tuberculosis occurring in close contacts of persons with MDR TB are also likely to have MDR TB.
<b>Failure of the initial treatment regimen</b>	Patients who fail to become sputum smear-negative while on treatment are likely to have drug-resistant organisms. However, the likelihood depends on a number of factors, including whether rifampicin was used in the continuation phase and whether DOT was used throughout treatment. Thus, a detailed history of drugs used is essential. This is especially true for patients treated by private providers, often with non-standard regimens.
<b>Relapse after apparently successful treatment</b>	In clinical trials most patients who relapse have fully susceptible organisms. However, under program conditions an apparent relapse, especially an early relapse, may, in fact, be an unrecognized treatment failure and thus have a higher likelihood of drug resistance.
<b>Return after default without recent treatment failure</b>	The likelihood of MDR TB varies substantially in this group, depending in part on the duration of treatment and the degree of adherence before default.
<b>Exposure in institutions that have outbreaks or a high prevalence of TB with any drug resistance</b>	Patients who frequently stay in homeless shelters, prisoners in many countries, and health care workers in clinics, laboratories, and hospitals can have high rates of TB with any drug resistance pattern.
<b>Residence in areas with high drug-resistant TB prevalence</b>	Drug-resistant TB rates in many areas of the world can be high enough to justify routine DST in all new cases.

<sup>155</sup> Modified from World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. WHO/HTM/TB/2008.402.

Drug susceptibility testing (DST) to the first-line antituberculosis drugs should be performed in laboratories that participate in an ongoing, rigorous quality assurance program. DST for first-line drugs is currently recommended for all patients with a history of previous antituberculosis treatment; patients who have failed treatment, especially those who have failed a standardized re-treatment regimen, are the highest priority.<sup>156</sup> Testing with Xpert MTB/RIF is recommended for patients judged to be at risk for having MDR tuberculosis.<sup>85</sup> Tests (other than Xpert MTB/RIF) for identifying drug resistance in *M. tuberculosis* are shown in Table 9. It should be noted that in some instances phenotypic DST may miss low level rifampicin resistance due to uncommon mutations in the *rpoB* gene, thus accounting for discordance between genotypic and phenotypic methods of performing DSTs.<sup>175,176</sup> The determination of the specificity of a molecular DST method based only on phenotypic DST as a reference may, therefore, underestimate the specificity of the molecular DST. In light of these findings, it is currently unclear whether and to what extent Xpert MTB/RIF might out-perform phenotypic DST methods for rifampicin resistance.<sup>77</sup>

Patients who develop tuberculosis and are known to have been in close contact with persons known to have MDR tuberculosis also should have DST performed on an initial isolate. Although HIV infection has not been conclusively shown to be an independent risk



factor for drug resistance, MDR tuberculosis outbreaks in HIV settings and high mortality rates in persons with MDR tuberculosis and HIV infection justify routine DST in all HIV-infected tuberculosis patients, resources permitting.<sup>159,160,162,168</sup>

All patients suspected of having XDR tuberculosis should have DST to isoniazid, rifampicin, the second-line injectable agents, and a fluoroquinolone. When epidemiological or other factors suggest that there is a risk for XDR tuberculosis in a person with HIV infection, liquid media or other validated rapid techniques for DST of first- and second-line drugs is recommended. HIV-infected patients with XDR tuberculosis have been observed to have a rapidly fatal course, thus, in patients (with or without HIV infection) who have a severe or rapidly progressive illness an empirical treatment regimen, based on international recommendations, should be initiated promptly, generally prior to having drug susceptibility test results.<sup>168</sup>

TABLE 9.

### WHO approved tests for identification of drug resistance

Tests	Purpose	Comments
Line probe assays: GenoType MTBDRplus assays	Rapid detection of rifampicin resistance	The GenoType MTBDR <sup>®</sup> assays have good sensitivity and specificity for rifampicin resistance in AFB positive sputum samples and positive cultures. <sup>177</sup> LPAs are approved by WHO <sup>86</sup>
Colorimetric redox-indicator (CRI) methods and nitrate reductase assays (NRA)	Rapid detection of rifampicin and isoniazid resistance	WHO recommends NRA and CRI as interim solutions, pending the development of capacities for genotypic DST. <sup>178,179</sup>
Microscopic Observation Drug Susceptibility [MODS]	Rapid detection of rifampicin and isoniazid resistance	MODS is suitable for use at reference laboratory level; <sup>180</sup> scaling-up and decentralization to lower level laboratories is not recommended. The WHO recommends MODS as interim solution, pending the development of capacities for genotypic DST.
Phenotypic drug susceptibility testing methods for first-line and second-line antituberculosis drugs:	Detection of resistance to first- and second-line drugs	DST for isoniazid and rifampicin shows good reliability and reproducibility when tested in commercial liquid and solid media. WHO recommends that among Rif-resistant or MDR TB cases, phenotypic testing for all fluoroquinolones (ofloxacin, moxifloxacin, levofloxacin) and second-line injectable agents (kanamycin, amikacin, and capreomycin) available to national TB programmes should be done. <sup>181</sup>  <b>Note:</b> Genotypic methods for detection of second-line drug susceptibility are available but not approved by WHO. <sup>182</sup>
Pyrosequencing for RIF resistance	Rapid detection of rifampicin resistance	Pyrosequencing is a highly sensitive and specific tool for the detection of RIF resistance in <i>M. tuberculosis</i> . Overall sensitivity and specificity were estimated at respectively 0.94 (95% CI 0.92–0.96) and 0.98 (95% CI 0.97–0.99). <sup>183</sup>  Pyrosequencing is considered the reference method for genotypic DST methods.

---

**STANDARD 12.** Patients with or highly likely to have tuberculosis caused by drug-resistant (especially MDR/XDR) organisms should be treated with specialized regimens containing quality-assured second-line antituberculosis drugs. The doses of antituberculosis drugs should conform to WHO recommendations. The regimen chosen may be standardized or based on suspected or confirmed drug susceptibility patterns. At least five drugs—pyrazinamide and four drugs to which the organisms are known or presumed to be susceptible, including an injectable agent—should be used in a 6–8 month intensive phase and at least 3 drugs to which the organisms are known or presumed to be susceptible, should be used in the continuation phase. Treatment should be given for at least 18–24 months beyond culture conversion. Patient-centered measures, including observation of treatment, are required to ensure adherence. Consultation with a specialist experienced in treatment of patients with MDR/XDR tuberculosis should be obtained.

### Rationale and Evidence Summary

Because randomized controlled treatment trials for MDR/XDR tuberculosis are difficult to design, none has been conducted to evaluate currently available regimens of second-line drugs. However, study designs similar to those used for new antiretroviral drugs in which a new drug plus an optimized regimen, based on DST, is compared to the optimized regimen are being used for studies of new drugs for MDR/XDR tuberculosis.<sup>184</sup> In the absence of clinical trial data, current recommendations for treating MDR/XDR tuberculosis are based on observational studies, general microbiological and therapeutic principles, extrapolation from available evidence from pilot MDR tuberculosis treatment projects, expert opinion,<sup>155,156,169,185–193</sup> and more recently, a carefully conducted individual patient meta-analysis.<sup>194</sup> The individual patient data meta-analysis examined the outcomes of treatment for MDR tuberculosis and concluded that treatment success, compared with failure/relapse or death, was associated with use of later generation fluoroquinolones, as well as ofloxacin, ethionamide or prothionamide, use of four or more likely effective drugs in the initial intensive phase, and three or more likely effective drugs in the continuation phase.<sup>156,174,194</sup> In addition, not surprisingly, outcomes in patients with XDR tuberculosis were worse when there was resistance to additional drugs beyond those that comprise the definition of XDR.<sup>172</sup>

There are three strategic options for treatment of MDR/XDR tuberculosis: standardized, empiric, and individualized regimens. The approach is dependent on having access to either reliable DST results for individual patients or population data on the prevalent resistance patterns. The choice among the three approaches should be based on availability of second-line drugs and DST for first- and second-line drugs, local drug resistance patterns, and the history of use of second-line drugs.<sup>155,156,187,193</sup> Basic principles involved in the design of any regimen include the use of at least four drugs with either certain or highly likely effectiveness, drug administration at least six days a week, drug dosage determined by patient weight, the use of an injectable agent (an aminoglycoside or capreomycin) for 6–8 months, treatment duration of approximately 20 months, and patient-centered DOT throughout the treatment course.

Based on their activity, efficacy, route of administration, tolerance, availability, and costs, antituberculosis drugs can be classified in five groups.<sup>187</sup> Group 1 consists of first-line



William: January, 2012. 19 years old, 33 kg MDR TB



William: July, 2012. 19 years old, 59 kg



*"My grandfather lived with my family and he was very sick with cough and losing weight. He had TB and was treated several times but never got cured. He died. Then I got sick."*

—William

*He has now completed treatment and is working as a volunteer in the TB program in Dar es Salaam.*

drugs: isoniazid, rifampicin, ethambutol, pyrazinamide, and rifabutin. Any of these drugs should be used if it is thought that susceptibility remains. Only one drug should be selected from Group 2 (injectable agents—kanamycin, amikacin, capreomycin, streptomycin) and Group 3 (fluoroquinolones), because of documented total or partial cross-resistance and similar toxicities within the groups. Group 4 consists of less potent oral agents: ethionamide, prothionamide, cycloserine, terizidone, *p*-aminosalicylic acid. Group 5 is composed of drugs for which antituberculosis action has not been documented in clinical trials (except for thioacetazone): clofazimine, linezolid, amoxicillin/clavulanate, thioacetazone, imipenem/cilastatin high-dose isoniazid, and clarithromycin. A drug that has been used within a failing regimen should not be counted in the total of four drugs for re-treatment, even if susceptibility is shown in the laboratory. The doses and adverse effects of second-line drugs are described in detail the ATS/CDC/IDSA Treatment of Tuberculosis.<sup>122</sup>

Standardized treatment regimens are based on representative drug resistance surveillance data or on the history of drug usage in the country.<sup>155</sup> Based on these assessments, regimens can be designed that will have a high likelihood of success. Advantages include less dependency on highly technical laboratories, less reliance on highly specialized clinical expertise required to interpret DST results, simplified drug ordering and logistics, and easier operational implementation. A standardized approach is useful in settings where second-line drugs have not been used extensively and where resistance levels to these drugs are consequently low or absent.

Empiric treatment regimens are commonly used in specific groups of patients while the DST results are pending.<sup>155,156</sup> Empiric regimens are strongly recommended to avoid clinical deterioration and to prevent transmission of MDR strains of *M. tuberculosis* to contacts while awaiting the DST results.<sup>155</sup> Once the results of DST are known, an empiric regimen may be changed to an individualized regimen. Ongoing global efforts to address the problem of MDR tuberculosis will likely result in broader access to laboratories performing DST and a faster return of results.

Individualized treatment regimens (based on DST profiles and drug history of individual patients or on local patterns of drug utilization) have the advantage of avoiding toxic and expensive drugs to which the MDR strain is resistant.<sup>155</sup> However, an individualized approach requires access to substantial human, financial, and technical (laboratory) capacity. DSTs for second-line drugs are notoriously difficult to perform, largely because of drug instability and the fact that critical concentrations for defining drug resistance are very close to the minimal inhibitory concentration (MIC) of individual drugs.<sup>195</sup> Laboratory proficiency testing results are not yet available for second-line drugs; as a result little can be said about the reliability of DST for these drugs.<sup>195</sup> Clinicians treating MDR tuberculosis

*Often second-line drugs are the last best hope for patients with drug-resistant tuberculosis, and it is crucial that such treatment be designed with the active participation of the patient.*

patients must be aware of these limitations and interpret DST results with this in mind.

A shorter course standardized regimen used in Bangladesh has been described with good results reported in a small observational study.<sup>196</sup> Although promising, at this point there is insufficient evidence to recommend the use of this regimen for treating MDR tuberculosis. A clinical trial is underway that should provide substantial new information on which to base recommendations. Current advice from WHO is that a short regimen for MDR tuberculosis should be used only under operational research conditions.<sup>197</sup>

Substantial treatment support that may include financial assistance is commonly needed to enable patients to complete a second-line regimen. MDR/XDR tuberculosis treatment is a complex health intervention and medical practitioners are strongly advised to obtain consultation with a specialist experienced in the management of these patients. Often second-line drugs are the last best hope for patients with drug-resistant tuberculosis, and it is crucial that such treatment be designed for maximal effectiveness with the active participation of the patient to overcome the challenges faced by both provider and patient with MDR/XDR tuberculosis.<sup>198</sup> Physicians undertaking treatment of patients with MDR TB must be committed to finding and administering a regimen using quality-assured drugs for the full recommended duration of treatment. Commonly this requires collaboration with public health tuberculosis control programs.

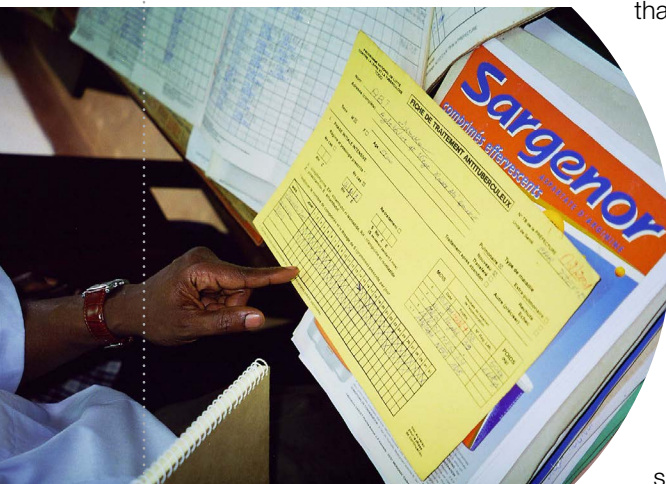
Two new second-line drugs, delamanid and bedaquiline,<sup>199-201</sup> have been introduced, although as of this writing only bedaquiline has been approved by the US FDA. Given the paucity of data describing outcomes and adverse events, the recommendation by WHO states that bedaquiline may be added to a WHO-recommended regimen in adult patients with pulmonary tuberculosis caused by MDR organisms.<sup>200</sup> The recommendations also specify fairly rigid conditions under which the drug should be used. Thus, informed consent should be obtained from the patient and there should be careful monitoring for adverse drug effects.

Of great concern, tuberculosis caused by organisms resistant to all drugs tested has been described in India, but likely exists elsewhere as well.<sup>202,203</sup> However, because of uncertainties about the connection between second-line DST results and patient outcomes it is not clear that there are no treatment options. Nevertheless, at least at this time there are no specific recommended treatment options for such patients and symptomatic or palliative care may be required. Although the number of such cases is likely to be small providers should be attuned to the possibility of such situations and be prepared to provide appropriate palliative management to relieve suffering caused by the disease.

**STANDARD 13.** An accessible, systematically maintained record of all medications given, bacteriologic response, outcomes, and adverse reactions should be maintained for all patients.

### Rationale and Evidence Summary

Recording and reporting of data are fundamental components of care for patients with tuberculosis and for control of the disease. Data recording and reporting are necessary to monitor trends in tuberculosis at global, national, and subnational levels; to monitor progress in the treatment and in the quality of care for individual patients and groups (cohorts) of patients; to ensure continuity when patients are referred between health care facilities; to plan, implement, and evaluate programmatic efforts; and to support advocacy for adequate funding for tuberculosis control programs.<sup>10</sup> When high quality data are available, successes can be documented and corrective actions taken to address problems that are identified.<sup>204,205</sup>




There is a sound rationale and clear benefits for individual patients of a well-maintained record keeping system. It is common for individual physicians to believe sincerely, generally without documentation, that a majority of the patients in whom they initiate antituberculosis therapy are cured. However, when systematically evaluated, it is often seen that only a minority of patients have successfully completed the full treatment regimen. The recording and reporting system enables targeted, individualized follow-up to identify patients who are failing therapy. It also helps in facilitating continuity of care, particularly in settings (e.g., large hospitals) where the same practitioner might not be seeing the patient during every visit. A good record of medications given, results of investigations such as smears, cultures, and chest radiographs, and progress notes on clinical improvement, adverse events, and adherence will provide for more uniform monitoring and ensure a high standard of care.

*Records are important to provide continuity when patients move from one care provider to another and enable tracing of patients who miss appointments.*

Records are important to provide continuity when patients move from one care provider to another and enable tracing of patients who miss appointments. In patients who default and then return for treatment, and patients who relapse after treatment completion, it is critical to review previous records in order to assess the likelihood of drug resistance. Lastly, management of complicated cases (e.g., MDR tuberculosis) is not possible without an adequate record of previous treatment, adverse events, and drug susceptibility results. It should be noted that, wherever patient records are concerned, care must be taken to assure confidentiality of the information, yet the records should be made available to the patient upon request.

It is anticipated that electronic data systems will play an increasing role in tuberculosis data collection and analysis.<sup>204</sup> Most health care workers in even the poorest countries are familiar with mobile phone technologies and many use them regularly in their daily lives. The spread of mobile and web-based technologies is dramatically reducing the barriers to implementing electronic systems that existed until the very recent past. In this context, it is not surprising that there is growing use of and interest in electronic recording and reporting of tuberculosis data.





# Standards for Addressing HIV Infection and Other Co-morbid Conditions

*Knowledge of a person's HIV status influences the approach to a diagnostic evaluation and treatment for tuberculosis.*

**STANDARD 14.** HIV testing and counseling should be conducted for all patients with, or suspected of having, tuberculosis unless there is a confirmed negative test within the previous two months. Because of the close relationship of tuberculosis and HIV infection, integrated approaches to prevention, diagnosis, and treatment of both tuberculosis and HIV infection are recommended in areas with high HIV prevalence. HIV testing is of special importance as part of routine management of all patients in areas with a high prevalence of HIV infection in the general population, in patients with symptoms and/or signs of HIV-related conditions, and in patients having a history suggestive of high risk of HIV exposure.

## **Rationale and Evidence Summary**

Tuberculosis is strongly associated with HIV infection and is estimated to cause more than a quarter of deaths among persons with HIV.<sup>21,206</sup> An autopsy study conducted among adults with HIV infection who died at home in a South African setting found microbiological evidence of tuberculosis in 34% and active tuberculosis in 19%.<sup>207</sup> Similarly, an autopsy study conducted in Kenya among adults with HIV infection who died after receiving a median 10 months of antiretroviral therapy (ART) found microbiological or histological evidence of tuberculosis in 52% and tuberculosis was thought to be the cause of death in 41% of people living with HIV who died within 3 months of ART initiation.<sup>208</sup>

Infection with HIV increases the likelihood of progression from infection with *M. tuberculosis* to active tuberculosis. The risk of developing tuberculosis in people living with HIV is between 20 and 37 times greater than among those who do not have HIV infection.<sup>206</sup> Although the prevalence of HIV infection varies widely between and within countries, among persons with HIV infection there is always an increased risk of tuberculosis. The wide differences in HIV prevalence mean that a variable percentage of patients with tuberculosis will have HIV infection as well. This ranges from less than 1% in low HIV prevalence countries up to 50–77% in countries with a high HIV prevalence, mostly sub-Saharan African countries.<sup>21</sup> Even though in low HIV prevalence countries few tuberculosis patients are HIV-infected, the connection is sufficiently strong and the impact on the patient sufficiently great that provider-initiated HIV counseling and testing should always be conducted in managing individual patients, especially among groups in which the prevalence

*Integrated care facilitates early detection and prompt treatment of tuberculosis resulting in a reduction of mortality and improved treatment success.*

of HIV is higher, such as injecting drug users. In countries having a high prevalence of HIV infection, the yield of positive results will be high and, again, the impact of a positive result on the patient will be great.<sup>209</sup> Thus, the indication for HIV testing is strong; co-infected patients will benefit by access to antiretroviral therapy and by administration of cotrimoxazole for prevention of opportunistic infections.<sup>209</sup> Testing for HIV among presumptive tuberculosis cases in sub-Saharan Africa also yields high HIV-positive results.<sup>210,211</sup> In addition, in South Africa testing household contacts of patients with tuberculosis for both HIV and tuberculosis resulted in detection of a large number of undiagnosed tuberculosis cases and persons with HIV infection.<sup>212</sup> A study in Thailand also showed higher HIV prevalence among contacts of tuberculosis patients living with HIV than among contacts of HIV-negative tuberculosis patients.<sup>213</sup>

Infection with HIV changes the clinical manifestations of tuberculosis.<sup>214,215</sup> Further, in comparison with non-HIV infected patients, patients with HIV infection who have pulmonary tuberculosis have a lower likelihood of having acid-fast bacilli detected by sputum smear microscopy.<sup>216</sup> Moreover, data consistently show that the chest radiographic features are atypical and the proportion of extrapulmonary tuberculosis is greater in patients with advanced HIV infection compared with those who do not have HIV infection. Consequently, knowledge of a person's HIV status influences the approach to a diagnostic evaluation for tuberculosis. For this reason it is important, particularly in areas in which there is a high prevalence of HIV infection, that provider-initiated HIV testing and counseling be implemented for persons suspected of having tuberculosis and those known to have tuberculosis.<sup>210,217</sup> In addition, the history and physical examination should include a search for indicators that suggest the presence of HIV infection. A comprehensive list of clinical criteria/algorithms for HIV/AIDS clinical staging is available in the WHO document *WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children*.<sup>218</sup>

Studies of integrated tuberculosis and HIV services have demonstrated that integrated care facilitates early detection and prompt treatment of tuberculosis resulting in a reduction of mortality and improved treatment success.<sup>219-223</sup> The integrated model of tuberculosis and HIV services in a single health facility also improves ART enrollment and ART update, and supports early initiation of ART.<sup>209,219-223</sup> Thus, integrated approaches to prevention, diagnosis, and treatment of tuberculosis and HIV are strongly recommended in areas of high HIV prevalence.

---

**STANDARD 15.** In persons with HIV infection and tuberculosis who have profound immunosuppression (CD4 counts less than 50 cells/mm<sup>3</sup>), ART should be initiated within 2 weeks of beginning treatment for tuberculosis unless tuberculous meningitis is present. For all other patients with HIV and tuberculosis, regardless of CD4 counts, antiretroviral therapy should be initiated within 8 weeks of beginning treatment for tuberculosis. Patients with tuberculosis and HIV infection should also receive cotrimoxazole as prophylaxis for other infections.

### **Rationale and Evidence Summary**

The evidence on effectiveness of treatment for tuberculosis in patients with HIV co-infection versus those who do not have HIV infection has been reviewed extensively.<sup>14,122,125,126,224-227</sup>

These reviews suggest that, in general, the outcome of treatment for tuberculosis is the same in HIV-infected and non-HIV-infected patients with the notable exception that death rates are greater among patients with HIV infection, presumably due in large part to complications of HIV infection. Tuberculosis treatment regimens are largely the same for HIV-infected and non-HIV-infected patients; however, the results are better if rifampicin is used throughout and treatment is given daily at least in the intensive phase.<sup>126</sup>



*ART should be initiated within 2 weeks after the start of tuberculosis treatment for patients with a CD4 count less than 50 cells/mm<sup>3</sup> and as early as possible within 8 weeks for the other HIV-positive tuberculosis cases.*

In patients with HIV-related tuberculosis, treating tuberculosis is the first priority. In the setting of advanced HIV infection, untreated tuberculosis can progress rapidly to death. As noted above, however, antiretroviral treatment may be lifesaving for patients with advanced HIV infection. Therefore, all patients with tuberculosis and HIV infection should receive antiretroviral therapy as early as possible regardless of CD4 counts.<sup>228</sup> Antiretroviral therapy results in remarkable reduction in mortality and AIDS-related morbidity, and greatly improves survival and quality of life of HIV-infected persons. ART is associated with reduction of mortality risk that in different studies has ranged from 54% to 95% in both resource-limited and high-income settings.<sup>229</sup> Recent clinical trials, STRIDE and SAPIT, showed reduction of deaths and AIDS-related events by 42% and 68%, respectively, with early ART in combination with tuberculosis treatment in persons with advanced HIV infection.<sup>230,231</sup> The CAMELIA trial found reduction of mortality by 34% when

ART was initiated 2 weeks compared with 8 weeks following initiation of tuberculosis treatment in patients with profound immunosuppression (median CD4 count of 25 cells/mm<sup>3</sup>).<sup>232</sup> Thus, evidence from these trials indicates that ART should be initiated within 2 weeks after the start of tuberculosis treatment for patients with a CD4 count less than 50 cells/mm<sup>3</sup> and as early as possible within 8 weeks for the other HIV-positive tuberculosis cases.<sup>209</sup> Caution should be given for early initiation of ART in HIV-positive patients with tuberculous meningitis because of its association with higher rate of adverse events compared with initiation of ART 2 months after start of tuberculosis treatment.<sup>233</sup>

There are some important issues associated with concomitant therapy for tuberculosis and HIV infection that should be considered. These include overlapping toxicity profiles for the drugs used, drug-drug interactions (especially with rifampicin and protease inhibitors), potential problems with adherence to multiple medications, and immune reconstitution inflammatory reactions.<sup>122,214</sup> There are few drug interactions with tuberculosis drugs and the nucleoside reverse transcriptase inhibitors (NRTIs) and no specific changes are recommended. However, rifampicin reduces drug levels of both non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors through induction of the cytochrome P450 liver enzyme system. Therefore, efavirenz should be used as the preferred NNRTI since its interactions with antituberculosis drugs are minimal. In several studies, ART with standard-dose efavirenz and two nucleosides was well tolerated and highly efficacious in achieving viral load suppression.<sup>14</sup> In HIV-positive tuberculosis patients who need an ART regimen containing a boosted protease inhibitor (PI), it is recommended to use a rifabutin-based regimen.<sup>14</sup> Patients should also be closely monitored to identify adverse drug reactions and to observe for immune reconstitution inflammatory syndrome (IRIS). Although some studies reported increased risk of IRIS when ART is started earlier, the mortality benefit of earlier ART initiation outweighs the IRIS risk, which usually is self-limited.<sup>234</sup>

Patients with tuberculosis and HIV infection should also receive cotrimoxazole (trimethoprim-sulfamethoxazole) as prophylaxis for other infections. Several studies have demonstrated the benefits of cotrimoxazole prophylaxis, and this intervention is currently recommended by the WHO as part of the TB/HIV management package.<sup>209,214,235-239</sup>

---

**STANDARD 16. Persons with HIV infection who, after careful evaluation, do not have active tuberculosis should be treated for presumed latent tuberculosis infection with isoniazid for at least 6 months.**

### **Rationale and Evidence Summary**

Early identification of symptoms consistent with tuberculosis followed by prompt diagnostic evaluation and appropriate treatment of the disease among people living with HIV increases survival and improves quality of life. Thus, screening for symptoms among persons with HIV infection is crucial for identifying both tuberculosis cases and persons who should receive isoniazid preventive therapy.<sup>46,47,240,241</sup> A comprehensive systematic review and meta-analysis found that the absence of four symptoms: current cough, night sweats, fever, or weight loss identified a large subset of PLHIV who are very unlikely to have active tuberculosis.<sup>47</sup> All persons with HIV infection should be regularly screened for tuberculosis using the clinical algorithm with the four symptoms: current cough, night sweats, fever or weight loss, at every visit to a health facility or contact with a health care worker.<sup>47,209,216,241</sup> PLHIV who report any one of the symptoms should be evaluated for tuberculosis and other diseases. Similarly, children living with HIV who have one of the following symptoms—poor weight gain, fever, current cough, or a history of contact with a person who has infectious tuberculosis should be evaluated for tuberculosis and other conditions.<sup>209,241</sup> The diagnostic evaluation for tuberculosis should be done in accordance with national and international guidelines. In HIV-prevalent settings, Xpert MTB/RIF should be used as the initial test.<sup>59,85</sup> PLHIV who do not have any one of the four screening symptoms cited above or a history of contact with a person who has infectious tuberculosis are unlikely to have active tuberculosis (negative predictive value 97.7%, 95% CI 97.4–98.0) and, therefore, are candidates for IPT.<sup>47,241</sup>

Isoniazid, given to PLHIV in whom tuberculosis has been excluded reduces the risk of tuberculosis by approximately 33% compared with placebo.<sup>242</sup> The protective effect decreases with time after treatment but may persist for 2–3 years. The benefit is most pronounced in persons with a positive tuberculin skin test (~64% reduction) and is substantially less (14%) in persons with negative or unknown tuberculin skin test results. After excluding active tuberculosis, isoniazid (approximately 5 mg/kg/day, 300 mg/day maximum for adults and 10 mg/kg/day up to 300 mg/day for children) should be given to persons with HIV infection who are known to have latent tuberculosis infection or who have been in contact with an infectious tuberculosis case. If performing a tuberculin skin test is not possible, isoniazid is recommended for all PLHIV.<sup>209,241</sup> There is a trend to lower tuberculosis incidence with a longer preventive therapy particularly in settings with high tuberculosis prevalence and transmission and among tuberculin skin test-positive PLHIV.<sup>243,244</sup>

In spite of there having been strong evidence-based recommendations for the use of IPT in PLHIV since 1998, implementation for these recommendations has been very limited.



*Screening for symptoms among persons with HIV infection is crucial for identifying both tuberculosis cases and persons who should receive isoniazid preventive therapy.*

The reluctance to use IPT is based, particularly, on concerns with creating drug resistance if active tuberculosis is not excluded. In a study conducted in Rio de Janeiro, Brazil, operational training of physicians to screen for tuberculosis in public HIV clinics combined with the use of tuberculin skin testing led to improved implementation of IPT.<sup>245</sup> There was a modest population level reduction in the incidence of tuberculosis (13% reduction) and death (24% reduction). After adjustment for important covariates (age, CD4 count, antiretroviral treatment), there was a 27% reduction in incidence and a 31% reduction in deaths. Adverse effects were minimal.

Treatment of latent tuberculosis infection with a regimen of once weekly rifapentine and isoniazid given for 3 months (12 doses) under direct observation has been shown in low tuberculosis incidence settings to be as effective as a 9-month isoniazid regimen in preventing tuberculosis.<sup>246</sup> Moreover, the treatment completion rate was significantly higher. The weekly rifapentine/isoniazid regimen also showed less toxicity than other drug combination or continuous isoniazid regimens.<sup>244,247</sup> However, this regimen has not been evaluated in high-prevalence settings and thus cannot be recommended at this time in those settings.

The combined use of IPT and antiretroviral therapy (ART) among PLHIV significantly reduces the incidence of tuberculosis. The combined use of ART and IPT can reduce tuberculosis incidence among PLHIV by up to 97% particularly among persons with positive tuberculin skin tests.<sup>248,249</sup> Earlier initiation of ART at a CD4 cell count of more than 350/ $\mu$ l can reduce tuberculosis incidence by 60% and the reduction is 84% if ART is started when the CD4 cell count is less than 200/ $\mu$ l.<sup>250</sup> A recent clinical trial among PLHIV who received ART showed that at 12 months isoniazid resulted in a 40% reduction of tuberculosis incidence regardless of the tuberculin skin test result.<sup>251</sup>



---

**STANDARD 17.** All providers should conduct a thorough assessment for co-morbid conditions and other factors that could affect tuberculosis treatment response or outcome and identify additional services that would support an optimal outcome for each patient. These services should be incorporated into an individualized plan of care that includes assessment of and referrals for treatment of other illnesses. Particular attention should be paid to diseases or conditions known to affect treatment outcome, for example, diabetes mellitus, drug and alcohol abuse, undernutrition, and tobacco smoking. Referrals to other psychosocial support services, or to such services as antenatal or well-baby care should also be provided.

### Rationale and Evidence Summary

In addition to the location, severity, and extent of tuberculosis, a number of other factors can affect the response to and outcome of treatment. These factors include concomitant illnesses (such as diabetes mellitus), psychosocial issues, and socioeconomic barriers to treatment completion. In working with a patient to treat tuberculosis, the provider must assess and address other contributing factors to ensure that there is the greatest chance of cure. Addressing co-morbid conditions commonly associated with tuberculosis can decrease treatment default, prevent drug resistance, and decrease treatment failures and deaths.

There are a number of conditions that are either risk factors for tuberculosis or are common in patients with the disease. Many of these can adversely affect treatment outcome. These include HIV (discussed previously), other immunosuppressive disorders, diabetes mellitus, malnutrition, alcoholism, other substance abuse, and tobacco use.<sup>252-256</sup>

Clinicians should take individual risk factors into account and carry out the necessary tests to evaluate co-morbid conditions relevant to tuberculosis treatment response and outcome. These should be provided free of charge to the patient.

Because of its increasing prevalence, diabetes mellitus is a particular concern.<sup>257</sup> Diabetes triples the risk of developing tuberculosis and can increase the severity of tuberculosis.<sup>258</sup> Conversely, tuberculosis can worsen blood glucose control in persons with diabetes. Tuberculosis must be considered in people with diabetes, and diabetes must be considered in people with tuberculosis. Individuals with both conditions require careful clinical management to ensure that optimal care is provided for both diseases.<sup>259</sup>

The same tuberculosis treatment regimen should be prescribed for patients with diabetes as for those without diabetes. However, because of the potential for reduced concentrations of rifampicin, careful observation of clinical response is necessary.<sup>260</sup> Where possible, patients with tuberculosis should be screened for diabetes at the start of their treatment. Management of diabetes in patients with tuberculosis should be provided in line with existing management guidelines.<sup>261</sup>

Coexisting non-infectious lung diseases, such as chronic obstructive pulmonary disease (COPD), may increase the risk for tuberculosis and complicate management. Both clinical and radiographic assessment of response may be confounded by coexisting lung disease. Tuberculosis is also a risk for the development of COPD and may be a major contributor to this emerging problem in low-resource settings.<sup>262</sup>



*Having a diagnosis of tuberculosis may serve as an entry point to health care and psychosocial services that can enhance treatment completion.*

Macro- and micronutritional deficiencies are both causes and consequences of tuberculosis and therefore very common at the time of tuberculosis diagnosis. All tuberculosis patients should have a nutritional assessment including weight and height in order to determine body mass index. Nutritional care should be provided according to the nutritional status of the patient in line with guidelines on nutritional care for people with tuberculosis. Nutritional support, for example a food package, should be considered for patients who do not have the financial means to meet their nutritional needs during tuberculosis treatment.<sup>263</sup>

Social factors<sup>13,142</sup> may also be important in influencing treatment response and outcome, and interventions should be considered to mitigate their impact. Homelessness, social isolation, migration for work, a history of incarceration, and unemployment have all been cited as barriers to treatment adherence and risk factors for poor treatment outcome.<sup>13,142</sup> Having a diagnosis of tuberculosis may serve as an entry point to health care and psychosocial services that can enhance treatment completion. Treatment support including psychosocial support is a cornerstone of the best practices for tuberculosis treatment described in detail in *Best Practice for the Care of Patients with Tuberculosis: a Guide for Low-income Countries*.<sup>16</sup> By providing patients with referrals to accessible services for co-morbid conditions of any kind, the provider enhances their chances for cure in the shortest possible time and contributes to increasing the overall health of the community.

It is recognized that not all necessary services are currently available in the areas most in need of this support. To the extent these services are available, they should be fully utilized to support tuberculosis patient treatment. Where they are not available, plans to enhance relevant capacities should be incorporated into local, regional, and national tuberculosis control strategies.

Other diseases and treatments, especially immunosuppressive treatments such as corticosteroids and tumor necrosis factor (TNF) alpha inhibitors, increase the risk of tuberculosis and may alter the clinical features of the disease.<sup>264,265</sup> Clinicians caring for patients with diseases or taking drugs that alter immune responsiveness must be aware of the increased risk of tuberculosis and be alert for symptoms that may indicate the presence of tuberculosis. Isoniazid preventive treatment may be considered for such patients if active tuberculosis is excluded.



# Standards for Public Health and Prevention

*This inability to conduct targeted contact investigations results in missed opportunities to prevent additional cases of tuberculosis, especially among children.*

**STANDARD 18.** All providers should ensure that persons in close contact with patients who have infectious tuberculosis are evaluated and managed in line with international recommendations. The highest priority contacts for evaluation are:

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

## Rationale and Evidence Summary

The determination of priorities for contact investigation is based on the likelihood that a contact: 1) has undiagnosed tuberculosis; 2) is at high risk of developing tuberculosis if infected; 3) is at risk of having severe tuberculosis if the disease develops; and 4) is at high risk of having been infected by the index case. The risk of acquiring infection with *M. tuberculosis* is correlated with intensity and duration of exposure to a person with infectious tuberculosis, generally called an index case. A contact is any person who has been exposed to an index case. Commonly contacts are divided into two groups, household and non-household. A person who shared the same enclosed living space for one or more nights, or for frequent or extended periods during the day with the index case during the 3 months before commencement of the current treatment episode, is defined as a household contact. Non-household contacts may also share an enclosed space, such as a social gathering place, workplace, or facility, for extended periods during the day with the index case during the 3 months before commencement of the current treatment episode and thus also be at risk of having acquired infection with *M. tuberculosis*. Contact investigation is considered an important activity, both to find persons with previously undetected tuberculosis and persons who are candidates for treatment of latent tuberculosis infection.<sup>266-268</sup>

Unfortunately, lack of adequate staff and resources in many areas makes contact investigation a challenging task. This inability to conduct targeted contact investigations results in missed opportunities to prevent additional cases of tuberculosis, especially among

children. Thus, more energetic efforts are necessary to overcome these barriers to optimum tuberculosis control practices.

Two systematic reviews of studies on household contact investigations in low- and middle-income settings showed that, on average, about 4.5% and 3.1% respectively of the contacts were found to have active tuberculosis.<sup>269,270</sup> The median number of household contacts that were evaluated to find one case of active tuberculosis was 19 (range 14–300). The median proportion of contacts found to have latent infection was just over 50% in both studies. The median number of contacts that were evaluated to find one person with latent tuberculosis infection was 2 (range 1–14). In the review by Fox et al,<sup>270</sup> longer term follow up demonstrated that the incidence of tuberculosis remained above the background rate for at least 5 years. Evidence from these reviews suggests that contact investigation in high-incidence settings is a high-yield strategy for case finding. Based on the evidence from the reviews, WHO developed recommendations for contact investigation in low resource settings.<sup>8</sup>

A systematic review and meta-analysis of the yield of investigation of contacts of persons with MDR/XDR tuberculosis found a pooled yield of 6.5% of contacts also had active tuberculosis.<sup>271</sup> Latent tuberculosis infection was found in 50.7%.

The main benefit of contact investigation for contacts of MDR/XDR index cases is early detection of active tuberculosis that should result in decreasing transmission of MDR/XDR organisms. In the systematic review, just over 50% of contacts with active tuberculosis had drug susceptibility profiles that were concordant with the index case. Unfortunately, there are no current recommendations for treatment of latent infection that is presumed to be with MDR/XDR organisms.

---

**STANDARD 19. Children <5 years of age and persons of any age with HIV infection who are close contacts of a person with infectious tuberculosis, and who, after careful evaluation, do not have active tuberculosis, should be treated for presumed latent tuberculosis infection with isoniazid for at least six months.**

#### **Rationale and Evidence Summary**

Children (particularly those under the age of five years) are a vulnerable group because of the high likelihood of progressing from latent infection to active tuberculosis. Children, especially if very young, are also more likely to develop disseminated and serious forms of tuberculosis such as meningitis. For these reasons it is recommended that, after active tuberculosis is excluded, children under the age of five years living in the same household as a sputum smear-positive tuberculosis patient should be treated with isoniazid, 10 mg/kg/day (up to a maximum of 300 mg), for 6 months on the presumption that they have been infected by the index case. The screening of children for active tuberculosis can be accomplished by a careful medical history and physical examination, as illustrated in Figure 1.<sup>114</sup>

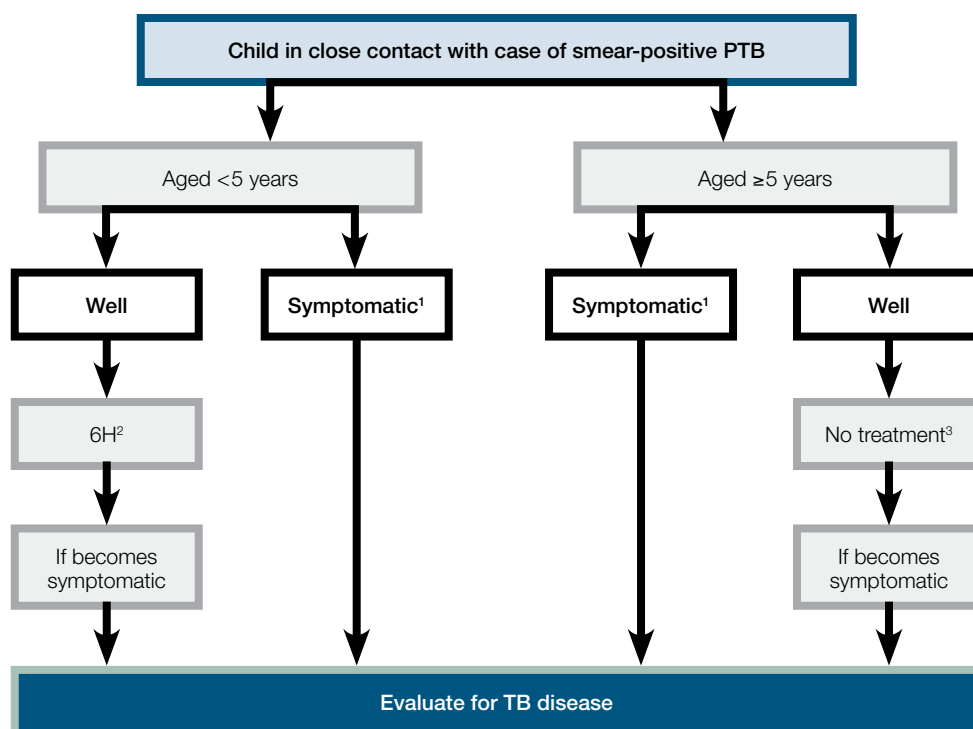
Likewise, PLHIV are highly vulnerable to developing tuberculosis if infected and, thus, should be carefully evaluated for the presence of active tuberculosis. Persons with HIV infection should be evaluated and treated as described in Standard 16.<sup>241</sup> Monitoring and

evaluation of IPT as a programmatic intervention should be undertaken as described in *Recommendations for Investigating Contacts of Persons with Infectious Tuberculosis in Low- and Middle-income Countries*.<sup>8</sup>

In persons other than children <5 years of age and PLHIV, the tuberculin skin test and interferon-gamma release assays may be used to identify those at increased risk for developing active tuberculosis and who are therefore candidates for treatment of latent infection once active tuberculosis is excluded.<sup>9</sup> Because the public health benefit of treatment for latent tuberculosis infection, other than for children and PLHIV, in low- and middle-income countries is not proven, it is not recommended as a programmatic approach. However, as a part of care for individuals with risk factors for tuberculosis who are exposed to a person with infectious tuberculosis, clinicians may choose to test for latent infection with a tuberculin skin test or interferon-gamma release assay and, if the test is positive and active tuberculosis is excluded, give treatment for latent tuberculosis infection as a preventive intervention.<sup>8</sup>

FIGURE 1.

**Approach to evaluation and management of children in contact with an infectious case of tuberculosis when a tuberculin skin test and chest radiograph are not available**



1. If tuberculosis is suspected evaluate as described in Standard 6

2. Treat with isoniazid 10 mg/kg/day for six months

3. No treatment should be given unless the child is HIV-infected in which case give isoniazid 10 mg/kg/day



**STANDARD 20.** Each health care facility caring for patients who have, or are suspected of having, infectious tuberculosis should develop and implement an appropriate tuberculosis infection control plan to minimize possible transmission of *M. tuberculosis* to patients and health care workers.

### Rationale and Evidence Summary

*M. tuberculosis* is spread nearly exclusively via the air, thus, the simple act of sharing air with a person who has infectious tuberculosis may result in transmission of the infection. There have been a number of well-documented outbreaks of tuberculosis including MDR and XDR tuberculosis that have occurred in health care facilities. Because of the concern with transmission of both drug-resistant and drug susceptible *M. tuberculosis* to patients and health care workers in facilities providing care for patients with tuberculosis, infection control is now recognized to be of considerable importance.<sup>17-19,272-274</sup>



Infection control for tuberculosis consists of managerial activities at the facility level and a hierarchy of three categories of control measures including administrative controls (most important), environmental controls, and the use of respirators (special masks designed to protect the wearer).

**Managerial Controls:** Facility-level managerial activities constitute the framework for setting up and implementing the other two categories of controls and should include the following: identification and strengthening of local coordinating bodies; development of a facility plan (including human resources) for implementation of infection control measures; and policies and procedures to ensure proper implementation of the control measures. In addition, policies that minimize the use of health care facilities, both for inpatients and outpatients, should be developed and implemented. Community approaches to providing care for persons with, or suspected of having, tuberculosis should be emphasized as a means of reducing visits to health care facilities.

Implementation of the control measures as a group reduces transmission of *M. tuberculosis* in health care facilities.<sup>275</sup> However, in health care facilities, administrative controls should be implemented as the first priority because they have been shown to be the most important measures in reducing transmission of tuberculosis. Consequently, all facilities, public and private, caring for patients with, or suspected of having, infectious tuberculosis should implement the set of measures in a manner that is best suited to the conditions that prevail in the facility, particularly local programmatic, climatic, and socioeconomic conditions. For example, infection control requirements will be less in programs that manage most patients with tuberculosis in the community compared with programs that routinely utilize hospitalization. The interventions should be consistent with and complement overall general infection control efforts and, particularly, those efforts targeting other airborne infections.

**Administrative Controls:** There are several administrative controls that are feasible in all settings that, taken together, could be predicted to minimize the likelihood of transmission occurring in the facility.<sup>275-278</sup> Administrative measures include careful screening and early

identification of patients with, or suspected of having, tuberculosis and separating them from other patients, especially from patients who are highly susceptible to tuberculosis. Organizing patient flow through sections of facilities, for example, rapid identification of coughing patients, systematic use of surgical masks for coughing patients, and directing these patients away from crowded waiting areas (fast-tracking) can minimize the potential for exposure and transmission. Separation of patients who are suspected of having tuberculosis will decrease risks to other patients and will enable health workers to take appropriate precautions. Patients with HIV infection and other forms of immunosuppression, in particular, should be physically separated from patients with suspected or confirmed infectious tuberculosis. Patients who have or are at risk of having MDR tuberculosis should be separated from other patients, including other patients with tuberculosis. Having a universally applied program in which patients taught proper cough etiquette will serve to reduce dissemination of infectious aerosols.

Prompt collection of sputum specimens for microscopy or other microbiological evaluations is an important step in infection control. Early identification of tuberculosis leads to early initiation of treatment and a consequent prompt major reduction in infectiousness, if the organisms causing the disease are not resistant to the drugs being used. In areas in which there is a high prevalence of drug resistance, rapid drug susceptibility/resistance testing would enable identification and appropriate treatment.<sup>276</sup> Diagnostic delays can be further minimized by using rapid molecular tests (including rapid drug susceptibility tests), by reducing the laboratory turnaround time for sputum examination, and by carrying out diagnostic investigations in parallel rather than in sequence.

All health workers should be given appropriate information and encouraged to undergo regular screening for tuberculosis and HIV testing and counseling. Those who are HIV-infected should be offered appropriate prevention and care services. Health workers with HIV infection should not work in areas where exposure to untreated tuberculosis is likely and especially should not be caring for patients with known MDR and XDR tuberculosis, or in settings where drug resistance is likely. Such workers should be provided with jobs in a lower risk area.

**Environmental Controls:** The choice of environmental controls is largely determined by building design and intended use, construction details, local climatic and socioeconomic conditions, and available resources. Effective ventilation should be given a high priority. Ventilation effectively reduces the number of infectious particles in the air and may be achieved by natural ventilation in some settings, by mixed natural and mechanical ventilation, and by mechanical ventilation systems. The obvious benefit of natural ventilation as an approach to infection control is that can be applied to all areas that have windows and doors that open to the outside.<sup>277</sup> However, around the clock natural ventilation cannot be applied other than in tropical climates, and even in these areas, windows may be closed during the night for security or comfort negating the effect of natural ventilation, thus, it is of limited utility. In settings where optimal natural ventilation cannot be achieved, properly placed and shielded upper room ultraviolet germicidal irradiation fixtures should be considered as a complementary control. This may be especially useful in cold climates where outdoor ventilation is limited.

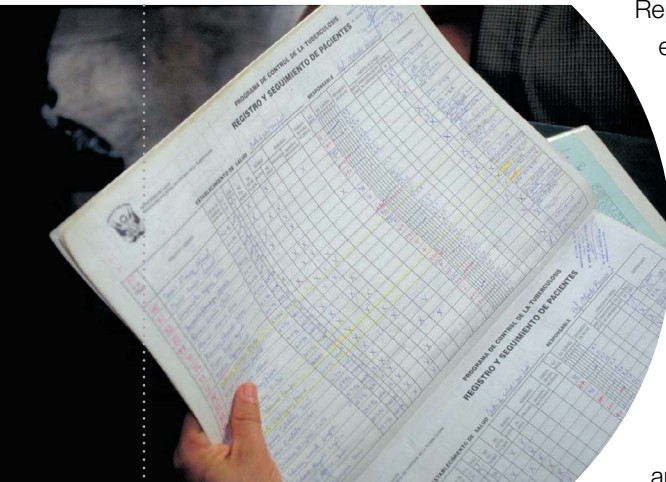
**Disposable Particulate Respirators (masks):** Particulate respirators protect the person wearing the device by filtering particles out of the inspired air.<sup>278</sup> Respirators that meet or exceed Centers for Disease Control and Prevention/National Institute for Occupational Services and Health (CDC/NIOSH)-certified N95 or CE-certified FFP2 standards (filter at least 95% of airborne particles  $\geq 0.3 \mu\text{m}$  in diameter) should be worn by health care providers in areas where the risk of transmission is high after appropriate training.<sup>17,19</sup>

Indications for using a respirator should be defined by the facility, but commonly include procedures in which aerosols are generated, such as bronchoscopy, or exposure to persons with untreated or ineffectively treated tuberculosis. In areas where drug resistance is common, however, every patient with tuberculosis should be considered potentially to have drug-resistant disease for purposes of infection control.

---

**STANDARD 21. All providers must report both new and re-treatment tuberculosis cases and their treatment outcomes to local public health authorities, in conformance with applicable legal requirements, regulations, and policies.**

#### Rationale and Evidence Summary



Reporting tuberculosis cases to the local tuberculosis control program is an essential public health function and in many countries is legally mandated. Ideally, the reporting system design, supported by a legal framework, should be capable of receiving and integrating data from several sources including laboratories and health care institutions, as well as from individual practitioners.

An effective reporting system that includes all providers enables a determination of the overall effectiveness of tuberculosis control programs, of resource needs, and of the true distribution and dynamics of the disease within the population as a whole, not just the population served by the government tuberculosis control program. In most countries tuberculosis is a notifiable disease. Such a system is useful not only to monitor progress and treatment outcomes of individual patients, but also to evaluate the overall performance of the tuberculosis control programs at the local, national, and global levels, and to indicate programmatic weaknesses.

A regularly updated recording and reporting system allows for targeted, individualized follow-up to help patients who are not making adequate progress (i.e., failing therapy).<sup>279</sup> The system also allows for evaluation of the performance of the practitioner, the hospital or institution, local health system, and the country as a whole. Finally, a system of recording and reporting ensures accountability.

An additional important function of a recording and reporting system is to identify serious adverse events resulting from antituberculosis drugs.<sup>280</sup> This surveillance is especially important as new drugs and regimens are introduced. In both the WHO and CDC recommendations regarding the use of bedaquiline, it is strongly recommended that there be ongoing surveillance and reporting of adverse events.<sup>200,281</sup> Clinical experience with the drug is limited, but because of the pressing need for new drugs to treat MDR TB,

*An effective reporting system that includes all providers enables a determination of the overall effectiveness of tuberculosis control programs, of resource needs, and of the true distribution and dynamics of the disease.*

bedaquiline was released for use under specific conditions. There are many instances of serious adverse effects of drugs being identified by post-marketing surveillance (phase IV studies). Similarly there is little systematic information on the adverse effects of many of the drugs and regimens used in treating MDR TB, thus pharmacovigilance is important in this group as well.

Although, on the one hand reporting to public health authorities is essential, on the other hand it is also essential that patient confidentiality be maintained. Thus, reporting must follow predefined channels using standard procedures that guarantee that only authorized persons see the information. Such safeguards must be developed by local and national tuberculosis control programs to ensure the confidentiality of patient information.

# References

1. World Health Organization. Systematic screening for active tuberculosis: Principles and recommendations. Geneva: World Health Organization, 2013. WHO/HTM/TB/2013.04.
2. World Health Organization. Global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva: World Health Organization 2014.
3. Hopewell PC, Pai M. Tuberculosis, vulnerability, and access to quality care. *JAMA*. 2005; **293**(22): 2790-3.
4. Hopewell PC, Pai M, Maher D, et al. International standards for tuberculosis care. *Lancet Infect Dis*. 2006; **6**(11): 710-25.
5. World Health Organization. Handbook for guideline development. Geneva: World Health Organization, 2012.
6. World Health Organization. Public-private mix for TB care and control: A toolkit. Geneva: World Health Organization, 2010. WHO/HTM/TB/2010.12.
7. Chakaya J, Uplekar M, Mansoor J, et al. Public-private mix for control of tuberculosis and TB-HIV in Nairobi, Kenya: outcomes, opportunities and obstacles. *Int J Tuberc Lung Dis*. 2008; **12**(11): 1274-8.
8. World Health Organization. Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. Geneva: World Health Organization, 2012. WHO/HTM/TB/2012.9.
9. World Health Organization. Integrating community-based tuberculosis activities into the work of nongovernmental and other civil society organizations. Geneva: World Health Organization, 2012. WHO/HTM/TB/2012/8.
10. World Health Organization. Definitions and reporting framework for tuberculosis. Geneva: World Health Organization, 2013. WHO/HTM/TB/2013.2.
11. Migliori GB, Zellweger JP, Abubakar I, et al. European Union standards for tuberculosis care. *Eur Resp J*. 2012; **39**(4): 807-19.
12. Pai M, Das J. Management of Tuberculosis in India: Time for a deeper dive into quality. *Nat Med J India*. 2013; **26**(2): 65-8.
13. World Health Organization. Adherence to long-term therapies: Evidence for action. Geneva: World Health Organization, 2003. WHO/MNC/03.01.
14. World Health Organization. Treatment of tuberculosis guidelines (Fourth edition). Geneva: World Health Organization, 2009. WHO/HTM/TB/2009.420.
15. American Thoracic Society, Centers for Disease Control and Prevention, Infectious Diseases Society of America. Controlling Tuberculosis in the United States. *MMWR* 2005; **54**(RR12): 1-81.
16. Ait-Khaled N, Alarcon E, Armengol R, et al. Management of tuberculosis: A guide to the essentials of good practice. Paris: International Union Against Tuberculosis and Lung Disease; 2010.
17. Centers for Disease Control and Prevention. Guidelines for preventing the transmission of Mycobacterium tuberculosis in health care settings, 2005. *MMWR* 2005; **54**(RR17):1-141.
18. World Health Organization. WHO policy on TB infection control in health-care facilities, congregate settings and households. Geneva: World Health Organization, 2009. WHO/HTM/TB/2009.419.
19. Sotgiu G, D'Ambrosio L, Centis R, et al. TB and M/XDR TB infection control in European TB reference centres: the Achilles' heel? *Eur Respir J*. 2011; **38**(5): 1221-3.
20. Lönnroth K, Raviglione M. Global epidemiology of tuberculosis: prospects for control. *Semin Respir Crit Care Med*. 2008; **29**(5): 481-91.
21. World Health Organization. Global Tuberculosis Report, 2013. Geneva: World Health Organization; 2013.
22. World Health Organization. Multidrug and extensively drug-resistant TB (M/XDR TB): 2010 global report on surveillance and response. Geneva: World Health Organization, 2010. WHO/HTM/TB/2010.3.
23. Malmborg R, Mann G, Squire SB. A systematic assessment of the concept and practice of public-private mix for tuberculosis care and control. *Int J Equity Health*. 2011; **10**(1): 49.
24. Dewan PK, Lal SS, Lönnroth K, et al. Improving tuberculosis control through public-private collaboration in India: literature review. *BMJ*. 2006; **332**(7541): 574-8.



25. van der Werf MJ, Langendam MW, Huitric E, Manisero D. Multidrug resistance after inappropriate tuberculosis treatment: a meta-analysis. *Eur Respir J*. 2012; **39**(6): 1511-9.
26. World Health Organization. Involving private practitioners in tuberculosis control: issues, interventions, and emerging policy framework. Geneva: World Health Organization, 2001. WHO/CDS/TB/2001.285.
27. Storla DG, Yimer S, Bjune GA. A systematic review of delay in the diagnosis and treatment of tuberculosis. *BMC Public Health*. 2008; **8**: 15.
28. Sreeramareddy CT, Panduru KV, Menten J, Van den Ende J. Time delays in diagnosis of pulmonary tuberculosis: a systematic review of literature. *BMC Infect Dis*. 2009; **9**: 91.
29. Davis J, Katamba A, Vasquez J, et al. Evaluating tuberculosis case detection via real-time monitoring of tuberculosis diagnostic services. *Am J Respir Crit Care Med*. 2011; **184**(3): 362-7.
30. Uplekar M, Pathania V, Raviglione M. Private practitioners and public health: weak links in tuberculosis control. *Lancet*. 2001; **358**(9285): 912-6.
31. Olle-Goig JE, Cullity JE, Vargas R. A survey of prescribing patterns for tuberculosis treatment amongst doctors in a Bolivian city. *Int J Tuberc Lung Dis*. 1999; **3**(1): 74-8.
32. Shah SK, Sadiq H, Khalil M, et al. Do private doctors follow national guidelines for managing pulmonary tuberculosis in Pakistan? *East Mediterr Health J*. 2003; **9**(4): 776-88.
33. Prasad R, Nautiyal RG, Mukherji PK, et al. Diagnostic evaluation of pulmonary tuberculosis: what do doctors of modern medicine do in India? *Int J Tuberc Lung Dis*. 2003; **7**(1): 52-7.
34. Lönnroth K, Thuong LM, Linh PD, Diwan VK. Delay and discontinuity--a survey of TB patients' search of a diagnosis in a diversified health care system. *Int J Tuberc Lung Dis*. 1999; **3**(11): 992-1000.
35. Cheng G, Tolhurst R, Li RZ, Meng QY, Tang S. Factors affecting delays in tuberculosis diagnosis in rural China: a case study in four counties in Shandong Province. *Trans R Soc Trop Med Hyg*. 2005; **99**(5): 355-62.
36. Uplekar M. Involving private health care providers in delivery of TB care: global strategy. *Tuberculosis*. 2003; **83**(1): 156-64.
37. Grenier J, Pinto L, Nair D, et al. Widespread use of serological tests for tuberculosis: data from 22 high-burden countries. *Eur Respir J*. 2012; **39**(2): 502-5.
38. World Health Organization. Commercial serodiagnostic tests for diagnosis of tuberculosis: Policy statement. Geneva, World Health Organization, 2011. WHO/HTM/TB/2011.5.
39. World Health Organization. Guidance on ethics of tuberculosis prevention, care, and control. Geneva: World Health Organization, 2010. WHO/HTM/TB/2010.16.
40. Ukwaja KN, Alobu I, Abimbola S, Hopewell PC. Household catastrophic payments for tuberculosis care in Nigeria: incidence, determinants, and policy implications for universal health coverage. *Infect Dis Poverty*. 2013; **2**: 21.
41. Ukwaja KN, Alobu I, Lgwenyi C, Hopewell PC. The high cost of free tuberculosis services: patient and household costs associated with tuberculosis care in ebonyi state, Nigeria. *PLoS One*. 2013; **8**: e73134.
42. World Health Organization. Early detection of tuberculosis: An overview of approaches, guidelines, and tools. Geneva, World health Organization, 2011. WHO/HTM/STB/PSI/2011.21.
43. Miller CR, Davis JL, Katamba A, et al. Sex disparities in tuberculosis suspect evaluation: a cross-sectional analysis in rural Uganda. *Int J Tuberc Lung Dis*. 2013; **17**(4): 480-5.
44. Ministry of Health, Cambodia. National tuberculosis prevalence survey, 2002. Phnom Penh: Royal Government of Cambodia, 2005.
45. Hoa NB, Sy DN, Nhung NV, Tiemersma EW, Borgdorff MW, Cobelens FG. National survey of tuberculosis prevalence in Viet Nam. *Bull World Health Organ*. 2010; **88**(4): 273-80.
46. Ayles H, Schaap A, Nota A, et al. Prevalence of tuberculosis, HIV and respiratory symptoms in two Zambian communities: implications for tuberculosis control in the era of HIV. *PLoS One*. 2009; **4**(5): e5602.
47. Getahun H, Kittikraisak W, Heilig CM, et al. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. *PLoS Med*. 2011; **8**(1): e1000391.

48. World Health Organization. Practical approach to lung health: Manual on initiating PAL implementation. Geneva, World Health Organization, 2008. WHO/HTM/TB/2008.410.
49. World Health Organization. Implementing the Stop TB strategy: A handbook for national tuberculosis control programmes. Geneva: World Health Organization, 2008. WHO/HTM/TB/2008.401.
50. World Health Organization. Toman's tuberculosis: Case detection, treatment, and monitoring. Geneva: World Health Organization, 2004. WHO/HTM/TB/2004.334.
51. World Health Organization. Respiratory care in primary care services: A survey in 9 countries. Geneva, World health Organization, 2004. WHO/HTM/TB/2004.333.
52. Santha T, Garg R, Subramani R, et al. Comparison of cough of 2 and 3 weeks to improve detection of smear-positive tuberculosis cases among out-patients in India. *Int J Tuberc Lung Dis.* 2005; **9**(1): 61-8.
53. Nyamande K, Laloo UG, John M. TB presenting as community-acquired pneumonia in a setting of high TB incidence and high HIV prevalence. *Int J Tuberc Lung Dis.* 2007; **11**(12): 308-13.
54. Cavallazzi R, Wiemken T, Christensen D, et al. Predicting Mycobacterium tuberculosis in patients with community-acquired pneumonia. *Eur Respir J.* 2014; **43**(1):178-84.
55. Lienhardt C, Rowley J, Manneh K, et al. Factors affecting time delay to treatment in a tuberculosis control programme in a sub-Saharan African country: the experience of The Gambia. *Int J Tuberc Lung Dis.* 2001, **5**(3):233-239.
56. Khan J, Malik A, Hussain H, et al. Tuberculosis diagnosis and treatment practices of private physicians in Karachi, Pakistan. *East Mediterr Health J.* 2003; **9**(4): 769-75.
57. Singla N, Sharma PP, Singla R, Jain RC. Survey of knowledge, attitudes and practices for tuberculosis among general practitioners in Delhi, India. *Int J Tuberc Lung Dis.* 1998; **2**(5): 384-9.
58. Suleiman BA, Houssein AI, Mehta F, Hinderaker SG. Do doctors in north-western Somalia follow the national guidelines for tuberculosis management? *East Mediterr Health J.* 2003; **9**(4): 789-95.
59. World Health Organization. Policy statement: Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system. Geneva: World Health Organization, 2011. WHO/HTM/TB/2011.4.
60. Centers for Disease Control and Prevention. Updated Guidelines for the Use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis. *MMWR.* 2009; **58**: 7-10.
61. Pinto L, Pai M, Dheda K, et al. Scoring systems using chest radiographic features for the diagnosis of pulmonary tuberculosis in adults: A systematic review *Eur Respir J.* 2013; **42**(2):480-94.
62. Steingart KR, Henry M, Ng V, et al. Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. *Lancet Infect Dis.* 2006; **6**(9): 570-81.
63. Steingart KR, Ng V, Henry M, et al. Sputum processing methods to improve the sensitivity of smear microscopy for tuberculosis: a systematic review. *Lancet Infect Dis.* 2006; **6**(10): 664-74.
64. Mase SR, Ramsay A, Ng V, et al. Yield of serial sputum specimen examinations in the diagnosis of pulmonary tuberculosis: a systematic review. *Int J Tuberc Lung Dis.* 2007; **11**(5): 485-95.
65. Davis JL, Cattamanchi A, Cuevas LE, et al. Diagnostic accuracy of same-day microscopy versus standard microscopy for pulmonary tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis.* 2013; **13**(2): 147-54.
66. Ling DI, Flores LL, Riley LW, Pai M. Commercial nucleic-acid amplification tests for diagnosis of pulmonary tuberculosis in respiratory specimens: Meta-analysis and meta-regression. *PLoS One.* 2008; **3**(2): e1536.
67. Greco S, Girardi E, Navarra S, Saltini C. The current evidence on diagnostic accuracy of commercial based nucleic acid amplification tests for the diagnosis of pulmonary tuberculosis. *Thorax.* 2006; **61**(9): 783-90.
68. Pai M, Flores LL, Hubbard A, et al. Nucleic acid amplification tests in the diagnosis of tuberculous pleuritis: a systematic review and meta-analysis. *BMC Infect Dis.* 2004; **4**(1): 6.
69. Pai M, Flores LL, Pai N, et al. Diagnostic accuracy of nucleic acid amplification tests for tuberculous meningitis: a systematic review and meta-analysis. *Lancet Infect Dis.* 2003; **3**(10): 633-43.
70. Daley P, Thomas S, Pai M. Nucleic acid amplification tests for the diagnosis of tuberculous lymphadenitis: a systematic review. *Int J Tuberc Lung Dis.* 2007; **11**(11): 1166-76.
71. Sarmiento OL, Weigle KA, Alexander J, et al. Assessment by meta-analysis of PCR for diagnosis of smear-negative pulmonary tuberculosis. *J Clin Microbiol.* 2003; **41**(7): 3233-40.

72. Dinnes J, Deeks J, Kunst H, et al. A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. *Health technology assessment (Winchester, England)* 2007; **11**(3): 1-196.
73. Steingart KR, Schiller I, Horne DJ, et al. Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults (Review). *Cochrane Database Syst Rev*. 2014; Issue 1. Art. No.: CD009593.
74. Cruciani M, Scarpato C, Malena M, et al. Meta-analysis of BACTEC MGIT 960 and BACTEC 460 TB, with or without solid media, for detection of mycobacteria. *J Clin Microbiol*. 2004; **42**(5): 2321-5.
75. Brent AJ, Mugo D, Musyimi R, et al. Performance of the MGIT TBc identification test and meta-analysis of MPT64 assays for identification of the Mycobacterium tuberculosis complex in liquid culture. *J Clin Microbiol*. 2011; **49**(12): 4343-6.
76. Parsons LM, Somoskövi A, Gutierrez C, et al. Laboratory diagnosis of tuberculosis in resource-poor countries: challenges and opportunities. *Clin. Microbiol. Rev*. 2011; **24**(2): 314-50.
77. World Health Organization. The use of the Xpert MTB/RIF® assay for the detection of pulmonary, extrapulmonary tuberculosis and rifampicin resistance in adults and children. Geneva; World health Organization, 2013, WHO/HTM/TB/2013.14.
78. Harries AD, Hargreaves NJ, Kemp J, et al. Deaths from tuberculosis in sub-Saharan African countries with a high prevalence of HIV-1. *Lancet*. 2001; **357**(9267): 519-23.
79. Maher D, Harries A, Getahun H. Tuberculosis and HIV interaction in sub-Saharan Africa: impact on patients and programmes; implications for policies. *Trop Med Int Health*. 2005; **10**(8): 734-42.
80. Rieder HL, Chiang CY, Rusen ID. A method to determine the utility of the third diagnostic and the second follow-up sputum smear examinations to diagnose tuberculosis cases and failures. *Int J Tuberc Lung Dis*. 2005; **9**(4): 384-91.
81. Steingart KR, Ramsay A, Pai M. Optimizing sputum smear microscopy for the diagnosis of pulmonary tuberculosis. *Expert Rev Anti Infect Ther*. 2007; **5**(3): 327-31.
82. World Health Organization. Fluorescent light-emitting diode (LED) microscopy for diagnosis of tuberculosis: Policy statement. Geneva, World health Organization, 2011. WHO/HTM/TB/2011.8.
83. World Health Organization. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system: Policy statement. Geneva: World Health Organization, 2011. WHO/HTM/TB/2011.4.
84. Weyer K, Mirzayev F, Migliori G, et al. Rapid molecular TB diagnosis: evidence, policy-making and global implementation of Xpert(R)MTB/RIF. *Eur Respir J*. 2012; **42**(1): 252-71.
85. World Health Organization. Rapid implementation of the Xpert MTB/RIF diagnostic test: Technical and operational 'how-to' practical considerations. Geneva: World Health Organization, 2011. WHO/HTM/TB/2011.2.
86. World Health Organization. Molecular line probe assays for rapid screening of patients at risk of multidrug-resistant tuberculosis (MDR TB): Policy statement. Geneva: World Health Organization, 2008.
87. Metcalfe JZ, Everett CK, Steingart KR, et al. Interferon-gamma release assays for active pulmonary tuberculosis diagnosis in adults in low- and middle-income countries: systematic review and meta-analysis. *J Infect Dis*. 2011; **204** Suppl 4: S1120-9.
88. Steingart KR, Flores LL, Dendukuri N, et al. Commercial serological tests for the diagnosis of active pulmonary and extrapulmonary tuberculosis: an updated systematic review and meta-analysis. *PLoS Med*. 2011; **8**(8): e1001062.
89. Sandgren A, Hollo V, van der Werf MJ. Extrapulmonary tuberculosis in the European Union and European Economic Area, 2002 to 2011. *Euro Surveill*. 2013 Mar 21; **18**(12). pii: 20431.
90. Udawadia ZF, Sen T. Pleural tuberculosis: an update. *Curr Opin Pulm Med*. 2010; **16**(4): 399-406.
91. Thwaites GE, Caws M, Chau TT, et al. Comparison of conventional bacteriology with nucleic acid amplification (amplified mycobacterium direct test) for diagnosis of tuberculous meningitis before and after inception of antituberculosis chemotherapy. *J Clin Microbiol*. 2004; **42**(3): 996-1002.
92. Mtei L, Matee M, Herfort O, et al. High rates of clinical and subclinical tuberculosis among HIV-infected ambulatory subjects in Tanzania. *Clin Infect Dis*. 2005; **40**(10): 1500-7.
93. Corbett EL, Bandason T, Duong T, et al. Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): a cluster-randomised trial. *Lancet*. 2010; **376**(9748): 1244-52.

94. World Health Organization. Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents: Recommendations for HIV-prevalent and resource-constrained settings. Geneva, World Health Organization, 2007. WHO/HTM/TB/2007.379 & WHO/HIV/2007.1.
95. Wilson D, Mbhele L, Badri M, et al. Evaluation of the World Health Organization algorithm for the diagnosis of HIV-associated sputum smear-negative tuberculosis. *Int J Tuberc Lung Dis.* 2011; **15**(7): 819-24.
96. Alamo ST, Kunutsor S, Walley J et al. Performance of the new WHO diagnostic algorithm for smear-negative pulmonary tuberculosis in HIV prevalent settings: a multisite study in Uganda. *Trop Med Int Health.* 2012; **17**: 884-95.
97. Hueriga H, Varaine F, Okwaro E. Performance of the 2007 WHO algorithm to diagnose smear-negative pulmonary tuberculosis in a HIV prevalent setting. *PLoS One.* 2012; **7**: e51336.
98. Bah B, Massari V, Sow O, et al. Useful clues to the presence of smear-negative pulmonary tuberculosis in a West African city. *Int J Tuberc Lung Dis.* 2002; **6**(7): 592-8.
99. Wilkinson D, De Cock KM, Sturm AW. Diagnosing tuberculosis in a resource-poor setting: the value of a trial of antibiotics. *Trans R Soc Trop Med Hyg.* 1997; **91**(4): 422-4.
100. Sterling TR. The WHO/IUATLD diagnostic algorithm for tuberculosis and empiric fluoroquinolone use: potential pitfalls. *Int J Tuberc Lung Dis.* 2004; **8**(12): 1396-400.
101. Migliori GB, Langendam MW, D'Ambrosio L, et al. Protecting the tuberculosis drug pipeline: stating the case for the rational use of fluoroquinolones. *Eur Resp J.* 2012; **40**(4): 814-22.
102. Chen TC, Lu PL, Lin CY, et al. Fluoroquinolones are associated with delayed treatment and resistance in tuberculosis: a systematic review and meta-analysis. *Int J Infect Dis.* 2011; **15**(3): 211-16.
103. Dowdy DW, Chaisson RE, Maartens G, et al. Impact of enhanced tuberculosis diagnosis in South Africa: a mathematical model of expanded culture and drug susceptibility testing. *Proc Natl Acad Sci U S A.* 2008; **105**(32):11293-8.
104. van Deun A. What is the role of mycobacterial culture in diagnosis and case finding? In: Frieden TR, ed. Toman's tuberculosis: Case detection, treatment and monitoring, 2nd Edition. Geneva: World Health Organization; 2004: 35-43.
105. Toman K. How many bacilli are present in a sputum specimen found positive by smear microscopy? In: Frieden TR, ed. Toman's tuberculosis: Case detection, treatment and monitoring, 2nd Edition. Geneva: World Health Organization; 2004: 11-3.
106. Toman K. How reliable is smear microscopy? In: Frieden TR, ed. Toman's tuberculosis: Case detection, treatment and monitoring, 2nd Edition. Geneva: World Health Organization; 2004: 14-22.
107. Pai M, Ramsay A, O'Brien R. Evidence-based tuberculosis diagnosis. *PLoS Med.* 2008; **5**(7): e156.
108. World Health Organization. Use of liquid TB culture and drug susceptibility testing (DST) in low and medium income settings. Geneva: World Health Organization, 2007.
109. Daley CL, Gotway MB, Jasmer RM. Radiographic Manifestations of Tuberculosis: A Primer for Clinicians. Second Edition. San Francisco: Curry International Tuberculosis Center, 2011. <http://www.currytbcenter.ucsf.edu/radiographic/>.
110. Ellis S M, Flower C, Ostensen H, Pettersson H. The WHO manual of diagnostic imaging: Radiographic anatomy and interpretation of the chest and the pulmonary system. Geneva: World health Organization, 2006. <http://www.who.int/iris/handle/10665/43293>.
111. Tuberculosis Coalition for Technical Assistance/Japan Antituberculosis Association. Handbook for District Hospitals in Resource Constrained Settings on Quality Assurance of Chest Radiography. [http://pdf.usaid.gov/pdf\\_docs/Pnadv465.pdf](http://pdf.usaid.gov/pdf_docs/Pnadv465.pdf).
112. Hesseling AC, Schaaf HS, Gie RP, et al. A critical review of diagnostic approaches used in the diagnosis of childhood tuberculosis. *Int J Tuberc Lung Dis.* 2002; **6**(12): 1038-45.
113. Gie RP, Beyers N, Schaaf HS, Goussard P. The challenge of diagnosing tuberculosis in children: a perspective from a high incidence area. *Paediatr Respir Rev.* 2004; **5 Suppl A**: S147-9.
114. World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. Geneva: World Health Organization, 2006. WHO/HTM/TB/2006.371.
115. Shingadia D, Novelli V. Diagnosis and treatment of tuberculosis in children. *Lancet Infect Dis.* 2003; **3**(10): 624-32.

116. Nicol MP Zar HJ. New specimens and laboratory diagnostics for childhood pulmonary TB: progress and prospects. *Paediatr Respir Rev*. 2011; **12**(1): 16-21.
117. Nelson LJ, Wells CD. Tuberculosis in children: considerations for children from developing countries. *Semin Pediatr Infect Dis*. 2004; **15**(3): 150-4.
118. Marais BJ, Gie RP, Hesseling AC, et al. A refined symptom-based approach to diagnose pulmonary tuberculosis in children. *Pediatrics*. 2006; **118**(5): e1350-9.
119. Graham SM. The use of diagnostic systems for tuberculosis in children. *Indian J Pediatr*. 2011; **78**(3): 334-9.
120. Pearce EC, Woodward JF, Nyandiko WM, Vreeman RC, Ayaya SO. A systematic review of clinical diagnostic systems used in the diagnosis of tuberculosis in children. *AIDS Res Treat*. 2012; **2012**: 401896.
121. World Health Organization. Management of the child with a serious infection or severe malnutrition: Guidelines for care at the first-referral level in developing countries. Geneva: World Health Organization, 2000. WHO/FCH/CAH/00.1.
122. 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**(4): 603-62.
123. Gelband H. Regimens of less than six months for treating tuberculosis. *Cochrane Database Syst Rev*. 2000; (2): CD001362.
124. Lew W, Pai M, Oxlade O, et al. Initial drug resistance and tuberculosis treatment outcomes: systematic review and meta-analysis. *Ann Intern Med*. 2008; **149**(2): 123-34.
125. Korenromp EL, Scano F, Williams BG, et al. Effects of human immunodeficiency virus infection on recurrence of tuberculosis after rifampin-based treatment: an analytical review. *Clin Infect Dis*. 2003; **37**(1): 101-12.
126. Ahmad Khan F, Minion J, Al-Motairi A, et al. An updated systematic review and meta-analysis on the treatment of active tuberculosis in patients with HIV infection. *Clin Infect Dis*. 2012; **55**(8): 1154-63.
127. Menzies D, Benedetti A, Paydar A, et al. . Effect of duration and intermittency of rifampin on tuberculosis treatment outcomes: a systematic review and meta-analysis. *PLoS Med*. 2009; **6**(9): e1000146.
128. Mitchison DA. Antimicrobial therapy for tuberculosis: justification for currently recommended treatment regimens. *Semin Respir Crit Care Med*. 2004; **25**(3): 307-15.
129. Mwandumba H, Squire S. Fully intermittent dosing with drugs for treating tuberculosis in adults. *Cochrane Database Syst Rev*. 2001; (4).
130. British Medical Research Council. Controlled trial of 4 three-times-weekly regimens and a daily regimen all given for 6 months for pulmonary tuberculosis. Second report: the results up to 24 months. Hong Kong Chest Service/British Medical Research Council. *Tubercle*. 1982; **63**(2): 89-98.
131. British Medical Research Council. Controlled trial of 2, 4, and 6 months of pyrazinamide in 6-month, three-times-weekly regimens for smear-positive pulmonary tuberculosis, including an assessment of a combined preparation of isoniazid, rifampin, and pyrazinamide. Results at 30 months. Hong Kong Chest Service/British Medical Research Council. *Am Rev Respir Dis*. 1991; **143**(4 Pt 1): 700-6.
132. Cao JP, Zhang LY, Zhu JQ, Chin DP. Two-year follow-up of directly-observed intermittent regimens for smear-positive pulmonary tuberculosis in China. *Int J Tuberc Lung Dis*. 1998; **2**(5): 360-4.
133. Caminero JA, Pavon JM, Rodriguez de Castro F, et al. Evaluation of a directly observed six months fully intermittent treatment regimen for tuberculosis in patients suspected of poor compliance. *Thorax*. 1996; **51**(11): 1130-3.
134. Bechan S, Connolly C, Short GM, et al. Directly observed therapy for tuberculosis given twice weekly in the workplace in urban South Africa. *Trans R Soc Trop Med Hyg*. 1997; **91**(6): 704-7.
135. Benator D, Bhattacharya M, Bozeman L, et al. Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial. *Lancet*. 2002; **360**(9332): 528-34.
136. Vernon A, Burman W, Benator D, et al. Acquired rifamycin mono-resistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. Tuberculosis Trials Consortium. *Lancet*. 1999; **353**(9167): 1843-7.
137. Lienhardt C, Cook SV, Burgos M, et al. Efficacy and safety of a 4-drug fixed-dose combination regimen compared with separate drugs for treatment of pulmonary tuberculosis: the Study C randomized controlled trial. *JAMA*. 2011; **305**(14): 1415-23.



138. Albanna AS, Smith BM, Cowan D, Menzies D. Fixed Dose Combination Anti-tuberculosis Therapy: A Systematic Review and Meta-Analysis. *ERJ Express*. 2013.
139. Blomberg B, Spinaci S, Fourie B, Laing R. The rationale for recommending fixed-dose combination tablets for treatment of tuberculosis. *Bull World Health Organ*. 2001; **79**(1): 61-8.
140. Panchagnula R, Agrawal S, Ashokraj Y, et al. Fixed dose combinations for tuberculosis: Lessons learned from clinical, formulation and regulatory perspective. *Methods Find Exp Clin Pharmacol*. 2004; **26**(9): 703-21.
141. Monedero I, Caminero JA. Evidence for promoting fixed-dose combination drugs in tuberculosis treatment and control: a review. *Int J Tuberc Lung Dis*. 2011; **15**(4): 433-9.
142. Munro SA, Lewin SA, Smith HJ, et al. Patient adherence to tuberculosis treatment: a systematic review of qualitative research. *PLoS Med*. 2007; **4**(7): e238.
143. Volmink J, Matchaba P, Garner P. Directly observed therapy and treatment adherence. *Lancet*. 2000; **355**(9212): 1345-50.
144. Volmink J, Garner P. Directly observed therapy for treating tuberculosis. *Cochrane Database Syst Rev*. 2003; (1): CD003343.
145. Pope DS, Chaisson RE. TB treatment: as simple as DOT? *Int J Tuberc Lung Dis*. 2003; **7**(7): 611-5.
146. Pasipanodya JG, Gumbo T. A meta-analysis of self-administered vs directly observed therapy effect on microbiologic failure, relapse, and acquired drug resistance in tuberculosis patients. *Clin Infect Dis*. 2013; **57**(1): 21-31.
147. Chaulk CP, Kazandjian VA. Directly observed therapy for treatment completion of pulmonary tuberculosis: Consensus Statement of the Public Health Tuberculosis Guidelines Panel. *JAMA*. 1998; **279**(12): 943-8.
148. Frieden TR. Can tuberculosis be controlled? *Int J Epidemiol*. 2002; **31**(5): 894-9.
149. Suarez PG, Watt CJ, Alarcon E, et al. The dynamics of tuberculosis in response to 10 years of intensive control effort in Peru. *J Infect Dis*. 2001; **184**(4): 473-8.
150. Tang S, Squire SB. What lessons can be drawn from tuberculosis (TB) control in China in the 1990s? An analysis from a health system perspective. *Health Policy*. 2005; **72**(1): 93-104.
151. World Health Organization. Integrated Management of Adolescent and Adult Illness (IMAI): General principles of good chronic care. Geneva: World Health Organization, 2004. WHO/CDS/IMAI/2004.3.
152. World Health Organization. Integrated Management of Adolescent and Adult Illness (IMAI): Chronic HIV care with ARV therapy and prevention. Geneva: World Health Organization, 2007. WHO/HTM/2007.02.
153. Hadley M, Maher D. Community involvement in tuberculosis control: lessons from other health care programmes. *Int J Tuberc Lung Dis*. 2000; **4**(5): 401-8.
154. Friedrich SO, Rachow A, Saathoff E. Evaluation of the Xpert® MTB/RIF assay as a rapid sputum biomarker of response to tuberculosis treatment: a prospective cohort study. *Lancet Respir Med*. 2013; **1**(6): 462-70.
155. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization, 2008. WHO/HTM/TB/2008.402.
156. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis: A 2011 update. Geneva: World Health Organization, 2011. WHO/HTM/TB/2011.6.
157. Hirpa S, Medhin G, Girma B, et al. Determinants of multidrug-resistant tuberculosis in patients who underwent first-line treatment in Addis Ababa: a case control study. *BMC Public Health*. 2013; **13**: 782.
158. Coninx R, Mathieu C, Debacker M, et al. First-line tuberculosis therapy and drug-resistant Mycobacterium tuberculosis in prisons. *Lancet*. 1999; **353**(9157): 969-73.
159. Edlin BR, Tokars JL, Grieco MH, et al. An outbreak of multidrug-resistant tuberculosis among hospitalized patients with the acquired immunodeficiency syndrome. *N Engl J Med*. 1992; **326**(23): 1514-21.
160. Fischl MA, Uttamchandani RB, Daikos GL, et al. An outbreak of tuberculosis caused by multiple-drug-resistant tubercle bacilli among patients with HIV infection. *Ann Intern Med*. 1992; **117**(3): 177-83.
161. Schaaf HS, Van Rie A, Gie RP, et al. Transmission of multidrug-resistant tuberculosis. *Pediatr Infect Dis J*. 2000; **19**(8): 695-9.

162. Small PM, Shafer RW, Hopewell PC, et al. Exogenous reinfection with multidrug-resistant *Mycobacterium tuberculosis* in patients with advanced HIV infection. *N Engl J Med*. 1993; **328**(16): 1137-44.
163. Zhao Y, Xu S, Wang L, et al. National survey of drug-resistant tuberculosis in China. *N Engl J Med*. 2012; **366**(23): 2161-70.
164. Royce S, Falzon D, van Weezenbeek C, et al. Multidrug resistance in new tuberculosis patients: burden and implications. *Int J Tuberc Lung Dis*. 2013; **17**(4): 511-3.
165. Skrahina A HH, Zalutskaya A, et al. Alarming levels of drug-resistant tuberculosis in Belarus: results of a survey in Minsk. *Eur Respir J*. 2012; **39**(6): 1425-35.
166. World Health Organization. Anti-tuberculosis drug resistance in the world. Fourth global report. Geneva: World Health Organization, 2008. WHO/HTM/TB/2008.394.
167. Caminero JA. Likelihood of generating MDR TB and XDR TB under adequate National Tuberculosis Control Programme implementation. *Int J Tuberc Lung Dis*. 2008; **12**(8): 869-77.
168. Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet*. 2006; **368**(9547): 1575-80.
169. Kim HR, Hwang SS, Kim HJ, et al. Impact of extensive drug resistance on treatment outcomes in non-HIV-infected patients with multidrug-resistant tuberculosis. *Clin Infect Dis*. 2007; **45**(10): 1290-5.
170. Migliori GB, Ortmann J, Girardi E, et al. Extensively drug-resistant tuberculosis, Italy and Germany. *Emerg Infect Dis*. 2007; **13**(5): 780-2.
171. Shah NS, Wright A, Bai GH, et al. Worldwide emergence of extensively drug-resistant tuberculosis. *Emerg Infect Dis*. 2007; **13**(3): 380-7.
172. Migliori GB, Sotgiu G, Gandhi NR, et al. Drug resistance beyond extensively drug-resistant tuberculosis: individual patient data meta-analysis. *Eur Respir J*. 2013; **42**(1): 169-79.
173. World Health Organization. "Totally drug-resistant" tuberculosis: A WHO consultation on the diagnostic definition and treatment options (21-22 March 2012). Geneva, 2012. <http://www.who.int/tb/challenges/xdr/xdrconsultation/en/>.
174. Falzon D, Gandhi N, Migliori GB, et al. Resistance to fluoroquinolones and second-line injectable drugs: impact on multidrug-resistant TB outcomes. *Eur Respir J*. 2013; **42**(1): 156-68.
175. Williamson DA, Basu I, Bower J.,. An evaluation of the Xpert MTB/RIF assay and detection of false-positive rifampicin resistance in *Mycobacterium tuberculosis*. *Diagn Microbiol Infect Dis*. 2012; **74**: 207-09.
176. van Deun A, Barrera L, Bastian I, et al. *Mycobacterium tuberculosis* strains with highly discordant rifampin susceptibility test results. *J Clin Microbiol*. 2009; **47**: 3501-6.
177. Ling DI, Zwerling A, Pai M. GenoType MTBDR assays for the diagnosis of multidrug-resistant tuberculosis: a meta-analysis. *Eur Respir J*. 2008; **32**: 1165-74.
178. Martin A, Portaels F, Palomino JC. Colorimetric redox-indicator methods for the rapid detection of multidrug resistance in *Mycobacterium tuberculosis*: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2007; **59**(2): 175-83.
179. Martin A, Panaiotov S, Portaels F, et al. The nitrate reductase assay for the rapid detection of isoniazid and rifampicin resistance in *Mycobacterium tuberculosis*: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2008; **62**(1): 56-64.
180. Minion J, Leung E, Menzies D, Pai M. Microscopic-observation drug susceptibility and thin layer agar assays for the detection of drug resistant tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2010; **10**(10): 688-98.
181. Horne DJ, Pinto LM, Arentz M, et al. Diagnostic accuracy and reproducibility of WHO-endorsed phenotypic drug susceptibility testing methods for first-line and second-line anti-tuberculosis drugs: a systematic review and meta-analysis. *J Clin Microbiol*. 2013; **51**(2): 393-401.
182. Feng Y, Liu S, Wang Q, et al. Rapid diagnosis of drug resistance to fluoroquinolones, amikacin, capreomycin, kanamycin and ethambutol using genotype MTBDRsl assay: a meta-analysis. *PLoS One*. 2013; **8**(2): e55292.
183. Guo Q, Zheng RJ, Zhu CT, et al. Pyrosequencing for the rapid detection of rifampicin resistance in *Mycobacterium tuberculosis*: a meta-analysis [Review article]. *Int J Tuberc Lung Dis*. 2013; **17**(8): 1008-13.
184. Mitnick CD, Castro KG, Harrington M, et al. Randomized trials to optimize treatment of multidrug-resistant tuberculosis. *PLoS Med*. 2007; **4**(11): e292.

185. Caminero JA. Management of multidrug-resistant tuberculosis and patients in retreatment. *Eur Respir J*. 2005; **25**(5): 928-36.
186. Caminero JA. Treatment of multidrug-resistant tuberculosis: evidence and controversies. *Int J Tuberc Lung Dis*. 2006; **10**(8): 829-37.
187. Francis J. Curry National Tuberculosis Center and California Department of Public Health. Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 2008. [www.currytbcenter.ucsf.edu/drtb](http://www.currytbcenter.ucsf.edu/drtb).
188. Keshavjee S, Gelmanova IY, Pasechnikov AD, et al. Treating multidrug-resistant tuberculosis in Tomsk, Russia: developing programs that address the linkage between poverty and disease. *Ann N Y Acad Sci*. 2008; **1136**: 1-11.
189. Kim DH, Kim HJ, Park SK, et al. Treatment outcomes and long-term survival in patients with extensively drug-resistant tuberculosis. *Am J Respir Crit Care Med*. 2008; **178**(10): 1075-82.
190. Mitnick CD, Shin SS, Seung KJ, et al. Comprehensive treatment of extensively drug-resistant tuberculosis. *N Engl J Med*. 2008; **359**(6): 563-74.
191. Mukherjee JS, Rich ML, Socci AR, et al. Programmes and principles in treatment of multidrug-resistant tuberculosis. *Lancet*. 2004; **363**(9407): 474-81.
192. Johnston JC, Shahidi NC, Sadatsafavi M, Fitzgerald JM (2009) Treatment Outcomes of Multi-drug-Resistant Tuberculosis: A Systematic Review and Meta-Analysis. *PLoS One*. 2009; (9): e6914.
193. Caminero JA. Guidelines for Clinical and Operational Management of Drug-Resistant Tuberculosis. Paris: International Union Against Tuberculosis and Lung Disease; 2013.
194. Ahuja SD, Ashkin D, Avendano M, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. *PLoS Med*. 2012; **9**(8): e1001300.
195. Kim SJ. Drug-susceptibility testing in tuberculosis: methods and reliability of results. *Eur Respir J*. 2005; **25**(3): 564-9.
196. van Deun A, Maug AK, Salim MA, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. *Am J Respir Crit Care Med*. 2010; **182**(5): 684-92.
197. World Health Organization. The use of short regimens for treatment of multidrug-resistant tuberculosis. Geneva: World Health Organization, 2012.
198. Toczek A, Cox H, du Cros P, et al. Strategies for reducing treatment default in drug-resistant tuberculosis: systematic review and meta-analysis. *Int J Tuberc Lung Dis*. 2013; **17**(3): 299-307.
199. Skripconoka V, Danilovits M, Pehme L, et al. Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. *Eur Respir J*. 2013; **41**(6): 1393-400.
200. World Health Organization. The use of bedaquiline to treat MDR TB: Interim policy guidance. Geneva, World Health Organization, 2013. WHO/HTM/TB/2013.6.
201. Diacon AH, Dawson R, von Groote-Bidlingmaier F, et al. 14-day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial. *Lancet*. 2012; **380**(9846): 986-93.
202. Udawadia ZF, Amale RA, Ajbani KK, Rodrigues C. Totally drug resistant tuberculosis in India. *Clin Infect Dis*. 2012; **54**: 579-81.
203. World Health Organization. "Totally drug-resistant" tuberculosis: a WHO consultation on the diagnostic definition and treatment options. (meeting report, 21-22 March 2012) <http://www.who.int/tb/challenges/xdr/xdrconsultation/en/>.
204. World Health Organization. Electronic recording and reporting for tuberculosis care and control. Geneva: World Health Organization, 2012. WHO/HTM/TB/2011.22.
205. Munsiff S, Ahuja SD, King L, et al. Ensuring accountability: the contribution of the cohort review method to tuberculosis control in New York City. *Int J Tuberc Lung Dis*. 2006; **10**: 1133-39.
206. Getahun H, Gunneberg C, Granich R, Nunn P. HIV infection-associated tuberculosis: the epidemiology and the response. *Clin Infect Dis*. 2010; **50** Suppl 3: S201-7.
207. Martinson N, Omar T, Lebina L, et al. Post mortem pulmonary pathology in adults dying at home: South Africa Conference on retroviruses and opportunistic infections. Atlanta, GA; 2013.
208. Some F, Mwangi A. Burden of tuberculosis among persons dying with HIV/AIDS while on antiretroviral therapy in Western Kenya. Conference on retroviruses and opportunistic infections. Atlanta, GA; 2013.

209. World Health Organization. WHO policy on collaborative TB/HIV activities: Guidelines for national programmes and other stakeholders. Geneva: World Health Organization, 2012. WHO/HTM/TB/2012.1.
210. Odhiambo J, Kizito W, Njoroge A, et al. Provider-initiated HIV testing and counselling for TB patients and suspects in Nairobi, Kenya. *Int J Tuberc Lung Dis*. 2008; **12**(3 Suppl 1): 63-8.
211. Srikantiah P, Lin R, Walusimbi M, et al. Elevated HIV seroprevalence and risk behavior among Ugandan TB suspects: implications for HIV testing and prevention. *Int J Tuberc Lung Dis*. 2007; **11**(2): 168-74.
212. Shapiro AE, Variava E, Rakgokong MH, et al. Community-based targeted case finding for tuberculosis and HIV in household contacts of patients with tuberculosis in South Africa. *Am J Respir Crit Care Med*. 2012; **185**: 1110-16.
213. Suggaravetsiri P, Yanai H, Chongsuvivatwong V, et al. Integrated counseling and screening for tuberculosis and HIV among household contacts of tuberculosis patients in an endemic area of HIV infection: Chiang Rai, Thailand. *Int J Tuberc Lung Dis*. 2003; **7**(12 Suppl 3): S424-31.
214. Harries AD, Zachariah R, Lawn SD. Providing HIV care for co-infected tuberculosis patients: a perspective from sub-Saharan Africa. *Int J Tuberc Lung Dis*. 2009; **13**(1): 6-16.
215. Maher D, Harries A, Getahun H. Tuberculosis and HIV interaction in sub-Saharan Africa: impact on patients and programmes; implications for policies. *Trop Med Int Health*. 2005; **10**(8): 734-42.
216. Getahun H, Harrington M, O'Brien R, Nunn P. Diagnosis of smear-negative pulmonary tuberculosis in people with HIV infection or AIDS in resource-constrained settings: informing urgent policy changes. *Lancet*. 2007; **369**(9578): 2042-9.
217. UNAIDS/WHO. Guidance on provider-initiated HIV testing and counseling in health facilities. Geneva: World Health Organization; 2007.
218. World Health Organization. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. Geneva: World Health Organization, 2007.
219. Lawn SD, Campbell L, Kaplan R, et al. Delays in starting antiretroviral therapy in patients with HIV-associated tuberculosis accessing non-integrated clinical services in a South African township. *BMC Infect Dis*. 2011; **11**: 258.
220. Pevzner ES, Vandebriel G, Lowrance DW, et al. Evaluation of the rapid scale-up of collaborative TB/HIV activities in TB facilities in Rwanda, 2005-2009. *BMC Public Health*. 2011; **11**: 550.
221. Phiri S, Khan PY, Grant AD, et al. Integrated tuberculosis and HIV care in a resource-limited setting: experience from the Martin Preuss centre, Malawi. *Trop Med Int Health*. 2011; **16**(11): 1397-403.
222. Louwagie G, Girdler-Brown B, Odendaal R, et al. Missed opportunities for accessing HIV care among Tshwane tuberculosis patients under different models of care. *Int J Tuberc Lung Dis*. 2012; **16**(8): 1052-8.
223. Legido-Quigley H, Montgomery CM, Khan P, et al. Integrating tuberculosis and HIV services in low- and middle-income countries: a systematic review. *Trop Med Int Health*. 2013; **18**(2):199-211.
224. Dlodlo RA, Fujiwara PI, Enarson DA. Should tuberculosis treatment and control be addressed differently in HIV-infected and -uninfected individuals? *Eur Respir J*. 2005; **25**(4): 751-7.
225. El-Sadr WM, Perlman DC, Denning E, et al. A review of efficacy studies of 6-month short-course therapy for tuberculosis among patients infected with human immunodeficiency virus: differences in study outcomes. *Clin Infect Dis*. 2001; **32**(4): 623-32.
226. Harries A. How does treatment of tuberculosis differ in persons infected with HIV? In: Frieden TR, ed. *Toman's tuberculosis: Case detection, treatment and monitoring*, 2nd Edition. Geneva: World Health Organization; 2004: 169-72.
227. Page K, Godfrey Faussett P, Chaisson R. Tuberculosis-HIV coinfection: Epidemiology, Clinical Aspects, and Interventions. In: Ravigliione M, ed. *Tuberculosis: A Comprehensive International Approach*. 3rd ed. New York: Informa Healthcare; 2006.
228. World Health Organization. The use of antiretroviral drugs for treating and preventing HIV infection. Geneva, World Health Organization, 2013.
229. Lawn SD, Kranzer K, Wood R. Antiretroviral therapy for control of the HIV-associated tuberculosis epidemic in resource-limited settings. *Clin Chest Med*. 2009; **30**(4):685-99.
230. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med*. 2011; **365**(16): 1482-91.

231. Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. *N Engl J Med*. 2011; **365**(16): 1492-501.
232. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med*. 2011; **365**(16): 1471-81.
233. Torok ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)-associated tuberculous meningitis. *Clin Infect Dis*. 2011; **52**(11):1374-83.
234. Laureillard D, Marcy O, Madec Y, et al. Paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome after early initiation of antiretroviral therapy in the camelia randomized trial. *AIDS*. 2013; **27**(16):2577-86.
235. Chimzizi R, Gausi F, Bwanali A, et al. Voluntary counselling, HIV testing and adjunctive cotrimoxazole are associated with improved TB treatment outcomes under routine conditions in Thyolo District, Malawi. *Int J Tuberc Lung Dis*. 2004; **8**(5): 579-85.
236. Chimzizi RB, Harries AD, Manda E, et al. Counselling, HIV testing and adjunctive cotrimoxazole for TB patients in Malawi: from research to routine implementation. *Int J Tuberc Lung Dis*. 2004; **8**(8): 938-44.
237. Grimwade K, Sturm AW, Nunn AJ, et al. Effectiveness of cotrimoxazole prophylaxis on mortality in adults with tuberculosis in rural South Africa. *AIDS*. 2005; **19**(2): 163-8.
238. Nunn P, Williams B, Floyd K, et al. Tuberculosis control in the era of HIV. *Nat Rev Immunol*. 2005; **5**(10): 819-26.
239. World Health Organization. TB/HIV: A clinical manual. Geneva: World Health Organization, 2004. WHO/HTM/T/2004.329.
240. Wood R, Middelkoop K, Myer L, et al. Undiagnosed tuberculosis in a community with high HIV prevalence: implications for tuberculosis control. *Am J Respir Crit Care Med*. 2007; **175**(1):87-93.
241. World Health Organization. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva: World Health Organization, 2011. WHO/HTM/TB/2011.11.
242. Woldebanna S, Volmink J. Treatment of Latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev*. 2010 Jan 20;(1):CD000171.
243. Samandari T, Agizew TB, Nyirenda S, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2011; **377**(9777):1588-98.
244. Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J Med*. 2011; **365**(1): 11-20.
245. Durovni B, Saraceni V, Moulton LH, et al. Effect of improved tuberculosis screening and isoniazid preventive therapy on incidence of tuberculosis and death in patients with HIV in clinics in Rio de Janeiro, Brazil: a stepped wedge, cluster-randomised trial. *Lancet Infect Dis*. 2013; **13**(10): 852-8.
246. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med*. 2011; **365**(23): 2155-66.
247. Schechter M, Zajdenverg R, Falco G, et al. Weekly rifapentine/isoniazid or daily rifampin/pyrazinamide for latent tuberculosis in household contacts. *Am J Respir Crit Care Med*. 2006; **173**(8):922-6.
248. Golub JE, Saraceni V, Cavalcante SC, et al. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. *AIDS*. 2007; **21**(11): 1441-8.
249. Golub JE, Pronyk P, Mohapi L, et al. Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. *AIDS*. 2009; **23**(5): 631-6.
250. Suthar AB, Lawn SD, del Amo J, et al. Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis. *PLoS Med*. 2012; **9**(7): e1001270.
251. Rangaka MX, Wilkinson RJ. Isoniazid prevention of HIV-associated tuberculosis. *Lancet Infect Dis*. 2013; **13**(10):825-7.
252. Lönnroth K, Jaramillo EE, Williams BG, et al. Drivers of tuberculosis epidemics: role of risk factors and social determinants. *Soc Sci Med*. 2009; **68**(12): 2240-6.
253. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. *PLoS Med*. 2008; **5**(7): e152.



254. World Health Organization/The International Union Against Tuberculosis and Lung Disease. Monograph on TB and tobacco control: Joining efforts to control two related global epidemics. Geneva: World Health Organization, 2007. WHO/HTM/TB/2007.390.
255. Wang CS, Yang CJ, Chen HC, et al. Impact of type 2 diabetes on manifestations and treatment outcome of pulmonary tuberculosis. *Epidemiol Infect.* 2009; **137**(2): 203-10.
256. Creswell J, Raviglione M, Ottmani S, et al. Tuberculosis and noncommunicable diseases: neglected links and missed opportunities. *Eur Respir J.* 2011; **37**(5): 1269-82.
257. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract.* 2010; **87**(1): 4-14.
258. Baker MA, Harries AD, Jeon CY, et al. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. *BMC Med.* 2011; **9**: 81.
259. World Health Organization. Collaborative framework for care and control of tuberculosis and diabetes. Geneva: World Health Organization, 2011. WHO/HTM/TB/2011.15.
260. Nijland HM, Ruslami R, Stalenhoef JE, et al. Exposure to rifampicin is strongly reduced in patients with tuberculosis and type 2 diabetes. *Clin Infect Dis.* 2006; **43**(7): 848-54.
261. American Diabetes Association. Standards of medical care in diabetes-2013. *Diabetes Care.* 2013; **36**(suppl): S 11-66.
262. Allwood BW Meyer L, Bateman ED. A systematic review of the association between pulmonary tuberculosis and the development of chronic airflow obstruction in adults. *Respiration.* 2013; **86**(1): 76-85.
263. World Health Organization. Nutritional care and support for people with tuberculosis. Geneva: World Health Organization, 2013.
264. Winthrop KL. Infections and biologic therapy in rheumatoid arthritis: our changing understanding of risk and prevention. *Rheumatic Dis Clin North Am.* 2012; **38**(4): 727-45.
265. Solovic I, Sester M, Gomez-Reino JJ, et al. The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. *Eur Respir J.* 2010; **36**(5): 1185-206.
266. Etkind SC, Veen J. Contact follow-up in high and low-prevalence countries. In: Raviglione M, ed. Tuberculosis: a comprehensive international approach, 3rd Edition. New York: Informa Healthcare; 2006: 555-82.
267. Rieder HL. Contacts of tuberculosis patients in high-incidence countries. *Int J Tuberc Lung Dis.* 2003; **7**(12 Suppl 3): S333-6.
268. Erkens CG, Kamphorst M, Abubakar I, et al. Tuberculosis contact investigation in low prevalence countries: a European consensus. *Eur Respir J.* 2010; **36**(4): 925-49.
269. Morrison JL, Pai M, Hopewell P. Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis. *Lancet Infect Dis.* 2008; **8**(6):359-68.
270. Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: a systematic review and meta-analysis. *Eur Respir J.* 2013; **41**(1): 140-56.
271. Shah NS Yuen C, Heo M, et al. Yield of Contact Investigations in Households of Drug-Resistant Tuberculosis Patients: Systematic Review and Meta-Analysis. *Clin Infect Dis.* 2013. Epub 2013 24 Sep.
272. Basu S, Andrews JR, Poolman EM, et al. Prevention of nosocomial transmission of extensively drug-resistant tuberculosis in rural South African district hospitals: an epidemiological modelling study. *Lancet.* 2007; **370**(9597): 1500-7.
273. Nardell E, Dharmadhikari A. Turning off the spigot: reducing drug-resistant tuberculosis transmission in resource-limited settings. *Int J Tuberc Lung Dis.* 2010; **14**(10): 1233-43.
274. Ling D, Menzies D. Occupation-related respiratory infections revisited. *Infect Dis Clin North Am.* 2010; **24**(3): 655-80.
275. Blumberg HM, Watkins DL, Berschling JD, et al. Preventing the nosocomial transmission of tuberculosis. *Ann Intern Med.* 1995; **122**(9): 658-63.
276. Escombe AR, Moore DA, Gilman RH, et al. The Infectiousness of tuberculosis patients coinfecting with HIV. *PLoS Med.* 2008; **5**(9): e188.
277. Escombe AR, Oeser CC, Gilman RH, et al. Natural ventilation for the prevention of airborne contagion. *PLoS Med.* 2007; **4**(2): e68.

278. Dharmadhikari AS, Mphahlele M, Stoltz A, et al. Surgical face masks worn by patients with multi-drug-resistant tuberculosis: impact on infectivity of air on a hospital ward. *Am J Respir Crit Care Med*. 2012; **185**(10): 1104-9.
279. Maher D, Raviglione MC. Why is a recording and reporting system needed, and what system is recommended? In: Frieden TR, ed. *Toman's tuberculosis: Case detection, treatment and monitoring*, 2nd Edition. Geneva: World Health Organization; 2004: 270-3.
280. World Health Organization. *A Practical Handbook on the Pharmacovigilance of Medicines Used in the treatment of Tuberculosis*. Geneva; World Health Organization 2013.
281. Centers for Disease Control and Prevention. Provisional CDC Guidelines for the Use and Safety Monitoring of Bedaquiline Fumarate (Sirturo TM) for the Treatment of Multidrug-Resistant Tuberculosis. *MMWR Recomm Rep*. 2013 Oct 25; **62**(RR-09):1-12.

# Annex 1

The steering committees responsible for editions 1 and 2 of the *ISTC* are listed below.

## Edition 1

- **Edith Alarcón** (nurse, international technical agency, NGO)
- **R. V. Asokan** (professional society)
- **Jaap Broekmans** (international technical agency, NGO)
- **Jose Caminero** (academic institution, care provider)
- **Kenneth Castro** (national tuberculosis program director)
- **Lakbir Singh Chauhan** (national tuberculosis program director)
- **David Coetzee** (TB/HIV care provider)
- **Sandra Dudereva** (medical student)
- **Saidi Egwaga** (national tuberculosis program director)
- **Paula Fujiwara** (international technical agency, NGO)
- **Robert Gie** (pediatrics, care provider)
- **Case Gordon** (patient advocate)
- **Philip Hopewell, Co-Chair** (professional society, academic institution, care provider)
- **Umesh Laloo** (academic institution, care provider)
- **Dermot Maher** (global tuberculosis control)
- **G. B. Migliori** (professional society)
- **Richard O'Brien** (new tools development, private foundation)
- **Mario Raviglione, Co-Chair** (global tuberculosis control)
- **D'Arcy Richardson** (nurse, funding agency)
- **Papa Salif Sow** (HIV care provider)
- **Thelma Tupasi** (multiple drug-resistant tuberculosis, private sector, care provider)
- **Mukund Uplekar** (global tuberculosis control)
- **Diana Weil** (global tuberculosis control)
- **Charles Wells** (technical agency, national tuberculosis program)
- **Karin Weyer** (laboratory)
- **Wang Xie Xiu** (national public health agency)

## Edition 2

- **Edith Alarcón** (nurse, international technical agency, NGO)
- **R. V. Asokan** (professional society)
- **Carmelia Basri** (national tuberculosis program)
- **Henry Blumberg** (infection control, academic institution)
- **Martien Borgdorff** (international technical agency)
- **Jose Caminero** (training, academic institution, care provider)
- **Martin Castellanos** (national tuberculosis program director)
- **Kenneth Castro** (national tuberculosis program director)
- **Richard Chaisson** (prevention, academic institution)
- **Jeremiah Chakaya** (professional society)
- **Lakbir Singh Chauhan** (national tuberculosis program director)
- **Lucy Chesire** (patient advocate)
- **Daniel Chin** (donor agency)
- **David Cohn** (prevention, academic institution)
- **Charles Daley** (role of radiographic evaluation, academic institution)

- **Saidi Egwaga** (national tuberculosis program director)
- **Elizabeth Fair** (case finding and contact investigation, academic institution)
- **Paula Fujiwara** (international technical agency, NGO)
- **Haileyesus Getahun** (TB/HIV, global tuberculosis control)
- **Robert Gie** (pediatrics, care provider)
- **Case Gordon** (patient advocate)
- **Ruben Granich** (TB/HIV, global tuberculosis control)
- **Malgosia Grzemska** (policy and liaison with WHO, global tuberculosis control)
- **Mark Herrington** (TB/HIV, NGO)
- **Philip Hopewell, Co-Chair** (professional society, academic institution, care provider)
- **Ernesto Jaramillo** (drug resistance, global tuberculosis control)
- **Anwar Jusuf** (professional society)
- **Salmaan Keshavjee** (drug resistance)
- **Umesh Laloo** (drug resistance, professional society)
- **Kitty Lambregts** (drug resistance, international technical agency)
- **Hadiarto Mangunegoro** (professional society)
- **Divide Manissero** (pediatric tuberculosis, regional tuberculosis control)
- **Eugene McCray** (TB/HIV, national tuberculosis control program)
- **G. B. Migliori** (professional society)
- **Ed Nardell** (infection control)
- **Paul Nunn** (drug resistance, global tuberculosis control)
- **Rick O'Brien** (diagnosis of smear-negative TB/role of new diagnostics, private foundation)
- **Madhukar Pai** (diagnosis of smear-negative TB/role of new diagnostics, academic institution)
- **Mario Raviglione, Co-Chair** (global tuberculosis control)
- **D'Arcy Richardson** (nursing, funding agency)
- **KJ Seung** (infection control)
- **Joseph Sitienei** (national tuberculosis program director)
- **Pedro Suarez** (role of radiographic evaluation)
- **Thelma Tupasi** (drug resistance, private sector, care provider)
- **Mukund Uplekar** (public private mix, global tuberculosis control)
- **Maarten Van Cleef** (international technical agency)
- **Cheri Vincent** (donor agency)
- **Diana Weil** (policy, global tuberculosis control)
- **Karin Weyer** (laboratory)
- **Wang Xie Xiu** (national public health agency)

# Annex 2

## Utilization of the ISTC

The *ISTC* is potentially a very powerful tool to improve the quality of tuberculosis care globally. Because of the way in which the *ISTC* was developed and the international endorsements it has received through the two previous editions, the document is broadly credible across categories of practitioners and, thus, carries substantial authority. This credibility and authority are major strengths of the *ISTC* and should be capitalized upon in its utilization.

Based on experience with the first (2006) and second (2009) editions of the *ISTC*, there are multiple uses for the document by both the public and private sectors. Many of these are described in the *Handbook for Utilizing the International Standards for Tuberculosis Care* which described utilization of the first edition of the *ISTC* (available at <http://www.istcweb.org>). Some of the more frequent uses are summarized below:

### Unifying Approaches to Tuberculosis Care Between the Public and Private Sectors

One of the intended uses of the *ISTC* is as a tool to unify approaches to diagnosis and treatment between the public and private sectors, especially in countries in which there is a strong private sector. The *ISTC*, by articulating widely accepted, authoritative approaches to tuberculosis care, can serve as a vehicle for bringing the two sectors together. As a product of the collaboration fostered by the *ISTC*, several countries and regions have utilized the *ISTC* as the framework for developing more local adaptations of the document.

Activities aimed at fostering public-private collaborations may be initiated by organizations representing either sector. Prior to developing activities based on the *ISTC*, the initiating organization must have a sound understanding of the individual standards and assess their ability to be in compliance with the standards. This likely will require internal assessment of capacity, planning, and development of specific strategies to address the standards. For example, if the goal is to involve the private sector more effectively, the NTP must be willing to adjust and accommodate, where necessary, to the needs of private providers. Planned *ISTC* activities should be clearly linked with the identified gaps to be filled. Overall objectives should also be formulated in relation to national tuberculosis control objectives and targets.

Obtaining endorsements by influential local organizations, including governments and professional societies, serves as a way of obtaining buy-in and commitment to the principles in the *ISTC*. Moreover, the influence of the *ISTC* is amplified with each endorsement received, and local endorsement paves the way for further *ISTC*-related activities, as described subsequently.

### Mobilizing Professional Societies

Professional societies and their leaders are often influential members of the private medical community, have direct access to a large number of practicing clinicians, and have influence that extends beyond their membership. The societies often include academic physicians who are influential in their own right. Professional societies can provide a convenient means, sometimes the only means, to access the private sector systematically by



utilizing society journals, newsletters, and other communications. Strategic thinking needs to be applied in determining the reasons for seeking professional society support, but the *ISTC* can serve as a means to identify and focus on common goals and objectives and can provide a framework for addressing and improving the quality of care delivered by private providers.

## Providing the Framework for Conducting a Feasibility Analysis

Because each of the major components of tuberculosis care is included in the *ISTC*, the standards provide a broad framework for a systematic “feasibility analysis” of local capabilities, and can serve as a vehicle for addressing any shortcomings. Conceptually, the *ISTC* feasibility analysis is a way for programs and providers to take stock of the standards that are or are not being met in their country. The feasibility analysis can be applied at any level in the health system national, state/provincial, district, or individual institutional level. The level at which the analysis is performed depends in part on the organization and funding of tuberculosis services. Conducting the analysis at a national level can provide an overall mapping and assessment of tuberculosis services across the country; this can be useful for general NTP planning purposes, for informing policy makers, and for advocacy efforts. Conducting the analysis at a district or local level may enable those participating to discuss more specific problems and to devise more specific solutions. For example, if the problem is limited access to laboratories, specific sharing of resources can be suggested. Within an individual institution, the *ISTC* may be used to assess the availability and quality of essential tuberculosis services provided by the institution and by the clinicians practicing within the institution.

## Quality and Performance Assessment

Similar to the feasibility analysis, the *ISTC* can serve as a means for assessing the quality of care. The individual standards within the *ISTC* can be utilized to measure the quality of tuberculosis services delivered by any provider, program, or sector. A major purpose of the *ISTC* is to improve the quality of tuberculosis care. Any or all of the standards may be used as tools for monitoring and evaluation of quality. Such assessments, just as with the feasibility analysis, can identify weaknesses in programs, institutions, or individual providers. Tailored interventions can then be employed to correct the weaknesses and improve quality.

## ISTC as an Advocacy Tool

Political commitment is a critical component of tuberculosis control, and its absence limits implementation of control measures. There has been considerable success in bringing high-level government attention and commitment to tuberculosis control. However, in most countries, at all levels of government, there has been a failure to translate this high-level political commitment into effective, country-level public policies that provide a framework for sustained tuberculosis control programs and activities. The *ISTC* provides a set of internationally recognized standards any government should seek to meet. In using the *ISTC* feasibility analysis tools, NTPs can identify gaps in meeting the standards, providing a powerful advocacy tool to seek improved tuberculosis care and control.

## Engaging Patients and Communities

The *ISTC* relates to this component in two ways: First, because the *ISTC* is backed by an international consensus and describes agreed upon elements of tuberculosis care that should be available everywhere, patients worldwide should expect that their care is in compliance with the *ISTC*. The *ISTC*, thus, provides patients with the backing they need to insist that they receive high quality care. Similarly, communities should expect that the care provided within their boundaries meets the standards, and thus is of high quality.

Second, the *Patients' Charter for Tuberculosis Care* was developed in tandem with the *ISTC* with the intent that they would be complimentary documents. The *PCTC* relies on the *ISTC* as its technical support. The *PCTC* describes both patients' rights and responsibilities. Implicit in both the statements of patients' rights and their responsibilities is that they will receive care that is in conformance with the *ISTC*. Patients' awareness of and support for the *ISTC* and the *PCTC* can be used to provide leverage in dealings with policy makers and funding agencies, empowering them to be effective advocates for high quality tuberculosis care.

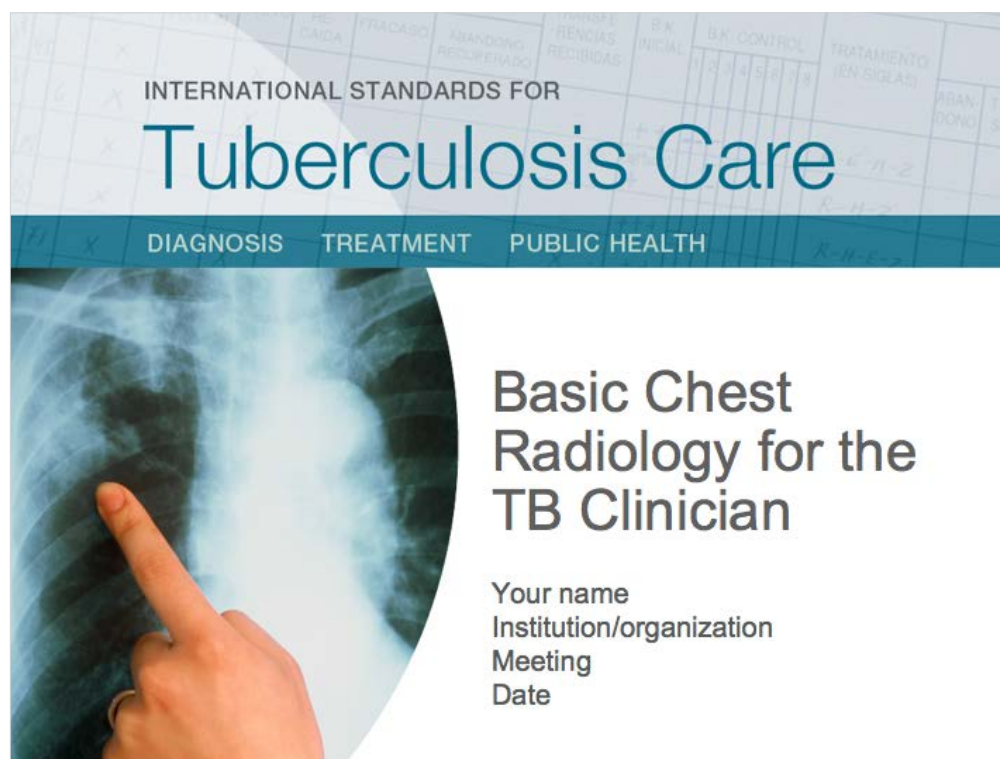
# Annex 3

## ISTC Tuberculosis Training Modules

The *ISTC Tuberculosis Training Modules* are educational resource tools developed to assist in the incorporation of the *ISTC* into training courses and curricula on tuberculosis. The modules currently available are based on edition 2 of the *ISTC*. Updates modules based on edition 3 will be available in September, 2014. However, the descriptions based on the 2009 update will be equally applicable to the modules based on edition 3. All training material can be downloaded at [www.istcweb.org](http://www.istcweb.org).

The modules are comprehensive in their coverage of core topics in the clinical evaluation and management of tuberculosis and the material is presented in a format that is flexible and adaptable to various training needs. While the modules may be used as core presentations for courses on tuberculosis, the *ISTC Tuberculosis Training Modules* material should also be viewed as a tuberculosis “training resource library” offering easy access to specific *ISTC* material, individual slides, images, or graphics as needed to update or augment existing tuberculosis training materials.

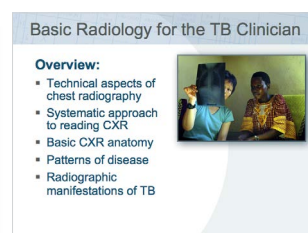
The planning and development of the *ISTC Tuberculosis Training Modules* was guided by members of the original *ISTC* steering committee and through significant input from *ISTC* implementation pilot countries. Through an informal assessment of needs from country-level input and steering committee members, a didactic PowerPoint slide format was chosen as most useful for easy adaptation for general training needs across a spectrum of capacity-building activities. The target audience is practicing physicians, both public and private. The modules may be adapted for pre-service trainees, nursing, and other health care providers.



INTERNATIONAL STANDARDS FOR  
**Tuberculosis Care**  
DIAGNOSIS TREATMENT PUBLIC HEALTH

**Basic Chest Radiology for the TB Clinician**

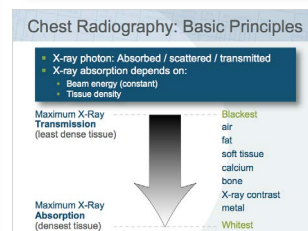
Your name  
Institution/organization  
Meeting  
Date



Basic Radiology for the TB Clinician

**Overview:**

- Technical aspects of chest radiography
- Systematic approach to reading CXR
- Basic CXR anatomy
- Patterns of disease
- Radiographic manifestations of TB



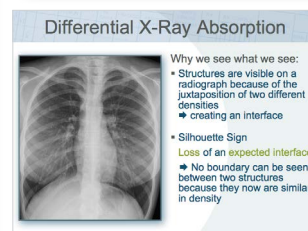
Chest Radiography: Basic Principles

- X-ray photon: Absorbed / scattered / transmitted
- X-ray absorption depends on:
  - Beam energy (constant)
  - Tissue density

Maximum X-Ray Transmission (least dense tissue)

Maximum X-Ray Absorption (densest tissue)

Blackest  
air  
fat  
soft tissue  
calcium  
bone  
X-ray contrast  
metal  
Whitest



Differential X-Ray Absorption

Why we see what we see:

- Structures are visible on a radiograph because of the juxtaposition of two different densities
  - creating an interface
- Silhouette Sign
  - Loss of an expected interface
  - No boundary can be seen between two structures because they now are similar in density

## Organization of Modules

Core topics in tuberculosis diagnosis, treatment, and public health responsibilities are covered in the modules, highlighting the relevant *ISTC* standards as they address the basic principles of care for persons with, or suspected of having, tuberculosis.

**ISTC Tuberculosis Training Modules** cover the following content areas:

Training Module Slide Sets 2009	
Standards for Diagnosis	
Clinical Presentation and Diagnosis of Tuberculosis	Standards 1, 2, 3, 4, 5, 6
Microbiological Evaluation of Tuberculosis	Standards 2, 3, 4, 5, 6, 10, 11
Pediatric Tuberculosis	Standards 2, 3, 4, 6
Standards for Treatment	
Initial Treatment of Tuberculosis	Standards 7, 8, 9, 10, 12,13
Fostering and Assessing Adherence to Treatment	Standard 9,17
Drug-resistant Tuberculosis	Standard 11, 12
Standards for Addressing HIV Infection and other Co-morbid Conditions	
TB and HIV infection: Introduction and Diagnosis	Standards 2, 3, 14
TB and HIV infection: Treatment	Standards 8, 15,16
Standards for Public Health	
Contact Evaluation	Standards 18
Isoniazid Preventive Therapy	Standards 16, 19
Tuberculosis Infection Control	Standards 20
Additional Training Modules/Slides	
Basic Chest Radiology for the TB Clinician	
Introduction to the ISTC Standards	

## Additional Training and Evaluation Tools

Additional materials provided with the slidesets include instructor Teaching Notes, a Facilitator's Guide (includes sample *ISTC* course agendas), instructions for producing Participant Manuals, and Evaluation and Training Tools (includes Training Module Test Questions).

**Teaching Notes:** Each *ISTC Tuberculosis Training Module* contains Teaching Notes to assist instructors by offering speaking points, background material, and interactive tips. The Teaching Note Summary serves as a quick reference document containing a complete set of Teaching Notes with “thumbnail” slide images for all modules.

**Facilitator's Guide:** The *Facilitator's Guide* explains the organization of the *ISTC Tuberculosis Training Modules* and includes suggestions for effective course development and facilitation, including:

- Sample course agendas
- Participant manual instructions

**Test Questions:** Questions based on module objectives are included which may be used as Pre- and Post- test evaluation or alternately as interactive discussion tools for module presentations.

**Other Evaluation and Training Tools:** Template forms for course evaluations and training course administrative tools for registration and certification are also available.

## Pilot Testing of the Training Modules

Draft versions of the *ISTC Tuberculosis Training Modules* have been pilot-tested in a variety of settings. The successful adaptation and incorporation of the *ISTC* material by these pilot groups offers examples of how the *ISTC* Training Modules may be used.

**Training curriculum for practicing physicians (private and public):** Materials from the *ISTC Tuberculosis Training Modules* were adapted for use in a comprehensive set of training material developed to teach providers about new national tuberculosis guidelines (which incorporated the *ISTC*) in the Caribbean. In-country educators piloted the material in three separate trainings sessions.

**Specialty workforce training:** Select materials from the *ISTC Tuberculosis Training Modules* were used by outside experts as part of a training course for physicians, nurses, and clinical staff at a new national MDR-referral hospital in Tanzania.

**Pre-service training:** Collaboration between the National Tuberculosis and Leprosy Program (NTLP) and six medical schools and Allied Health Sciences in Tanzania resulted in a unified curriculum on tuberculosis integrating the *ISTC*. Materials from the *ISTC Tuberculosis Training Modules* were used in the development of the final curriculum.

**Professional Societies:** *ISTC Tuberculosis Training Modules* were adapted for use as core material for an extensive country-wide training plan developed by a collaborative effort of professional society members and the NTP as part of the *ISTC* task force mission in Indonesia.



## 2009 Revisions and Online Access

The first version of the training material was released in 2008. The current 2009 version has been updated to reflect the revisions within this document. New modules (radiology, pediatrics, isoniazid preventive therapy, and infection control) have been added as well. All training material can be downloaded at [www.istcweb.org](http://www.istcweb.org).



# Photo Credits

## **Cover - top**

Peru 1997  
Photographer: Jad Davenport  
Credits: WHO/TBP/Davenport  
Source: World Lung Foundation

## **Cover - middle**

India 2004  
Photographer: Gary Hampton  
Credits: WHO/TBP/Gary Hampton  
Source: World Lung Foundation

## **Cover - bottom**

Uganda 2003  
Photographer: Gary Hampton  
Credits: WHO/TBP/Gary Hampton  
Source: World Lung Foundation

## **Page 4**

Ethiopia 2003  
Photographer: Jan van den Hornbergh  
Credits: WHO/TBP/Jan van den Hornbergh  
Source: World Lung Foundation

## **Page 8**

Tanzania 2012  
Photographer: Phil Hopewell  
Credits: Curry International TB Center, UCSF  
Source: Photographer

## **Page 14**

Uganda 2003  
Photographer: Gary Hampton  
Credits: WHO/TBP/ Gary Hampton  
Source: World Lung Foundation

## **Page 20**

Myanmar 2001  
Photographer: Virginia Arnold  
Credits: WHO/TBP/Arnold  
Source: World Lung Foundation

## **Page 22**

Thailand 2007  
Photographer: Wanda Walton  
Credits: CDC/DTBE  
Source: Photographer

## **Page 25**

Uganda 2010  
Credits: ©FIND/Ajay Thirumala

## **Page 28**

Peru 1997  
Photographer: Jad Davenport  
Credits: WHO/TBP/Davenport  
Source: World Lung Foundation

## **Page 31**

Photographer: Gary Hampton  
Credits: WHO/TBP/Hampton  
Source: World Lung Foundation

## **Page 33**

Photographer: Sarah England  
Credits: WHO/TBP/England  
Source: World Lung Foundation

## **Page 34**

South Africa 2003  
Photographer: Gary Hampton  
Credits: WHO/TBP/Hampton  
Source: World Lung Foundation

## **Page 37**

Ghana 2004  
Photographer: Pierre Viro  
Credits: WHO/TBP/Viro  
Source: World Lung Foundation

## **Page 41**

Photographer: Gary Hampton  
Credits: WHO/TBP/Hampton  
Source: World Lung Foundation

## **Page 42**

Photographer: Phil Hopewell  
Credits: Curry International TB Center, UCSF  
Source: Photographer

## **Page 47**

Tanzania 2012  
Photographer: Phil Hopewell  
Credits: Curry International TB Center, UCSF  
Source: Photographer

## **Page 49**

Photographer: Sarah England  
Credits: WHO/TBP/England  
Source: World Lung Foundation

## **Page 50**

Uganda 2003  
Photographer: Gary Hampton  
Credits: WHO/TBP/Gary Hampton  
Source: World Lung Foundation

## **Page 52**

Uganda 2003  
Photographer: Gary Hampton  
Credits: WHO/TBP/Gary Hampton  
Source: World Lung Foundation

## **Page 56**

Saipan 2009  
Photographer: Richard Brostrom  
Credits: CNMI Tuberculosis Control Program  
Source: Photographer

## **Page 57**

Tanzania 2012  
Photographer: Phil Hopewell  
Credits: Curry International TB Center, UCSF  
Source: Photographer

## **Page 60**

Tanzania 2012  
Photographer: Phil Hopewell  
Credits: Curry International TB Center, UCSF  
Source: Photographer

## **Page 62**

Peru 1997  
Photographer: Jad Davenport  
Credits: WHO/TBP/Davenport  
Source: World Lung Foundation

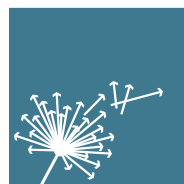
## **Back Cover**

Bangladesh 2001  
Photographer: Sarah England  
Credits: WHO/TBP/England  
Source: World Lung Foundation



University of California  
San Francisco

*advancing health worldwide™*



CURRY  
INTERNATIONAL  
TUBERCULOSIS  
CENTER

[www.currytbcenter.ucsf.edu](http://www.currytbcenter.ucsf.edu)