INTERNATIONAL STANDARDS FOR

Tuberculosis Care

DIAGNOSIS TREATMENT PUBLIC HEALTH

Developed by the Tuberculosis Coalition for Technical Assistance (TBCTA)

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List of Abbreviations

AFB	Acid-fast bacilli
ATS	American Thoracic Society
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DOT	Directly observed treatment
DOTS	The internationally recommended strategy for tuberculosis control
DST	Drug susceptibility testing
EMB	Ethambutol
FDC	Fixed-dose combination
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
IDSA	Infectious Diseases Society of America
INH	Isoniazid
IMAAI	Integrated Management of Adolescent and Adult Illness
IMCI	Integrated Management of Childhood Illness
ISTC	International Standards for Tuberculosis Care
IUATLD	International Union Against Tuberculosis and Lung Disease (The Union)
KNCV	Royal Netherlands Tuberculosis Foundation
LTBI	Latent tuberculosis infection
MIC	Minimal inhibitory concentration
MDR	Multiple drug resistance
NAAT	Nucleic acid amplification test
NTP	National tuberculosis control program
PZA	Pyrazinamide
RIF	Rifampicin
RR	Risk ratio
STI	Sexually transmitted infection
TB	Tuberculosis
TBCTA	Tuberculosis Coalition for Technical Assistance
USAID	United States Agency for International Development
WHO	World Health Organization
ZN	Ziehl-Neelsen staining

Summary

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, or are suspected of having, tuberculosis. The *Standards* are intended to facilitate the effective engagement of all care providers in delivering high-quality care for patients of all ages, including those with sputum smear-positive, sputum smear-negative, and extra pulmonary tuberculosis, tuberculosis caused by drug-resistant *Mycobacterium tuberculosis* complex (*M. tuberculosis*) organisms, and tuberculosis combined with human immunodeficiency virus (HIV) infection.

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 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 effective treatment are not only essential for good patient care—they are the key elements in the public health response to tuberculosis and 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 assuming an important public health function that entails a high level of responsibility to the community, as well as to the individual patient.

The Standards are intended to facilitate the effective engagement of all care providers in delivering high-quality care for patients of all ages and all forms of TB including drug-resistant TB and TB combined with HIV infection.

Although government tuberculosis program providers are not exempt from adherence to the *Standards*, non-program providers are the main target audience. 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 *Standards*. Such accommodations may be necessary, for example, to facilitate treatment supervision and contact investigations.

In addition to healthcare 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 as described in the *Patients' Charter for Tuberculosis Care*. 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* are intended to be complementary to local and national tuberculosis control policies that are consistent with World Health Organization (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 *Standards* 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.

The *Standards* are also intended to serve as a companion to and support for the *Patients' Charter for Tuberculosis Care* developed in tandem with the *Standards*. 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.

Standards for Diagnosis

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

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

Standard 3. For all patients (adults, adolescents, and children) suspected of having extrapulmonary tuberculosis, appropriate specimens from the suspected sites of involvement should be obtained for microscopy and, where facilities and resources are available, for culture and histopathological examination.

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

Standard 5. The diagnosis of sputum smear-negative pulmonary tuberculosis should be based on the following criteria: at least three negative sputum smears (including at least one early morning specimen); chest radiography findings consistent with tuberculosis; and lack of response to a trial of broad-spectrum antimicrobial agents. (NOTE: Because the fluoroquinolones are active against *M. tuberculosis complex* and, thus, may cause transient improvement in persons with tuberculosis, they should be avoided.) For such patients, if facilities for culture are available, sputum cultures should be obtained. In persons with known or suspected HIV infection, the diagnostic evaluation should be expedited.

Standard 6. The diagnosis of intrathoracic (i.e., pulmonary, pleural, and mediastinal or hilar lymph node) tuberculosis in symptomatic children with negative sputum smears should be based on the finding of chest radiographic abnormalities consistent with tuberculosis and either a history of exposure to an infectious case or evidence of tuberculosis infection (positive tuberculin skin test or interferon gamma release assay). For such patients, if facilities for culture are available, sputum specimens should be obtained (by expectoration, gastric washings, or induced sputum) for culture.

Standards for Treatment

Standard 7. Any practitioner treating a patient for tuberculosis is assuming an important public health responsibility. To fulfill this responsibility the practitioner must not only prescribe an appropriate regimen but, also, be capable of assessing the adherence of the patient to the regimen and addressing poor adherence when it occurs. By so doing, the provider will be able to ensure adherence to the regimen until treatment is completed.

Standard 8. All patients (including those with HIV infection) who have not been treated previously should receive an internationally accepted first-line treatment regimen using drugs of known bioavailability. The initial phase should consist of two months of isoniazid, rifampicin, pyrazinamide, and ethambutol. The preferred continuation phase consists of isoniazid and rifampicin given for four months. Isoniazid and ethambutol given for six months is an alternative continuation phase regimen that may be used when adherence cannot be assessed, but it is associated with a higher rate of failure and relapse, especially in patients with HIV infection.

The doses of antituberculosis drugs used should conform to international recommendations. Fixed-dose combinations of two (isoniazid and rifampicin, three (isoniazid, rifampicin, and pyrazinamide), and four (isoniazid, rifampicin, pyrazinamide, and ethambutol) drugs are highly recommended, especially when medication ingestion is not observed.

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

Standard 10. All patients should be monitored for response to therapy, best judged in patients with pulmonary tuberculosis by follow-up sputum microscopy (two specimens) at least at the time of completion of the initial phase of treatment (two months), at five months, and at the end of treatment. Patients who have positive smears during the fifth month of treatment should be considered as treatment failures and have therapy modified appropriately. (See Standards 14 and 15.) In patients with extrapulmonary tuberculosis and in children, the response to treatment is best assessed clinically.

Follow-up radiographic examinations are usually unnecessary and may be misleading.

Standard 11. A written record of all medications given, bacteriologic response, and adverse reactions should be maintained for all patients.

Standard 12. In areas with a high prevalence of HIV infection in the general population and where tuberculosis and HIV infection are likely to co-exist, HIV counseling and testing is indicated for all tuberculosis patients as part of their routine management. In areas with lower prevalence rates of HIV, HIV counseling and testing is indicated for tuberculosis patients with symptoms and/or signs of HIV-related conditions and in tuberculosis patients having a history suggestive of high risk of HIV exposure.

Standard 13. All patients with tuberculosis and HIV infection should be evaluated to determine if antiretroviral therapy is indicated during the course of treatment for tuberculosis. Appropriate arrangements for access to antiretroviral drugs should be made for patients who meet indications for treatment. Given the complexity of co-administration of antituberculosis treatment and antiretroviral therapy, consultation with a physician who is expert in this area is recommended before initiation of concurrent treatment for tuberculosis and HIV infection, regardless of which disease appeared first. However, initiation of treatment for tuberculosis should not be delayed. Patients with tuberculosis and HIV infection should also receive cotrimoxazole as prophylaxis for other infections.

Standard 14. An assessment of the likelihood of drug resistance, based on history of prior treatment, exposure to a possible source case having drug-resistant organisms, and the community prevalence of drug resistance, should be obtained for all patients. Patients who fail treatment and chronic cases should always be assessed for possible drug resistance. For patients in whom drug resistance is considered to be likely, culture and drug susceptibility testing for isoniazid, rifampicin, and ethambutol should be performed promptly.

Standard 15. Patients with tuberculosis caused by drug-resistant (especially multiple-drug resistant [MDR]) organisms should be treated with specialized regimens containing second-line antituberculosis drugs. At least four drugs to which the organisms are known or presumed to be susceptible should be used, and treatment should be given for at least 18 months. Patient-centered measures are required to ensure adherence. Consultation with a provider experienced in treatment of patients with MDR tuberculosis should be obtained.

Standards for Public Health Responsibilities

Standard 16. All providers of care for patients with tuberculosis should ensure that persons (especially children under 5 years of age and persons with HIV infection) who are in close contact with patients who have infectious tuberculosis are evaluated and managed in line with international recommendations. Children under 5 years of age and persons with HIV infection who have been in contact with an infectious case should be evaluated for both latent infection with *M. tuberculosis* and for active tuberculosis.

Standard 17. All providers must report both new and retreatment tuberculosis cases and their treatment outcomes to local public health authorities, in conformance with applicable legal requirements and policies.

Research Needs

As part of the process of developing the *ISTC*, several key areas that require additional research were identified. Systematic reviews and research studies (some of which are underway currently) in these areas are critical to generate evidence to support rational and evidence-based care and control of tuberculosis. Research in these operational and clinical areas serves to complement ongoing efforts focused on developing new tools for tuberculosis control.

Introduction

Purpose

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, or are suspected of having, tuberculosis. The *Standards* are intended to facilitate the effective engagement of all care providers in delivering high-quality care for patients of all ages, including those with sputum smear-positive, sputum smear-negative, and extrapulmonary tuberculosis, tuberculosis caused by drug-resistant *Mycobacterium tuberculosis* complex (*M. tuberculosis*) organisms, and tuberculosis combined with HIV infection. A high standard of care is essential to restore the health of individuals with tuberculosis, to prevent the disease in their families and others with whom they come into contact, and to protect the health of communities.[1] Substandard care will result in poor patient outcomes, continued infectiousness with transmission of *M. tuberculosis* to family and other community members, and generation and propagation of drug resistance. For these reasons, substandard care is not acceptable.

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

The standards in this document differ from existing guidelines in that standards present **what** should be done, whereas, guidelines describe **how** the action is to be accomplished. Standards provide the foundation on which care can be based; guidelines provide the framing for the whole structure of care. Guidelines and standards are, thus, complementary to one another. A standard does not provide specific guidance on disease management but, rather, presents a principle or set of principles that can be applied in nearly all situations. In general, standards do not require adaptation to local circumstances. Guidelines must be tailored to local conditions. In addition, a standard can be used as an indicator of the overall adequacy of disease management against which individual or collective practices can be measured, whereas guidelines are intended to assist providers in making informed decisions about appropriate health interventions.[2]

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 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 effective 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 tubercu-

losis 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 assuming an important public health function that entails a high level of responsibility to the community, as well as to the individual patient. Adherence to the standards in this document will enable these responsibilities to be fulfilled.

Audience

The *Standards* are addressed to all healthcare providers, private and public, who care for persons with proven tuberculosis or with symptoms and signs suggestive of tuberculosis. In general, providers in government tuberculosis programs that follow existing international guidelines are in compliance with the *Standards*. However, in many instances (as described under Rationale), clinicians (both private and public) who are not part of a tuberculosis control program lack the guidance and systematic evaluation of outcomes provided by government control programs, and, commonly, would not be in compliance with the *Standards*. Thus, although government program providers are not exempt from adherence to the *Standards*, non-program providers are the main target audience. 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 *Standards*. Such accommodations may be necessary, for example, to facilitate treatment supervision and contact investigations.

In addition to healthcare 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 as described in the *Patients' Charter for Tuberculosis Care*. 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 healthcare providers in the community adhere to a high standard of tuberculosis care.[3] The community should expect that care for tuberculosis will be up to the accepted standard.

Scope

Three categories of activities are addressed by the *Standards*: diagnosis, treatment, and public health responsibilities of all providers. Specific prevention approaches, laboratory performance, and personnel standards are not addressed. The *Standards* are intended to be complementary to local and national tuberculosis control policies that are consistent with World Health Organization (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 Standards are also intended to serve as a companion to and support for the Patients' Charter for Tuberculosis Care.

To meet the requirements of the *Standards*, approaches and strategies (guidelines), 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 the level of care can, and should, go beyond what is specified in the *Standards*. Local conditions, practices, and resources also will determine the degree to which this is the case.

The *Standards* are also intended to serve as a companion to and support for the *Patients' Charter for Tuberculosis Care* (http://www.worldcarecouncil.org) developed in tandem with the *ISTC*. This *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.

There are several critical areas that the *Standards* do not address. Their exclusion should not be regarded as an indication of their lack of importance but, rather, their being beyond the scope of this document. The *Standards* do not address the extremely important concern with overall 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 the *Standards* will address.[1]

Also not addressed by the *Standards* is the necessity of having a sound, effective government tuberculosis control program. The requirements of such programs are described in a number of international recommendations from the WHO, the US Centers for Disease Control and Prevention (CDC), and the International Union Against Tuberculosis and Lung Disease (The Union). 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 laboratory services to the private sector.

In providing care for patients with, or suspected of having, tuberculosis, clinicians and persons responsible for healthcare facilities should take measures that reduce the potential for transmission of *M. tuberculosis* to healthcare workers and to other patients by following either local, national, or international guidelines for infection control. This is especially true in areas or specific populations with a high prevalence of HIV infection. Detailed recommendations are contained in the WHO *Guidelines for Prevention of Tuberculosis in Health Care Facilities in Resource-Limited Settings*, and the updated CDC guidelines for preventing the transmission of *M. tuberculosis* in healthcare settings.[4,5]

The *Standards* 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. For example, rather than expecting full implementation of all diagnostic elements at once, priorities

should be set based on local circumstances and capabilities. Pursuing this example, once high-quality sputum smear microscopy is universally available, the first priority activity to be accomplished would be performing sputum cultures for persons suspected of having tuberculosis but who have negative sputum smears, especially those in areas of high HIV prevalence. The second priority would consist of obtaining cultures and drug susceptibility testing for patients at high risk of having tuberculosis caused by drug-resistant organisms. A third priority would be performing cultures for all persons suspected of having tuberculosis. In some settings, as a fourth priority, drug susceptibility testing should be performed for isolates of *M. tuberculosis* obtained from patients not responding to standardized treatment regimens and, finally, for initial isolates from all patients.

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 and growing global health problem.[6–9] One-third of the world's population is infected with *M. tuberculosis*, mostly in developing countries, where 95% of cases occur.[8] In 2003, there were an estimated 8.8 million new cases of tuberculosis, of which 3.9 million were sputum smear-positive and, thus, highly infectious.[6,7] The number of tuberculosis cases that occur in the world each year is still growing, although the rate of increase is slowing. In the African region of the WHO, the tuberculosis case rate continues to increase, both because of the epidemic of HIV infection in sub-Saharan countries and the poor or absent primary care services in parts of the region.[6,7] In Eastern Europe, after a decade of increases, case rates have only recently reached a plateau, the increases being attributed 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.[6,7,9] In many other 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, prisoners, 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.

It is widely recognized that many providers are involved in the diagnosis and treatment of tuberculosis.[10-13] Traditional healers, general and specialist physicians, nurses, clinical officers, academic physicians, unlicensed practitioners, physicians in private practice, practitioners of alternative medicine, 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.[11] A recent global situation assessment reported by WHO suggested that delays in diagnosis were common.[12] The delay was more often in receiving a

diagnosis rather than in seeking care, although both elements are important.[14] This survey and other studies also show that clinicians, in particular those who work in the private healthcare sector, often deviate from standard, internationally recommended, tuberculosis management practices.[11,12] These deviations include: under-utilization of sputum 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.[11,12,15–21] Anecdotal evidence also suggests over-reliance on poorly validated or inappropriate diagnostic tests, such as serologic assays, often in preference to conventional bacteriological evaluations.

Together these findings highlight flaws in healthcare 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.[1] Likewise, any community with no or inadequate access to appropriate diagnostic and treatment services for tuberculosis is a vulnerable community.[1] The development of the *ISTC* is an attempt to reduce vulnerability of individuals and communities to tuberculosis by promoting high-quality care for persons with, or suspected of having, tuberculosis.

Companion and Reference Documents

The *Standards* in this document are complementary to two other important companion documents. The first, *Patients' Charter for Tuberculosis Care* (http://www.worldcarecouncil.org), specifies the rights and responsibilities of patients and has been developed in tandem with this document. Second, the International Council of Nurses has developed a set of standards, *TB/MDR-TB Nursing Standards* (www.icn.ch/tb/standards.htm), that define in detail the critical roles and responsibilities of nurses in the care and control of tuberculosis. As a single-source reference for many of the practices for tuberculosis care, we refer the reader to *Toman's Tuberculosis: Case Detection, Treatment, and Monitoring* (second edition).[22]

There are many guidelines and recommendations on various aspects of tuberculosis care and control. (For listing, see http://www.nationaltbcenter.edu/international/.) The *Standards* draw from many of these documents to provide their evidence base. In particular, we have relied on guidelines that are generally accepted because of the process by which they were developed, and by their broad use. However, existing guidelines, although implicitly based on standards, do not present standards that define the acceptable level of care in such a way as to enable assessment of the adequacy of care by patients themselves, by communities, and by public health authorities.

In providing the evidence base for the *Standards*, 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 itself. Throughout the document we have used the terminology recommended in the "Revised International Definitions in Tuberculosis Control."[23]

Standards for Diagnosis

Not all patients with respiratory symptoms receive an adequate evaluation for tuberculosis. 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.

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

Rationale and Evidence Summary

The most common symptom of pulmonary tuberculosis is persistent, productive cough, 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.

Although most 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. Although the presence of cough for 2–3 weeks is nonspecific, traditionally, having cough of this duration has served 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.[22–25]

In a recent survey conducted in primary healthcare services of nine low- and middle-income countries, 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. 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.[26] Other

studies have shown that 4–10% of adults attending outpatient health facilities in developing countries may have a persistent cough of more than 2–3 weeks in duration.[27] This percentage varies somewhat, depending on whether there is active questioning concerning the presence of cough. Respiratory conditions, therefore, constitute a substantial proportion of the burden of diseases in patients presenting to primary healthcare services.[26,27]

Data from India, Algeria, and Chile generally show that the percentage of patients with positive sputum smears increases with increasing duration of cough from 1–2 weeks, increasing to 3–4, and >4 weeks.[28] However, in these studies even patients with shorter duration of cough had an appreciable prevalence of tuberculosis. A more recent assessment from India demonstrated that by using a threshold of ≥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.[29] 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, but in addition, 7% of patients who did not volunteer that they had cough, but on questioning admitted to having cough ≥2 weeks, had positive smears.[29]

Choosing a threshold of 2–3 weeks is an obvious compromise, and it should be recognized that, while using this threshold reduces the clinic and laboratory workload, some cases would be missed. In patients presenting with chronic cough, the proportion of cases attributable to tuberculosis will depend on the prevalence of tuberculosis in the community.[27] 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.

Overall, by focusing on adults and children presenting with chronic cough, the chances of identifying patients with pulmonary tuberculosis are maximized. Unfortunately, several studies suggest that not all patients with respiratory symptoms receive an adequate evaluation for tuberculosis.[12,15,17–20,30] 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.

STANDARD 2. All patients (adults, adolescents, and children who are capable of producing sputum) suspected of having pulmonary tuberculosis should have at least two, and preferably three, sputum specimens obtained for microscopic examination. When possible, at least one early morning specimen should be obtained.

Rationale and Evidence Summary

To prove a diagnosis of tuberculosis, every effort must be made to identify the causative agent of the disease. A microbiological diagnosis can only be confirmed by culturing *M. tuberculosis* complex (or, under appropriate circumstances, identifying specific nucleic acid sequences in a clinical specimen) from any suspected site of disease. In practice,

however, there are many resource-limited settings in which culture is not feasible currently. Fortunately, microscopic examination of stained sputum is feasible in nearly all settings, and the diagnosis of tuberculosis can be strongly inferred by finding acid-fast bacilli by microscopic examination. In nearly all clinical circumstances in high-prevalence areas, finding acid-fast bacilli in stained sputum is highly specific and, thus, is the equivalent of a confirmed diagnosis. In addition to being highly specific for *M. tuberculosis* complex, identification of acid-fast bacilli by microscopic examination is particularly important for three reasons: it is the most rapid method for determining if a person has tuberculosis; it identifies persons who are at greatest risk of dying from the disease*; and it identifies the most likely transmitters of infection.

Failure to perform a proper diagnostic evaluation before initiating treatment potentially exposes the patient to the risks of unnecessary or wrong treatment with no benefit and may delay accurate diagnosis and proper treatment.

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 microscopy laboratories. Moreover, it is crucial that such laboratories undergo assessments of quality and have programs for quality improvement. These quality assessments are generally the responsibility of a government system (usually the NTP).

Failure to perform a proper diagnostic evaluation before initiating treatment 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 5 years of age and older can generate a specimen. Adolescents, although often classified as children at least until the age of 15 years, can generally produce sputum. Thus, age alone is not sufficient justification for failing to attempt to obtain a sputum specimen from a child or adolescent.

The information summarized below describes the results of various approaches to sputum collection, processing, and examination. The application of the information to actual practices and policies should be guided by local considerations.

The optimum number of sputum specimens to establish a diagnosis has been examined in a number of studies. In a recent review of data from a number of sources, it was stated that, on average, the initial specimen was positive in about 83–87% of all patients ultimately found to have acid-fast bacilli detected, in an additional 10–12% with the second specimen, and in a further 3–5% on the third specimen.[34] A rigorously conducted systematic review of 41 studies on this topic found a very similar distribution of results: on average, the second smear detected about 13% of smear-positive cases, and the third smear detected 4% of all smear-positive cases.[35] In studies that used culture as the reference standard, the mean incremental yield in sensitivity of the second smear was 9% and that of the third smear was 4%.[35]

* It should be noted that in persons with HIV infection, mortality rates are greater in patients with clinically-diagnosed tuberculosis who have negative sputum smears than among HIV-infected patients who have positive sputum smears.[31-33]

A recent re-analysis of data from a study involving 42 laboratories in four high-burden countries showed that the incremental yield from a third sequential smear ranged from 0.7–7.2%.[36] 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 three specimens adds minimally to the number of positive specimens obtained.[35] In addition, a third specimen is useful as confirmatory evidence if only one of the first two smears has a positive result. Ideally, the results of sputum microscopy should be returned to the clinician within no more than one working day from submission of the specimen. The timing of specimen collection is also important. The yield appears to be greatest from early morning (overnight) specimens.[35,37–39] Thus, although it is not practical to collect only early morning specimens, at least one specimen should be obtained from an early morning collection.

A variety of methods have been used to improve the performance of sputum smear microscopy.[40–42] In general, the sensitivity of microscopy (as compared to culture) is higher with concentration by centrifugation and/or sedimentation (usually after pretreatment with chemicals such as bleach, NaOH, and NaLC) or both, as compared to direct (unconcentrated) smear microscopy. A comprehensive, systematic review of 83 studies describing the effects of various physical and/or chemical methods for concentrating and processing sputum prior to microscopy found that concentration resulted in a higher sensitivity (15–20% increase) and smear-positivity rate, when compared with direct smears.[40] Although there are demonstrable advantages to concentration of sputum, there are also disadvantages. Centrifugation is more complex, requires electrical power, and may be associated with increased infection risk to laboratory personnel. Consequently, it is not clear that the advantages offset the disadvantages in low-resource settings.

Fluorescence microscopy, 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 systematic review, 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, suggests that fluorescence microscopy is the more sensitive method.[41] The results of this review have been verified in a more comprehensive, systematic review of 43 studies. This review showed that fluorescence microscopy is on average 10% more sensitive than conventional light microscopy.[42] The specificity of fluorescence microscopy was comparable to Ziehl-Neelsen staining. The combination of increased sensitivity with little or no loss of specificity makes fluorescence microscopy a more accurate test, although the increased cost and complexity might make it less applicable in many areas. For this reason, fluorescence staining is probably best 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.

STANDARD 3. For all patients (adults, adolescents, and children) suspected of having extrapulmonary tuberculosis, appropriate specimens from the suspected sites of involvement should be obtained for microscopy and, where facilities and resources are available, for culture and histopathological examination.

Although appropriate specimens may be difficult to obtain, bacteriological comfirmation of a diagnosis of extrapulmonary tuberculosis should be sought.

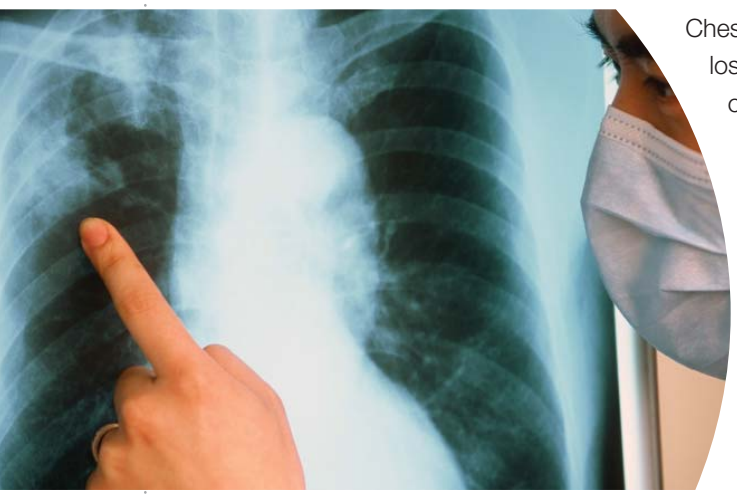
Rationale and Evidence Summary

Extrapulmonary tuberculosis (without associated lung involvement) accounts for 15–20% of tuberculosis in populations with a low prevalence of HIV infection. 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 culture is more important. For example, 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. Given the low yield of microscopy, both culture and histopathological examination of tissue specimens, such as may be obtained by needle biopsy of lymph nodes, are important diagnostic tests. In addition to the collection of specimens from the sites of suspected tuberculosis, examination of sputum and a chest film may also be useful, especially in patients with HIV infection, in whom there is an appreciable frequency of subclinical pulmonary tuberculosis.[43]

In patients who have an illness compatible with tuberculosis that is severe or progressing rapidly, initiation of treatment should not be delayed pending the results of microbiological examinations. Treatment should be started while awaiting results and then modified, if necessary, based on the microbiological findings.

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

Rationale and Evidence Summary



Chest radiography is a sensitive but nonspecific test to detect tuberculosis.[44] Radiographic examination (film or fluoroscopy) of the thorax or other suspected sites of involvement may be useful to identify persons for further evaluation. However, a diagnosis of tuberculosis cannot be established by radiography alone. Reliance on the chest radiograph as the only diagnostic test for tuberculosis will result in both over-diagnosis of tuberculosis and missed diagnoses of tuberculosis and other diseases. In a study from India in which 2,229 outpatients were examined by photofluorography, 227 were classified as having tuberculosis by radiographic criteria.[45,46] Of the 227, 81 (36%) had negative sputum cultures, whereas of the remaining 2,002 patients, 31 (1.5%) had positive cultures. Looking at these results in terms of the sensitivity of chest radiography, 32 (20%) of 162 culture-positive cases would have been missed by radiography. Given these and other data, it is clear that the use of radiographic examinations alone to diagnose tuberculosis is not an acceptable practice.

A diagnosis of tuberculosis cannot be established by radiography alone.

Chest radiography is useful to evaluate persons who have negative sputum smears to attempt to find evidence for pulmonary tuberculosis and to identify other abnormalities that may be responsible for the symptoms. With regard to tuberculosis, radiographic examination is most useful when applied as part of a systematic approach in the evaluation of persons whose symptoms and/or findings suggest tuberculosis, but who have negative sputum smears. (See Standard 5.)

STANDARD 5. The diagnosis of sputum smear-negative pulmonary tuberculosis should be based on the following criteria: at least three negative sputum smears (including at least one early morning specimen); chest radiography findings consistent with tuberculosis; and lack of response to a trial of broad-spectrum antimicrobial agents. (NOTE: Because the fluoroquinolones are active against *M. tuberculosis complex* and, thus, may cause transient improvement in persons with tuberculosis, they should be avoided.) For such patients, if facilities for culture are available, sputum cultures should be obtained. In persons with known or suspected HIV infection, the diagnostic evaluation should be expedited.

Rationale and Evidence Summary

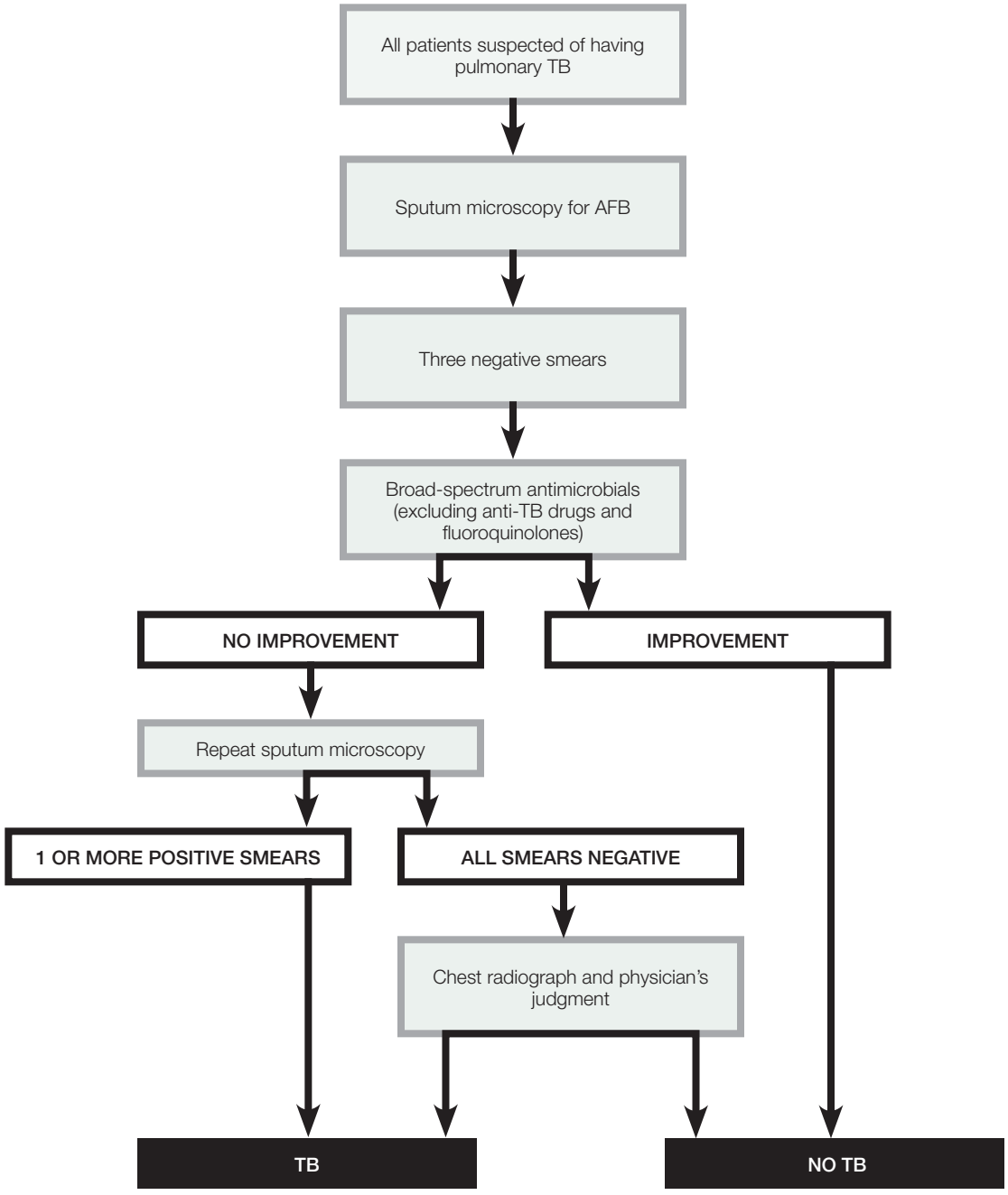
The designation of "sputum smear-negative tuberculosis" presents a difficult diagnostic dilemma. As noted above, on average, sputum smear microscopy is only about 50–60% sensitive when compared with culture. Nevertheless, given the nonspecific nature of the symptoms of tuberculosis and the multiplicity 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 three adequate sputum smears are negative. Because patients with HIV infection and tuberculosis frequently have negative sputum smears, and because of the broad differential diagnosis (including *Pneumocystis jiroveci* pneumonia and bacterial and fungal lower respiratory infections) in this group, such a systematic approach is crucial. It is important, however, 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; 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 based on the above three criteria, 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 17).

A number of algorithms have been developed as a means to systematize the diagnosis of smear-negative tuberculosis, although none has been adequately validated under field conditions.[47,48] In particular, there is little information or experience on which to base approaches to the diagnosis of smear-negative tuberculosis in persons with HIV infection. Figure 1 is modified from an algorithm developed by WHO and is included as an example of a systematic approach.[24] It should be recognized that, commonly, the steps in the algorithm are not followed in a sequential fashion by a single provider. The algorithm should be viewed as presenting an approach to diagnosis that incorporates the main components of, and a framework for, the diagnostic evaluation.

There are several points of caution regarding the algorithm. First, completion of all of the steps requires a substantial amount of time; thus, it should not be used for patients with an illness that is worsening rapidly. This is especially true in patients with HIV infection in whom tuberculosis may be rapidly progressive. Second, several studies have shown that patients with tuberculosis may respond, at least transiently, to broad spectrum

FIGURE 1.

An illustrative approach to the diagnosis of sputum smear-negative pulmonary tuberculosis[24]



AFB = acid-fast bacilli; **TB** = tuberculosis

Source: Modified from WHO, 2003[24]

antimicrobial treatment.[49–52] 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.[53] Third, the approach outlined in the algorithm may be quite costly to the patient and deter her/him from continuing with the diagnostic evaluation. Given all these concerns, application of such an algorithm in patients with at least three negative sputum smear examinations must be done in a flexible manner. Ideally, the evaluation of smear-negative tuberculosis should be guided by locally validated approaches, suited to local conditions.

Although sputum microscopy is the first bacteriologic diagnostic test of choice where resources permit and adequate, quality-assured laboratory facilities are available, culture should be included in the algorithm for evaluating patients with negative sputum smears. Properly done, culture adds a significant layer of complexity and cost but also increases sensitivity, which should result in earlier case detection.[54,55] Although the results of culture may not be 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.

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%.[56,57] In contrast, a properly performed culture can detect far lower numbers of acid-fast bacilli (detection limit is about 100 organisms per ml).[54] 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 drug susceptibility testing in patients in whom there is reason to suspect drug-resistant tuberculosis.[54] The disadvantages of culture are its cost, technical complexity, and the time required to obtain a result, thereby imposing a diagnostic delay if there is less reliance on sputum smear microscopy. In addition, ongoing quality assessment is essential for culture results to be credible. Such quality assurance measures are not available widely in most low-resource settings.

In many countries, although culture facilities are not uniformly available, there is the capacity to perform culture 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 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. Liquid media systems such as BACTEC® utilize the release of radioactive CO_2 from C-14 labeled palmitic acid in the media to identify growth. The MGIT® system, also using liquid medium, has the advantage of having growth detected by the appearance of fluorescence in a silicone plug at the bottom of the tube, thereby avoiding radioactivity. Decisions to provide culture facilities for diagnosing tuberculosis depend on financial resources, trained personnel, and the ready availability of reagents and equipment service.

Nucleic acid amplification tests (NAATs), although widely distributed, do not offer major advantages over culture at this time. Although a positive result can be obtained more quickly than with any of the culture methods, the NAATs are not sufficiently sensitive for a negative result to exclude tuberculosis.[58–63] In addition, NAATs are not sufficiently sensitive to be useful in identifying *M. tuberculosis* in specimens from extrapulmonary sites of disease.[59–61,63] Moreover, cultures must be available if drug susceptibility testing is to be performed. Other approaches to establishing a diagnosis of tuberculosis, such as serological tests, are not of proven value and should not be used in routine practice at this time.[58]

STANDARD 6. The diagnosis of intrathoracic (i.e., pulmonary, pleural, and mediastinal or hilar lymph node) tuberculosis in symptomatic children with negative sputum smears should be based on the finding of chest radiographic abnormalities consistent with tuberculosis and either a history of exposure to an infectious case or evidence of tuberculosis infection (positive tuberculin skin test or interferon gamma release assay). For such patients, if facilities for culture are available, sputum specimens should be obtained (by expectoration, gastric washings, or induced sputum) for culture.

Rationale and Evidence Summary

Children with tuberculosis commonly have paucibacillary disease without evident lung cavitation but with involvement of intrathoracic lymph nodes. Consequently, compared with adults, sputum smears from children are more likely to be negative. Therefore, cultures of sputum or other specimens, radiographic examination of the chest, and tests to detect tuberculous infection (generally, a tuberculin skin test) are of relatively greater importance. Because many children less than 5 years of age do not cough and produce sputum effectively, culture of gastric washings obtained by naso-gastric tube lavage or induced sputum has a higher yield than spontaneous sputum.[64]

Compared with adults, sputum smears from children are more likely to be negative.

Several recent reviews have examined the effectiveness of various diagnostic tools, scoring systems and algorithms to diagnose tuberculosis in children.[64–67] Many of these approaches lack standardization and validation and, thus, are of limited applicability. Table 1 presents the approach recommended by the Integrated Management of Childhood Illness (IMCI) program of WHO that is widely used in first-level facilities in low- and middle-income countries.[68]

TABLE 1.

An approach to the diagnosis of tuberculosis in children[68]

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

A history of:

- unexplained weight loss or failure to grow normally
- unexplained fever, especially when it continues for more than two weeks
- chronic cough
- exposure to an adult with probable or definite pulmonary infectious tuberculosis

On examination:

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

Source: Reproduced from WHO/FCH/CAH/00.1

Standards for Treatment

Treatment for tuberculosis is not only a matter of individual health; it is also a matter of public health. All providers, public and private, who undertake to treat a patient with tuberculosis, must have the knowledge to prescribe a standard treatment regimen and the means to assess adherence to the regimen and to address poor adherence in order to ensure that treatment is completed.

STANDARD 7. **Any practitioner treating a patient for tuberculosis is assuming an important public health responsibility. To fulfill this responsibility, the practitioner must not only prescribe an appropriate regimen but, also, be capable of assessing the adherence of the patient to the regimen and addressing poor adherence when it occurs. By so doing, the provider will be able to ensure adherence to the regimen until treatment is completed.**

Rationale and Evidence Summary

As described in the Introduction, the main interventions to prevent the spread of tuberculosis in the community are the detection of patients with infectious tuberculosis and providing them with 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 diabetes mellitus); 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 standard treatment regimen and the means to assess adherence to the regimen and address poor adherence to ensure that treatment is completed.[69] National tuberculosis programs commonly possess approaches and tools 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 (including those with HIV infection) who have not been treated previously should receive an internationally accepted first-line treatment regimen using drugs of known bioavailability. The initial phase should consist of two months of isoniazid, rifampicin, pyrazinamide and ethambutol.* The preferred continuation phase consists of isoniazid and rifampicin given for four months. Isoniazid and ethambutol given for six months is an alternative continuation phase regimen that may be used when adherence cannot be assessed but is associated with a higher rate of failure and relapse, especially in patients with HIV infection.**

The doses of antituberculosis drugs used should conform to international recommendations. Fixed-dose combinations of two (isoniazid and rifampicin), three (isoniazid, rifampicin, and pyrazinamide) and four (isoniazid, rifampicin, pyrazinamide, and ethambutol) drugs are highly recommended, especially when medication ingestion is not observed.

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.[24,25,69] These are referenced and data will not be reviewed in this document. All these data indicate that 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. 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. There are several variations in the frequency of drug administration that have been shown to produce acceptable results.[24,25,69]

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.

Two systematic reviews of regimens of less than six months have found that shorter durations of treatment have an unacceptably high rate of relapse.[70,71] Thus, the current international standard for smear or culture-positive tuberculosis is a regimen administered for a minimum duration of six months.[24,69]

Although the six-month regimen is the preferred option, an alternative continuation phase regimen, consisting of isoniazid and ethambutol given for six months, making the total duration of treatment eight months, may also be used. It should be recognized, however, that this regimen, presumably because of the shorter duration of rifampicin administration, is associated with a higher rate of failure and relapse, especially in patients with HIV infection.[72–74] Nevertheless, the eight-month regimen may be used when adherence to treatment throughout the continuation phase cannot be assessed.[24] The rationale for this approach is that if the patient is nonadherent, the emergence of resistance to rifampicin

* Ethambutol may be omitted in the initial phase of treatment for adults and children who have negative sputum smears, do not have extensive pulmonary tuberculosis or severe forms of extrapulmonary disease, and who are known to be HIV negative.

will be minimized. A retrospective review of the outcomes of treatment of tuberculosis in patients with HIV infection shows that tuberculosis relapse is minimized by the use of a regimen containing rifampicin throughout a six-month course.[72] Thus, the six-month regimen containing rifampicin throughout the entire course is preferable in patients with HIV infection to minimize the risk of relapse; however, the patient's HIV stage, the need for and availability of antiretroviral drugs, and the quality of treatment supervision/support must be considered in choosing an appropriate continuation phase of therapy.

Intermittent administration of antituberculosis drugs enables supervision to be provided more efficiently and economically with no reduction in efficacy. The evidence on effectiveness of intermittent regimens was reviewed recently.[75,76] These reviews, based on several trials,[77–82] 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. However, WHO and The Union do not recommend the use of twice-weekly intermittent regimens because of the potentially greater consequences of missing one of the two doses.[24,25,83] A simplified version of the current WHO recommendations for treating persons who have not been treated previously is shown in Table 2.[24]

TABLE 2.

Recommended treatment for persons not treated previously[24]

RANKING	INITIAL PHASE	CONTINUATION PHASE
Preferred	INH, RIF, PZA, EMB[1,2] daily, 2 months INH, RIF, PZA, EMB[1,2] 3x/week, 2 months	INH, RIF daily, 4 months INH, RIF 3x/week, 4 months
Optional	INH, RIF, PZA, EMB[2] daily, 2 months	INH, EMB daily, 6 months[3]

INH = isoniazid; **RIF** = rifampicin; **PZA** = pyrazinamide; **EMB** = ethambutol

1 Streptomycin may be substituted for ethambutol.
2 Ethambutol may be omitted in the initial phase of treatment for adults and children who have negative sputum smears, do not have extensive pulmonary tuberculosis or severe forms of extra-pulmonary disease, and who are known to be HIV negative.
3 Associated with higher rate of treatment failure and relapse; should generally not be used in patients with HIV infection.

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,[24] The Union,[25] ATS, CDC, the Infectious Diseases Society of America (IDSA),[69] and others.[83,84] The recommended doses for daily and thrice-weekly administration are shown in Table 3.

TABLE 3.

Doses of first-line antituberculosis drugs in adults and children

DRUG	Recommended dose in mg/kg body weight (range) DAILY	THREE TIMES WEEKLY
isoniazid	5 (4–6), maximum 300 daily	10
rifampicin	10 (8–12), maximum 600 daily	10 (8–12), maximum 600 daily
pyrazinamide	25 (20–30)	35 (30–40)
ethambutol	children 20 (15–25)* adults 15 (15–20)	30 (25–35)
streptomycin	15 (12–18)	15 (12–18)

* The recommended daily dose of ethambutol is higher in children (20 mg/kg) than in adults (15mg/kg), because the pharmacokinetics are different. (Peak serum ethambutol concentrations are lower in children than in adults receiving the same mg/kg dose.)

Treatment of tuberculosis in special clinical situations, such as 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 WHO and ATS/CDC/IDSA treatment guidelines.[24,69]

Although there is no evidence that fixed-dose combinations (FDCs) are superior to individual drugs, expert opinion suggests that they may minimize inadvertent monotherapy and may decrease the frequency of acquired drug resistance and medication errors.[24,69] FDCs also reduce the number of tablets to be consumed and may thereby increase patient adherence to recommended treatment regimens.[85,86]

STANDARD 9. **To foster and assess adherence, a patient-centered approach to administration of drug treatment, based on the patient's needs and mutual respect between the patient and the provider, should be developed for all patients. Supervision and support should be gender-sensitive and age-specific and should draw on the full range of recommended interventions and available support services, including patient counseling and education. A central element of the patient-centered strategy is the use of measures to assess and promote adherence to the treatment regimen and to address poor adherence when it occurs. These measures should be tailored to the individual patient's circumstances and be mutually acceptable to the patient and the provider. Such measures may include direct observation of medication ingestion (directly observed therapy—DOT) by a treatment supporter who is acceptable and accountable to the patient and to the health system.**

Rationale and Evidence Summary

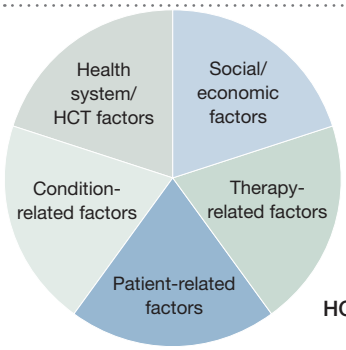
Assuming an appropriate drug regimen is prescribed, success of treatment for tuberculosis depends largely on patient adherence.

The approach described 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.[87] The success 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. Antituberculosis drug regimens, as described previously, 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 milieu, belief system, and living circumstances. Consequently, it is not surprising that, without appropriate treatment support, a significant proportion of patients with tuberculosis discontinue treatment before completion of the planned duration or are erratic in drug taking. Yet, failure to complete treatment for tuberculosis leads to prolonged infectivity, poor outcomes, and drug resistance.[88]

Adherence is a multi-dimensional phenomenon determined by the interplay of five sets of factors (dimensions), as illustrated in Figure 2 and Table 4.[87]

FIGURE 2.

The five dimensions of adherence[87]



HCT = Healthcare Team

Source: WHO, 2003[87]

TABLE 4.

Factors affecting adherence[87]

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

DOT = directly observed therapy; TB = tuberculosis;
(+) = factors having a positive effect on adherence; (-) = factors having a negative effect on adherence
Source: Modified from WHO, 2003[87]

When a second individual directly observes a patient swallowing medications, there is greater certainty that the patient is actually receiving the prescribed medications. This approach results in a high cure rate and a reduction in the risk of drug resistance.

Despite evidence to the contrary, there is a widespread tendency to focus on patient-related factors as the main cause of poor adherence.[87] Sociological and behavioral research during the past 40 years has shown that patients need to be supported, not blamed.[87] Less attention is paid to provider and health system-related factors. Several studies have evaluated various interventions to improve adherence to tuberculosis therapy. (These interventions are listed in Table 4.) There are a number of reviews that examine the evidence on the effectiveness of these interventions.[69, 87, 89, 90–95]

Among the interventions evaluated, DOT has generated the most debate and controversy.* The third component of the global DOTS strategy, now widely recommended as the most effective strategy for controlling tuberculosis worldwide, is the administration of a standardized, rifampicin-based regimen using case management interventions that are appropriate to the individual and the circumstances.[23,24,69,97] These interventions may include DOT as one of a range of measures to promote and assess adherence to treatment.

The main advantage of DOT is that treatment is carried out entirely under close, direct supervision.[92] 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. This approach, therefore, results in a high cure rate and a reduction in the risk of drug resistance. Also, because there is a close contact between the patient and the treatment supporter, adverse drug effects and other complications can be identified quickly and managed appropriately.[92] Moreover, such case management can also serve to identify and assist in addressing the myriad other problems experienced by patients with tuberculosis, such as undernutrition, poor housing, and loss of income, to name a few.

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, stigma, and physical hardship, all factors that can have an important effect on adherence.[87] Ideally, a flexible mix of health facility-based and community-based DOT should be available.

In a Cochrane systematic review that synthesized the evidence from six controlled trials comparing DOT with self-administered therapy,[89,90] the authors found that patients allocated to DOT and those allocated to self-administered therapy had similar cure rates (Risk Ratio [RR] 1.06, 95% Confidence Interval [CI] 0.98, 1.14); and rates of cure plus treatment completion (RR 1.06, 95% CI 1.00, 1.13). They concluded that direct observation of medication ingestion did not improve outcomes.[89,90]

In contrast, other reviews have found DOT to be associated with high cure and treatment completion rates.[24,69,91,92,98] Also, programmatic studies on the effectiveness of the DOTS strategy have shown high rates of treatment success in several countries.[87] It is likely that these inconsistencies across reviews are due to the fact that primary studies are often unable to separate the effect of DOT alone from the overall DOTS strategy.[87,94] In a retrospective review of programmatic results, the highest rates of success were achieved with

* There is an important distinction between directly observed treatment (DOT) and the DOTS strategy for tuberculosis control: DOT is one of a range of measures used to promote and assess adherence to tuberculosis treatment, whereas the DOTS strategy consists five components and forms the platform on which tuberculosis control programs are built.[96]

Treatment support measures, and not the treatment regimen itself, must be individualized to suit the unique needs of the patient.

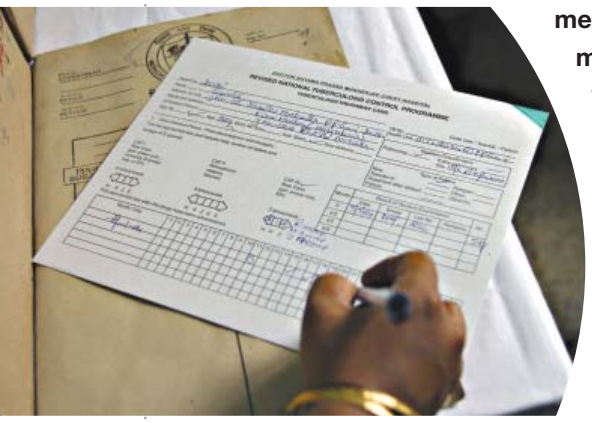
"enhanced DOT," which consisted of "supervised swallowing" plus social supports, incentives, and enablers as part of a larger program to encourage adherence to treatment.[91] Such complex interventions are not easily evaluated within the conventional randomized controlled trial framework.[87]

Interventions other than DOT have also shown promise.[87, 95] For example, interventions that used incentives, peer assistance, repeated motivation of patients, and staff training and motivation all have been shown to improve adherence significantly.[95] In addition, adherence may be enhanced by provision of more comprehensive primary care, as described in the Integrated Management of Adolescent and Adult Illness (IMAAI),[99-101] as well as by provision of specialized services such as opiate substitution for injection drug users.

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.[87] 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.

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.[3] Not only should the community expect that optimum treatment for tuberculosis is provided, but it also should expect and play a role in promoting conditions that facilitate and assist in ensuring that the patient will adhere to the prescribed regimen.

STANDARD 10. All patients should be monitored for response to therapy, best judged in patients with pulmonary tuberculosis by follow-up sputum smear microscopy (two specimens) at least at the time of completion of the initial phase of treatment (two months), at five months, and at the end of treatment. Patients who have positive smears during the fifth month of treatment should be considered as treatment failures and have therapy modified appropriately. (See Standards 14 and 15.) In patients with extrapulmonary tuberculosis and in children, the response to treatment is best assessed clinically. Follow-up radiographic examinations are usually unnecessary and may be misleading.



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. For the latter function, contact between the patient and a provider is necessary. To judge response of pulmonary tuberculosis to treatment, the most expeditious method is sputum smear microscopy. Ideally, where quality-assured laboratories are available, sputum cultures, as well as smears, should be performed for monitoring.

Patient monitoring is necessary to evaluate the response of the disease to treatment and to identify adverse drug reactions.

Having a positive sputum smear at completion of five months of treatment defines treatment failure, indicating the need for determination of drug susceptibility and initiation of a retreatment regimen.[23] Radiographic assessments, although used commonly, have been shown to be unreliable for evaluating response to treatment.[102] Similarly, clinical assessment can be unreliable and misleading in the monitoring of patients with pulmonary tuberculosis.[102] In patients with extrapulmonary tuberculosis and in children, clinical evaluations may be the only available means of assessing the response to treatment.

STANDARD 11. A written record of all medications given, bacteriologic response, and adverse reactions should be maintained for all patients.

Rationale and Evidence Summary

There is a sound rationale and clear benefits of a record keeping system.[103] It is common for individual physicians to believe sincerely 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.[103] The recording and reporting system enables targeted, individualized follow-up to identify patients who are failing therapy.[103] 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 to 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., multidrug-resistant 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 insure confidentiality of the information.

STANDARD 12. In areas with a high prevalence of HIV infection in the general population where tuberculosis and HIV infection are likely to co-exist, HIV counseling and testing is indicated for all tuberculosis patients as part of their routine management. In areas with lower prevalence rates of HIV, HIV counseling and testing is indicated for tuberculosis patients with symptoms and/or signs of HIV-related conditions and in tuberculosis patients having a history suggestive of high risk of HIV exposure.

Rationale and Evidence Summary

Infection with HIV both increases the likelihood of progression from infection with *M. tuberculosis* to active tuberculosis and changes the clinical manifestations of the disease.[32,104,105] 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.[32,104,105] 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 would influence 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 the history and physical examination include a search for indicators that suggest the presence of HIV infection. Table 5 presents clinical features that are suggestive of HIV infection.[105] A comprehensive list of clinical criteria/algorithms for HIV/AIDS diagnosis and clinical staging is available in the WHO document *Scaling up Antiretroviral Therapy in Resource-Limited Settings: Guidelines for a Public Health Approach* (Geneva, 2002).[106]

Tuberculosis is highly associated with HIV infection worldwide.[7,107] Although the prevalence of HIV infection varies widely among and within countries, in persons with HIV infection there is always an increased risk of tuberculosis. The 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 to 50–70% in countries with a high HIV prevalence, mostly sub-Saharan African countries.[7] Even though in low-HIV-prevalence countries few tuberculosis patients will be HIV-infected, the connection is sufficiently strong and the impact on the patient sufficiently great that the test should always be considered in managing individual patients, especially among groups in

Even though in low HIV prevalence countries few tuberculosis patients will be HIV-infected, the test should always be considered in managing individual patients, especially among groups in which the prevalence of HIV is higher.

which the prevalence 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. Thus, the indication for HIV testing is strong; co-infected patients may benefit by access to antiretroviral therapy as HIV treatment programs expand or through administration of co-trimoxazole for prevention of opportunistic infections, even when antiretroviral drugs are not available locally.[105,107,108]

TABLE 5.

Clinical features suggestive of HIV infection in patients with tuberculosis[105]

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

Source: Modified from WHO, 2004[105]

STANDARD 13. All patients with tuberculosis and HIV infection should be evaluated to determine if antiretroviral therapy is indicated during the course of treatment for tuberculosis. Appropriate arrangements for access to antiretroviral drugs should be made for patients who meet indications for treatment. Given the complexity of co-administration of antituberculosis treatment and antiretroviral therapy, consultation with a physician who is expert in this area is recommended before initiation of concurrent treatment for tuberculosis and HIV infection, regardless of which disease appeared first. However, initiation of treatment for tuberculosis should not be delayed. Patients with tuberculosis and HIV infection should also receive co-trimoxazole as prophylaxis for other infections.

All patients with tuberculosis and HIV infection either currently are, or will be, candidates for antiretroviral therapy.

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.[24,69,72,105,109–112] 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. With two exceptions, tuberculosis treatment regimens are the same for HIV-infected and non-HIV-infected patients. The first exception is that thioacetazone, a drug used commonly in the past but no longer recommended, is contraindicated in patients with HIV infection. Thioacetazone is associated with a high risk of severe skin reactions in HIV-infected individuals and should not be used.[24,105] Second, the results of treatment are better if a rifampicin-containing regimen is used throughout the six-month course of treatment.[72] Thus, the six-month regimen containing rifampicin throughout the entire course is preferable in patients with HIV infection to minimize the risk of relapse; however, the patient's HIV stage, the need for (and availability of) antiretroviral drugs, and the quality of treatment supervision/support must be considered in choosing an appropriate continuation phase of therapy.

All patients with tuberculosis and HIV infection either currently are, or will be, candidates for antiretroviral therapy. Antiretroviral therapy results in remarkable reductions in morbidity and mortality in HIV-infected persons and may improve the outcomes of treatment for tuberculosis. Highly active antiretroviral therapy (HAART) is the internationally accepted standard of care for persons with advanced HIV infection.

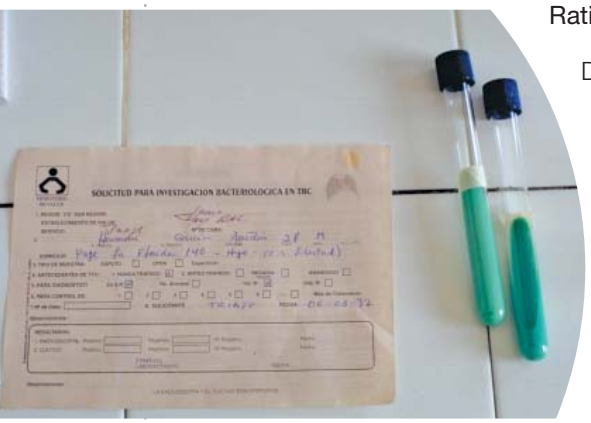
In patients with HIV-related tuberculosis, treating tuberculosis is the first priority. In the setting of advanced HIV infection, untreated tuberculosis can progress rapidly to death. As noted above, however, antiretroviral treatment may be lifesaving for patients with advanced HIV infection. Consequently, concurrent treatment may be necessary in patients with advanced HIV disease (e.g., circulating CD4+ T lymphocyte count <200/μL). It should be emphasized, however, that treatment for tuberculosis should not be interrupted in order to initiate antiretroviral therapy, and, in patients with early stage HIV infection, it may be safer to defer antiretroviral treatment until at least the completion of the initial phase of tuberculosis treatment.[105]

There are a number of problems associated with concomitant therapy for tuberculosis and HIV infection. These include overlapping toxicity profiles for the drugs used, drug-

drug interactions (especially with rifamycins and protease inhibitors), potential problems with adherence to multiple medications, and immune reconstitution reactions.[69,105] Consequently, consultation with an expert in HIV management is needed in deciding when to start antiretroviral drugs, the agents to use, and the plan for monitoring for adverse reactions and response to both therapies. (For a single-source reference on the management of tuberculosis in patients with HIV infection see the WHO manual *TB/HIV: A Clinical Manual*.[105])

Patients with tuberculosis and HIV infection should also receive co-trimoxazole (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.[105,107,113–118]

STANDARD 14. An assessment of the likelihood of drug resistance, based on history of prior treatment, exposure to a possible source case having drug-resistant organisms, and the community prevalence of drug resistance, should be obtained for all patients. Patients who fail treatment and chronic cases should always be assessed for possible drug resistance. For patients in whom drug resistance is considered to be likely, culture and drug susceptibility testing for isoniazid, rifampicin, and ethambutol should be performed promptly.



Rationale and Evidence Summary

Drug resistance is largely man-made and is a consequence of suboptimal regimens and treatment interruptions. Clinical errors that commonly lead to the emergence of drug resistance include: failure to provide effective treatment support and assurance of adherence; failure to recognize and address patient non-adherence; inadequate drug regimens; adding a single new drug to a failing regimen; and failure to recognize existing drug resistance.[119] In addition, co-morbid conditions associated with reduced serum levels of antituberculosis drugs (e.g., malabsorption, rapid transit diarrhea, HIV infection, or use of antifungal agents) may also lead to the acquisition of drug resistance.[119]

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.[119] Patients with drug-resistant tuberculosis can spread the disease to their contacts. Transmission of drug-resistant strains of *M. tuberculosis* has been well described in congregate settings and in susceptible populations, notably HIV-infected persons.[120–123] 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 China, the Baltic States, and countries of the former Soviet Union.

The strongest factor associated with drug resistance is previous antituberculosis treatment, as shown by the WHO/IUATLD Global Project on Anti-TB Drug Resistance Surveillance, started in 1994.[124] In previously treated patients, the odds of any resistance are at least fourfold higher and that of MDR at least tenfold higher than in new (untreated)

Clinical errors that commonly lead to the emergence of drug resistance include: failure to provide effective treatment support and assurance of adherence; failure to recognize and address patient non-adherence; inadequate drug regimens; adding a single new drug to a failing regimen; and failure to recognize existing drug resistance.

patients.[124] Patients with chronic tuberculosis (sputum-positive after retreatment) and those who fail treatment (sputum-positive after five months of treatment) are at highest risk of having MDR tuberculosis, especially if rifampicin was used throughout the course of treatment.[124] 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.[119–124]

Drug susceptibility testing (DST) to the first-line antituberculosis drugs should be performed in specialized reference 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 retreatment regimen, and chronic cases are the highest priority.[119] 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.[119]

STANDARD 15. Patients with tuberculosis caused by drug-resistant (especially MDR) organisms should be treated with specialized regimens containing second-line antituberculosis drugs. At least four drugs to which the organisms are known or presumed to be susceptible should be used, and treatment should be given for at least 18 months. Patient-centered measures are required to ensure adherence. Consultation with a provider experienced in treatment of patients with MDR tuberculosis should be obtained.

Rationale and Evidence Summary

Because randomized controlled treatment trials for MDR tuberculosis would be extremely difficult to design, none have been conducted. Current recommendations are, therefore, based on observational studies, general microbiological and therapeutic principles, extrapolation from available evidence from pilot MDR tuberculosis treatment projects, and expert opinion.[125,126] Three strategic options for treatment of MDR tuberculosis are currently recommended by WHO: standardized regimens, empiric regimens, and individualized treatment regimens. The choice among these 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.[119] 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 at

least six months, treatment duration of 18–24 months, and DOT throughout the treatment course.

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

Three strategic options for treatment of MDR tuberculosis are currently recommended by WHO: standardized regimens, empiric regimens, and individualized treatment regimens.

Empiric treatment regimens are commonly used in specific groups of patients while the DST results are pending. Unfortunately, most of the available DST methods have a turnaround time of several months. 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.[119] 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 previous 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. However, an individualized approach requires access to substantial human, financial, and technical (laboratory) capacity. DST 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.[127] 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.[124,127] Clinicians treating MDR tuberculosis patients must be aware of these limitations and interpret DST results with this in mind.

Current WHO recommendations for treatment of MDR tuberculosis can be found at (http://www.who.int/tb/en/).[119] MDR tuberculosis treatment is a complex health intervention, and medical practitioners are strongly advised to consult colleagues experienced in the management of these patients.

Standards for Public Health Responsibilities

The 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 barriers to optimum tuberculosis control practices.

STANDARD 16. All providers of care for patients with tuberculosis should ensure that persons (especially children under 5 years of age and persons with HIV infection) who are in close contact with patients who have infectious tuberculosis are evaluated and managed in line with international recommendations. Children under 5 years of age and persons with HIV infection who have been in contact with an infectious case should be evaluated for both latent infection with *M. tuberculosis* and for active tuberculosis.

Rationale and Evidence Summary

The risk of acquiring infection with *M. tuberculosis* is correlated with intensity and duration of exposure to a person with infectious tuberculosis. Close contacts of patients with tuberculosis, therefore, are at high risk for acquiring the infection. 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 (LTBI).[128,129]

The potential yield of contact investigation in high- and low-incidence settings has been reviewed previously.[128,129] In low-incidence settings (e.g., United States), it has been found that, on average, 5–10 contacts are identified for each incident tuberculosis case. Of these, about 30% are found to have latent tuberculosis infection, and another 1–4%

have active tuberculosis.[128,130,131] Much higher rates of both latent infection and active disease have been reported in high-prevalence countries, where about 50% of household contacts have latent infection, and about 10–20% have active tuberculosis at the time of initial investigation.[129] A recent systematic review of more than 50 studies on household contact investigations in high incidence settings showed that, on average, about 6% (range 0.5–29%; N=40 studies) of the contacts were found to have active tuberculosis.[132] The median number of household contacts that were evaluated to find one case of active tuberculosis was 19 (range 14–300).[132] The median proportion of contacts found to have latent infection was 49% (range: 7–90%; N= 34 studies).[132] The median number of contacts that were evaluated to find one person with latent tuberculosis infection was 2 (range 1–14).[132] Evidence from this review suggests that contact investigation in high-incidence settings is a high-yield strategy for case finding.

Among close contacts, there are certain subgroups that are particularly at high risk for acquiring the infection with *M. tuberculosis* and progressing rapidly to active disease—children and persons with HIV infection. Children (particularly those under the age of 5 years) are a vulnerable group, not only because of the high likelihood of progressing from latent infection to active disease, but because they are more likely to develop disseminated and serious forms of tuberculosis such as meningitis. The Union, therefore, recommends that children under the age of 5 years living in the same household as a sputum smear-positive tuberculosis patient should be targeted for preventive therapy (after exclusion of tuberculosis to prevent *de facto* monotherapy of tuberculosis).[65,129] Similarly, contacts who have HIV infection are at substantially greater risk for progressing to active tuberculosis.

Unfortunately, lack of adequate staff and resources in many areas makes contact investigation difficult.[65,129] 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.

STANDARD 17. All providers must report both new and retreatment tuberculosis cases and their treatment outcomes to local public health authorities, in conformance with applicable legal requirements and policies.

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 healthcare institutions, as well as individual practitioners.

An effective reporting system 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 reportable disease. A system of recording and reporting information on tuberculosis cases and their treatment outcomes is one of the key elements of the DOTS strategy.[103] 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.[103]

Reporting tuberculosis cases to the local tuberculosis control program is an essential public health function. The recording and reporting system allows for targeted, individualized follow-up to help patients.

The recording and reporting system allows for targeted, individualized follow-up to help patients who are not making adequate progress (i.e., failing therapy).[103] 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.

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.

Research Needs

Research in operational and clinical areas serves to complement ongoing efforts focused on developing new tools for tuberculosis control—new diagnostic tests, drugs, and vaccines.

As part of the process of developing the *ISTC*, several key areas that require additional research were identified (Table 6). Systematic reviews and research studies (some of which are underway currently) in these areas are critical to generate evidence to support rational and evidence-based care and control of tuberculosis. Research in these operational and clinical areas serves to complement ongoing efforts focused on developing new tools for tuberculosis control—new diagnostic tests,[133] drugs,[134] and vaccines.[135]

Key areas requiring additional research include:

- Diagnosis and case finding
- Treatment, monitoring, and support
- Public health and operational research

TABLE 6.

Priority areas for research and evaluation

AREA OF RESEARCH	SPECIFIC RESEARCH QUESTIONS
Diagnosis and case finding	■ What is the sensitivity and specificity of various thresholds for chronic cough (e.g., two versus three weeks) as a screening test to determine who should be evaluated for tuberculosis? How do local conditions such as the prevalence of tuberculosis, HIV infection, asthma, and chronic obstructive pulmonary disease (COPD) influence the threshold? ■ What is the optimal diagnostic strategy/algorithm for establishing a diagnosis of tuberculosis in patients suspected of having the disease but who have negative sputum smears? Should the strategy be modified in patients with HIV infection? ■ What is the optimal diagnostic algorithm for children with suspected tuberculosis? ■ What is the role of therapeutic antibiotic trials in the diagnosis of smear-negative tuberculosis? ■ What is the value and role of sputum concentration in improving the accuracy and yield of smear microscopy? ■ What is the impact of bleach treatment of sputum on the accuracy and yield of sputum smear microscopy? ■ What is the role, feasibility, and applicability of fluorescent microscopy in routine field conditions in areas of both high and low HIV prevalence? ■ Is there a role for more intensive case finding in high-HIV-endemic settings? ■ What is the contribution of routine use of culture in tuberculosis care and control in high-prevalence areas? ■ Is there a role for rapid culture methods in tuberculosis control programs? ■ What factors lead to delays in establishing a diagnosis of tuberculosis? ■ What is the impact of engaging former (or current) TB patients and/or patient organizations in active case finding? ■ What is the role reporting by components of the healthcare system other than direct patient care providers?
Treatment, monitoring, and support	■ What interventions are effective in improving patient (adults and children) adherence to antituberculosis therapy? ■ What is the efficacy of direct observation of treatment (DOT) versus other measures to improve adherence to treatment? ■ What is the role of fixed-dose combinations (FDCs) in improving adherence? ■ What is the optimal duration of antituberculosis therapy for patients who are HIV-positive? ■ What interventions help in reducing mortality among tuberculosis patients who have HIV infection? ■ What is the effectiveness of standardized versus individualized treatment regimens in the management of mono-resistant and MDR tuberculosis? ■ What is the relevance of second-line drug susceptibility test results in determining individualized retreatment regimens? ■ What are the optimal drug doses and duration of treatment for children? ■ What is the impact of engaging former (or current) TB patients or patient organizations in improving adherence?
Public health and operational research	■ What is the effect of the DOTS strategy on tuberculosis transmission in populations with high rates of MDR tuberculosis? ■ What is the impact of HIV infection on the effectiveness of DOTS programs? ■ What interventions or measures are helpful in improving tuberculosis management practices in private practitioners? ■ What is the impact of treatment of latent tuberculosis infection on tuberculosis burden in high-HIV-prevalence settings? ■ What is the impact of engaging former (or current) patients and/or patient organizations in improving tuberculosis control programs in regions with insufficient human resources? ■ What are the optimum models for integration of tuberculosis and HIV care?

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