

Compendium of WHO guidelines and associated standards: ensuring optimum delivery of the cascade of care for patients with tuberculosis

Second edition - June 2018

END TB STRATEGY
POLICY
SCREENING
EARLIER DETECTION
DIAGNOSIS
TREATMENT
THE COMPENDIUM
DRUG-RESISTANCE
XDR-TB
TB/HIV
MONITORING & EVALUATION
COMMUNITY ENGAGEMENT
LTBI
COMORBID CONDITIONS
PATIENT CARE AND SUPPORT
MDR-TB
TB IN CHILDREN
PALLIATIVE CARE
COMMUNITY
DIGITAL HEALTH
ETHICS
INFECTION CONTROL

THE
END TB
STRATEGY



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of WHO guidelines
and associated standards:
ensuring optimum delivery of the cascade
of care for patients with tuberculosis**

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Foreword

Tuberculosis (TB) is the single leading infectious cause of mortality. Ending the TB epidemic is one of the targets of the Sustainable Development Goals (SDGs) that requires intensive action by all countries, especially those with a high TB burden. The World Health Organization (WHO) End TB Strategy encompasses a package of interventions organized around the three pillars of integrated patient-centered care and prevention, bold policies and supportive systems and intensified research and innovation that should be adapted at country level. The End TB strategy requires the implementation of a combination of biomedical, public health and socioeconomic activities to accelerate the decline in global TB incidence and mortality rates while addressing all of the determinants of the TB epidemic with high-level commitment and a multisectoral approach.

The Global Ministerial Conference in Moscow in November 2017 created a new wave of hope for tackling several of the major hurdles hampering progress in the response to TB. The Moscow Declaration to End TB set out the commitments by Member States, and calls for specific actions by WHO and by partners, including civil society, at global and country level. These actions include ensuring sufficient and sustainable financing, pursuing science, research and innovation while recognizing that acceleration of progress toward the goal of ending TB requires action across the health sector and beyond. The Moscow Declaration also called for the development of a multisectoral accountability framework for TB that can be used to galvanize and sustain political commitment and action on TB at both global and national levels.

The global TB response is on the brink of a new era and the Moscow Declaration has helped to pave the way for the UN General Assembly High-Level Meeting on TB to be held in New York in September 2018. The UNGA High Level Meeting represents a unique opportunity to raise the profile of TB and secure the political commitment at the level of Heads of State to catalyze change towards reinvigorated and transformative TB efforts.

The Compendium of WHO TB guidelines and associated standards has been updated as a necessary guide to facilitate access to quality-assured diagnosis, treatment and care for all persons affected by TB.

Dr Tereza Kasaeva
Global TB Programme

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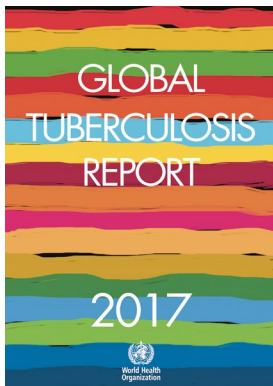
Abbreviations

aDSM	active TB drug safety monitoring and management
ART	antiretroviral therapy
BCG	bacille Calmette–Guérin
CPT	co-trimoxazole preventive therapy
CXR	chest X-ray
DOT	directly observed treatment
DST	drug-susceptibility testing
EPTB	extrapulmonary tuberculosis
FDC	fixed-dose combination
IGRA	interferon gamma release assay
LF-LAM	lateral flow urine lipoarabinomannan assay
LPA	line probe assay
LTBI	latent tuberculosis infection
MDGs	Millennium Development Goals
MDR-TB	multidrug-resistant tuberculosis
NGO	nongovernmental organization
NTP	National tuberculosis programme
RR-TB	rifampicin-resistant tuberculosis
SAT	self-administered treatment
SDGs	Sustainable Development Goals
TB	tuberculosis
TB-LAMP	loop-mediated isothermal amplification for detection of <i>Mycobacterium tuberculosis</i>
TST	tuberculin skin test
UV	ultraviolet
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

1. Introduction

The World Health Organization (WHO) estimates that 10.4 million persons developed tuberculosis (TB) worldwide in 2016, corresponding to a global incidence of 140 TB cases per 100 000 population. Of those who developed TB, 1.0 million cases (10%) occurred among persons living with HIV. The worldwide total for 2016 also included 490 000 cases of multidrug-resistant TB (MDR-TB) and 110 000 cases of rifampicin-resistant TB (RR-TB), needing the same second-line treatment regimen. In the same year, 1.67 million deaths were caused by TB, including 374 000 among persons living with HIV and nearly 240 000 among patients with MDR-TB or RR-TB.¹ These numbers make TB the top infectious killer worldwide, well above the number of deaths from HIV/AIDS or malaria, and one of the top 10 causes of deaths in 2016.

domestically and internationally, through new mechanisms, notably The Global Fund to Fight AIDS, Tuberculosis and Malaria, established in 2002 and currently providing nearly 85% of international financing for TB services.² As a result of these efforts the MDG-related target to “have halted by 2015 and begun to reverse” TB incidence was achieved; 53 million lives were saved; and mortality was reduced by 37% since 1990. However, the annual decline in incidence rate has been only 1.4% on average worldwide, or 19% since 2000, suggesting that much more needs to be done and more resources invested to combat the disease, both in terms of implementing existing measures and performing research to develop new tools. With the end of the MDG era in 2015, it was clear that reinvigorated and intensified prevention, care and control efforts would be crucial to accelerating the decline of incidence and deaths.



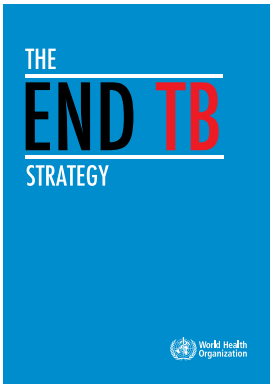
Global Tuberculosis Report 2017¹

Serious challenges remain in tackling the TB epidemic, among them more than 4 million missed cases (undetected or not notified), the MDR-TB crisis, a suboptimal response to the TB and HIV co-epidemics, catastrophic costs for TB patients, the slow uptake of new tools, and significant gaps in financing for research and for service delivery. These gaps culminate in patients with TB not receiving the best possible care, despite significant technological innovations introduced during the past 10 years.

Since the beginning of the Millennium Development Goal (MDG) era in 2000, efforts to control TB have been intensified, with increased commitments to implementing practices aligned with WHO’s recommendations. An era of increased financing followed, both

1 Global tuberculosis report 2017. Geneva: World Health Organization; 2017 (WHO/HTM/TB/2017.23; http://www.who.int/tb/publications/global_report/en/, accessed 1 May 2018).
2 Tuberculosis. In: The Global Fund [website]. Geneva: The Global Fund to Fight AIDS, Tuberculosis and Malaria; 2017 (<http://www.theglobalfund.org/en/tuberculosis/>, accessed 1 May 2018).

1.1 The END TB Strategy

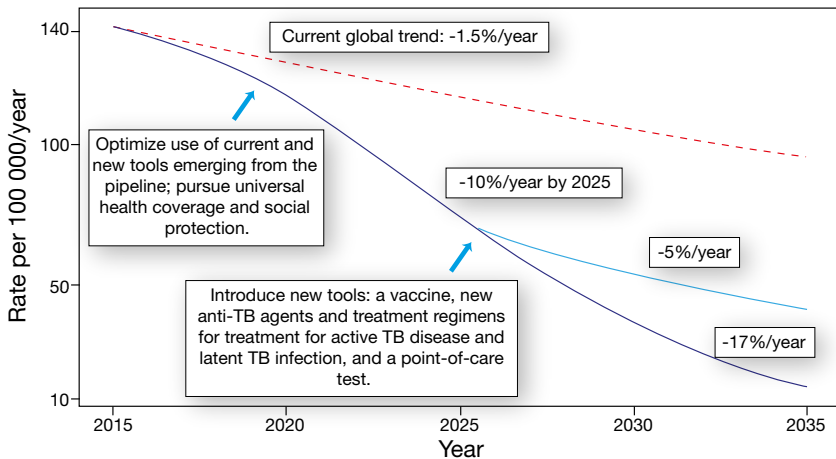


The End TB Strategy³

WHO’s End TB Strategy³, developed within the context of the United Nations Sustainable Development Goals (SDGs), is a logical evolution, reflecting a paradigm shift from past global TB

strategies. The original WHO DOTS strategy of 1994 created the basis for effective TB control activities by standardizing the requirements for addressing the epidemic. WHO’s Stop TB Strategy of 2006 broadened this response by addressing the emerging challenges of HIV-associated TB and MDR-TB⁴. It contributed to improving access to quality TB care by engaging all public and private care providers, and civil society organizations and communities, and it encouraged investment in research to develop better tools and approaches. Ending the TB epidemic is one of the SDG targets that requires the implementation of a mix of biomedical, public health and socioeconomic interventions, often extending beyond the health sector, along with major breakthroughs in research and innovation to accelerate the decline in global TB incidence rates to reach the 2030 and 2035 targets for the End TB Strategy (Fig. 1).³

Fig. 1. Projected global trajectory of TB incidence rate 2015-2035 required to reach 2035 targets of the End TB Strategy



3 The End TB Strategy: global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva: World Health Organization; 2014 (http://www.who.int/tb/strategy/End_TB_Strategy.pdf, accessed 1 May 2018).

4 The Stop TB Strategy: building on and enhancing DOTS to meet the TB-related Millennium Development Goals. Geneva: World Health Organization; 2006 (WHO/HTM/TB/2006.368; http://apps.who.int/iris/bitstream/10665/69241/1/WHO_HTM_STB_2006.368_eng.pdf, accessed 1 May 2018).

WHO's End TB Strategy was endorsed by all Member States through a resolution at the Sixty-seventh World Health Assembly in 2014. The End TB Strategy encompasses a comprehensive package of interventions based on three fundamental pillars and four underlying principles (Fig. 2). The essential components for implementing the End TB Strategy⁵ (*The Essentials*) provide a framework that allows countries to adopt and to adapt their approach to ending the TB epidemic.



END TB Strategy (*The Essentials*)⁵

Fig. 2. WHO's End TB Strategy: three fundamental pillars and four underlying principles



1.2 Scope of the Compendium

This document focuses on the first pillar of WHO's End TB strategy – that is, activities related to integrated, patient-centred care and prevention for early detection, treatment and care of all TB patients, including children. Implementing this approach requires close collaboration among all stakeholders, including the social sector, civil society and local communities. The aim is to ensure that the patient's needs, values, preferences and rights inform the access and delivery of services.

The operational and financing approaches to enable universal access to quality care are addressed in the guidance provided in "*The Essentials*" document and other tools for national strategic planning and operational implementation.

This Compendium is organized to follow the pathway of persons with signs or symptoms of TB in seeking care and also to include cross-cutting elements essential to the patient-centred approach to care delivery that is recommended by WHO. The document also

5 Implementing The End TB Strategy: the essentials. Geneva: World Health Organization; 2015 (WHO/HTM/TB/2015.31; http://www.who.int/tb/publications/2015/end_tb_essential.pdf?ua=1 accessed 1 May 2018).

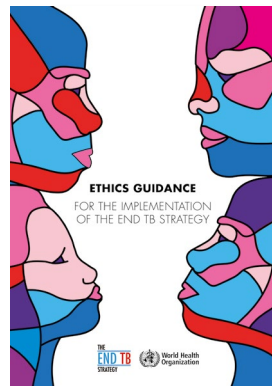
addresses TB preventive care, principally treatment for latent TB infection. It consolidates all WHO policy recommendations, and outlines WHO’s standards for patient-centred care. This compilation of standards, prepared on the lines of the International Standards of TB Care⁶ and enriched further with easy access to source documents, is meant to meet the needs not only of national TB programmes (NTPs) and public health physicians but also the clinicians working in the private, corporate and voluntary sectors.

1.3 Ethical Considerations

WHO’s End TB Strategy and the UN SDGs, which target ending the TB epidemic by 2030, call for due attention to equity, human rights and ethics. The “protection and promotion of human rights, ethics and equity” is one of the four key principles of the Strategy.

As stated in WHO’s Constitution, “the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition”⁷. Similarly, the International Covenant on Economic, Social and Cultural Rights establishes “the right of everyone to the enjoyment of the highest attainable standard of physical and mental health” (that is, the right to health), and specifically calls on states to take steps necessary for “the prevention, treatment and control of epidemic, endemic, occupational and other diseases”.⁸ Promoting social justice and equity in TB programmes should take into account the needs of all patients and, in particular, the special needs of socially vulnerable groups for whom tailored interventions should be proactively developed. Interventions should be gender-sensitive and address different types of vulnerabilities.

Governments and national TB programmes, with the support of the international community, have an ethical obligation to provide universal access to TB care according to international standards, including as a critical part of that care, providing quality-assured essential medicines, care and social support. WHO’s ethics guidance for the implementation of the End TB Strategy presents a comprehensive review and discussion of the most relevant considerations for clinical and programmatic management of TB prevention, diagnosis, treatment and care⁹.



Ethics Guidance for implementing the End TB Strategy⁹

1.4 Community Engagement

National TB programmes should systematically implement integrated, community-based TB activities by engaging communities, nongovernmental organizations (NGOs) and other civil society organizations. Community-based TB activities are wide-ranging and contribute to preventing and diagnosing TB, and improving treatment adherence and care to positively influence the outcomes of drug-sensitive, drug-resistant and HIV-associated TB.

6 International Standards for Tuberculosis Care; 2014 (third edition).

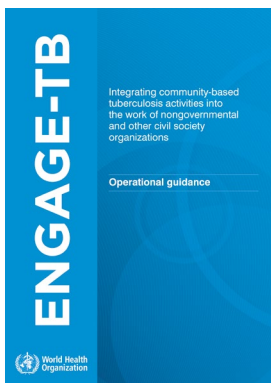
http://www.who.int/tb/publications/ISTC_3rdEd.pdf?ua=1

7 Constitution of the World Health Organization. In: Basic documents. Geneva: World Health Organization; 2006 (http://www.who.int/governance/eb/who_constitution_en.pdf, accessed 1 May 2018).

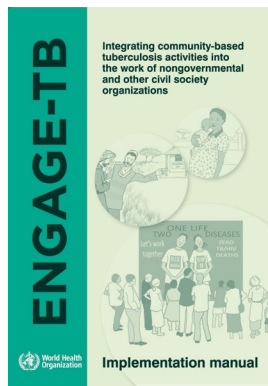
8 International Covenant on Economic, Social and Cultural Rights. Geneva: Office of the United Nations High Commissioner for Human Rights; 1966 (<http://www.ohchr.org/Documents/ProfessionalInterest/cescr.pdf>, accessed 1 May 2018).

9 Ethics Guidance for implementing the End TB Strategy. Geneva. World Health Organization; 2017 (WHO/HTM/TB 2017.07) <http://apps.who.int/iris/bitstream/10665/254820/1/9789241512114-eng.pdf?ua=1>, accessed 1 May 2018).

These activities include mobilizing communities to promote effective communication and participation among community members to generate demand for TB prevention, diagnosis, treatment and care services. Although diagnostic tests continue to be performed in clinical settings due to a lack of simple diagnostic methods, community-based TB activities are conducted outside formal health facilities (such as hospitals, health centres and clinics) and in community-based settings (such as schools, places of worship and other congregate settings) and homes. To improve synergies and the impact of such activities, community-based TB interventions should be integrated with other activities that support primary health-care services, including those targeting HIV infection, maternal and child health, and noncommunicable diseases. Community-based TB activities utilize mechanisms through which community members, community-based organizations and groups interact to coordinate and deliver their responses to the challenges and needs affecting their communities. WHO's ENGAGE-TB approach provides policy and programme guidance to promote the systematic engagement of NGOs and other civil society organizations in delivering integrated community-based TB activities.^{10, 11}



Engage TB Approach – Operational Guidance¹⁰



Engage TB Approach – Implementation Manual¹¹



1.5 Public-Private Mix to engage all care providers

Engaging all relevant health care providers in TB care through public-private mix (PPM) approaches is an essential component of the WHO End TB Strategy. PPM for TB prevention and care represents a comprehensive approach for systematic involvement of all relevant health care providers in TB care to promote the use of International Standards for TB Care and contribute constructively to achieve national and global End TB targets. Global guidelines on various aspects of TB care are often developed for the purpose of NTPs. This compendium presents a handy guide not only for NTPs but also for public and private physicians to enable them to put evidence-based WHO policies and international standards into routine practice. PPM encompasses diverse collaborative strategies such as public-private (between NTP and the private sector), public-public (between NTP and other public sector care providers such as general hospitals, prison or military health services and social security organizations), and private-private (between an NGO or a private hospital and the neighborhood private



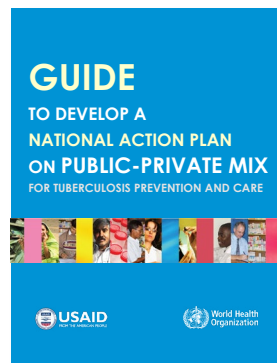
10 Engage-TB: integrating community-based tuberculosis activities into the work of nongovernmental and other civil society organizations. Operational guidance. Geneva: World Health Organization; 2012 (WHO/HTM/TB/2012/8; http://apps.who.int/iris/bitstream/10665/75997/1/9789241504508_eng.pdf?ua=1, accessed 1 May 2018).

11 Engage-TB: integrating community-based tuberculosis activities into the work of nongovernmental and other civil society organizations. Implementation manual. Geneva: World Health Organization; 2013 (WHO/HTM/TB/2013.10; http://apps.who.int/iris/bitstream/10665/96900/1/9789241506540_eng.pdf?ua=1, accessed 1 May 2018).

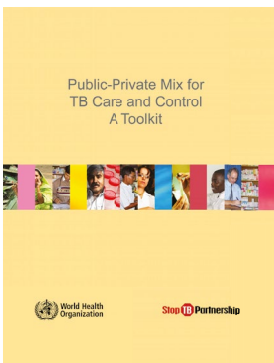
providers) collaboration. These collaborations are required because individual and institutional care providers especially in the private sector are often unable to carry out, on their own, all the clinical and public health tasks essential in the delivery of high-quality TB care. PPM also implies engaging relevant care providers in prevention and management of MDR-TB and in the implementation of TB/HIV collaborative activities.

The WHO policy and accompanying toolkit¹² on engaging all care providers in TB prevention and care provides guidance on practical steps that countries should undertake to involve various providers in efforts to combat TB. A guide to develop a national TB PPM action plan¹³ has been developed as an important addition to the PPM toolkit. The Guide – is a planning document designed to facilitate the integration of strong PPM components into national TB strategic plans that are the basis for Global Fund proposals and national budgeting processes. In addition, the PPM national action plan development process provides an opportunity to engage multisectoral stakeholders, and raise awareness and commitment about the need to leverage the entire health system in order to reach public health goals in TB and beyond.

It is crucial that PPM is planned based on a national situation assessment. NTPs are mandated to shoulder the stewardship role, to ensure that technical standards are met, drugs are provided free of charge to patients, and that all aspects of coordination, training, contracting, supervision and surveillance are carried out as per NTP guidelines. Suitable roles for different health care providers should be defined and enabled according to the need of the programme, and the capacity and willingness of different health care providers.



Guide to develop a national action plan on public-private mix for tuberculosis prevention and care¹³



Public-Private Mix Toolkit¹²

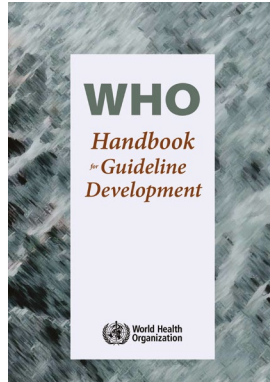
12 Public-private mix for TB care and control: A toolkit. Geneva: World Health Organization; 2010. http://apps.who.int/iris/bitstream/10665/44450/1/9789241500487_eng.pdf?ua=1&ua=1, accessed 1 May 2018).

13 Guide to develop a national action plan on public-private mix for tuberculosis prevention and care. Geneva: World Health Organization; 2018.

http://www.who.int/tb/publications/2017/Final_Tool_PPM_action_plan.pdf?ua=1, accessed 1 May 2018).

2. WHO's policy development process

WHO uses the GRADE (Grading of Recommendations Assessment, Development and Evaluation)¹⁴ approach to assess the quality of a body of evidence, and to develop and report recommendations. The detailed policy recommendations referred to in this compendium of guidelines qualify their strength as well as the certainty of the evidence on which they are based. The recommendation should be read along with the accompanying remarks that summarize the evidence upon which the recommendation was made, the anticipated desirable and undesirable effects of the interventions (to assess the balance between expected benefits and risks), and other considerations that are important for the implementation of the policies. The certainty of evidence is categorized into four levels (Table 1).



WHO Handbook for Guideline Development¹⁴

Table 1. Certainty of evidence and definitions

Certainty of evidence	Definition
High (⊕⊕⊕⊕)	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate (⊕⊕⊕)	Further research is likely to have an important impact on our confidence in the effect and may change the estimate.
Low (⊕⊕)	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very Low (⊕)	Any estimate of effect is very uncertain.

A number of factors may increase or decrease the certainty of evidence. The highest rating is usually assigned to data from randomized controlled trials (or RCTs) while evidence from observational studies is usually assigned a low or very low quality value at the start of the process. Quality of the evidence can be down-graded or up-graded based on the specific elements of the GRADE evidence assessment process as outlined in the WHO Handbook on Guideline Development.

A recommendation may be strong or conditional. Apart from the quality of evidence, the strength of a recommendation is determined by the balance between desirable and undesirable effects, values and preferences, and considerations of equity, resource use and feasibility. For strong recommendations, the GRADE assessment shows that the desirable effects of an intervention clearly outweigh the undesirable effects and that the intervention will benefit most (if not all) public health

14 Handbook for Guideline Development 2nd Ed. Geneva: World Health Organization; 2014 http://www.who.int/publications/guidelines/handbook_2nd_ed.pdf?ua=1, accessed 1 May 2018.

programmes and patients. The reverse may also hold, ie. that undesirable effects clearly outweigh anticipated benefits, which would lead to a strong recommendation against an intervention. For conditional recommendations, the GRADE assessment considers that desirable effects probably outweigh the undesirable effects in most settings and for most public health programmes and patients. Conditional recommendations therefore always outline the desired considerations/conditions for implementation of the actual WHO policy guidance. The conditionality

of any recommendation by WHO should therefore never be an impediment to national TB programmes to adopting and scaling-up innovations to improve TB diagnosis, treatment and care. At times a clinical question remains unanswered after review of available data; in such a situation no evidence-informed recommendation is possible. The decision to make no recommendation is different from a negative recommendation (for which there is evidence against the use of a certain intervention).

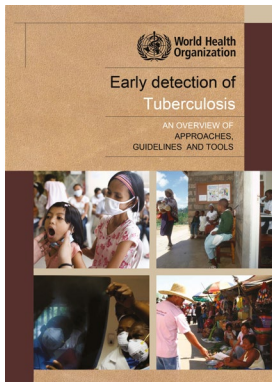
3. Early detection of TB

WHO TB Standard 1. For persons with signs or symptoms consistent with TB, performing prompt clinical evaluation is essential to ensure early and rapid diagnosis.

Health-care workers may delay or fail to undertake promptly the clinical evaluation of persons presenting with symptoms suggestive of TB. Therefore, all health-care workers in all relevant public and private health-care facilities should be sensitive to the need to identify and evaluate persons suspected of having TB, especially those with respiratory symptoms¹⁵. Health-care workers should also be aware of the need to pay special attention to risk groups that are common to all settings and those that are specific to the settings in which they work.

- with known or suspected immunocompromising conditions, particularly HIV infection;
- who have been in contact with patients with MDR-TB or extensively drug-resistant (XDR) TB.

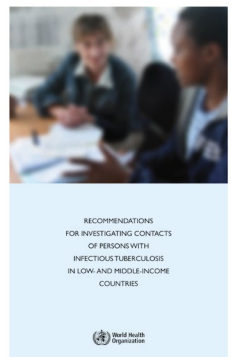
Evidence indicates that in both high- and low-incidence countries, the prevalence of TB among contacts is high, particularly among household members¹⁶. Evidence also suggests that contact investigations could be particularly useful for identifying childhood TB. Furthermore, contact investigation can help identify persons who require careful follow up, such as those who were exposed to an index case with MDR- or XDR- TB and persons infected with HIV or who have other factors that put them at risk for rapid progression to active TB. Effective investigation of TB contacts within national TB programmes and other services can result in the detection of a significant number of cases. Early identification means a better chance of cure and, potentially, a reduction in further transmission. Furthermore, contact investigation allows for the identification of persons who have latent infection and are at a high risk for active TB, so they can receive preventive treatment.



An overview of approaches guidelines and tools¹⁵

WHO TB Standard 2. All persons who have been in close contact with patients who have pulmonary TB should be evaluated. The highest priority contacts for evaluation are those:

- with signs or symptoms suggestive of TB;
- aged < 5 years;



Investigating contacts of persons with infectious tuberculosis¹⁶

15 Early detection of tuberculosis: An overview of approaches, guidelines and tools. Geneva: World Health Organization (WHO/HTM/STB/PSI/2011.21 http://apps.who.int/iris/bitstream/handle/10665/70824/WHO_HTM_STB_PSI_2011.21_eng.pdf?sequence=1&isAllowed=y, accessed 1 May 2018).

16 Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. Geneva: World Health Organization (WHO/HTM/TB/2012.9 http://apps.who.int/iris/bitstream/10665/77741/1/9789241504492_eng.pdf?ua=1, accessed 1 May 2018).

WHO TB Standard 3. All persons living with HIV and workers who are exposed to silica should always be screened for active TB in all settings. Other high risk groups should be prioritized for screening based on the local TB epidemiology, health system capacity, resource availability and feasibility of reaching the risk groups.

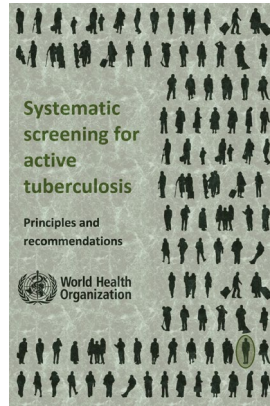
Indiscriminate mass screening should be avoided while risk groups should be prioritized for screening based on careful assessment of local TB epidemiology, potential benefits and risks of harm of screening, and alternative interventions to improve early TB detection^{17, 18}. People with very high risk of TB or severe consequences of delayed TB diagnosis should be prioritized first:

- persons in prisons and other penal institutions, and prison staff;
- persons with an untreated fibrotic lesion on chest X-ray (CXR);
- persons in settings where there is a high burden of TB (an estimated prevalence >100/100 000 in the general population) who are seeking care or who are in care and belong to selected risk groups), and health-care workers in these settings;
- geographically defined subpopulations with extremely high levels of undetected TB (>1% prevalence) and other subpopulations with very poor access to health care.

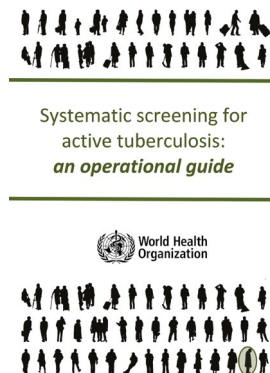
Early detection of TB is essential to further improve health outcomes for people with TB, and to reduce TB transmission more effectively. Systematic screening in high risk groups is a possible complement to efforts to improve the patient-initiated pathway to TB diagnosis.

The available evidence suggest that screening, if done in the right way and targeting the right people, may reduce suffering and death. There

is a need to balance potential benefits against the risks and costs of screening. Some risk groups should always be screened, whereas the prioritization of other risk groups as well as the choice of screening approach depend on the epidemiology, the health-system context, and the resources available.



Systematic screening for active tuberculosis. Principles and recommendations¹⁷



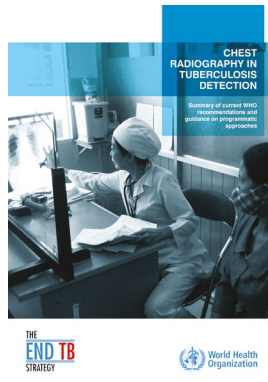
Systematic screening for active tuberculosis: An operational guide¹⁸

17 Systematic screening for active tuberculosis. Principles and recommendations. Geneva: World Health Organization, 2013. (WHO/HTM/TB/2013.04. http://apps.who.int/iris/bitstream/10665/84971/1/9789241548601_eng.pdf?ua=1&ua=1, accessed 1 May 2018).

18 Systematic screening for active tuberculosis: an operational guide. Geneva: World Health Organization, 2015. (WHO/HTM/TB/2015.16 http://apps.who.int/iris/bitstream/10665/181164/1/9789241549172_eng.pdf?ua=1&ua=1, accessed 1 May 2018).

WHO TB Standard 4. Chest radiography, or CXR, is an important tool for triaging and screening for pulmonary TB, and it is also useful to aid diagnosis when pulmonary TB cannot be confirmed bacteriologically. CXR can be used to select individuals for referral for bacteriological confirmation, and the role of radiology remains important when bacteriological tests cannot provide a clear answer.

Access to high-quality radiography is limited in many settings. Ensuring the wider and quality-assured use of CXR for TB detection in combination with the laboratory-based diagnostic tests recommended by WHO, can contribute to earlier TB diagnosis and, potentially, to closing the TB case-detection gap when CXR is used in algorithms as part of a framework of health-system and laboratory strengthening.¹⁹



Chest Radiography in Tuberculosis Detection¹⁹

19 Chest radiography in tuberculosis detection. Summary of current WHO recommendations and guidance on programmatic approaches. Geneva: World Health Organization, 2016(WHO/HTM/TB/2016.20 <http://apps.who.int/iris/bitstream/10665/252424/1/9789241511506-eng.pdf?ua=1>, accessed 1 May 2018).

4. Diagnosing TB disease

WHO TB Standard 5. To safely and efficiently diagnose TB and drug-resistant TB requires a functional network of quality assured laboratories with appropriate biosafety measures in place for performing different technical procedures. As such, TB programmes require a tiered network of integrated laboratories in which different levels use complementary tools to diagnose TB and HIV, and have mechanisms for referring specimens between the different levels of the network.

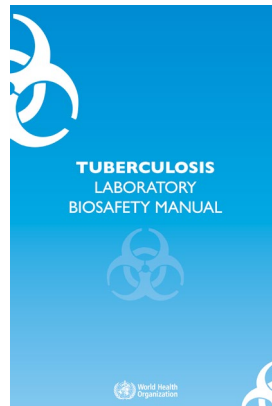
A policy framework for implementing tuberculosis diagnostics presents a structure for introducing WHO's recommended diagnostic techniques for TB.²⁰ It is expected that countries will adapt this generic policy framework within the contexts of their own epidemiological situation and resources. No single policy framework can address all issues in detail due to the diversity of resources and needs in different countries, as well as the geographical variation in the epidemiology of TB, HIV-associated TB and drug-resistant TB. Sputum smear microscopy remains the primary diagnostic technique in many high TB burden setting. Performing microscopy on two sputum specimens collected from persons provided with instruction on how to produce a good quality sputum specimen collected at any time of day (spot specimen) yields equivalent results as microscopy on specimens collected from patients in the early morning. Sputum-smear microscopy is a relatively insensitive test. The sensitivity is further reduced in patients with extrapulmonary TB, children and in those who are co-infected with HIV. Microscopy for acid-fast bacilli cannot distinguish MTB from nontuberculous mycobacteria; it cannot distinguish viable from nonviable organisms; and it cannot distinguish drug-susceptible strains from drug-resistant strains. TB programmes should transition to replacing microscopy as the

initial diagnostic test with WHO-recommended rapid diagnostics that allow for the simultaneous detection of TB and drug-resistant TB.



Policy framework for implementing TB diagnostics²⁰

WHO's *Tuberculosis laboratory biosafety manual* uses an approach based on risk assessment that promotes the development of appropriate biosafety practices in laboratories and takes into account the combination of test procedures, staff expertise and facilities present in each laboratory.²¹



Tuberculosis laboratory biosafety manual²¹

20 Implementing tuberculosis diagnostics: policy framework. Geneva: World Health Organization; 2015 (WHO/HTM/TB/2015.11; http://apps.who.int/iris/bitstream/10665/162712/1/9789241508612_eng.pdf?ua=1&ua=1, accessed 1 May 2018).

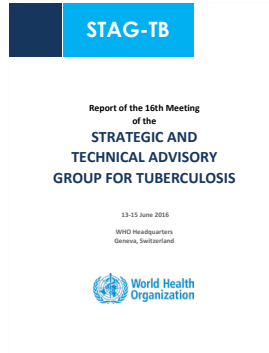
21 Tuberculosis laboratory biosafety manual. Geneva: World Health Organization; 2012 (WHO/HTM/TB/2012.11; http://apps.who.int/iris/bitstream/10665/77949/1/9789241504638_eng.pdf, accessed 1 May 2018).

WHO TB Standard 6. All patients with signs and symptoms of pulmonary TB who are capable of producing sputum should have as their initial diagnostic test at least one sputum specimen submitted for Xpert MTB/RIF Ultra assay. This also includes children who are able to provide a sputum sample. A second Xpert MTB/RIF Ultra assay may be performed for all patients who initially test negative by Xpert MTB/RIF Ultra but whose signs and symptoms of TB persist.

The End TB Strategy calls for early diagnosis and prompt treatment for persons of all ages who have any form of TB. This requires ensuring access to WHO-recommended rapid diagnostics and universal access to drug-susceptibility testing (DST) for all patients with signs and symptoms of TB. WHO defines universal access to DST as rapid DST for at least rifampicin among all patients with bacteriologically confirmed TB, and further DST for at least fluoroquinolones and second-line injectable agents among all TB patients with rifampicin resistance.²²

The sensitivity of the Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, United States) for detecting TB is similar to that of solid culture (88% when compared with liquid culture as a reference standard); the specificity is also high (99%).

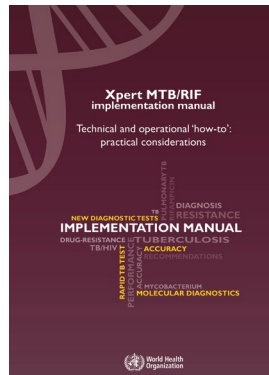
The Xpert MTB/RIF assay is the only WHO-recommended diagnostic test that simultaneously detects TB and rifampicin resistance, and it is suitable for use at lower levels of the health system. The Xpert MTB/RIF assay has 95% sensitivity and 98% specificity for detecting rifampicin resistance when compared with phenotypic reference standards.^{23, 24}



Report of the 16th meeting of the Strategic and Technical Advisory Group for Tuberculosis²²



Xpert MTB/RIF assay: Policy update²³



Xpert MTB/RIF assay: Implementation manual²⁴

22 Report of the 16th meeting of the Strategic and Technical Advisory Group for Tuberculosis. Geneva: World Health Organization; 2016 (WHO/HTM/TB/2016.10; http://www.who.int/tb/advisory_bodies/stag_tb_report_2016.pdf?ua=1, accessed 1 May 2018).

23 Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy update. Geneva: World Health Organization; 2013 (WHO/HTM/TB/2013.16; http://apps.who.int/iris/bitstream/10665/112472/1/9789241506335_eng.pdf, accessed 1 May 2018).

24 Xpert MTB/RIF implementation manual. Technical and operational 'how-to': practical considerations. Geneva: World Health Organization; 2014 (WHO/HTM/TB/2014.1; http://apps.who.int/iris/bitstream/10665/112469/1/9789241506700_eng.pdf?ua=1, accessed 1 May 2018).

The Xpert MTB/RIF Ultra assay has a higher sensitivity than the Xpert MTB/RIF assay, particularly in smear-negative, culture-positive specimens and in specimens from HIV-positive patients. It has at least as good accuracy for detecting rifampicin resistance. However, as a result of the increased sensitivity, the Xpert MTB/RIF Ultra assay also detects non-replicating and non-viable bacilli, particularly in patients with a recent history of TB, which reduces the overall specificity of the Xpert MTB/RIF Ultra assay in high-burden settings. Nonetheless, in low-burden settings and when testing specimens to diagnose EPTB and paediatric TB, false-positive results were not a major concern.²⁵

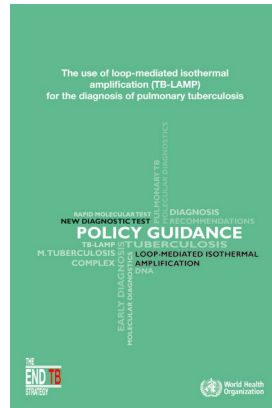


Non-inferiority analysis of Xpert MTB/RIF Ultra compared to Xpert MTB/RIF²⁵

WHO recommends using the **Xpert MTB/RIF Ultra assay** as the **initial diagnostic test** to detect TB and rifampicin resistance for all patients with signs and symptoms of TB. This includes children and patients (if they are able to provide a sputum sample). However, the majority of children will have negative results with all of the available bacteriological tests; therefore, a negative test result does not exclude TB in children.

Loop-mediated isothermal amplification for detecting TB (TB-LAMP), another molecular diagnostic test, may be used as a replacement

test or as a follow-on test to sputum-smear microscopy for diagnosing pulmonary TB in adults with signs and symptoms consistent with TB.²⁶ These recommendations apply to settings where it is possible to perform conventional sputum-smear microscopy. TB-LAMP should not replace rapid molecular tests that detect TB and resistance to rifampicin, especially among populations at risk of MDR-TB.



Loop-mediated isothermal amplification for detecting TB (TB-LAMP)²⁶

WHO TB Standard 7. The Xpert MTB/RIF Ultra assay should be used in preference to conventional microscopy and culture as the initial diagnostic test for cerebrospinal fluid specimens from patients being evaluated for TB meningitis. The Xpert MTB/RIF Ultra assay is recommended as a replacement test for usual practice (including conventional microscopy, culture or histopathology) for testing specific non-respiratory specimens (lymph nodes and other tissues) from patients suspected of having EPTB.

Given the urgency of rapid diagnosis when a patient is evaluated for TB meningitis, the Xpert MTB/RIF Ultra assay should be used. Pleural fluid is a suboptimal specimen for the bacterial

25 WHO meeting report of a technical expert consultation: non-inferiority analysis of Xpert MTB/RIF Ultra compared to Xpert MTB/RIF. Geneva: World Health Organization; 2017 (WHO/HTM/TB/2017.04; <http://apps.who.int/iris/bitstream/10665/254792/1/WHO-HTM-TB-2017.04-eng.pdf>, accessed 1 May 2018).

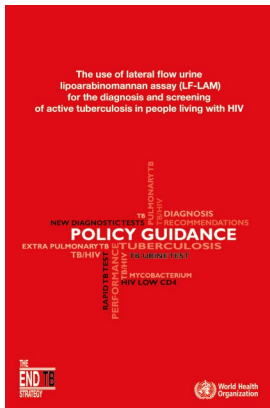
26 The use of loop-mediated isothermal amplification (TB-LAMP) for the diagnosis of pulmonary tuberculosis: policy guidance. Geneva: World Health Organization; 2016 (WHO/HTM/TB/2016.11; <http://apps.who.int/iris/bitstream/10665/249154/1/9789241511186-eng.pdf?ua=1>, accessed 1 May 2018).

confirmation of pleural TB using any method. These recommendations currently do not apply to specimens of stool, urine or blood, given the insufficient data on the utility of Xpert MTB/RIF Ultra in these specimens. Standard operating procedures for processing extrapulmonary specimens are provided in the Xpert MTB/RIF implementation manual.

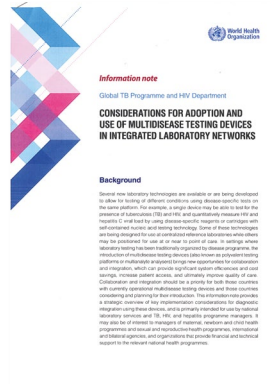
WHO TB Standard 8. For persons living with HIV, the Xpert MTB/RIF Ultra assay should be used as an initial diagnostic test. The lateral flow urine lipoarabinomannan assay (LF-LAM) can be used to assist in the diagnostic process for HIV-positive patients who are seriously ill.

LF-LAM is recommended to assist in the diagnosis of TB in HIV-positive adult inpatients with signs and symptoms of TB (pulmonary or extrapulmonary, or both) who have a CD4 cell count ≤ 100 cells/ μ L, and for HIV-positive patients who are seriously ill regardless of their CD4 count, and for those with an unknown CD4 count.²⁷

Several new laboratory technologies are available or being developed to allow the same platform to be used to test for multiple conditions. For example, a single device may be able to test for the presence of TB and HIV, as well as quantitatively measure the viral load of HIV and hepatitis C. Some of these technologies are designed for reference laboratories, whereas others may be used at the point of care. A number of issues should be considered before adopting devices that test for multiple diseases, including how to coordinate planning, whether the devices have regulatory approval and they have been validated in a setting similar to where they will be used, the choice of product and site where they will be placed. Details can be found in *Considerations for adoption and use of multi-disease testing devices in integrated laboratory networks*.²⁸



Lateral flow urine lipoarabinomannan assay (LF-LAM)²⁷



Multi-disease testing devices in integrated laboratory networks²⁸

27 The use of lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis and screening of active tuberculosis in people living with HIV: policy guidance. Geneva: World Health Organization; 2015 (WHO/HTM/TB/2015.25; http://apps.who.int/iris/bitstream/10665/193633/1/9789241509633_eng.pdf?ua=1&ua=1, accessed 1 May 2018).

28 Considerations for adoption and use of multi-disease testing devices in integrated laboratory networks. Geneva: World Health Organization; 2017. (WHO/HTM/TB/2017.06; <http://apps.who.int/iris/bitstream/10665/255693/1/WHO-HTM-TB-2017.06-eng.pdf?ua=1>, accessed 1 May 2018).

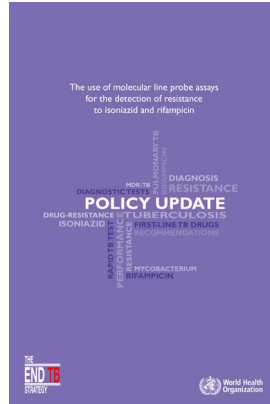
WHO TB Standard 9. DST using WHO-recommended rapid tests should be performed for all TB patients prior to starting therapy, including new patients and patients who require retreatment. If rifampicin resistance is detected, rapid molecular tests for resistance to isoniazid, fluoroquinolones and second-line injectable agents should be performed promptly to inform the treatment of MDR-TB and XDR-TB.

WHO recommends using commercially available molecular line probe assays (LPAs) as the initial test, instead of phenotypic culture-based DST, to detect resistance to rifampicin and isoniazid for persons with a sputum smear-positive specimen (direct testing) or a culture isolate of *Mycobacterium tuberculosis* complex (indirect testing). Commercially available molecular LPAs have good accuracy when used for either direct or indirect testing for resistance to rifampicin. Culture-based DST may still be necessary when an LPA does not detect isoniazid resistance.²⁹

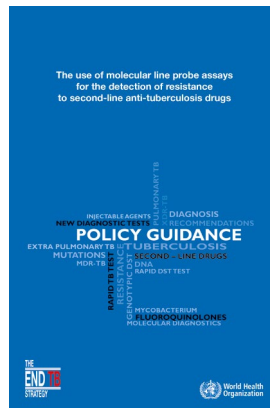
WHO recommends using molecular LPAs for second-line anti-TB agents, instead of phenotypic culture-based DST, as the initial test to detect resistance to fluoroquinolones and second-line injectable agents in patients with confirmed RR-TB or MDR-TB.³⁰ WHO recommends using second-line LPAs to test sputum specimens (direct testing) and culture isolates of *M. tuberculosis* complex (indirect testing) from both pulmonary and extrapulmonary sites.

Mutations conferring resistance to second-line injectable agents that are detected by second-line LPA tests are highly correlated with the results of culture-based phenotypic DST. Mutations conferring resistance to fluoroquinolones that are detected by second-

line LPA are highly correlated with the results of culture-based phenotypic DST. Second-line LPA can be used to identify persons eligible for enrolment on the shorter MDR-TB regimen.



Molecular line probe assays for the detection of resistance to isoniazid and rifampicin: Policy update²⁹



Molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs: Policy guidance³⁰

29 The use of molecular line probe assays for the detection of resistance to isoniazid and rifampicin: policy update. Geneva: 2016 update. Geneva: World Health Organization; 2016. (WHO/HTM/TB/2016.12; <http://apps.who.int/iris/bitstream/10665/250586/1/9789241511261-eng.pdf?ua=1>, accessed 1 May 2018).

30 The use of molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs: policy guidance. Geneva: World Health Organization; 2016 (WHO/HTM/TB/2016.07; <http://apps.who.int/iris/bitstream/10665/246131/1/9789241510561-eng.pdf?ua=1>, accessed 1 May 2018).

WHO TB Standard 10. Culture-based (phenotypic) drug susceptibility testing for selected medicines should be performed for patients enrolled in treatment for drug-resistant TB.

Drug-susceptibility testing (DST) serves three main purposes: first, it can be used to guide the choice of chemotherapy for a patient. Second, it is valuable in confirming that resistance has emerged when a patient has failed to have a satisfactory response to treatment. Third, it can be used for the surveillance of resistance to anti-TB medicines.

DST uses critical concentrations of anti-TB medicines to determine the susceptibility or resistance of a culture of *M. tuberculosis*. The critical concentration is defined as the lowest concentration of an anti-TB medicines *in vitro* that will inhibit the growth of 99% of phenotypically wild type strains of *M. tuberculosis* complex.

WHO and FIND issued in 2018 a Technical Report³¹ summarising the current evidence for determining critical concentrations in different media for performing DST for specific medicines used in treatment of drug-resistant TB. Critical concentrations for the new and repurposed anti-TB agents bedaquiline, delamanid, linezolid and clofazimine are included. In addition,

revised consensus critical concentrations for fluoroquinolones and second-line injectable agents are presented.

A clinical breakpoint for the higher dose of moxifloxacin (800mg/day) was established for the first time. The clinical breakpoint is defined as the concentration above the critical concentration that separates strains that will likely respond to treatment from those that will likely not to respond to treatment. These strains may be effectively treated with the higher daily dose of 800 mg moxifloxacin.



Critical concentrations for drug susceptibility testing³¹

31 Technical report on critical concentrations for drug susceptibility testing of medicines used in the treatment of drug-resistant tuberculosis. Geneva: World Health Organization;2018 (WHO/CDS/TB/2018.5) (<http://apps.who.int/iris/bitstream/10665/260470/1/WHO-CDS-TB-2018.5-eng.pdf> accessed 1 May 2018).

5. Diagnosing latent TB infection

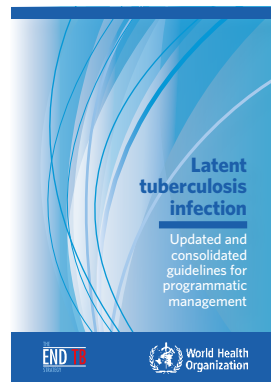
WHO TB Standard 11. Either a tuberculin skin test (TST) or an interferon gamma release assay (IGRA) can be used to test for latent TB infection (LTBI). A TST or IGRA is not a requirement before initiating tuberculosis preventive therapy in persons living with HIV and for children less than five years who are contacts of people with active TB disease.

No tool allows direct measurement of *M. tuberculosis* infection in humans, and the diagnosis of LTBI is based on a positive result by either tuberculin skin test (TST) or interferon-gamma release assay (IGRA), indicating an immune response to *M. tuberculosis*. However, these tests cannot accurately predict the risk of developing active TB disease. WHO recommends that either a TST or IGRA be used to test for LTBI in both high- and low- TB-burden countries and that active TB disease be ruled out prior to prescribing preventive treatment, as per WHO guidelines. There is no strong evidence that one LTBI test should be preferred over the other. The choice will depend on the availability, cost and the health infrastructure. The evidence reviewed and the recommendations in the 2018 consolidated guidelines on LTBI apply to the use of the TST and commercially available IGRAs (QuantiFERON®-TB Gold In-Tube and T-SPOT®.TB only). Any new or generic test should be subjected to adequate validation in the settings of intended use.

WHO recommends expansion of at-risk populations that should be prioritized for LTBI testing and treatment. While people living with HIV and HIV-negative household child

TB contacts less than 5 years of age have been key target risk groups globally, WHO has now identified HIV-negative children aged ≥ 5 years, adolescents and adults who are household contacts of TB patients, as well as household contacts of patients with multidrug-resistant TB (MDR-TB), as additional high-risk groups for programmatic management of LTBI. Additionally, HIV negative clinical risk groups such as patients initiating anti-TNF treatment, patients receiving dialysis treatment, patients preparing for an organ or haematological transplant and patients with silicosis should be systematically tested and treated regardless of the TB burden of the country.

Neither the TST nor IGRA can be used to diagnose *active TB disease* nor for the diagnostic workup of adults suspected of having active TB.³²



Updated and consolidated guidelines for the programmatic management of latent tuberculosis infection ³²

³² Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva: World Health Organization; 2018 (WHO/CDS/TB/2018.4) (<http://apps.who.int/iris/bitstream/handle/10665/260233/9789241550239-eng.pdf;jsessionid=9A5133F378D172D22981BCC52A9E7EB1?sequence=1> Accessed 1 May 2018)

6. Treating TB

6.1 Treating drug-susceptible TB

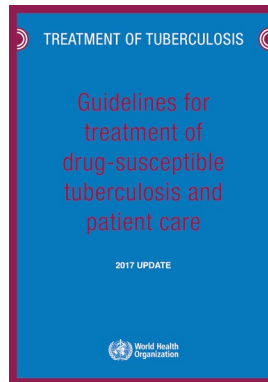
WHO TB Standard 12. While awaiting DST results, patients with drug-susceptible TB and TB patients who have not been treated previously with anti-TB agents and do not have other risk factors for drug resistance should receive a WHO-recommended first-line treatment regimen using quality assured anti-TB agents. The initial phase should consist of 2 months of isoniazid, rifampicin, pyrazinamide and ethambutol. The continuation phase should consist of 4 months of isoniazid and rifampicin. Daily dosing should be used throughout treatment. The doses of anti-TB agents should conform to WHO's recommendations. Fixed-dose combination (FDC) anti-TB agents may provide a more convenient form of administration.

The standard 6-month regimen for drug-susceptible TB (2 months of isoniazid, rifampicin, pyrazinamide and ethambutol followed by 4 months of isoniazid and rifampicin, denoted as 2HRZE/4HR) is the recommended regimen, and it showed better outcomes than other regimens using first-line anti-TB agents for treating drug-susceptible TB³³. Any deviation from this TB treatment recommendation should only be conducted under proper research conditions. Shorter 4-month regimens containing fluoroquinolones are associated with significantly higher rates of relapse compared with the standard 6-month rifampicin-containing regimen; therefore, these shorter regimens are not recommended.

Evidence has shown that FDCs are non-inferior and as effective as separate formulations of anti-TB agents in terms of treatment failure, death, treatment adherence and adverse

events. Patients' greater satisfaction with FDC treatment is an advantage of using these formulations. FDCs may provide programme benefits by making it easier to order medication, simplifying supply chain management, reducing the occurrence of stock-outs, and facilitating the delivery of anti-TB agents and the preparation of prescriptions. FDCs may also provide other benefits, especially in settings with a large number of TB patients and a limited number of health-care workers, by reducing the need for additional health-care staff and additional training in the dosing and dispensing of medications, as well as by lowering the number of pills that patients need to take.

In patients with pulmonary TB who are being treated with a first-line regimen, sputum testing should be done by the end of months 2, 5 and 6 (at the end of treatment). If a specimen obtained at the end of month 2 is sputum smear-positive and culture positive, DST for resistance to at least rifampicin should be performed to guide the therapy. Xpert MTB/RIF is not suitable for monitoring of patients during treatment.



Treatment of drug-susceptible tuberculosis and patient care: 2017 update³³

33 Guidelines for treatment of drug-susceptible tuberculosis and patient care: 2017 update. Geneva: World Health Organization; 2017 (WHO/HTM/TB/2017.05; <http://apps.who.int/iris/bitstream/10665/255052/1/9789241550000-eng.pdf?ua=1>, accessed 1 May 2018).

WHO TB Standard 13. In patients who require retreatment for TB, the category II regimen should no longer be prescribed and DST should be conducted to inform the choice of treatment regimen.

There are several reasons why the category II regimen should no longer be used. With the advent of widespread DST, the standard of care is to perform DST on specimens from persons whose treatment has been interrupted or who have had a recurrence of disease, and then to treat them based on the drug-resistance profile. Not carrying out DST and, instead, empirically treating with the substandard category II regimen creates an inequitable treatment situation, delays proper treatment for drug-resistant TB (which fuels resistance and leads to worse outcomes not only for patients with drug-resistant TB but also for the community) and unnecessarily exposes patients with drug-susceptible disease to the toxicities of streptomycin.

One of the basic principles of TB treatment is that a single anti-TB agent should not be added to an unsuccessful regimen. Adding streptomycin to a previously unsuccessful regimen of isoniazid, rifampicin, ethambutol and pyrazinamide violates this principle and fuels the development of resistance, which will lead to the loss of streptomycin as a second-line agent for MDR-TB therapy. Patients whose first-line TB treatment has been interrupted, failed or who have had a recurrence of disease tend to have a higher risk of resistance than new TB patients. Using a category II regimen for these patients runs contrary to basic treatment principles and will accelerate the emergence of drug resistance.

WHO TB Standard 14. In patients with tuberculous meningitis or tuberculous pericarditis, adjuvant corticosteroid therapy should be used in addition to an appropriate TB treatment regimen.

In patients with tuberculous meningitis, lower rates of mortality, death or severe disability, and disease relapse occur when patients are treated with corticosteroids in addition to their anti-TB treatment. Additionally, rates of adverse events and severe adverse events, including severe hepatitis, are lower in patients receiving corticosteroids. In patients with tuberculous pericarditis, use of corticosteroid in addition to anti-TB treatment reduces the risk of death and constrictive pericarditis and promotes treatment adherence. The benefit of preventing constrictive pericarditis outweighs the potential harms of corticosteroid therapy.

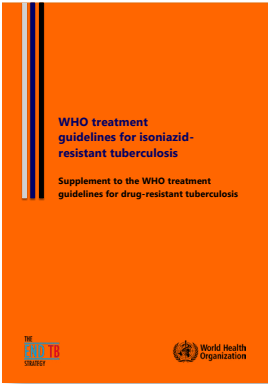
6.2 Treating drug-resistant TB

WHO TB Standard 15. In patients with rifampicin-susceptible, isoniazid-resistant TB, 6 months of combination treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin, with or without isoniazid, is recommended.

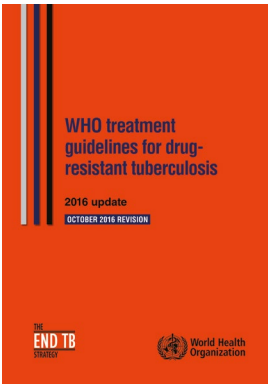
This recommendation aims to increase cure rates in patients with isoniazid-resistant TB (HR-TB), in whom a 2HRZE/4HR regimen is more likely to fail than in isoniazid-susceptible TB patients^{34, 35}. Levofloxacin is only to be used after rifampicin-resistance has been excluded with rapid molecular testing. Ideally, HR-TB treatment is only started after isoniazid resistance and susceptibility to fluoroquinolone have been reliably confirmed. Extending the duration of treatment beyond 6 months may be necessary when HR-TB is detected in the course of a first-line TB treatment or in patients with extensive disease. Streptomycin and other injectable agents are not usually recommended for the treatment of HR-TB.

34 WHO treatment guidelines for isoniazid-resistant tuberculosis. 2017 Supplement to the WHO treatment guidelines for drug-resistant tuberculosis. Geneva, World Health Organization; 2017 (WHO/CDS/TB/2018.7) <http://apps.who.int/iris/bitstream/handle/10665/260494/9789241550079-eng.pdf;jsessionid=DDB265E7A18A215D085673BCC978D4EC?sequence=1>, accessed 1 May 2018.

35 WHO treatment guidelines for drug-resistant tuberculosis: 2016 update. October 2016 revision. Geneva: World Health Organization; 2016 (WHO/HTM/TB/2016.04; <http://apps.who.int/iris/bitstream/10665/250125/1/9789241549639-eng.pdf?ua=1>, accessed 1 May 2018).



WHO treatment guidelines for isoniazid-resistant TB³⁴



WHO treatment for drug-resistant TB³⁵
(under revision)

WHO TB Standard 16. Patients with multidrug- or rifampicin-resistant TB (MDR/RR-TB) require second-line treatment regimens. MDR/RR-TB patients may be treated using a 9–11 month MDR-TB treatment regimen (the shorter

regimen) unless they have resistance to second-line anti-TB agents or meet other exclusion criteria. In these cases, a longer (individualized) regimen with at least five effective anti-TB agents in the intensive phase and four agents in the continuation phase is recommended for 20 months or more. Partial resection surgery has a role in treating MDR-TB.

Most adults and children with pulmonary forms of MDR/RR-TB who do not have additional resistance to fluoroquinolones and injectable agents may be effectively cured with a shorter MDR-TB regimen (Fig. 3).³⁶ Any deviation from this TB treatment recommendation should only be conducted under proper research conditions. Longer regimens are usually composed of at least pyrazinamide, a fluoroquinolone, an injectable agent and two other second-line medicines from group C (see Table 2), adjusted on the basis of individual drug-susceptibility test results, contraindications and clinical manifestations. Bedaquiline or delamanid may be included in longer regimens to improve outcomes.^{37, 38, 39} Both bedaquiline and delamanid have been registered to be used for a duration of 24 weeks. Data on the safety and the added value of continuing these medicines beyond 24 weeks remain limited. However, clinicians and national TB programmes may be compelled to offer to selected MDR-TB patients the use these medicines beyond 24 weeks; this practice should be conducted under specific conditions, including careful selection of eligible patients, aDSM and patient informed consent⁴⁰. In HIV-positive patients with MDR- or XDR-TB, the early introduction of antiretroviral agents

36 Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization; 2014 (WHO/HTM/TB/2014.11; http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf, accessed 1 May 2018).

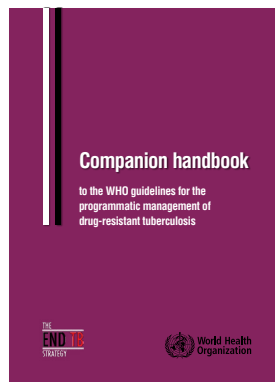
37 The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance. Geneva: World Health Organization; 2013 (WHO/HTM/TB/2013.6; http://apps.who.int/iris/bitstream/10665/84879/1/9789241505482_eng.pdf, accessed 1 May 2018).

38 The use of delamanid in the treatment of multidrug-resistant tuberculosis: interim policy guidance. Geneva: World Health Organization; 2014 (WHO/HTM/TB/2014.23; http://apps.who.int/iris/bitstream/10665/137334/1/WHO_HTM_TB_2014.23_eng.pdf, accessed 1 May 2018). (under revision).

39 The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents: interim policy guidance. Geneva: World Health Organization; 2016 (WHO/HTM/TB/2016.14; <http://apps.who.int/iris/bitstream/10665/250614/1/9789241549899-eng.pdf?ua=1>, accessed 1 May 2018). (under revision).

40 WHO best-practice statement on the off-label use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis. Geneva: World Health Organization; 2017 (WHO/HTM/TB/2017.20; <http://apps.who.int/iris/bitstream/handle/10665/258941/WHO-HTM-TB-2017.20-eng.pdf?sequence=1&isAllowed=y>, accessed 1 May 2018).

is strongly recommended. Consultation with specialists experienced in treating adult and paediatric TB patients, including surgeons, may be necessary.



The programmatic management of drug-resistant TB requires good practices in many aspects of care, including using approved diagnostics to confirm drug resistance, using quality assured medicines, complying with WHO’s recommended doses, supporting patients to improve adherence to treatment (including using enablers and evidence-informed digital technologies), and monitoring patients’ response and adverse events. Regular microscopy and culture of sputum or other specimens remains important to ensure that treatment failure is detected early.⁴¹

Companion Handbook for the treatment of drug-resistant TB³⁶ (under revision)

Table 2. General steps in designing a longer treatment regimen for multidrug-resistant TB (MDR-TB)^a (under revision)

Steps	Medicine: groups and options	
1. Add one later-generation fluoroquinolone	A	Levofloxacin Moxifloxacin Gatifloxacin
2. Add one second-line injectable agent	B	Amikacin Capreomycin Kanamycin (Streptomycin ^b)
3. Add two or more second-line agents	C	Ethionamide or prothionamide Cycloserine or terizidone Linezolid Clofazimine
4. Add pyrazinamide and any other first-line agent if they will strengthen the regimen	D1	Pyrazinamide Ethambutol High-dose isoniazid
5. Add bedaquiline or delamanid	D2	Bedaquiline Delamanid
6. Add any of these agents if the regimen cannot be composed otherwise	D3	p-aminosalicylic acid Imipenem + cilastatin Meropenem Amoxicillin + clavulanic acid (Thioacetazone ^c)

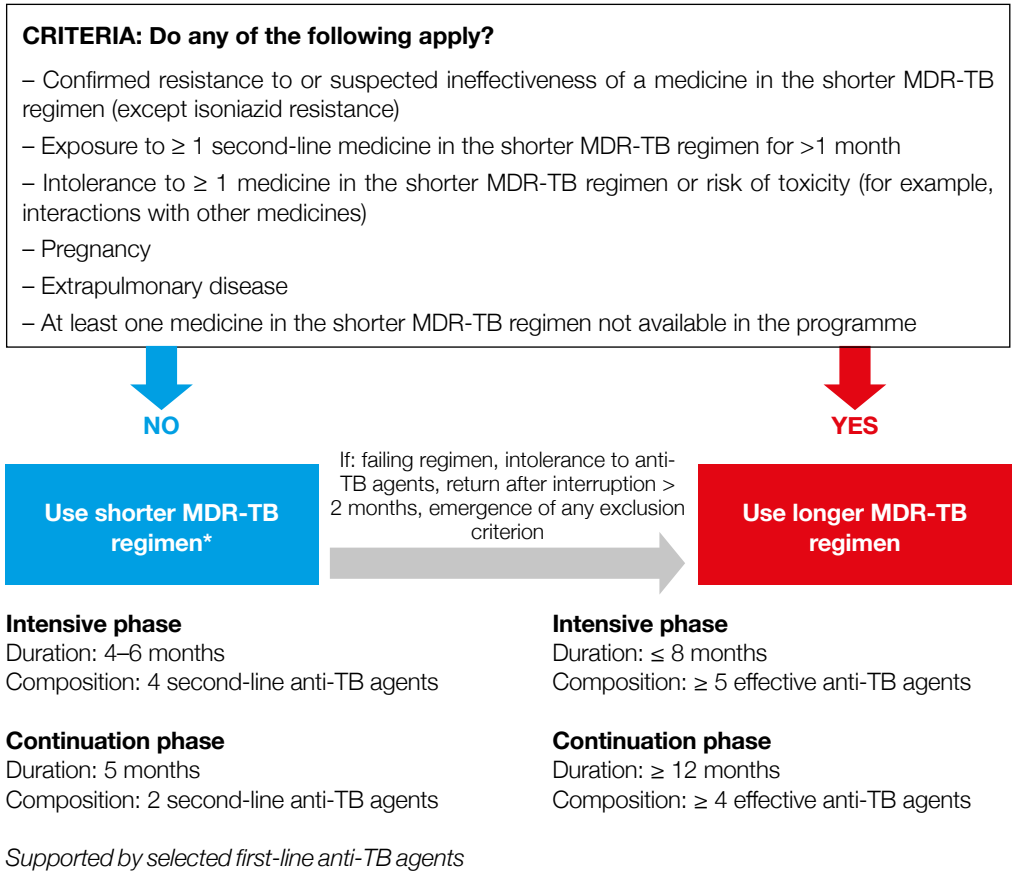
^a WHO treatment guidelines for drug-resistant tuberculosis: 2016 update. October 2016 revision. WHO/HTM/TB/2016.04 Geneva: World Health Organization; 2016 (WHO/HTM/TB/2016.04; <http://apps.who.int/iris/bitstream/10665/250125/1/9789241549639-eng.pdf?ua=1>, accessed 1 May 2018).

^b Refer to the 2016 guidelines for the conditions under which streptomycin may substitute other injectable agents.

^c HIV-status must be confirmed to be negative before thiacetazone is started.

41 Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Geneva: World Health Organization; 2011 (WHO/HTM/TB/2011.6; http://apps.who.int/iris/bitstream/10665/44597/1/9789241501583_eng.pdf, accessed 1 May 2018).

Fig. 3. Choosing a treatment regimen for patients with multidrug-resistant TB (MDR-TB) or rifampicin-resistant TB

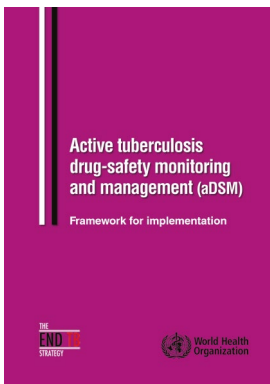


* 4-6 Km-Mfx-Pto-Cfz-Z-H_{high-dose}-E/5Mfx-Cfz-Z-E**

** Km = Kanamycin; Mfx = Moxifloxacin; Pto = Prothionamide; Cfz = Clofazamine; Z = Pyrazinamide; H_{high-dose} = high-dose Isoniazid; E = Ethambutol

WHO TB Standard 17. A system to actively monitor and manage harms caused by anti-TB agents is required whenever drug-resistant TB patients are treated with novel or repurposed medicines and MDR-TB regimens.

Active TB drug-safety monitoring and management (aDSM) for anti-TB agents refers to the systematic clinical and laboratory assessment of patients being treated with new anti-TB agents or novel MDR-TB or XDR-TB regimens to detect, manage and report suspected or confirmed toxicities.⁴² Although all detected adverse events need to be managed clinically, active TB drug-safety monitoring and management requires the reporting of only serious adverse events. As part of a comprehensive safety monitoring and management programme, treatment sites with additional resources may also monitor other adverse events that are clinically significant or of special interest to the programme. Programmes may phase in active safety monitoring and management to eventually cover TB patients being treated with any second-line agents.



Active tuberculosis drug-safety monitoring and management (aDSM)⁴²



6.3 Treating latent TB infection

WHO TB Standard 18. Persons living with HIV, HIV-negative children and adult household or close contacts of persons with pulmonary TB, as well as household contacts of patients with multi-drug resistant TB and who, after an appropriate clinical evaluation, are found not to have active TB but to have LTBI should be treated.

The systematic diagnosis and treatment of LTBI is part of the new End TB Strategy, and achieving $\geq 90\%$ LTBI treatment coverage among persons living with HIV, all adult, adolescent and child household or close contacts of persons with pulmonary TB, as well as contacts of patients with multi-drug resistant TB is a global priority target. Additionally, HIV negative clinical risk groups such as patients initiating anti-TNF treatment, patients receiving dialysis treatment, patients preparing for an organ or haematological transplant and patients with silicosis should be systematically tested and treated regardless of the TB burden of the country.

WHO recommends that either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) be used to test for LTBI in both high- and low- TB- burden countries and that active TB disease be ruled out by a WHO-recommended test prior to prescribing preventive treatment.

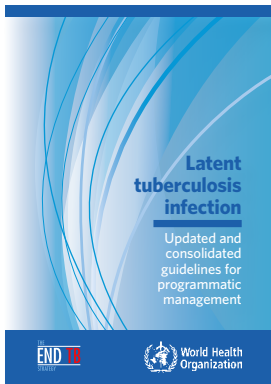
A TST or IGRA is not a requirement before initiating isoniazid preventive therapy (known as IPT) in persons living with HIV or child household contacts aged < 5 years.⁴³

Adults and adolescents living with HIV should be screened for TB according to a clinical algorithm. Those who do not report any of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered preventive treatment, regardless of their ART status. Chest radiography may be

⁴² Active tuberculosis drug-safety monitoring and management (aDSM). Geneva: World Health Organization; 2015 (WHO/HTM/TB/2015.28; http://apps.who.int/iris/bitstream/10665/204465/1/WHO_HTM_TB_2015.28_eng.pdf?ua=1, accessed 1 May 2018).

offered to people living with HIV and on ART and preventive treatment given to those with no abnormal radiographic findings. The absence of any symptoms of TB and the absence of abnormal chest radiographic findings may be used to rule out active TB disease among HIV-negative household contacts aged ≥ 5 years and other at-risk groups before preventive treatment.

Isoniazid monotherapy for 6 months is recommended for treatment of LTBI in both adults and children in countries with high and low TB incidence.



Updated and consolidated guidelines for the programmatic management of latent tuberculosis infection⁴³

In high TB incidence settings the following regimens **may be** offered as an alternative to 6 months of isoniazid monotherapy:

- (a) rifampicin plus isoniazid daily for 3 months as preventive treatment for children and adolescents aged < 15 years;
- (b) rifapentine and isoniazid weekly for 3 months as preventive treatment for both adults and children in countries with a high TB incidence.

In low TB incidence settings the following regimens **should be** offered as an alternative to 6 months of isoniazid monotherapy:

- (a) 9 months of isoniazid, or
- (b) a 3-month regimen of weekly rifapentine plus isoniazid, or
- (c) 3–4 months of isoniazid plus rifampicin, or
- (d) 3–4 months of rifampicin alone.

In settings with high TB incidence and transmission, adults and adolescents living with HIV who have an unknown or a positive TST and are unlikely to have active TB disease should receive at least 36 months of IPT, regardless of whether they are receiving ART. IPT should also be given irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy.

In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualised risk assessment and a sound clinical justification.

To implement the programmatic management of LTBI, it is also important to monitor and manage adverse events, provide support to improve adherence to and completion of treatment, and implement monitoring and evaluation systems that use standardized indicators. Tools to support monitoring and evaluation are encouraged. The WHO has developed a mobile phone app to support programmatic management of LTBI; the app is available for adaptation (http://www.who.int/tb/areas-of-work/preventive-care/ltbi/ltbi_app/en/).

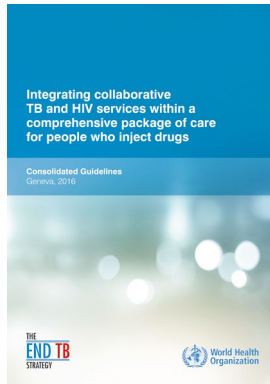
43 Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva: World Health Organization; 2018 (WHO/CDS/TB/2018.4) <http://apps.who.int/iris/bitstream/handle/10665/260233/9789241550239-eng.pdf;jsessionid=9A5133F378D172D22981BCC52A9E7EB1?sequence=1>, accessed 1 May 2018).

7. HIV infection and other co-morbid conditions

WHO TB Standard 19. HIV testing should be routinely offered to all patients with presumptive TB and those who have been diagnosed with TB.

Collaborative TB–HIV activities are a key component of the End TB Strategy, and achieving 100% HIV testing is one of the core targets set for 2025. Persons living with HIV are more likely to have poor TB treatment outcomes than HIV-negative TB patients. Close to 40% of persons living with HIV do not know their HIV status. Offering HIV testing and counselling to persons presenting with diagnosed or presumptive TB provides them with access to the continuum of prevention, care, support and treatment for HIV and for TB.

Studies in sub-Saharan Africa and in Asia have shown that a high number of HIV-positive people can be identified when patients presumed to have TB are tested for HIV even when they turn out not to have active TB disease; thus, HIV testing provides a further opportunity to ensure that HIV-positive people enter the HIV continuum of care and receive preventive treatment for TB. The principles that apply to all models of HIV testing in all circumstances are consent, confidentiality, counselling, correct test results and connection to care and treatment. Partners of known HIV-positive TB patients should also be offered voluntary HIV testing and counselling with mutual disclosure. HIV self-testing may be used as an additional strategy to extend HIV testing services to those who may be unable or reluctant to attend for HIV testing.^{44, 45, 46}



Integrating collaborative TB and HIV services⁴⁴

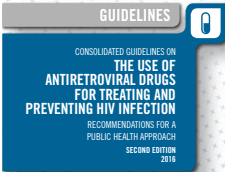


WHO policy on collaborative TB/HIV activities⁴⁵

44 Integrating collaborative TB and HIV services within a comprehensive package of care for people who inject drugs: consolidated guidelines. Geneva: World Health Organization; 2016 (WHO/HTM/TB/2016.02; http://apps.who.int/iris/bitstream/10665/204484/1/9789241510226_eng.pdf?ua=1, accessed 1 May 2018).

45 WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders. Geneva: World Health Organization; 2012 (WHO/HTM/TB/2012.1; http://apps.who.int/iris/bitstream/10665/44789/1/9789241503006_eng.pdf?ua=1&ua=1, accessed 1 May 2018).

46 Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2nd ed. Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf?ua=1, accessed 1 May 2018).



Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection⁴⁶

WHO TB Standard 20. Persons living with HIV should be screened for TB by using a clinical algorithm.

Because persons living with HIV are at a much higher risk of developing active TB disease, HIV services present an ideal opportunity to engage in routine TB case-finding at each visit. Adults and adolescents who report any one of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases.

WHO-approved rapid molecular diagnostic tests (for example, the Xpert MTB/RIF Ultra assay) should be used as the first test for persons living with HIV because these tests improve the yield and speed of diagnosis for both drug-sensitive and drug-resistant TB among this population; the use of these tests should be scaled up in all clinical settings supporting people with HIV. For HIV-positive persons who are seriously ill, LF-LAM can be used to assist diagnosis. Testing for TB in persons with HIV should always be expedited, and anti-TB treatment should be initiated as soon as possible after diagnosis. In peripheral settings where TB investigations are not available, clinical assessment and judgement should be used to provide presumptive TB treatment for individuals who are seriously ill.

Persons living with HIV in whom active TB has been ruled out should receive TB preventive treatment.

WHO TB Standard 21. Antiretroviral therapy (ART) and routine co-trimoxazole preventive therapy (CPT) should be initiated among all TB patients living with HIV, regardless of their CD4 cell count.

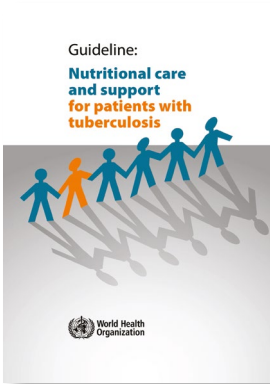
The early initiation of ART for patients with HIV-associated TB is critical to reducing morbidity and mortality. TB treatment should be initiated first, and ART should be started as soon as possible within the first 8 weeks of TB treatment. HIV-positive adults and adolescents with TB who have profound immunosuppression (for example, CD4 counts <50 cells/mm³) should receive ART within the first 2 weeks of initiating TB treatment. Caution is needed in persons living with HIV who have TB meningitis because immediately initiating ART is significantly associated with more severe adverse events compared with initiating ART 2 months after starting TB treatment. Patients should be followed up carefully to assess whether side effects related to co-treatment occur and whether TB-associated immune reconstitution inflammatory syndrome develops, which is common in patients with TB who start ART, but it is usually self-limiting. The early use of ART is also recommended for HIV-positive TB patients who are treated with second-line anti-TB regimens for drug-resistant TB.

Co-trimoxazole (sulfamethoxazole + trimethoprim) is a broad spectrum antimicrobial agent that prevents a range of secondary bacterial and parasitic infections in HIV-positive adults and children. TB patients living with HIV should receive CPT, and it should be implemented as an integral component of the HIV chronic care package.

HIV and TB programmes should coordinate to ensure that patients diagnosed with HIV-associated TB receive timely treatment and care, and programmes must also ensure the uninterrupted and integrated provision of CPT and ART to all HIV-positive persons who have active TB wherever they receive their care. Programmes should also ensure that TB and HIV services, including TB prevention, are integrated within services for maternal and child health, persons who inject drugs, and for other high risk or vulnerable groups, such as prisoners and miners.

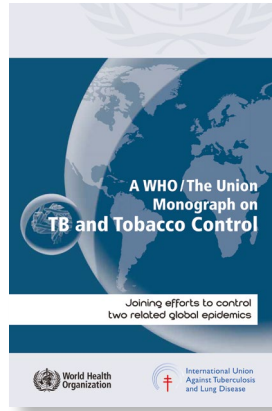
WHO TB Standard 22. A thorough assessment should be conducted to evaluate co-morbid conditions and other factors that could affect the response to or outcome of TB treatment. Particular attention should be given to diseases or conditions known to affect treatment outcomes, such as diabetes mellitus, drug and alcohol abuse, undernutrition and tobacco smoking.

All individuals with active TB should receive an assessment of their nutritional status and appropriate counselling based on their status at diagnosis and throughout treatment. Whether additional specific nutritional care and support are needed depends on these assessments and a number of other factors that make individuals more vulnerable.⁴⁷



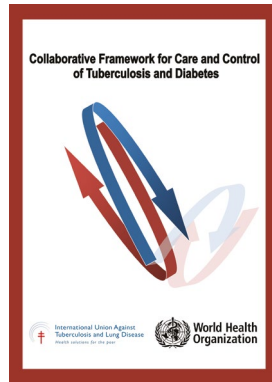
Nutritional care and support for patients with tuberculosis⁴⁷

Persons diagnosed with TB should be asked about smoking and offered advice about cessation if necessary.⁴⁸



TB and tobacco control⁴⁸

Patients with TB should be screened for diabetes at the start of their treatment if resources are available. The management of diabetes in TB patients should be in line with guidelines for managing diabetes.⁴⁹



Framework for care and control of tuberculosis and diabetes⁴⁹

The screening for and management of other co-morbid conditions depends on the epidemiology of the disease and the available resources. Co-morbid conditions may include, for example, the harmful use of alcohol, or other substance abuse and mental health problems.⁵⁰

47 Guideline: nutritional care and support for patients with tuberculosis. Geneva: World Health Organization; 2013 (http://apps.who.int/iris/bitstream/10665/94836/1/9789241506410_eng.pdf?ua=1&ua=1, accessed 1 May 2018).

48 WHO/The Union monograph on TB and tobacco control: joining efforts to control two related global epidemics. Geneva: World Health Organization; 2007 (WHO/HTM/TB/2007.390; http://www.who.int/tobacco/resources/publications/tb_tobac_monograph.pdf, accessed 1 May 2018).

49 Collaborative framework for care and control of tuberculosis and diabetes. Geneva: World Health Organization; International Union Against Tuberculosis and Lung Disease; 2011 (WHO/HTM/TB/2011.15; http://apps.who.int/iris/bitstream/10665/44698/1/9789241502252_eng.pdf, accessed 1 May 2018).

50 Lönnroth K, Williams BG, Jaramillo E, Stadlin S, Dye C. Alcohol use as a risk factor for tuberculosis – a systematic review. BMC Public Health. 2008;8:289. doi: 10.1186/1471-2458-8-289.

8. Managing TB in children

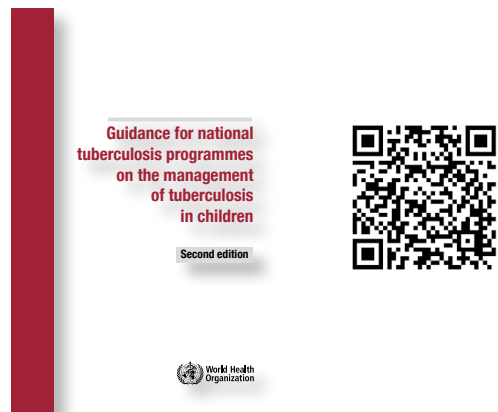
WHO TB Standard 23. The diagnosis of TB in children relies on the thorough assessment of all evidence derived from a careful history (including history of TB contacts and symptoms consistent with TB), clinical examination (including growth assessment), a TST, CXR (if available), bacteriological confirmation whenever possible, investigations for suspected pulmonary TB and suspected EPTB, and HIV testing. Whenever possible, the Xpert MTB/RIF Ultra assay should be used as the initial diagnostic test in children suspected of having any form of TB.

At least 1 million children become ill with TB every year. In 2015, 210 000 children died of TB, a number that includes 40 000 deaths among children who were HIV-positive.

Children can present with TB disease at any age, but in countries where TB is endemic this occurs most commonly when children are between 1 and 4 years old. Pulmonary TB is the most common type of TB in children. Extrapulmonary disease is also common (occurring in around 30–40% of cases) and can present in a variety of anatomical sites. Children who develop TB disease usually do so within one year of infection, which is why the presentation of TB in children is an indicator of recent and ongoing transmission of *M. tuberculosis* in the community. Risk factors for childhood TB include having a household or other close contact with pulmonary TB (especially bacteriologically confirmed pulmonary TB), and being younger than 5 years, HIV-positive and severely malnourished. Infants and young children (especially those younger than 2 years) are at greatest risk of developing severe, disseminated disease and at risk for high morbidity and death.

TB in children is often missed due to the non-specific symptoms (cough, fever and weight loss) and difficulties in diagnosis due to the paucibacillary nature of the disease and the

lack of suitable, child-friendly diagnostic tools (young children are unable to produce sputum spontaneously). In addition, to provide sputum specimens, children need to be admitted to hospital because primary health-care workers are usually not trained in sputum aspiration and induction. The majority of children will have negative results on all bacteriological tests; therefore, a negative test result does not exclude TB⁵¹.



Guidance for the management of tuberculosis in children⁵¹

WHO TB Standard 24. The principles of treating TB in children are the same as for treating TB in adults: first-line treatment of drug-sensitive TB consists of a 2 month intensive phase with isoniazid, rifampicin, pyrazinamide and, depending on the setting and type of disease, ethambutol, followed by a continuation phase with isoniazid and rifampicin for at least 4 months; however, the dose of first-line anti-TB agents differs from that administered in adults.

HIV-positive children with TB require ART and CPT in addition to TB treatment. Infants aged 0–3 months with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis should be promptly treated with

51 Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2nd ed. Geneva: World Health Organization; 2014 (WHO/HTM/TB/2014.03; http://apps.who.int/iris/bitstream/10665/112360/1/9789241548748_eng.pdf?ua=1, accessed 1 May 2018).

the standard treatment regimens, however, experts in treating TB in children advise that treatment may require dose adjustments to reconcile the effects of age and possible toxicity in younger infants.

Children with suspected or confirmed tuberculous meningitis and children with suspected or confirmed osteoarticular TB should be treated with a four-drug regimen (isoniazid, rifampicin, pyrazinamide and ethambutol, known as HRZE) for 2 months, followed by a two-drug regimen (isoniazid and rifampicin, HR) for 10 months, with the total duration of treatment being 12 months. The most recent guidelines on treating children with drug-resistant TB include specific recommendations for treating RR-TB and MDR-TB in children).

For children with mild forms of MDR- or RR-TB, a regimen without injectable agents can be used. If the minimum number of effective TB medicines cannot be composed as described above, delamanid may also be used alongside longer MDR-TB regimens in patients aged 6–17 years.

Although there are no formulations of second-line anti-TB agents for children, treatment outcomes in children are generally good, provided that treatment starts promptly and adherence is maintained until completion. The risk of adverse events is low when the recommended treatment regimens are used. Children should be regularly assessed until treatment is completed. Doses should be adjusted to take into account any weight gain.

WHO TB Standard 25. In settings where TB is highly endemic or where there is a high risk of exposure to TB, a single dose of bacille Calmette–Guérin (BCG) vaccine should be given to all infants; however, HIV-positive children should not be given BCG vaccine. After considering local factors, BCG vaccine should be given to all infants except those who are HIV-positive for whom BCG is contraindicated.

BCG is a live, attenuated vaccine derived from *M. bovis* and with a protective efficacy that varies widely between settings. However, neonatal BCG vaccination provides substantial protection against the more severe types of disseminated TB, such as miliary TB and tuberculous meningitis, to which infants and young children are particularly susceptible. There is no evidence that revaccination with BCG provides any additional protection; therefore, revaccination is not recommended.^{52, 53}

BCG vaccine should not be used in HIV-positive children because of the increased risk of severe and potentially fatal disseminated BCG disease. However, BCG is given routinely at birth in settings where TB is endemic before HIV infection can be reliably determined. Hence, several factors need to be considered locally to establish a risk–benefit balance for such approaches.

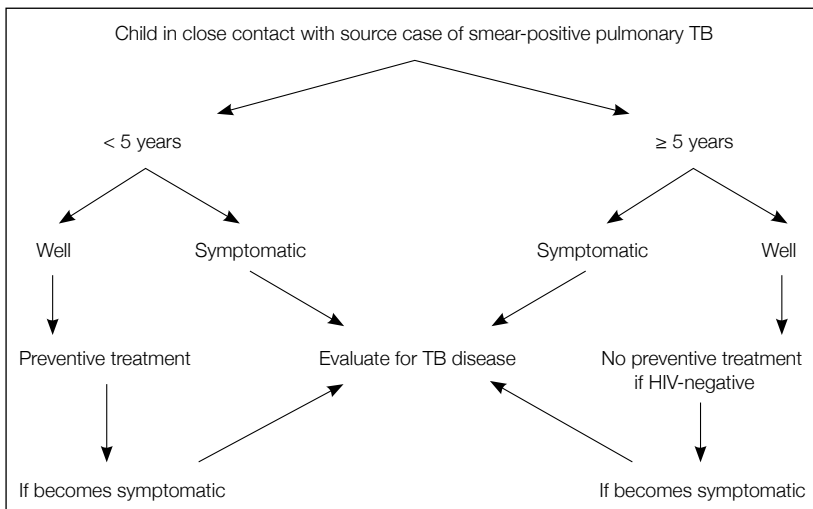
52 Global Advisory Committee on Vaccine Safety, 29–30 November 2006: safety of BCG vaccine in HIV-infected children. *Wkly Epidemiol Rec.* 2007;82:22 (<http://www.who.int/wer/2007/wer8203.pdf>, accessed 1 May 2018).

53 Global Advisory Committee on Vaccine Safety, 3–4 December 2009: use of BCG vaccine in HIV-infected infants. *Wkly Epidemiol Rec.* 2010;85:32–33 (<http://www.who.int/wer/2010/wer8505.pdf?ua=1>, accessed 1 May 2018).

WHO TB Standard 26. All children younger than 5 years and HIV-positive children of any age should be included in contact screening and management efforts, with the aim of identifying undiagnosed TB disease and providing preventive therapy for contacts without TB disease who are susceptible to developing disease following exposure to a contact with active TB disease.

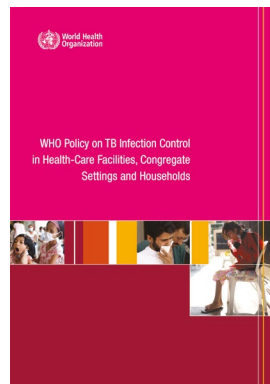
Fig. 4 presents the recommended simple algorithm that can be applied in any setting and requires information only about age, HIV status and the presence or absence of symptoms. Only symptomatic contacts require referral to a secondary level for further assessment; asymptomatic contacts may be prescribed preventive treatment by health workers at the community or primary care level.

Fig. 4. Symptom-based screening algorithm for managing care of children who are close contacts of people with TB



WHO's 2009 recommendations for infection control in health facilities, congregate settings and households do not specifically mention children but are equally relevant to children.⁵⁴

Because children with TB or at risk of TB will enter community or primary health-care services outside the TB programme (such as maternal and child health, nutrition, or HIV services), national TB programmes are encouraged to build links and effective collaboration with these programmes.



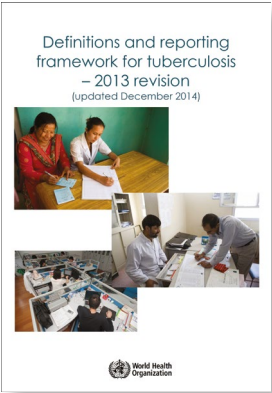
WHO policy on TB infection control in health-care facilities, congregate settings and households⁵⁴

54 WHO policy on TB infection control in health-care facilities, congregate settings and households. Geneva: World Health Organization; 2009 (WHO/HTM/TB/2009.419; http://apps.who.int/iris/bitstream/10665/44148/1/9789241598323_eng.pdf, accessed 1 May 2018).

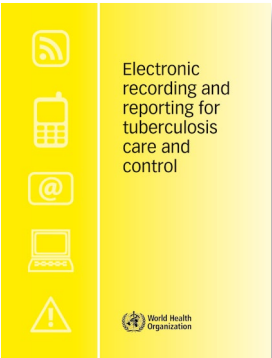
9. Monitoring and evaluation

WHO TB Standard 27. All providers must report both new and re-treatment TB cases and their treatment outcomes to national public health authorities in conformance with applicable legal requirements and policies; TB mortality should be monitored by using standard cause-of-death data from vital registration systems.

The routine monitoring of TB case notifications and treatment outcomes at the national and global levels is long established.⁵⁵ National systems generally started as paper-based reporting systems, with aggregated results reported upwards from the lowest administrative level (the Basic Management Unit). Subsequently, many countries have transitioned to electronic case-based reporting systems containing electronic records for which an episode of TB is the unit of analysis. For each episode, records contain relevant information about the person with TB (for example, age, sex, residence, previous history of treatment, personal identification number) and her or his treatment.⁵⁶ In cases in which these systems meet quality and coverage standards, they are the best way to track TB incidence. They are also the best way to compile and store data about TB cases, allowing for better quality data, the deduplication of records, greater data access and the timely analysis of any variables that are captured so that these may inform response strategies. Analyses may include data disaggregated by age, sex and location. In addition, core laboratory indicators should be routinely compiled to monitor access to rapid molecular detection of TB, progress towards universal access to DST, and the overall quality of laboratory services.⁵⁷



Definitions and reporting framework for tuberculosis⁵⁵



Electronic recording and reporting for tuberculosis care and control⁵⁶

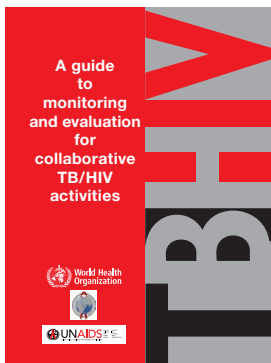
55 Definitions and reporting framework for tuberculosis – 2013 revision. Updated December 2014. Geneva: World Health Organization; 2013 (WHO/HTM/TB/2013.2; http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf, accessed 1 May 2018).

56 Electronic recording and reporting for tuberculosis care and control. Geneva: World Health Organization; 2012 (WHO/HTM/TB/2011.22; http://apps.who.int/iris/bitstream/10665/44840/1/9789241564465_eng.pdf, accessed 1 May 2018).



Framework of indicators and targets for laboratory strengthening⁵⁷

Ongoing monitoring of implementation and scale-up of collaborative TB/HIV activities and evaluation of their impact is critically important. The guide to monitoring and evaluation for collaborative TB/HIV activities aims to strengthen implementation of activities and improve quality of care.⁵⁸



A guide to monitoring and evaluation for collaborative TB/HIV activities⁵⁸

Periodic studies will remain necessary to monitor progress towards targets for reducing TB incidence and mortality, especially in

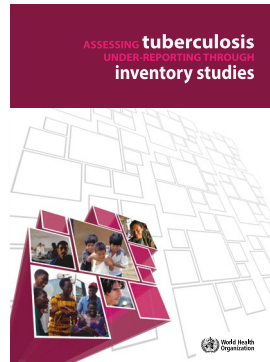
57 Framework of indicators and targets for laboratory strengthening under the End TB strategy. Geneva: World Health Organization; 2016 (WHO/HTM/TB/2016.18; <http://apps.who.int/iris/bitstream/10665/250307/1/9789241511438-eng.pdf?ua=1>, accessed 1 May 2018).

58 A guide to monitoring and evaluation for collaborative TB/HIV activities. Geneva: World Health Organization; 2015 (WHO/HTM/TB/2015.01; http://apps.who.int/iris/bitstream/10665/150627/1/9789241508278_eng.pdf?ua=1, accessed 1 May 2018).

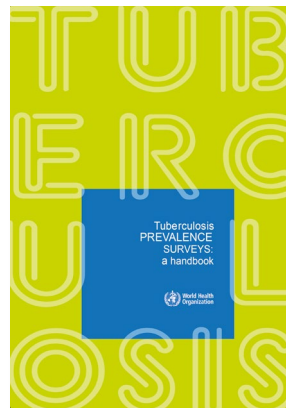
59 Assessing tuberculosis under-reporting through inventory studies. Geneva: World Health Organization; 2012 (WHO/HTM/TB/2012.12; http://apps.who.int/iris/bitstream/10665/78073/1/9789241504942_eng.pdf?ua=1, accessed 1 May 2018).

60 Tuberculosis prevalence surveys: a handbook. Geneva: World Health Organization; 2011 (WHO/HTM/TB/2010.17, http://apps.who.int/iris/bitstream/10665/44481/1/9789241548168_eng.pdf?ua=1&ua=1, accessed 1 May 2018).

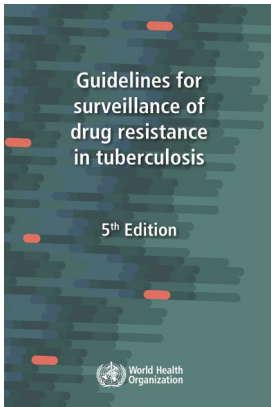
countries without case-based electronic surveillance and high-quality vital registration systems with broad coverage. These studies may include inventory studies to measure the underreporting of detected cases,⁵⁹ national TB prevalence surveys undertaken in countries that lack any direct measurement of TB burden,⁶⁰ drug-resistance surveys⁶¹ and health-facility surveys of costs faced by TB patients and their households.



Assessing tuberculosis under-reporting through inventory studies⁵⁹



Tuberculosis prevalence surveys⁶⁰



Drug-resistance surveillance⁶¹

The best way to track deaths from all causes, including TB, is through national vital registration systems that use standard coding for the cause of death and that adhere to international standards. Such systems have been in place for more than a century in some countries, but in others they need to be built or further developed to enable reliable monitoring of progress made towards TB mortality targets.⁶²

WHO methods and data sources
for country-level causes of death
2000–2015

Department of Informatics, Evidence and Research
WHO Geneva
January 2017



Global Health Estimates Technical Paper WHO/HTM/TB/2016.04



WHO methods and data sources for country-level causes of death 2000–2015⁶²

61 Guidelines for the surveillance of drug resistance in tuberculosis. 5th ed. Geneva: World Health Organization; 2012 (WHO/HTM/TB/2015.13; http://apps.who.int/iris/bitstream/10665/174897/1/9789241549134_eng.pdf?ua=1, accessed 1 May 2018).

62 WHO methods and data sources for country-level causes of death 2000–2015. Geneva: World Health Organization; 2016 (http://www.who.int/healthinfo/global_burden_disease/GlobalCOD_method_2000_2015.pdf, accessed 1 May 2018).

10. Supportive approaches

10.1 Digital health

WHO TB Standard 28. Digital technologies can be adapted to increase the effectiveness or efficiency of different components of TB programmes.

The potential for information and communication technologies to help combat TB remains largely untapped.⁶³ Many countries and partners have embarked on eHealth (or electronic health) and mHealth (or mobile health) interventions to enhance patient care, surveillance, programme management, communication and human resource development.

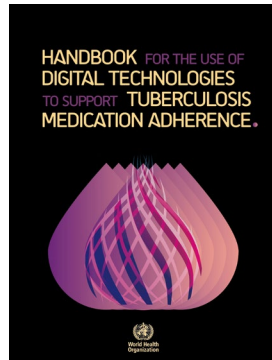
These developments have created new, exciting possibilities to improve patient care by turning data into useful information for individuals and for programme management. They have the potential to transform the delivery of different dimensions of services, bringing the notion of patient-centred care within reach, even under very basic conditions.



Digital health for the End TB Strategy⁶³

One important application of digital health in TB patient care is the support that it can lend to medication adherence. TB programmes have already been using short message service (SMS), video-supported treatment (VOT) and

medication event monitoring systems (MEMS)⁶⁴ to help patients complete treatment and health-care workers to monitor both daily dosing and treatment continuity. It is important to invest in digital health products for which evidence already exists and to collect data about their use and impacts, and users' preferences to continue to improve digital technologies.



Handbook: Digital technologies to support TB medication adherence⁶⁴

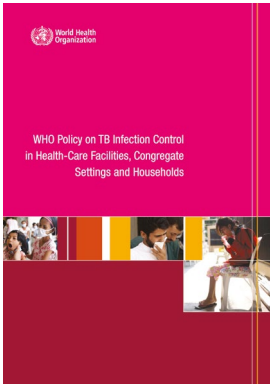
10.2 Infection control

WHO TB Standard 29. Promptly identify persons with TB symptoms (triage); provide an adequately ventilated waiting area for them; educate them about cough etiquette and respiratory hygiene; ensure they are prioritized for TB testing; and separate infectious patients.

Triage and separation of patients who have symptoms of TB should be implemented in ways that improve patient flow through the health-care facility. These controls are necessary to minimize the exposure of uninfected patients (particularly those who are immunocompromised) to infectious patients. The controls should be implemented irrespective of the likely or known drug-susceptibility pattern⁶⁵.

63 Digital health for the End TB Strategy: an agenda for action. Geneva: World Health Organization; 2015 (WHO/HTM/TB/2015.21; http://apps.who.int/iris/bitstream/10665/205222/1/WHO_HTM_TB_2015.21_eng.pdf, accessed 1 May 2018).

64 Handbook for the use of digital technologies to support tuberculosis medication adherence. Geneva: World Health Organization; 2018 (WHO/HTM/TB/2017.30; <http://apps.who.int/iris/bitstream/10665/259832/1/9789241513456-eng.pdf?ua=1>, accessed 1 March 2018).



WHO policy on TB infection control in health-care facilities, congregate settings and households⁶⁵

To minimize the spread of droplet nuclei, any patient with a cough and respiratory infection – in particular, patients with or suspected of having TB – should be educated about cough etiquette and respiratory hygiene; that is, they must be told about the need to cover their nose and mouth when sneezing or coughing. Such etiquette also applies to health workers, visitors and families. Physical barriers that can be used to minimize the spread of droplets include a piece of cloth, a tissue or a surgical mask; and such items should be properly disposed of as part of good respiratory hygiene practice.

Hospitalization is generally not recommended to evaluate persons suspected of having TB or to manage the treatment of patients with drug-susceptible TB, except for patients who have concomitant medical conditions that require it. If persons with symptoms of TB are hospitalized, they should not be placed in the same area as susceptible patients or patients with infectious TB. To avoid nosocomial transmission of TB (that is, hospital- or health-care-acquired TB), patients should spend as little time as possible in health-care facilities, including

clinics; this can be achieved, for example, by reducing diagnostic delays. Health workers should ensure that high-quality clinical care is provided to infectious patients and minimize the time spent with such patients in areas that are overcrowded or poorly ventilated.

The choice of ventilation system will be based on an assessment of the facility and informed by local programmatic, climatic and socioeconomic conditions. The ventilation system must be monitored regularly and have regular maintenance. Upper-room ultraviolet (UV) germicidal irradiation (known as UVGI) devices are potentially hazardous if improperly designed or installed. In well-designed systems, the principal hazard is inadvertent eye exposure by workers climbing into the high-UV zone for tasks such as painting, cleaning and maintenance. As with any engineering control, UV germicidal irradiation devices must be properly designed, installed, operated and maintained.

Additionally, a comprehensive programme should be implemented to train health workers how to use particulate respirators because the correct and continual use of respirators involves significant behavioural change on the part of health workers. Consideration should be given to including fit testing for respirators.

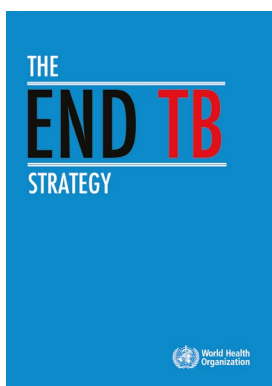
All health workers should be given appropriate information and encouraged to undergo a diagnostic investigation for TB if they have signs and symptoms suggestive of TB. Similarly, all health workers should be given appropriate information about HIV and encouraged to undergo HIV testing and counselling if necessary. If diagnosed with HIV, they should be offered a package of prevention, treatment and care that includes regular screening for active TB and access to ART.

65 WHO policy on TB infection control in health-care facilities, congregate settings and households. Geneva: World Health Organization; 2009 (WHO/HTM/TB/2009.419; http://apps.who.int/iris/bitstream/10665/44148/1/9789241598323_eng.pdf, accessed 1 May 2018).

10.3 Patient care and support

WHO TB Standard 30. A patient-centred approach to treatment should be developed to promote adherence, improve quality of life and relieve suffering. This approach should be based on the patient's needs and on mutual respect between the patient and the provider.

Integrated, patient-centred care and prevention focuses on prevention, early detection and treatment and care of all TB patients, including children. Implementing this approach requires close collaboration among all stakeholders, including the social sector, civil society and local communities. The human and financial resources required for implementation should be commensurate with the enhanced scope of core functions that are integrated effectively within delivery. The aim is to ensure that the patient's needs, values, preferences and rights inform the access and delivery of services.⁶⁶ Integrated, patient-centred care is fundamental, as well as broader social protection, to the target of eliminating the catastrophic costs for TB patients and affected households by 2020, as set out in the End TB Strategy.

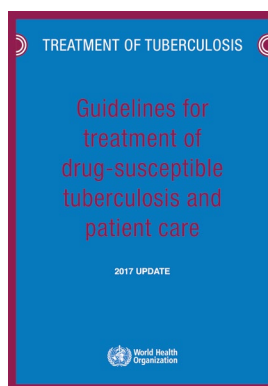


The End TB Strategy⁶⁶



WHO TB Standard 31. Prior to starting TB treatment, each patient's need for support should be assessed, and interventions to encourage adherence to treatment be offered to improve outcomes.

Patients have better outcomes when interventions to encourage treatment adherence are used, either individually or combined in a package – for example, there are higher rates of treatment success, treatment completion, cure and adherence, and there are lower rates of mortality and loss to follow up. When patients receive treatment adherence interventions in conjunction with directly observed treatment (DOT) or self-administered treatment (SAT), treatment outcomes are significantly improved compared with DOT or SAT alone. Recommended adherence interventions are shown in Table 4. Interventions should be selected after assessing the patient's needs, providers' resources and conditions for implementation⁶⁷.



Guidelines for treatment of drug-susceptible tuberculosis and patient care⁶⁷

66 The End TB Strategy: global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva: World Health Organization; 2014 (http://www.who.int/tb/strategy/End_TB_Strategy.pdf, accessed 1 May 2018).

67 Guidelines for treatment of drug-susceptible tuberculosis and patient care: 2017 update. Geneva: World Health Organization; 2017 (WHO/HTM/TB/2017.05; <http://apps.who.int/iris/bitstream/10665/255052/1/9789241550000-eng.pdf?ua=1>, accessed 1 May 2018).

Table 4. Recommended adherence interventions for patients being treated for TB and their providers

Intervention	Description
Patient education	Health education and counselling about TB and its treatment
Staff education	Education, charts or other visual reminders, educational tools and desktop aids for decision-making
Material support	Food or financial support, such as meals, food baskets, food supplements, food vouchers, transport subsidies, living allowance, housing incentives or a financial bonus; this intervention addresses the indirect costs incurred by patients or their caregivers while accessing health services, and tries to mitigate the consequences of income loss related to the disease
Psychological support	Counselling sessions or peer-group support
Communication with patient	Home visits or mobile telephone communication, such as SMS text messages or telephone calls
Digital medication monitor	A device that measures the time between each opening of a pill box; the monitor may give audible reminders or send SMS text messages to remind patients to take their medications, as well as recording when the box is opened

WHO TB Standard 32. Before starting TB treatment, all patients should be assessed to determine the risk of treatment interruption, and appropriate options for treatment administration should be offered to each patient. Community- or home-based DOT is recommended over health facility-based DOT or unsupervised treatment; and DOT administered by trained lay providers or health-care workers is recommended over DOT administered by family members. Video-observed treatment may replace DOT when the technology is available and can be organized and operated by health-care providers and patients.

Overall, the evidence is inconsistent about whether DOT alone or SAT alone is more likely to encourage treatment adherence. However, some subgroups of patients (such as HIV-positive TB patients) who have other factors affecting treatment adherence are likely to benefit from DOT; also, some specific types of DOT delivery (that is, certain locations of DOT or DOT providers) are more likely to work than others. Community-based or home-based DOT is more likely to encourage adherence than health facility-based DOT, but family members

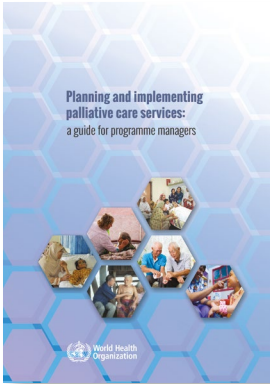
should not be the first option for administering DOT. Therefore, DOT is better provided at home or in the community by trained lay providers or health-care workers.

The advantage of using video technology is its potential to allow observation of adherence from a distance, even when a patient is travelling and cannot visit or be visited by a DOT provider. Video technology also offers more flexibility because a patient's adherence can be observed at different times of day. Potentially, it could help achieve better levels of patient adherence at a much lower cost and less inconvenience than in-person DOT. Video technology can be used in addition to or interchangeably with in-person DOT. For instance, it is not expected that a patient will use video technology throughout the duration of their treatment.

10.4 Palliative care

Palliative care refers to all measures taken to relieve the suffering of persons affected by a life-threatening condition. Because mortality in TB remains unacceptably high, the priority is to ensure timely access to life-saving treatment. Patients with limited effective treatment options,

such as those with MDR-TB, are at high risk of suffering due to the disease, the toxicity of treatment and the sequelae of both.⁶⁸



Planning and implementing palliative care services⁶⁸



WHO TB Standard 33. All forms of suffering associated with TB should be addressed by ensuring that patients have proper access to care and to the management of adverse reactions to treatment, management of psychological distress, means to prevent and mitigate stigma and discrimination, and by providing access to social protection mechanisms to reduce indirect costs.

Palliative care is not given instead of treatment but in addition to treatment, whenever possible, to patients with limited options for effective treatment. Care that relieves suffering is an integral part of caring for all persons with TB at all times during the course of their illness. National TB programmes and all health-care providers should be aware that suffering is more severe in patients with XDR-TB due to its chronic nature and the limited options for effective treatment; this group should be prioritized for palliative care until highly effective regimens are developed.

Persons with TB for whom all treatment options have been exhausted usually remain a source of TB transmission. The only option for protecting public health while delivering palliative and end-of-life care is to ensure that proper infection control measures are in place at the patient's home, hospital or hospice.

68 Planning and implementing palliative care services: a guide for programme managers. Geneva: World Health Organization; 2016 (<http://apps.who.int/iris/bitstream/10665/250584/1/9789241565417-eng.pdf>, accessed 1 May 2018).

THE
END TB
STRATEGY



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