WHO consolidated guidelines on tuberculosis

Module 1: Prevention

Tuberculosis preventive treatment

World Health Organization

WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment

ISBN 978-92-4-000150-3 (electronic version)

ISBN 978-92-4-000151-0 (print version)

ISBN 978-92-4-000267-8 (epub)

Suggested citation. WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Design by Inis Communication

WHO consolidated guidelines on tuberculosis

Module 1: Prevention

Tuberculosis preventive treatment

World Health Organization

Table of Contents

Acknowledgements iv
Abbreviations & acronyms vi
Definitions vii
Executive summary viii
Introduction 1
1. Recommendations 3
2. Monitoring and evaluation 26
3. Research gaps 28
4. References 31
Supplementary Table 38

Online annexes

Annex 1. Methods and Expert panels
Annex 2. GRADE Summary of Evidence Tables
Annex 3. GRADE Evidence to Decision Tables

Acknowledgements

The production of the *WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment* was coordinated and written by Dennis Falzon, Avinash Kanchar and Matteo Zignol under the overall direction of Tereza Kasaeva, Director of the WHO Global TB Programme. The WHO Global TB Programme gratefully acknowledges the contribution of all experts involved in the production of these guidelines.[1]

Guideline Development Group

The Guideline Development Group (GDG) was composed of Mohammed Al Lawati (Consultant Physician, Oman); Helen Ayles (Infectious Diseases and International Health, LSHTM, Lusaka, Zambia); Rolando Cedillos (Service of Infectious Diseases and Integrated Programme for STI/HIV/AIDS, El Salvador); Padmapriyadarsini Chandrasekaran (National Institute for Research in Tuberculosis, India); Diana Gibb (Medical Research Council, United Kingdom of Great Britain and Northern Ireland (UK)); Yohhei Hamada (Research Institute of Tuberculosis (RIT), Japan Anti-Tuberculosis Association (JATA), Japan); Anthony D Harries (International Union Against Tuberculosis and Lung Disease, Paris, France; London School of Hygiene and Tropical Medicine, London, UK); Alexander Kay (Baylor College of Medicine, Global TB Program, Eswatini); Nasehi Mahshid (Department of TB and Leprosy Control, Centre for Control of Communicable Diseases, Ministry of Health and Medical Education, Iran); Alberto Matteelli (University of Brescia, WHO Collaborating Centre for TB/HIV and TB Elimination, Italy); Lindiwe Mvusi (National Department of Health, South Africa); Kuldeep Singh Sachdeva (National Tuberculosis Elimination Programme, India); Nandi Siegfried (Medical Research Council / University of Cape Town, South Africa); Ezio Távora dos Santos Filho (Civil Society Task Force, Brazil); Marieke van der Werf (European Centre for Disease Prevention and Control, Sweden); Wim Vandevelde (Global TB Community Advisory Board, South Africa); and Irina Vasilyeva (Ministry of Health, Russian Federation). The co-chairs of the GDG were Lindiwe Mvusi and Nandi Siegfried. Dr Siegfried was also the GRADE methodologist

External Reviewers

The External Review Group (ERG) was composed of Connie Erkens (KNCV TB Foundation, Netherlands); Steve Graham (Center for International Child Health University of Melbourne, Australia); Giovanni B. Migliori (Istituti Clinici Scientifici Maugeri, IRCCS and WHO Collaborating Centre for TB and Lung Diseases, Italy); Rohit Sarin (National Institute of TB and Respiratory Diseases, India); James Seddon (Imperial College, UK); Alena Skrahina (Republican Scientific and Practical Centre for Pulmonology and TB, Belarus); and Carrie Tudor (International Council of Nurses, South Africa). Edits to the draft guidelines were also provided by people who responded to the call for public review on 1 July 2019.

Evidence reviewers

The following persons contributed to the reviews and summarization of evidence for the guidelines:

Mayara Bastos, Jonathon Campbell and Richard (Dick) Menzies (McGill University, Canada) provided the first draft of estimates and footnotes for the GRADE summary of evidence table from the trials of four months of daily rifampicin (PICO 6).

[1] More information on the areas of expertise, gender and geographical distribution, declarations of interests and the management of potential conflict for members of the GDG and ERG are summarised in **Annex 1** (online).

Richard Chaisson and Ritesh Ramchandani (Johns Hopkins University, USA) and Susan Swindells (University of Nebraska Medical Center, USA) provided the first draft of estimates and footnotes for the GRADE summary of evidence table from the BRIEF-TB/A5279 trial of one month of daily rifapentine and isoniazid (PICO 7).

Yohhei Hamada (RIT/JATA, Japan) researched and wrote the report on the systematic review and meta-analysis of the safety of isoniazid preventive treatment in pregnancy (PICO 9), with support from Carmen Figueroa (WHO Global TB Programme), and Mario Sánchez (WHO Management of Non-communicable Diseases, Disability, Violence & Injury Prevention). Lynne M. Mofenson (Consultant, WHO HIV Department) contributed with a qualitative review of the safety of isoniazid in pregnancy. Amita Gupta and Nicole Salazar-Austin (Johns Hopkins University, USA) provided unpublished information from their studies to complete the evidence review.

WHO Guideline Steering Group

The WHO Guideline Steering Group was composed of Annabel Baddeley, Annemieke Brands, Dennis Falzon, Carmen Figueroa, Medea Gegia, Christopher Gilpin, Philippe Glaziou, Avinash Kanchar and Matteo Zignol from the WHO Global TB Programme; Françoise Renaud and Satvinder Singh from the WHO Department of HIV/AIDS; Andreas Reis from the Department of Information, Evidence and Research; and Lorenzo Moja from the Department of Essential Medicines and Health Products. Wilson Were from the WHO Department of Maternal, Newborn, Child and Adolescent Health also reviewed the guidelines.

Others

The following persons participated as observers at the GDG meetings: Sevim Ahmedov (US Agency for International Development (USAID), USA); Draurio Barreira Cravo Neto (UNITAID, Switzerland); Anand Date (Centers for Disease Control and Prevention, USA); Lucia Gonzalez Fernandez (International AIDS Society, Switzerland); Harry Hausler (TBHIV Care, South Africa); Cecily Miller (University of California San Francisco, USA); Surbhi Modi (Centers for Disease Control and Prevention, USA); Suvanand Sahu (Stop TB Partnership, Switzerland); Anna Scardigli (Global Fund to Fight AIDS, TB and Malaria, Switzerland).

WHO acknowledges the contribution of the Guideline Review Committee and its WHO secretariat in reviewing and approving the guidelines ahead of their publication.

Funding for the guidelines update in 2019–2020 derived from WHO grants provided by USAID and the Russian Federation.

Abbreviations & acronyms

1HP	One month of daily rifapentine plus isoniazid
3HP	Three months of weekly rifapentine plus isoniazid
3HR	Three months of daily rifampicin plus isoniazid
4R	Four months of daily rifampicin monotherapy
6H	Six months of daily isoniazid monotherapy
9H	Nine months of daily isoniazid monotherapy
ART	antiretroviral treatment
BCG	bacille Calmette-Guérin (vaccine)
CI	confidence interval
ERG	External Review Group
GDG	Guideline Development Group
GRADE	grading of recommendations assessment, development and evaluation
HIV	human immunodeficiency virus
Hr-TB	isoniazid-resistant, rifampicin-susceptible TB
IGRA	interferon-gamma release assay
IPT	isoniazid preventive treatment (or monotherapy)
LTBI	latent tuberculosis infection
MDR-TB	multidrug-resistant tuberculosis
mITT	modified intention to treat (population)
OR	odds ratio
PICO	population, intervention, comparator and outcomes
PLHIV	people living with HIV
PMTPT	programmatic management of tuberculosis preventive treatment
RCT	randomized controlled trial
RR	relative risk
RR-TB	rifampicin-resistant tuberculosis
TST	tuberculin skin test
TB	tuberculosis

Definitions

Note: The definitions listed below apply to the terms as used in these guidelines. They may have different meanings in other contexts.

Adolescent: A person aged 10–19 years

Adult: A person over 19 years of age

Bacteriologically confirmed TB: TB diagnosed in a biological specimen by smear microscopy, culture or a WHO-approved molecular test such as Xpert® MTB/RIF

Child: A person under 10 years of age

Contact: Any person who was exposed to a person with tuberculosis

Contact investigation: A systematic process for identifying previously undiagnosed people with TB among the contacts of an index case. Contact investigation consists of identification and prioritization and clinical evaluation. It may also include testing for LTBI to identify candidates for TB preventive treatment.

High TB transmission setting: A setting with a high frequency of individuals with undetected or undiagnosed active TB, or where infectious TB patients are present and there is a high risk of TB transmission. TB patients are most infectious when they are untreated or inadequately treated. Spread is increased by aerosol-generating procedures and by the presence of highly susceptible individuals.

Household contact: A person who shared the same enclosed living space as the index case for one or more nights or for frequent or extended daytime periods during the 3 months before the start of current treatment.

Index case (index patient) of TB: The initially identified person of any age with new or recurrent TB in a specific household or other comparable setting in which others may have been exposed. An index case is the person on which a contact investigation is centred but is not necessarily the source case.

Infant: A child under 1 year (12 months) of age

Latent tuberculosis infection (LTBI): A state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of clinically manifest active TB. This is also at times referred to as TB infection. There is no gold standard test for direct identification of *M. tuberculosis* infection in humans. Most infected people have no signs or symptoms of TB but are at risk for active TB disease.

People who use drugs: People who engage in the harmful or hazardous use of psychoactive substances, which could impact negatively on the user's health, social life, resources and legal situation.

Programmatic management of tuberculosis preventive treatment (PMTPT): All coordinated activities by public and private health caregivers and the community aimed at scaling up TB preventive treatment to people who need it.

TB preventive treatment (TPT): Treatment offered to individuals who are considered at risk of TB disease in order to reduce that risk. Also referred to as treatment of TB infection, LTBI treatment or TB preventive therapy.

Tuberculosis (TB): The disease state due to *M. tuberculosis*. In this document, it is commonly referred to as "active" TB or TB "disease" in order to distinguish it from TB infection.

Underweight: in adults usually refers to a body mass index <18.5 and in children < 10 years to a weight-for-age < –2 z-scores

Executive summary

Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of clinically manifest active TB. It is estimated that about a quarter of the world's population is infected with TB. TB preventive treatment (TPT) is one of the key interventions recommended by WHO to achieve the End TB Strategy targets, as upheld by the UN High Level Meeting on TB in September 2018. TPT fits within a larger framework of preventive actions envisaged by Pillars 1 and 2 of the End TB Strategy, ranging from screening for active TB, infection control, prevention and care of HIV and other co-morbidities and health risks, access to universal health care, social protection and poverty alleviation.

WHO guidelines on LTBI consider the probability of progression to active TB disease in specific risk groups, the epidemiology and burden of TB, and the likelihood of a broad public health impact. Recommendations are meant primarily for staff in ministries of health and for other policy-makers working on TB, HIV, infectious diseases and maternal and child health. The 2020 *WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment* builds upon the previous edition of the document. Its main objectives were to reflect new evidence on shorter rifamycin-containing preventive regimens from trials reported after the 2018 edition of the guidelines were released and to improve the clarity and global applicability of its recommendations. These guidelines supersede previous WHO policy documents on the management of LTBI in people living with HIV (PLHIV), household contacts of people with TB and other risk groups.

The *WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment* were prepared in accordance with the requirements of the Guideline Review Committee. The Guideline Development Group (GDG) considered the quality of the latest available evidence on effectiveness and harms, as well as certainty of the evidence, values and preferences, and issues of equity, resource use, acceptability and feasibility of implementation when updating or formulating new recommendations and determining their strength. The GDG considered the implications of the best available evidence for each population subgroup at risk, their likelihood of progression from infection to active TB and the incidence of active TB as compared with that in the general population. The GDG used the guiding principle that individual benefit outweighs risk as the mainstay of recommendations on LTBI testing and TPT. LTBI testing is desirable whenever feasible to identify persons at highest risk for developing active TB. Any additional resources needed to implement the guidance should not be viewed as a barrier but should stimulate programmatic action to mobilise appropriate levels of funding.

The 18 recommendations in the *WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment* cover critical steps in the programmatic management of TPT (PMTPT) and follow the cascade of preventive care: identification of populations at risk (PLHIV as part of the HIV care package, household contacts and others), ruling out active TB disease, testing for LTBI, providing treatment, and monitoring adverse events, adherence and completion of treatment (**Table 1**). Most of the recommendations dating from the 2018 update remain largely unchanged. The changes introduced in 2020 relate primarily to the inclusion of a 1-month daily rifapentine and isoniazid regimen and a 4-month daily rifampicin regimen as alternative TB preventive treatment options in all settings subject to specific conditions. Advice on isoniazid preventive treatment in pregnancy and on the concomitant use of rifapentine and dolutegravir now reflects findings from latest available studies. Certain recommendations – previously restricted by national TB incidence thresholds out of concerns of intensity of TB transmission, programmatic capacity to rule out active TB, and resource implications

to implement a new intervention at scale – are now applicable to any country subject to setting-specific conditions. The operational limitations that need to be urgently overcome by countries to achieve global targets are highlighted. The publication of the new guidelines will be followed shortly after with the release of an operational guide containing practical details on the programmatic implementation of the updated guidance. These two publications are being issued as modular components of a new consolidated set of guidelines and operational guides that will group together other WHO normative documents on TB.

Table 1. Recommendations in the *WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment*[2]

1.1. Identifying populations for LTBI testing and TB preventive treatment
People living with HIV
1. Adults and adolescents living with HIV who are unlikely to have active TB should receive TB preventive treatment as part of a comprehensive package of HIV care. Treatment should also be given to those on antiretroviral treatment, to pregnant women and to those who have previously been treated for TB, irrespective of the degree of immunosuppression and even if LTBI testing is unavailable.
2. Infants aged < 12 months living with HIV who are in contact with a person with TB and who are unlikely to have active TB on an appropriate clinical evaluation or according to national guidelines should receive TB preventive treatment.
3. Children aged ≥ 12 months living with HIV who are considered unlikely to have active TB on an appropriate clinical evaluation or according to national guidelines should be offered TB preventive treatment as part of a comprehensive package of HIV prevention and care if they live in a setting with high TB transmission, regardless of contact with TB.
4. All children living with HIV who have successfully completed treatment for TB disease may receive TB preventive treatment.
Household contacts (regardless of HIV status)
5. Children aged < 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have active TB on an appropriate clinical evaluation or according to national guidelines should be given TB preventive treatment even if LTBI testing is unavailable.
6. Children aged ≥ 5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have active TB by an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment.
7. In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualized risk assessment and a sound clinical justification.
Other people at risk
8. People who are initiating anti-TNF treatment, or receiving dialysis, or preparing for an organ or haematological transplant, or who have silicosis should be systematically tested and treated for LTBI.
9. Systematic LTBI testing and treatment may be considered for prisoners, health workers, immigrants from countries with a high TB burden, homeless people and people who use drugs.
10. Systematic LTBI testing and treatment is not recommended for people with diabetes, people who engage in the harmful use of alcohol, tobacco smokers and underweight people unless they also belong to other risk groups included in the above recommendations.

[2] The recommendations in the current update are compared with those in the 2018 guidelines in the Supplementary Table.

1.2. Algorithms to rule out active TB disease

11. 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.

12. Adults and adolescents living with HIV who are screened for TB according to a clinical algorithm and who report any 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 and offered preventive treatment if active TB is excluded.

13. Chest radiography may be offered to people living with HIV on ART and preventive treatment given to those with no abnormal radiographic findings.

14. Infants and children living with HIV who have poor weight gain, fever or current cough or who have a history of contact with a person with TB should be evaluated for TB and other diseases that cause such symptoms. If TB disease is excluded after an appropriate clinical evaluation or according to national guidelines, these children should be offered TB preventive treatment, regardless of their age.

15. 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 risk groups before preventive treatment.

1.3. Testing for LTBI

16. Either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) can be used to test for LTBI.

1.4. TB preventive treatment options

17. The following options are recommended for the treatment of LTBI regardless of HIV status: 6 or 9 months of daily isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or a 3 month regimen of daily isoniazid plus rifampicin. A 1-month regimen of daily rifapentine plus isoniazid or 4 months of daily rifampicin alone may also be offered as alternatives.

18. In settings with high TB transmission, adults and adolescents living with HIV who have an unknown or a positive LTBI test and are unlikely to have active TB disease should receive at least 36 months of daily isoniazid preventive therapy (IPT). Daily IPT for 36 months should be given whether or not the person is on ART, and irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy in settings considered to have a high TB transmission as defined by national authorities.

Main changes to the guidance in the current update

(see also Supplementary Table)

- the text of five recommendations was edited to reflect their applicability regardless of the TB burden in the country or setting, and additional commentary added to highlight the implications for their use in settings that differ in TB burden and resources
- recommendations and accompanying considerations for TB preventive treatment in contacts and clinical and occupational risk groups have been slightly reworded to remove any undue stress on their application to HIV negative individuals only
- three previous recommendations on the systematic LTBI testing and TB preventive treatment in low burden settings and in PLHIV and household contacts under 5 years of age before the start of treatment are now presented amongst the implementation considerations
- one recommendation has been updated to include both 1HP and 4R as options for TB preventive treatment in all settings
- three previous recommendations on the use of 6H, 3HR in people under 15 years of age and 3HP in high TB prevalence settings no longer feature by themselves as these regimen options are now covered by one recommendation that lists all acceptable TB preventive treatment options in any setting
- the variable durations of 3–4 months of daily rifampicin and 3–4 months of daily rifampicin plus isoniazid in the previous recommendation have been simplified to 4 and 3 months respectively, being the length of time for which these treatments are usually given
- a single algorithm replaces the four in the 2018 guidance, harmonizing the key decision points for LTBI testing and TB preventive treatment of individuals at risk
- the content of the guidelines has been updated, citing recent references and latest available evidence, such as on use of rifapentine with dolutegravir and isoniazid preventive treatment in pregnant women with HIV
- the research gaps have been updated to reflect the latest evidence reviewed

Introduction

1. Background

Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of clinically manifest active TB (1)[3]. As there is no "gold standard" test for TB infection, the global burden is not known with certainty; however, about one fourth of the world's population is estimated to be infected with *M. tuberculosis* (2),(3). The vast majority have no signs or symptoms of TB disease and are not infectious, although they are at risk of developing active TB disease and becoming infectious. Several studies have shown that in recent decades, on average, 5–10% of those infected will develop active TB disease over the course of their lives, usually within the first 5 years after initial infection (4),(5). The risk for active TB disease after infection depends on several factors, the most important being immunological status (1). At the first United Nations high-level meeting on TB in 2018, Member States committed to provide TB preventive treatment to at least 30 million people in 2018–2022: 6 million people living with HIV (PLHIV), 4 million children < 5 years who are household contacts of people with TB, and 20 million other household contacts (6).

Prevention of active TB disease by TB preventive treatment is a critical component of the WHO End TB Strategy and efforts to eliminate TB (7),(8),(9). The efficacy of currently available TB preventive treatment ranges from 60% to 90% (1). The potential benefit of treatment should, however, be carefully balanced against the risk for drug-related adverse events. Mass, population-wide LTBI testing and treatment are not feasible because the tests are imperfect, there are risks of serious and potentially fatal adverse drug reactions, with a high cost and unproven public health impact. The benefits of TB preventive treatment are more likely to outweigh harms in infected individuals belonging to population groups in whom the risk for progression to active disease significantly exceeds that of the general population. The programmatic management of TB preventive treatment (PMTPT) involves a comprehensive package of interventions: identifying and testing those individuals who should be tested, delivering effective, safe treatment in such a way that the majority of those starting a treatment regimen will complete it with no or minimal risk of adverse events, and monitoring and evaluation of the process. PMTPT fits within a larger framework of preventive actions envisaged by Pillars 1 and 2 of the End TB Strategy, ranging from screening for active TB, infection control, prevention and care of HIV and other co-morbidities and health risks, access to universal health care, social protection and poverty alleviation.

2. Rationale

WHO guidelines on PMTPT are premised upon the probability that the condition will progress to active TB disease in specific risk groups, on the underlying epidemiology and burden of TB, the feasibility of the intervention, and the likelihood of a broader public health impact. They are expected to provide the basis for the development of national guidelines for LTBI management, adapted to the local circumstances. Although these revised guidelines envisage a massive expansion in population level treatment of LTBI, global coverage of the intervention is still very low even in the priority target groups

[3] Given that the main difference from active TB is the absence of disease and given that infection cannot always be considered latent, the condition is sometimes referred to as TB infection (TBI).

(10). The *Latent TB Infection : Updated and consolidated guidelines for programmatic management* released by WHO in 2018 brought together recommendations previously dispersed in several other guidelines to facilitate access to the most recent policies that are still valid for PLHIV (11), for children under 5 years who are household contacts of people with pulmonary TB (12), for other contacts of people with TB, and for clinical risk groups (13),(14),(15),(16). In addition, the 2018 guidelines updated 7 previous recommendations and included 7 new ones. Since the publication of these guidelines in early 2018 new evidence became available that made it necessary to revisit some of the recommendations once more.

3. Scope of the current update

The current update considered evidence for three questions, worded in PICO format[4], namely:

- In people of all ages at risk of active TB, does a 4-month daily rifampicin regimen safely prevent TB disease compared to other recommended TB preventive treatment regimens? (PICO 6)
- In people of all ages at risk of active TB, does a 1-month daily rifapentine plus isoniazid regimen safely prevent TB disease compared to other recommended TB preventive treatment regimens? (PICO 7)
- In pregnant and postpartum women, is isoniazid preventive treatment for TB as safe as other preventive treatment regimens? (PICO 9)

In addition to these new questions the wording of some of the recommendations dating from before the current update, along with their accompanying conditions, was revised to improve clarity. Some recommendations in previous guidelines applied differently to high and low TB incidence countries and settings (using a threshold of 100 TB cases per 100,000 population nationally to differentiate), primarily out of concerns about variable intensity of background TB transmission, as well as programmatic capacity to rule out active TB reliably and to provide adequately for newer treatments regimens and care. In 2019, the GDG that produced the *WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment* decided to stress these conditions under implementation considerations instead of restricting the recommendations based upon a TB incidence threshold.

When making their decisions about the wording and strength of the recommendations the GDG members took into account not only the evidence for effectiveness and safety of an intervention but also considered other dimensions important to both patient and programme, namely values, preferences, resource requirements, cost, impact on health equity, acceptability and feasibility. This is detailed in the GRADE Evidence to Decision Tables (**Annex 3**).

4. Target audience

The *WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment* provides a comprehensive set of recommendations for PMTPT geared towards the implementers of the WHO End TB Strategy and also for countries intent upon TB elimination (9). The guidelines are to be used primarily in national TB and HIV and maternal and child programmes or their equivalents in ministries of health and for other policy-makers working on TB, HIV, infectious diseases and maternal and child health. They are also appropriate for staff of ministries of justice, correctional services and other government agencies which deliver healthcare, including prison services, social services and immigration. The guidelines are also intended for clinicians in the public or the private sectors working on TB, HIV, infectious diseases, prevention, child health and noncommunicable diseases such as chronic kidney disease and cancer. The persons directly affected by the guidelines are risk groups for whom TB preventive treatment is recommended.

[4] **P**opulation, **I**ntervention, **C**omparator and **O**utcome. The three PICOs in the current update were renumbered to position them within the sequence of questions covered by the 2018 guidelines update (16). See **Annex 2** for a complete listing of PICOs and evidence summaries made for both the 2018 and the current (2019) updates

1. Recommendations

1.1. Identification of populations for testing of latent tuberculosis infection and TB preventive treatment

Among individuals infected with *M. tuberculosis* it is estimated that the lifetime risk of progressing to active TB averages to about 5–10% (4). The risk is particularly elevated among children under the age of 5 years and among people with compromised immunity (1). As any treatment entails risk of harms and opportunity costs, TB preventive treatment should be selectively targeted to population groups at highest risk of progression to active TB disease, who would benefit most from it. When identifying populations at increased risk, consideration should be given to the epidemiology and pattern of TB transmission in the country, so that treatment is optimized to offer lasting protection. A comprehensive individual clinical assessment that considers the balance between the risks and benefits for the person receiving treatment is critical. The three parts of this section describe recommendations for LTBI in population groups considered at highest risk and/or vulnerability to poor outcomes.

Adults and adolescents living with HIV

1. Adults and adolescents living with HIV who are unlikely to have active TB should receive TB preventive treatment as part of a comprehensive package of HIV care. Treatment should be given to those on antiretroviral treatment, to pregnant women and to those who have previously been treated for TB, irrespective of the degree of immunosuppression and even if LTBI testing is unavailable. *(Strong recommendation, high certainty in the estimates of effect)*

Justification and evidence

TB is the most frequent cause of AIDS-related deaths worldwide, despite progress in access to ART (17). TB caused about 251,000 deaths among PLHIV in 2018, representing about one third of all HIV deaths (10). Global data indicate that PLHIV are about 20 times more likely to develop active TB than those without HIV infection.

The recommendation for TB preventive treatment of all PLHIV was first published by WHO in 2011 (11). A systematic review of 12 randomized controlled trials (RCTs) found that preventive treatment reduced the overall risk for TB by 33% (relative risk [RR] 0.67, 95% confidence interval [CI] 0.51; 0.87) among the 8,578 PLHIV included (18). For those who were TST positive, the reduction increased to 64% (RR 0.36, 95% CI 0.22; 0.61). Although not statistically significant, the reduction was 14% among TST-negative people (RR 0.86, 95% CI 0.59; 1.26) and those of unknown TST status (RR 0.86, 95% CI 0.48; 1.52). Most of the studies in the review were, however, conducted before ART became available, and there is now increasing evidence from observational studies and RCTs of the efficacy of TB preventive treatment in people receiving ART. TB incidence has been reported to be high among all PLHIV who did not receive isoniazid preventive treatment (IPT), including those with CD4>350 per cu mm and who were TST negative (19). One double-blind RCT of 1,329 PLHIV receiving ART indicated that those on ART with negative TST or IGRA benefited more from IPT than those who were TST or IGRA positive (20).

An RCT of 2,056 PLHIV showed additive benefits of TB preventive treatment plus ART in reducing both TB incidence and overall mortality (21),(22). The protective effect lasted for more than 5 years.

The GDG reviewed the evidence from the systematic reviews and discussed each population risk group identified in detail for the prevalence of LTBI, risk of progression to active TB and the incidence of active TB as compared with the general population. They concluded that the evidence shows a clear benefit of systematic testing and treatment of LTBI for PLHIV. The wording of the recommendation now refers to LTBI testing rather than TST given that IGRA is also an option (see **Recommendation 16**). Preventive treatment should be given to adults and adolescents living with HIV, regardless of their immune status and whether they are on ART, given the evidence of additional protective effect to ART. A systematic review of studies conducted before ART became available showed the value of providing preventive treatment immediately after successful completion of TB treatment among PLHIV in countries with a TB incidence >100 / 100,000 population (11),(23). Therefore, preventive treatment is recommended for people who were previously treated for TB. No evidence was found, however, for preventive treatment of people who had successfully completed treatment for multidrug-resistant TB (MDR-TB) or extensively drug-resistant TB (XDR-TB). The effect of repeated courses of preventive treatment is unclear and hence no recommendation on this is made in the present guidelines; this is the subject of ongoing studies (e.g. WHIP3TB (24)). In settings with high TB transmission, however, daily IPT for 36 months or longer is recommended conditionally (25) (see **Recommendation 18**). The relative risk of TB transmission is determined by the local authorities on the basis of risk of exposure (e.g. TB incidence, occurrence of undiagnosed or inadequately treated disease, population density, environmental factors) and host immune response (see **Definitions**, (26)).

Pregnant women living with HIV are at risk for TB, which can have severe consequences for both the mother and the foetus, with increased risk of maternal and infant death (27). Pregnancy should not disqualify women living with HIV from receiving preventive treatment with medicines commonly used to treat active TB that are generally considered safe for use in pregnancy, such as isoniazid and rifampicin (classified as Pregnancy Category C by US FDA (28),(29)). **Section 1.4** presents the position of the GDG in 2019 on the use of isoniazid preventive treatment in pregnancy based on an updated evidence review.

Infants and children living with HIV

2. Infants aged < 12 months living with HIV who are in contact with a person with TB and who are unlikely to have active TB on an appropriate clinical evaluation or according to national guidelines should receive TB preventive treatment. *(Strong recommendation, moderate certainty in the estimates of effect)*

3. Children aged ≥ 12 months living with HIV who are considered unlikely to have active TB on an appropriate clinical evaluation or according to national guidelines should be offered TB preventive treatment as part of a comprehensive package of HIV prevention and care if they live in a setting with high TB transmission, regardless of contact with TB. *(Strong recommendation, low certainty in the estimates of effect)*

4. All children living with HIV who have successfully completed treatment for TB disease may receive TB preventive treatment. *(Conditional recommendation, low certainty in the estimates of effect)*

Justification and evidence

These recommendations were first published by WHO in 2011 (11). A systematic review conducted for the original guidelines included two studies, both conducted in South Africa. One suggested a

considerable reduction in mortality and protection against TB among HIV-infected children who received isoniazid for 6 months (30). The other RCT, however, showed no benefit of preventive treatment in HIV-infected infants identified in the first 3–4 months of life in whom there was no known exposure to active TB and who were rapidly placed on ART and monitored carefully every month for new exposure to TB or disease (31). Few RCTs included children on ART. In one trial of 167 children on ART, the incidence of TB was lower in those given TB preventive treatment than in those who were not, but the difference was not statistically significant (incidence rate ratio 0.51, 95% CI 0.15; 1.75)(32). A cohort study suggested an additive protective effect of preventive treatment in children receiving ART (33).

For infants aged <12 months living with HIV, the GDG noted that TB preventive treatment should be given only to those infants who have a history of household contact with a person with TB and do not have TB disease according to investigations conducted in line with national guidelines because of limited data on the benefits. The GDG strongly recommended preventive treatment for children aged ≥ 12 months living with HIV without clinical manifestations suggestive of active TB, despite the low quality of the evidence, because of the clear benefits seen in adults with HIV and the high risk for active TB among PLHIV. Children ≥ 12 months living with HIV who have clinical manifestations or who are contacts should be evaluated further and treated for active TB or LTBI as indicated (see also **Fig. 1**).

The GDG noted that, although the evidence for the efficacy of preventive treatment in children on ART is limited, it is biologically plausible, given the evidence of additive effects in adults with HIV receiving ART. Thus, preventive treatment is recommended for children, regardless of whether they are on ART or not.

There is no evidence on the value of preventive treatment in children living with HIV after successful completion of TB treatment. However, children living with HIV who are at risk of reinfection would benefit from preventive treatment. Therefore, based on this judgement, the GDG conditionally recommended that all children living with HIV who have been successfully treated for TB and are living in settings with high TB transmission (as defined by national authorities; see also **Definitions**) may receive a course of TB preventive treatment. This can be started immediately after the last dose of TB curative treatment or later, according to clinical judgement.

Household contacts of pulmonary TB[5]

5. Children aged < 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have active TB on an appropriate clinical evaluation or according to national guidelines should be given TB preventive treatment even if LTBI testing is unavailable. *(Strong recommendation, high certainty in the estimates of effect)*

6. Children aged ≥ 5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have active TB by an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment. *(Conditional recommendation, low certainty in the estimates of effect)*

Justification and evidence

The first recommendation was initially published by WHO in 2015 and the second in 2018 (13),(16). A systematic review conducted for the 2015 guidelines was updated in 2018, focusing on household contacts in countries with a TB incidence >100 / 100,00 population (13),(14) (see PICO 1 in **Annex 2**). The aim of the review was to determine the prevalence of LTBI, progression to active TB disease and the cumulative prevalence of active TB among household contacts, stratified by age. Another

[5] Regardless of HIV status

19 studies published between 2014 and 2016 were added. Whilst the evidence reviewed related to HIV-negative child contacts, children living with HIV who are a household contact of a person with bacteriologically confirmed pulmonary TB should also receive investigations and treatment as necessary. The recommendation was thus reworded slightly in the current update to remove undue restriction on its application to HIV negative children alone.

The prevalence of LTBI was higher among children and adolescents aged > 15 years and adults than in children < 5 years, who were at greatest risk for progression to active TB disease. In comparison with child household contacts < 5 years, the pooled risk ratios for progression to active TB were lower in children aged 5–15 years (0.28, 95% CI 0.12; 0.65, four studies) and for those > 15 years (0.22, 95% CI 0.08; 0.60, three studies). All household contacts, regardless of their age or LTBI status, were nevertheless at a substantially higher risk for progression to active TB than the general population (**Table 2**).

Table 2. Pooled estimates of risk for active TB among household contacts stratified by age and baseline LTBI status as compared with the general population

Age (years)	LTBI-positive at baseline				Regardless of baseline LTBI status			
	Follow-up < 12 months		Follow-up < 24 months		Follow-up < 12 months		Follow-up < 24 months	
	No. of studies	Risk ratio	No. of studies	Risk ratio	No. of studies	Risk ratio	No. of studies	Risk ratio
General population	–	1.0 (reference)	–	1.0 (reference)	–	1.0 (reference)	–	1.0 (reference)
0–4	2	24.3 (0.73–811.0)	3	22.9 (7.7–68.6)	3	25.9 (16.9–39.7)	5	14.8 (9.8–22.3)
5–14	2	27.1 (17.5–54.1)	3	8.2 (2.3–29.4)	3	24.1 (16.9–34.4)	5	6.3 (2.9–13.7)
≥ 15	1	30.7 (17.5–54.1)	2	13.4 (9.5–18.8)	1	24.7 (14.2–43.0)	3	11.7 (7.6–18.0)

Both recommendations may apply to HIV-negative and to HIV-positive children. The GDG noted the significantly higher risk of infants and young children < 5 years to develop active TB. Furthermore, the disease can develop rapidly in young children, and they are at greatest risk of severe and disseminated disease, associated with high morbidity and mortality. Therefore, the GDG strongly recommended preventive treatment for child household contacts aged < 5 years, regardless of HIV status and background epidemiology of TB, but only after active TB disease has been ruled out.

Preventive treatment is also conditionally recommended for household contacts in other age groups, according to clinical judgement on the balance between harm and benefit for individuals and the national and local epidemiology of TB, with special consideration of ongoing transmission of TB. In this group the confirmation of LTBI using either IGRA or TST would be desirable (see **Section 1.3**). Based on evidence of moderate to high quality, the 2015 LTBI guidelines strongly recommended the systematic LTBI testing and TB preventive treatment for contacts regardless of age in countries with a TB incidence lower than 100/100,000 population (13). In the current update, the GDG considered that this recommendation could be applied to any country regardless of TB burden if tests for LTBI and to rule out active TB were available and reliable. Treatment may be justifiable without a LTBI test based on an assessment of the individual's risk of exposure and for the development of active TB in a given setting. The GDG noted that the capacity of the health caregiver to assess the intensity of

exposure, risk of infection and reinfection, the risk for development of active TB, and the ascertainment of LTBI by testing, as well as capacity to weigh harm versus benefit of treatment and ability to exclude active TB disease before initiation of treatment are important considerations in the implementation of these recommendations.

Contacts of multidrug-resistant tuberculosis patients

7. In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualized risk assessment and a sound clinical justification. *(Conditional recommendation, very low certainty in the estimates of effect)*

Justification and evidence

This recommendation was added in the 2018 update of the guidelines. Ahead of this a systematic review of the effectiveness of preventive treatment for contacts of people with MDR-TB conducted for the 2015 LTBI guidelines was updated (14).

The updated review comprised 10 studies (6 newly identified and 4 from the previous review) that allowed comparisons between participants who received preventive treatment for MDR-TB and those who did not (see PICO 10 in **Annex 2**). Because of clinical heterogeneity among the studies, a meta-analysis could not be performed. Of the 10 studies, one was excluded because only isoniazid monotherapy was used, and an additional five studies were excluded as fewer than 20 participants completed preventive TB treatment. Therefore, the quality of the evidence was based on only four studies. No active TB was reported in either the intervention or the control group in one study (34), while one person with active TB due to a drug-susceptible strain that was different from the presumed source was reported in another study (35). The remaining two studies addressed the efficacy of preventive treatment (36),(37). In one cohort of 119 contacts, 104 with LTBI initiated fluoroquinolone-based preventive treatment, of whom 93 (89%) completed treatment, and none developed active TB; while 3 of 15 (20%) contacts who refused treatment developed MDR-TB (OR 0.02, 95% CI 0.00; 0.39) (36). In the other study, confirmed or probable TB developed in 2 of 41 (4.9%) children receiving tailored preventive treatment and in 13 of 64 (20.3%) children who did not receive proper preventive treatment (OR 0.2, 95% CI 0.04; 0.94) (37).

Most TB infection globally is with rifampicin-susceptible strains but recent modelling suggests that MDR-TB infection may increase in future (38). Overall, the GDG judged that the potential benefits of targeted preventive treatment for MDR-TB contacts, based on individual risk assessments, outweighs the harm but acknowledged uncertainty about the efficacy of the intervention due to the lack of RCT evidence. The GDG stressed that treatment should be given to selected individuals after a careful risk assessment, including intensity of exposure, certainty of the source of disease, reliable information on the drug resistance pattern of the source and potential adverse drug reactions. It should be given only to household contacts at high risk (e.g. children, people on immunosuppressive therapy, PLHIV) in whom the provision of MDR-TB preventive treatment would be more acceptable. The recommendation may also apply to HIV-negative individuals. Confirmation of infection by LTBI testing is usually required before treatment is initiated.

Other people at risk

8. People who are initiating anti-TNF treatment, or receiving dialysis, or preparing for an organ or haematological transplant, or who have silicosis should be systematically tested and treated for LTBI. *(Strong recommendation, low to very low certainty in the estimates of effect)*

9. Systematic LTBI testing and treatment may be considered for prisoners, health workers, immigrants from countries with a high TB burden, homeless people and people who use drugs. *(Conditional recommendation, low to very low certainty in the estimates of effect)*

10. Systematic LTBI testing and treatment is not recommended for people with diabetes, people who engage in the harmful use of alcohol, tobacco smokers and underweight people unless they also belong to other risk groups included in the above recommendations. *(Conditional recommendation, very low certainty in the estimates of effect)*

Justification and evidence

These recommendations were first published by WHO in 2015 (13). The GDG considered evidence from three systematic reviews that were conducted for the previous LTBI guidelines to determine which of the 24 defined at-risk population groups should be prioritized for LTBI testing and treatment (13),(14). Evidence of an increased prevalence of LTBI, an increased risk of progression from LTBI to active TB disease and an increased incidence of active TB was available for the following 15 risk groups: adult and child TB contacts, healthcare workers and students, PLHIV, patients on dialysis, immigrants from countries with a high TB burden (incidence of >100 TB cases per 100,000 population), patients initiating anti-TNF therapy, people who use drugs, prisoners, homeless people, patients preparing for an organ or haematological transplant, patients with silicosis, patients with diabetes, people who engage in the harmful use of alcohol, tobacco smokers and underweight people. An increased risk for progression to active TB was reported for 4 of the 15 groups: PLHIV; adult and child TB contacts; patients on dialysis and underweight people.

The GDG judged that people in clinical risk groups, such as patients initiating anti-TNF treatment, patients on dialysis, patients preparing for organ or haematological transplant and patients with silicosis, would benefit most from testing for and treatment of LTBI regardless of the background TB epidemiology. The GDG considered that the benefits of TB preventive treatment to lower the risk of progression to disease would usually outweigh the potential harm in these groups and made a strong recommendation despite a low to very low certainty in the evidence.

The GDG concluded from the evidence that the benefits of systematic LTBI testing and TB preventive treatment may not always outweigh the harm in healthcare workers and students, immigrants from countries with a high TB burden, prisoners, homeless people and people who use drugs. The GDG judged, however, that the benefits are more likely to outweigh potential harm when the risks for reinfection are lower. In 2019 the GDG updated this recommendation to make it applicable to both high and low TB prevalence countries on condition that the decision to systematically test for LTBI and offer TB preventive treatment in these population groups considers the local TB epidemiology and context, health infrastructure, capacity to exclude active TB reliably, any adverse impact on health equity and overall health priorities. Greater benefit is expected in individuals who were recently infected with TB, as documented by conversion from negative to positive on IGRA or TST (see **Section 1.3**). The GDG also concluded that recent immigrants, particularly those from countries with a higher TB burden to the one in the host country, may be prioritized[6], especially within the first few years after entry.

Despite evidence for increased prevalence of LTBI and active TB in patients with diabetes, people who engage in the harmful use of alcohol, tobacco smokers and underweight people, the GDG noted the paucity of data from clinical trials on the benefits and harm of systematic LTBI testing and treatment.

They concluded that systematic, routine testing and treatment in people with these risks alone may not outweigh the potential harms, regardless of background TB epidemiology. This should not, however, be construed as a blanket, negative recommendation for any form of testing and treatment among these populations on a case-by-case basis.

The GDG agreed that prioritization of groups based on their risk and the local and national context would be acceptable to people with LTBI and to key stakeholders, including clinicians and programme managers. It noted that the high risk for ongoing TB transmission of certain groups, such as frontline healthcare workers (including students), prisoners (and prison staff), immigrants from areas with a higher TB burden than the host country[6], homeless people and people who use drugs requires attention, so that the benefit of treatment is not compromised by subsequent reinfection. TB preventive treatment should articulate well with other preventive components of the programme aimed at active TB case-finding, infection control and early treatment of active TB (26).

Implementation considerations

In their normative and planning documents, national TB and HIV authorities and other stakeholders should clearly define the populations to prioritize for PMTPT. This position should aim to provide lasting protection from progression to active TB to a maximum of individuals at risk, thus limiting continued transmission and reinfection and reducing TB incidence over time. PLHIV and household contacts were primarily targeted for global action by Member States at the UN High Level Meeting in 2018 (6). The GDG stressed that the best available evidence should be used to ensure that benefits outweigh risks to the individuals belonging to these groups and to make the best possible use of resources. This could yield savings for the entire healthcare system. Any additional resources needed to implement the guidance should not be viewed as a barrier but should stimulate programmatic action to mobilise more funding. The GDG noted the value of ART in preventing TB in PLHIV, striving for universal access to ART as per WHO policy (39).

TB preventive treatment for PLHIV should be a core component of the HIV package of care and should be primarily the responsibility of national HIV/AIDS programmes and HIV service providers (39),(40). Care needs to be coordinated with the healthcare services responsible for TB. It should be viewed as one of a comprehensive set of interventions. It is also expected that some household contacts and other people eligible for TB preventive treatment (e.g. people receiving dialysis, prisoners) will also be HIV positive and would therefore require individual attention to minimize their likelihood of developing active TB.

Confirmation of LTBI using either IGRA or TST and reliable exclusion of active TB with chest radiography would be desirable before starting TB preventive treatment. In situations where these tests are not available TB preventive treatment should not be withheld from eligible people if active disease has been excluded on clinical grounds alone (see **Section 1.2**).

The capacity of the programme to provide MDR-TB preventive treatment in addition to other LTBI efforts should be carefully planned for. Providing a component on MDR-TB within PMTPT requires that all the necessary resources be in place, including the capacity to rule out active TB, to perform quality-assured testing for drug susceptibility (in the presumed source case), to deliver the necessary medications and to monitor closely for adverse events and for the emergence of active disease. The choice of MDR-TB preventive treatment is discussed further in **Section 1.4**.

The identification of populations for LTBI testing and TB preventive treatment raises a range of ethical issues (41),(42). First, LTBI is an asymptomatic and non-contagious state. This makes the ethical obligations different from those associated with active TB. For example, the absence of an immediate risk of transmission makes it unethical to restrict movement of someone with LTBI who refuses treatment. Shortage of evidence for benefit of systematic testing and treatment in certain

[6] Estimated TB incidence rates for all countries are updated annually by WHO (10).

populations (e.g. people with diabetes or who are underweight) should not stop efforts to offer preventive treatment to individuals with these conditions who are judged to be at increased risk of progression. Secondly, the absence of tests that can measure individual risk for the development of active TB may pose a challenge to communication. Informed consent requires effective, adequate communication to each person about the uncertainty of current LTBI tests to predict progression to active TB, individual host variabilities, and the protective benefit expected of treatment versus adverse reactions. Appropriate mechanisms to obtain informed consent should comply with international human rights standards and account for different languages and literacy skills, and legal status. Risk and uncertainty must be communicated in a way that is culturally and linguistically appropriate to people, including those whose first language is foreign to the local setting, for children, as well as people in prison. User feedback collected during screening programmes is useful to inform implementation. Thirdly, LTBI disproportionately affects individuals and groups that are already disadvantaged due to disease, socio-economic situation, or legal status among others. Therefore, efforts must be made to address existing inequities in access to services and to uphold human rights, so that the vulnerability of target groups does not impede their access to screening and treatment or violate their rights. Any intervention for vulnerable groups – including those who are criminalized, those in prisons, and children – should include measures to minimize the risk for stigmatization, such as protecting confidentiality of personal data and informed consent. The GDG emphasized that a person's status – testing positive for LTBI or receiving TB preventive treatment – should not affect the immigration procedure or deny entry. This should be reflected in existing laws or other policy regulations. People should be tested for LTBI and receive TB preventive treatment in strict adherence to human rights and ethical considerations (43). Policies should be evaluated by end-users from an ethical perspective and the views and experiences of affected populations gathered after implementation, both to consider possible unexpected effects and to ensure that the evidence on which they are based remains current and relevant (44). Person-centred LTBI care entails, among others, that it is provided in an equitable fashion without placing marginalized and vulnerable populations at an added disadvantage; it focuses on the human rights aspects of TB preventive treatment interventions so that there are appropriate safeguards in law, policy and practice to minimise additional stigma, discrimination, violation of bodily integrity or restrictions on freedom of movement; and people offered testing and treatment appreciate the associated uncertainties to help them participate in care options. These guiding principles would best draw upon a set of established human rights principles, such as consent, non-coercion, confidentiality (42).

1.2. Ruling out active tuberculosis disease

Giving TB preventive treatment to someone who has active TB can delay resolution of disease and favour the emergence of drug resistance. Excluding active TB disease before initiating preventive treatment is one of the critical steps in the LTBI care pathway. This section proposes approaches to rule out active TB and diagnose LTBI in people at risk of infection following key decision points, namely HIV status, symptoms, household contact, other risk factors, age, LTBI test results and abnormality on chest radiography (**Fig. 1**). The evidence and the recommendations underpinning these steps are also briefly discussed.

People living with HIV

11. 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. *(Strong recommendation, moderate certainty in the estimates of effect)*

12. Adults and adolescents living with HIV who are screened for TB according to a clinical algorithm and who report any 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 and offered preventive treatment if active TB is excluded. *(Strong recommendation, moderate certainty in the estimates of effect)*

13. Chest radiography may be offered to people living with HIV on ART and preventive treatment be given to those with no abnormal radiographic findings. *(Conditional recommendation, low certainty in the estimates of effect)*

14. Infants and children living with HIV who have poor weight gain[7], fever or current cough or who have a history of contact with a person with TB should be evaluated for TB and other diseases that cause such symptoms. If TB disease is excluded after an appropriate clinical evaluation or according to national guidelines, these children should be offered TB preventive treatment, regardless of their age. *(Strong recommendation, low certainty in the estimates of effect)*

Justification and evidence

The first two recommendations featured already in the 2015 guidelines and were updated in 2018 (13),(16). The third recommendation on chest radiography was first released in 2018, updating a position made in the 2011 guidelines (11). In 2011, WHO conducted a systematic review and a meta-analysis of individual patient data and recommended a symptom-screening rule of a combination of current cough, weight loss, night sweats and fever to exclude active TB in adults and adolescents (45). The review showed that the rule had a sensitivity of 79%, a specificity of 50% and a negative predictive value of 97.7% at a TB prevalence of 5%. Most PLHIV in studies included in the systematic review were not receiving ART.

During the 2018 update of the guidelines, a systematic review was undertaken to compare the performance of the four-symptom screen in PLHIV who were and were not receiving ART (see PICOs 2 and 3 in **Annex 2** and Table 2 of (46)). Data from 17 studies were included in this analysis. The pooled sensitivity of the four-symptom screen for PLHIV on ART was 51.0% (95% CI 28.4; 73.2), and the specificity was 70.7% (95% CI 47.7; 86.4); in PLHIV who were not receiving ART the pooled sensitivity was 89.3% (95% CI 82.6; 93.6), and the specificity was 27.2% (95% CI 17.3; 40.0). Two studies provided data on addition of abnormal chest radiographic findings to the screening rule for PLHIV on ART (47),(48). The pooled sensitivity was higher (84.6%, 95% CI 69.7; 92.9), but the specificity was lower (29.8%, 95% CI 26.3; 33.6) when compared with the symptom screen alone.

In all studies, the median prevalence of TB among PLHIV on ART was 1.5% (interquartile range, 0.6–3.5%). At a 1% prevalence of TB, the negative predictive value of the symptom screening rule was 99.3%; addition of abnormal chest radiographic findings increased the negative predictive value by 0.2%. No studies of the addition of chest radiography to the symptom rule for pregnant women were found in the review.

In infants and children, a systematic review conducted for the 2011 guidelines identified limited evidence on the best approach to screening (11). Based on these few studies and expert opinion, the

[7] *Poor weight gain* is here defined as reported weight loss, very low weight-for-age (< –3 Z-scores), underweight (weight-for-age < –2 Z-scores), confirmed weight loss (> 5%) since the last visit or growth curve flattening

previous GDG recommended a screening rule consisting of poor weight gain, fever, current cough and a history of contact with a person with TB. Another systematic review to assess the performance of this screening rule was attempted for the 2018 update. The only publication found was a conference abstract of a study of 176 hospitalized children with HIV aged ≤ 12 years in Kenya (49). The study had a sensitivity of 100% (95% CI, 76.8; 100.0) and a specificity of 4.3% (95% CI, 1.8; 8.7).

The GDG agreed that in adults and adolescents living with HIV the four-symptom screen – current cough, fever, weight loss or night sweats – is very useful for ruling out active TB, regardless of ART use. Confirmation of LTBI using IGRA or TST would be desirable before starting TB preventive treatment. It noted the potential benefits of adding an abnormal chest radiographic finding to the rule, while recognizing that the improvement in performance was marginal. Moreover, increased use of chest radiography would add more false-positive results to the screening rule, which would require more investigations for TB and other illnesses. Therefore, the GDG reiterated that chest radiography may be added as an additional investigation only if it does not pose a barrier to the provision of preventive treatment for PLHIV. It should not be a requirement for initiating preventive treatment. Although no study was found of the additive role of chest radiography in testing pregnant women, the GDG noted that pregnant women living with HIV could also benefit, as long as good practices are observed to prevent harmful radiation exposure to the foetus (50).

Infants and children living with HIV should be screened for TB as part of standard, routine clinical care, regardless of whether they are receiving TB preventive treatment or ART. The GDG noted that less data were available on the performance of a standardized screening rule for children living with HIV when compared with the screen rule for adults and adolescents. The single study showed that the symptom screening rule currently used in children living with HIV performs well, but no study has been reported on the harm or challenges of the rule, such as resource requirements for implementation. Symptom-based screening is generally acceptable to caregivers and people and is feasible even in resource-limited settings. Therefore, the GDG decided to make a strong recommendation for use of the symptom screen in children living with HIV. In those who have one or more symptoms, active TB should be ruled out. The GDG also noted that clinicians should broaden the differential diagnosis to include other diseases that may cause current cough, fever and poor weight gain in children with HIV. If the evaluation shows no signs of active TB and the clinician has decided not to treat for TB disease, children with HIV should be offered TB preventive treatment, regardless of their age. However, infants < 12 months of age should be given TB preventive treatment only if they have a history of household contact with a person with TB and active TB has been excluded according to national guidelines. Guidance on further testing for TB in PLHIV who have suggestive clinical features is available elsewhere (39).

Household contacts of a person with pulmonary TB

Infants and children < 5 years of age[8]

Justification and evidence

In 2012, a systematic review was carried out to assess the sensitivity and specificity of different combinations of one or more symptoms and/or chest radiography to screen for bacteriologically confirmed active pulmonary TB in HIV-negative persons and persons with unknown HIV status (51)[9]. While updating this review ahead of the 2018 guidelines only one study was identified for young children (mean age, 19.2 months) in which various symptoms were evaluated, such as failure to thrive and prolonged cough (52). This study did not discuss the value of symptoms for excluding TB. Symptom-based screening has been reported to be a safe and feasible contact management

[8] For LTBI testing and TB preventive treatment in <5 years see recommendations in **Section 1.1** and the algorithm in **Fig. 1**.

[9] Bacteriological confirmation may be by smear microscopy, culture or a WHO-approved molecular test such as Xpert® MTB/RIF (see **Definitions**).

strategy in children, even in resource-limited settings (53),(54). A modelling study using high TB burden setting parameters also suggested that providing preventive treatment without LTBI testing is cost-effective for child contacts under 5 years of age (55). See also **Section 1.1** for more background on the recommendation for LTBI testing and treatment in this risk group.

Household contacts aged ≥ 5 years and other risk groups

15. 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 risk groups before preventive treatment. *(Conditional recommendation, very low certainty in the estimates of effect)*

Justification and evidence

This is a conditional recommendation based on very low-quality evidence, newly released in the 2018 guidelines (16). It is based on the systematic review used to determine the sensitivity and specificity of screening based on symptoms and/or chest radiography for ruling out active TB in HIV-negative people and people of unknown HIV status for the 2015 guidelines (see PICO 3 in **Annex 2**) (51). To illustrate how the various screening and diagnostic algorithms are expected to rule out active TB, a simple model was constructed to compare the following six screening criteria: (i) any TB symptom, (ii) any cough, (iii) cough for 2–3 weeks, (iv) chest radiographic abnormality suggestive of TB, (v) any chest radiographic abnormality and (vi) a combination of any chest radiographic abnormality or any TB symptom. The model suggested that the combination of any chest radiographic abnormality and the presence of any symptoms suggestive of TB (i.e. any cough of any duration, haemoptysis, fever, night sweats, weight loss, chest pain, shortness of breath and fatigue) would offer the highest sensitivity (100%) and negative predictive value (100%) for ruling out TB. Ahead of the 2018 guidelines update this review was updated focusing on household contacts aged ≥ 5 years of pulmonary TB patients in high TB burden countries (56). Seven studies evaluating the accuracy of 'any CXR abnormality' had a pooled sensitivity of 94.1% (95%CI 85.8–97.7) and pooled specificity 86.8% (95%CI 79.7–91.7). In a hypothetical population of 10,000 HIV-negative individuals and at a TB prevalence of 2%, use of any TB symptoms alone would wrongly classify 54 TB patients as not having active TB and they would be offered TB preventive treatment. In contrast, use of any abnormal chest radiography finding would result in 12 TB patients being offered preventive treatment. Use of the combination of any TB symptoms plus any chest radiography abnormal findings would result in no patients with active TB being incorrectly offered preventive treatment. At a TB prevalence of 2%, use of any TB symptoms alone would require TB investigations of 16 extra non-TB patients for every TB case identified, whereas use of any abnormal chest radiography finding would require TB investigations of 7 extra non-TB patients for every TB case identified. Use of the combination of any TB symptoms plus any chest radiography abnormal finding would increase the number of individuals requiring TB investigations to 15 extra non-TB patients for every TB case identified.

In conclusion, a screening algorithm using any symptom of TB and any abnormal chest radiographic findings is likely to offer high sensitivity. This implies that the absence of any TB symptoms and chest radiographic abnormality can be used to exclude active pulmonary TB before initiating TB preventive treatment among household contacts.

The GDG noted the shortage of new data and agreed to continue using the existing symptom-based algorithms for infants and children who are household contacts of a person with TB. The GDG reiterated that national guidelines should specify what investigations are necessary to rule out active TB. It noted that screening of child contacts could include LTBI testing and chest radiography, although the absence of those investigations should not pose a barrier for either diagnosis of active TB disease or provision of preventive treatment. In the absence of these tests, clinical assessment alone

is sufficient to decide on initiation of TB preventive treatment particularly for household contacts < 5 years of a bacteriologically confirmed pulmonary TB.

The GDG concluded that symptom screening with or without the addition of chest radiography should be acceptable for individuals and programme managers. Chest radiography could increase the confidence of healthcare providers that active TB has been ruled out and lower concerns that TB preventive treatment is being administered inappropriately.

Implementation considerations

Fig. 1 is an algorithm for LTBI testing and treatment with separate entry points for PLHIV, household contacts or other persons at risk for LTBI.

The four-symptom screening method is recommended for all PLHIV at every visit to a health facility or contact with a health worker to ensure early detection of active TB. Other clinical features may also be helpful (e.g. poor weight gain in pregnant women). Other diseases that cause any of the four symptoms should be investigated in accordance with national guidelines and sound clinical practice. Individuals found not to have active TB should then be assessed for preventive treatment.

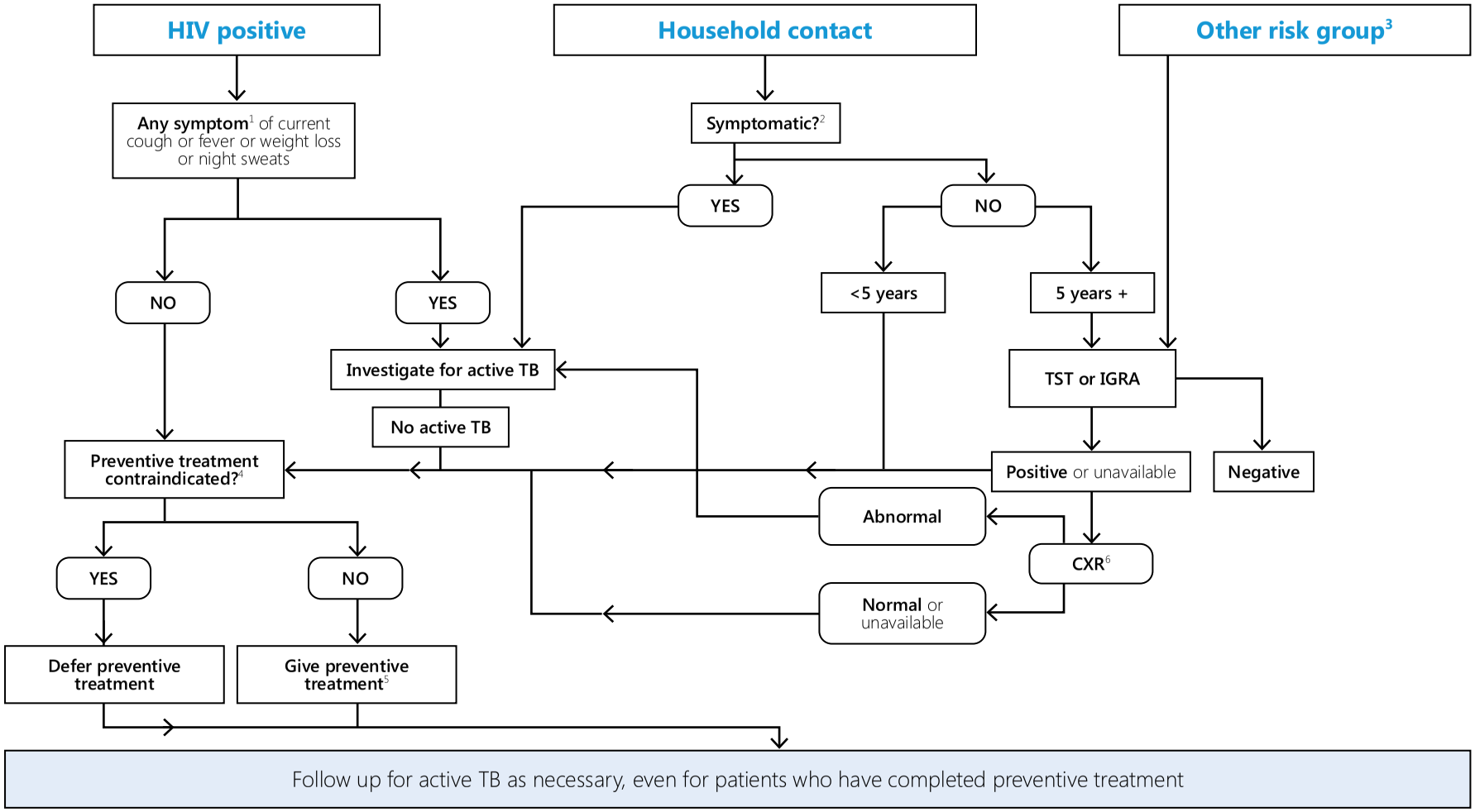
Where radiography or expert interpretation is not available, the absence of any TB symptoms alone may be considered sufficient before TB preventive treatment. This would offer the highest sensitivity among symptom-based screening rules, and its negative predictive value is high in most settings. The addition of abnormal chest radiographic findings to the symptom screening rule would increase logistical and infrastructural requirements, cost to individuals and health services, and need for qualified staff. The optimal frequency of chest radiography in regular TB screening of PLHIV is uncertain. Carrying out a chest radiograph in addition to symptom screening at every visit represents a significant burden on the individual and the health system. Local authorities should define its application and frequency based on their local epidemiology, health infrastructure and resources. Radiologists or other trained healthcare workers must be available to interpret chest radiography.

The GDG noted that chest radiography should not be a prerequisite or a barrier for initiating TB preventive treatment in PLHIV because of the need for additional resources, in view of the marginal gain in negative predictive value. Conversely, in PLHIV with low CD4 counts, active TB may occur despite a normal chest radiography. PLHIV who have any of the four symptoms or abnormal chest radiographic findings may have active TB and should be investigated for TB and other diseases. Xpert® MTB/RIF should be used as the initial diagnostic test.

Preventive treatment should not be withheld in an asymptomatic individual at risk of infection should LTBI testing and/or chest radiography be unavailable. It is conceivable that some people may have two risks (e.g. PLHIV who are also contacts of TB patients), in which case the triage shown in the figure would need to be adapted.

It is critical to ensure proper follow-up and evaluation for TB and other diseases in household contacts with abnormal chest radiographic findings or TB symptoms. The investigations should be performed in accordance with national guidelines and sound clinical practice. Contacts found not to have active TB need to be assessed for preventive treatment. Although LTBI testing is not a requirement for initiating TB preventive treatment, it may be done as a part of eligibility screening where feasible (see **Section 1.3**). A previous history of TB or TB preventive treatment should not be a contraindication for preventive treatment in case of exposure, following the exclusion of reactivated disease. These individuals, including those with fibrotic radiological lesions, may be at increased risk of progression (57),(58). Choice of TB preventive treatment also depends on presence of contraindication (e.g. active hepatitis; symptoms of peripheral neuropathy when isoniazid is considered) or likelihood of drug-drug interactions (see **Section 1.4**).

Fig. 1. Algorithm for LTBI testing and TB preventive treatment in individuals at risk



1. If <10 years, any one of current cough or fever or history of contact with TB or reported weight loss or confirmed weight loss >5% since last visit or growth curve flattening or weight for age <-2 Z-scores. Asymptomatic infants <1 year with HIV are only treated for LTBI if they are household contacts of TB. TST or IGRA may identify PLHIV who will benefit most from preventive treatment. Chest radiography (CXR) may be used in PLHIV on ART, before starting LTBI treatment.

2. Any one of cough or fever or night sweats or haemoptysis or weight loss or chest pain or shortness of breath or fatigue. In children <5 years, they should also be free of anorexia, failure to thrive, not eating well, decreased activity or playfulness to be considered asymptomatic.

3. Including silicosis, dialysis, anti-TNF agent treatment, preparation for transplantation or other risks in national guidelines.

4. Including acute or chronic hepatitis; peripheral neuropathy (if isoniazid is used); regular and heavy alcohol consumption. Pregnancy or a previous history of TB are not contraindications.

5. Regimen chosen based on considerations of age, strain (drug susceptible or otherwise), risk of toxicity, availability and preferences.

6. CXR may have been carried out earlier on as part of intensified case finding.

1.3. Testing for latent tuberculosis infection

Testing for LTBI increases the certainty that individuals targeted for treatment will benefit from it. However, there is no gold standard test to diagnose LTBI. Both currently available tests – TST and IGRA – are indirect and require a competent immune response to identify people infected with TB. A positive test result by either method is not by itself a reliable indicator of the risk of progression to active disease. The evidence and the recommendations for LTBI testing are discussed in this section.

16. Either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) can be used to test for LTBI. *(Strong recommendation, very low certainty in the estimates of effect)*

Justification and evidence

This recommendation was first published in the 2018 WHO guidelines (16). A previous systematic review was updated to compare the predictive performance of IGRA and TST for identifying incident active TB in countries with a TB incidence >100 / 100,00 population (59). Only studies in which TST was compared with IGRA in the same population ("head-to-head" studies) were included. Relative risk ratios for TB for people who tested positive and those who tested negative with TST and IGRA were estimated (see the GRADE evidence summaries for PICO 4 in **Annex 2**).

Five prospective cohort studies were identified, with a total of 7,769 participants; four were newly identified. Three of the studies were conducted in South Africa and two in India (20),(60),(61),(62),(63). The studies included PLHIV, pregnant women, adolescents, healthcare workers and household contacts. The pooled risk ratio estimate for TST was 1.49 (95% CI, 0.79; 2.80), and that for IGRA was 2.03 (95% CI, 1.18; 3.50). Although the estimate for IGRA was slightly higher than that for TST, the 95% CIs for the estimates for TST and IGRA overlapped and were imprecise. Furthermore, there was limited evidence for the predictive utility of the tests in specific at-risk populations.

The evidence reviewed and the recommendations apply only to the use of the two commercially available IGRAs (QuantiFERON®-TB Gold In-Tube and T-SPOT®.TB). The GDG concluded that the comparison of TST and IGRA in the same population does not provide strong evidence that one test should be preferred over the other for predicting progression to active TB disease. TST may require significantly fewer resources than IGRA and may be more familiar to practitioners in resource-constrained settings; however, recurrent global shortages and stock-outs of TST reduce prospects for its scale-up in PMTPT.

The GDG also noted that equity and access could affect the choice and type of test used. The preferences of people to be tested and programmes depend on several factors, such as the requirement for adequately equipped laboratory (e.g. for IGRA) and possible additional costs for people being tested (e.g. for travel) and programmes (e.g. for infrastructure and testing). The GDG strongly recommended the two tests as equivalent options, with relatively similar advantages and disadvantages.

The GDG stressed that the global shortage of TST should be addressed urgently and called for more investment into research on novel tests for LTBI with better predictive value.

The GDG cautioned that imperfect performance of these tests can lead to false-negative results, particularly for young children and immunocompromised individuals such as PLHIV with low CD4 counts. The GDG noted the importance of the tests to identify recent conversion from negative to positive, particularly among contacts of people with pulmonary TB, which is good practice when initiating TB preventive treatment. Nevertheless, recent studies among healthcare workers tested serially for LTBI in the USA showed that conversions from negative to positive and reversions from positive to negative are more commonly identified with IGRA than with TST (64). Thus, clinical judgement must still be used to interpret the results of serial LTBI tests.

Although some studies suggest otherwise (19),(20), the GDG maintained the past position that PLHIV who have a positive test for LTBI benefit more from TB preventive treatment than those who have a negative LTBI test (11),(16). LTBI testing can be used, where feasible, to identify such individuals. However, based upon evidence of moderate certainty, the GDG strongly emphasised that LTBI testing by TST or IGRA should not be a prerequisite to start TB preventive treatment in PLHIV and household contacts aged < 5 years, particularly in settings with a high TB incidence (e.g. >100 TB cases/ 100,000 population), given that benefits clearly outweigh the risks. A negative LTBI test in these two groups, as well as in HIV-negative infant household contacts, should be followed by a case-by-case assessment for the potential benefit and harms of TB preventive treatment.

Implementation considerations

LTBI testing is desirable whenever feasible to identify persons at highest risk for developing active TB. However it is not required in PLHIV or in household contacts aged < 5 years. In HIV-negative household contacts aged 5 years and more and in other risk groups LTBI tests are recommended, but their unavailability should not be a barrier to treat people who were judged to be at higher risk.

The GDG noted that the availability and affordability of the tests could determine which LTBI test is used. Other considerations include the structure of the health system, feasibility of implementation and infrastructure requirements.

The incremental cost-effectiveness of IGRAs and TSTs appears to be influenced mainly by their accuracy. Bacille Calmette-Guérin (BCG) vaccination plays a decisive role in reducing the specificity of TST. The GDG noted, however, that the impact of BCG vaccination on the specificity of TST depends on the strain of vaccine used, the age at which the vaccine is given and the number of doses administered. When BCG is given at birth, as is the case in most parts of the world, it has a variable, limited impact on TST specificity (65). Therefore, the GDG agreed that a history of BCG vaccination has a limited effect on interpretation of TST results later in life; hence, BCG vaccination should not be a determining factor in selecting a test.

IGRA testing is more costly than TST and requires appropriate laboratory services. Operational difficulties should be considered in deciding which test to use. For example, IGRA requires a phlebotomy, which can be difficult, particularly in young children; it requires a laboratory infrastructure, technical expertise and expensive equipment; its sensitivity is reduced in children aged <2 years and those with HIV. However, only a single visit is required to do an IGRA test (although patients may have to make a second visit to receive the result). TST is less costly and can be performed in the field, but it requires a cold chain, two healthcare visits and training in intradermal injection, reading and interpretation. One other practical advantage of IGRAs over TST is that they are not susceptible to a "booster response", which makes a two-step approach necessary in situations where the reactivity to TST has waned since infection.

Neither TST nor IGRA are to be used to diagnose active TB disease nor for diagnostic workup of adults suspected of having active TB.

1.4. Tuberculosis preventive treatment options

TB preventive treatment for an infection with strains presumed to be drug-susceptible can be broadly categorized into two types: monotherapy with isoniazid for at least 6 months (or isoniazid preventive therapy, IPT) and treatment with regimens containing a rifamycin (rifampicin or rifapentine). IPT has been the most widely used form of TB preventive treatment but the shorter duration of rifamycin regimens presents a clear advantage. Preventive treatment for MDR-TB requires a different approach using a fluoroquinolone or other second-line agents. The recommendations for these treatment options, as well as the conditions under which they apply, are discussed in different parts of this section.

17. The following options are recommended for the treatment of LTBI regardless of HIV status: 6 or 9 months of daily isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or a 3 month regimen of daily isoniazid plus rifampicin. *(Strong recommendation, moderate to high certainty in the estimates of effect)*. A 1-month regimen of daily rifapentine plus isoniazid or 4 months of daily rifampicin alone may also be offered as alternatives. *(Conditional recommendation, low to moderate certainty in the estimates of effect)*.

18. In settings with high TB transmission, adults and adolescents living with HIV who have an unknown or a positive LTBI test and are unlikely to have active TB disease should receive at least 36 months of daily isoniazid preventive treatment (IPT). Daily IPT for 36 months should be given whether or not the person is on ART, and irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy in settings considered to have a high TB transmission as defined by national authorities. *(Conditional recommendation, low certainty in the estimates of effect)*

Regimens containing isoniazid or rifamycins

Both recommendations already featured in WHO guidance from 2015 (13),(25). A strong recommendation for TB preventive treatment alternatives to 6H, based on evidence of low to high certainty, featured in previous WHO guidance (12),(13),(16). In 2019 the GDG made edits to the text of this recommendation to add the two new conditional recommendations for daily rifapentine plus isoniazid for 1 month (1HP) and daily rifampicin monotherapy for 4 months (4R) in all settings. These new recommendations are based, respectively, on low to moderate certainty in the estimates of effect. In addition, instead of a previous range of 3–4 months, the GDG now recommends a duration of 3 months for daily isoniazid plus rifampicin (3HR) and of 4 months for daily rifampicin alone (4R) to reflect the usual length of time for which these regimens are currently employed. Moreover, three previous recommendations on the use of 6H, 3HR in people <15 years and 3HP in high TB prevalence settings that featured separately in previous guidance are now proposed as alternative options. The revised recommendation makes all LTBI options applicable to all settings.

Justification and evidence

Daily isoniazid monotherapy

The efficacy of daily isoniazid monotherapy for six months (6H) or more in different populations and settings has been shown in a number of systematic reviews (18),(66),(67). A systematic review of RCTs in PLHIV showed isoniazid monotherapy reduces the overall risk for TB by 33% (RR 0.67; 95% CI 0.51; 0.87), and the that preventive efficacy reached 64% for people with a positive TST (RR 0.36; 95% CI 0.22; 0.61) (18). Furthermore, the efficacy of the 6-month regimen was not significantly different from that of 12 months' daily isoniazid monotherapy (RR 0.58; 95% CI 0.3; 1.12). A recent systematic review of RCTs also showed a significantly greater reduction in TB incidence among participants given the 6-month regimen than in those given a placebo (Odds ratio [OR] 0.65; 95% CI 0.50; 0.83)(68). No controlled clinical trials were found of daily isoniazid monotherapy for 9 months (9H) versus 6H. Re-analysis and modelling of the United States Public Health Service trials of isoniazid conducted in the 1950s and 1960s, however, showed that the benefit of isoniazid increases progressively when it is given for up to 9–10 months and stabilizes thereafter (69). For this reason, 9H is retained as an alternative regimen to 6H in the recommended TB preventive treatment options.

Regarding the second recommendation above, a systematic review and meta-analysis of three RCTs of PLHIV in settings with high TB prevalence and transmission showed that continuous IPT can reduce the risk for active TB by 38% more than 6 months' isoniazid (70). The effect was greater in people with

a positive TST (49% for active TB and 50% for death). In those with a negative TST, neither effect was significant, although the point estimate indicated a reduction in TB incidence of 27%. In two of the studies reviewed ART was not used and in the third ART coverage was low at baseline but increased during the period of observation.

Daily rifampicin plus isoniazid for 3 months (3HR)

A systematic review updated in 2017 showed that the efficacy and the safety profile of 3–4 months' daily rifampicin plus isoniazid were similar to those of 6 months' isoniazid (68),(71). A previous GDG therefore strongly recommended that daily rifampicin plus isoniazid could be used as an alternative to isoniazid in settings with a TB incidence <100 / 100,000 population (13). A new review to compare the effectiveness of rifampicin plus isoniazid daily for 3 months with isoniazid for 6 or 9 months in children identified one RCT and two observational studies (72),(73),(74) (see also GRADE evidence summaries for PICO 5 in **Annex 2**). The RCT (73) reported no clinical disease in either group and used new radiographic findings suggestive of active TB as a proxy for clinical disease. Fewer participants given daily rifampicin plus isoniazid than those given 9 months of isoniazid developed radiographic changes (RR 0.49, 95% CI 0.32; 0.76). The authors also reported a lower risk for adverse events (RR 0.33, 95% CI 0.20; 0.56) and a higher adherence rate (RR 1.07, 95% CI 1.01; 1.14) among children given daily rifampicin plus isoniazid. Similar findings were reported in the observational studies (72),(74).

Daily rifampicin monotherapy for 4 months (4R)

A previous systematic review conducted for the 2015 LTBI guidelines and updated in 2017, found similar efficacy for 3–4 months' daily rifampicin and 6H (odds ratio, 0.78; 95% CI, 0.41;1.46) (68),(71). The review also showed that individuals given rifampicin daily for 3–4 months had a lower risk for hepatotoxicity than those treated with isoniazid monotherapy (OR 0.03; 95% CI 0.00;0.48).

In 2019, the GDG discussed the implications of using 4R in high TB burden settings based on findings from RCTs of 4R vs 9H that included adults and children from such countries(75),(76),(77),(78). In study participants >17 years, the difference in rate of confirmed TB between 4R and 9H (4R arm minus 9H arm) was <0.01 cases per 100 person-years (95%CI, −0.14; 0.16); the difference in treatment completion was 15.1% (95% CI, 12.7; 17.4); the difference for Grade 3–5 adverse events was −1.1% (95% CI, −1.9; -0.4). In individuals <18 years, the difference in rate of active TB between 4R and 9H was -0.37 cases per 100 person-years (95% CI, −0.88; 0.14); the difference in treatment completion was 13.4% (95% CI, 7.5; 19.3); the difference in risk for adverse events attributed to the medicine used and resulting in discontinuation was −0.0 (95% CI, −0.1; 0.1). The evidence underpinning this revised recommendation is summarised in the GRADE tables for PICO 6 in **Annexes 2** and **3**.

Daily rifapentine plus isoniazid for 1 month (1HP)

In 2019, the GDG considered data from the only known published study of the 1HP regimen: a randomized, open-label, phase 3 non-inferiority trial comparing the efficacy and safety of 1HP with 9 months of isoniazid alone ("9H") in PLHIV who were in areas of high tuberculosis prevalence or who had evidence of LTBI (79). Enrolment was restricted to individuals ≥13 years old who were not pregnant or breastfeeding. Noninferiority would be shown if the upper limit of the 95% confidence interval for the between-group difference in the number of events per 100 person-years was less than 1.25. Among all study participants, the difference in incidence rate of TB (including deaths from any cause) between 1HP and 9H (i.e. 1HP arm minus 9H arm) was −0.02 per 100 person-years (95% confidence interval [CI], −0.35; +0.30); the relative risk (RR) for treatment completion of 1HP over 9H was 1.04 (95% CI, 0.99; 1.10); the RR for Grade 3–5 adverse events was 0.86 (95% CI, 0.58; 1.27); hazard ratio of death from any cause was 0.75 in favour of 1HP (95% CI, 0.42; 1.31); RR for emergence of resistance to isoniazid and rifampicin were, respectively, 1.63 (95% CI, 0.17; 15.99) and 0.81 (95% CI, 0.06; 11.77). Overall non-inferiority as defined by the study protocol was thus shown in the modified intention to treat (mITT) population. Non-inferiority was also shown for the sub-group with confirmed

LTBI infection (incidence rate difference per 100 person-years = 0.069 [-0.830 to 0.690]), as well as in males and females, and among those on or without ART at start of study. The number of patients with a CD4+ <250 cells per cu mm was small, and neither inferiority or noninferiority of 1HP was shown in this stratum. The evidence underpinning this new recommendation is summarised in the GRADE tables for PICO 7 in **Annexes 2** and **3**.

Weekly rifapentine plus isoniazid for 3 months (3HP)

A systematic review was conducted for the 2018 guidelines update to compare the effectiveness of a 3-month weekly regimen of rifapentine plus isoniazid (3HP) with that of isoniazid monotherapy. The review covered four RCTs (80),(81),(82),(83), which were analysed for three subgroups: adults with HIV infection, adults without HIV infection and children and adolescents, who could not be stratified according to HIV status because the relevant studies were lacking. The evidence underpinning this revised recommendation is summarised in the GRADE tables for PICO 8 in **Annexes 2** and **3**.

Two of the RCTs involved adults with HIV from South Africa, Peru and a number of countries with a TB incidence <100 / 100,000 population. No significant difference was found in the incidence of active TB between participants given a 3HP and 6H or 9H (RR 0.73, 95% CI 0.23; 2.30). Furthermore, the risk for hepatotoxicity was significantly lower with 3HP in adult PLHIV (RR 0.26, 95% CI 0.12; 0.55) and in those without HIV (RR 0.16, 95% CI 0.10; 0.27). The 3HP regimen was also associated with a higher completion rate in all subgroups (adults with HIV: RR 1.25, 95% CI 1.01; 1.55; adults without HIV: RR 1.19, 95% CI 1.16; 1.22; children and adolescents: RR 1.09, 95% CI 1.03; 1.15). One RCT included a comparison between 3HP and continuous isoniazid monotherapy in adult PLHIV (80). No significant difference in TB incidence was found in an intention-to-treat analysis; however, a per-protocol analysis showed a lower rate of TB infection or death in participants given continuous isoniazid. In all the studies, 3HP was given under direct observation. In a study of 3HP in 112 pregnant women, the rates of spontaneous abortion and birth defects were similar to those in the general US population (84).

Implementation considerations

The decision on which treatment to offer should not be confined to the manner in which it was studied in a trial (e.g. 1HP to replace 9H). The GDG agreed that the benefits of all the treatment options being recommended outweigh the potential harm. The programmes and clinicians should also consider the characteristics of the individual concerned to maximise the likelihood that treatment is completed as expected. Regimen choice is determined by considerations such as age, risk of toxicity or interaction, co-morbidity, drug susceptibility of the strain of the most likely source case, availability and the individual's preferences.

On the basis of existing practice, albeit in the absence of a direct comparison, the GDG judged that 9H is an equivalent option to 6H in countries with a strong health infrastructure. It noted, however, that 6H is preferable to 9H from the point of view of feasibility, resource requirements and acceptability to patients.

All recommended treatment options are possible in PLHIV. The recommendation to give at least 36 months of daily isoniazid monotherapy in PLHIV in high TB transmission settings is conditional and based on evidence that longer-term IPT significantly adds benefit to ART. The efficacy, safety and convenience of repeated treatment with shorter rifapentine regimens is being studied in PLHIV in such settings. The definition of a high TB transmission setting should be established by the national authorities (see also **Definitions**). Testing for LTBI is not a prerequisite for TB preventive treatment in PLHIV but its use is encouraged because people who are TST positive have a greater protective benefit from TB preventive treatment. PLHIV with a negative TST should not receive 36 months of daily IPT.

The GDG agreed unanimously that the benefits of 3HR for infants and children < 15 years of age outweigh the harm, given its safety profile, the higher rate of completion as compared with isoniazid monotherapy and the availability of child-friendly, fixed-dose combinations of rifampicin and isoniazid.

The GDG therefore made a strong recommendation despite the low quality of the evidence. There are no or very limited data on the performance and pharmacology of rifapentine in children < 2 years. The 3HP regimen is only recommended for use in children aged 2 years and more while the 1HP regimen in individuals aged 13 years and more.

The 2019 GDG considered that there was moderate certainty that 4R is not inferior to 9H, and when also considering the good safety profile of the 4R regimen and its reduced length, it recommended that this regimen may also be used in high TB-burden settings. When deciding to make a conditional recommendation the GDG considered that most people would value a shorter regimen, but raised concerns regarding variability in acceptability, uncertainty in resource requirements given its higher cost, and potential for reducing equity should it deflect resources and decrease treatment coverage of more vulnerable individuals. The GDG agreed that the introduction of 4R needs to be accompanied by mobilization of appropriate resources from the start to avoid shortages in other programmatic needs. The GDG also observed that impact on equity could change if the price and policy of use of 4R also change (see also **Annex 3** for more details on the GDG decisions).

With respect to 1HP, the 2019 GDG concluded that there was low certainty that its effectiveness would be non-inferior to 9H when used under programmatic settings in different populations at risk. When taking also into account the good safety profile of 1HP and its much shorter length when compared with other approved LTBI regimens, the GDG recommended that this regimen may also be used in high TB-burden settings and in people without HIV infection. The GDG considered that most people would value its much shorter duration than other options, that its implementation would be feasible, but raised concerns regarding uncertainty in resources requirements and the potential for reducing equity, leading to a conditional recommendation (see also **Annex 3** for more details on the GDG decisions).

In the current update, the GDG considered that all regimens could be used in any setting, regardless of TB burden, provided that the health infrastructure can ensure the treatment is given correctly without creating inequities, and that active TB can be excluded reliably before the initiation of treatment.

The GDG noted that all the treatment options can be self-administered. An RCT showed that self-administered treatment of the 3HP is not inferior to directly observed treatment (85); however, there is little further evidence on self-administration of this regimen. The GDG noted that a requirement for a direct observation could be a significant barrier to the implementation. People receiving TB preventive treatment should also be supported through access to advice on treatment and management of adverse events at their encounters with the health services. The GDG further noted that individuals receiving treatment, clinicians providing treatment and programme managers would prefer shorter to longer regimens.

Drug-drug interactions

Rifamycins induce certain cytochrome P-450 enzymes and may therefore interfere with medicines that depend on this metabolic pathway, accelerating their elimination. These include ART as well as many other medicines such as anticonvulsants, antiarrhythmics, quinine, oral anticoagulants, antifungals, oral or injectable contraceptives, corticosteroids, cyclosporine, fluoroquinolones and other antimicrobials, oral hypoglycaemic agents, methadone, and tricyclic antidepressants. Such medicines may therefore need to be avoided when rifampicin or rifapentine containing regimens are given, or that their dosages are adjusted.

Regimens containing rifamycins should be prescribed with caution to PLHIV who are on ART because of potential drug–drug interactions. These regimens should not be administered to people receiving protease inhibitors or nevirapine, including HIV-exposed infants on preventive treatment. Rifampicin can decrease the concentrations of other antiviral agents: atazanavir, darunavir, fosamprenavir, lopinavir, saquinavir and tipranavir. It should not be used with saquinavir/ritonavir. No dose adjustment is required when rifampicin is co-administered with efavirenz. The dose of dolutegravir however

needs to be increased to 50 mg twice daily when given together with rifampicin (86), a dose that is usually well tolerated and gives equivalent efficacy in viral suppression and recovery of CD4 cell count compared with efavirenz.

The 3HP regimen can be administered to patients receiving efavirenz-based antiretroviral regimens without dose adjustment, according to a study of pharmacokinetics (87). Administration of rifapentine with raltegravir was found to be safe and well tolerated (88). A drug interaction study in healthy volunteers of dolutegravir with once weekly HP reported toxicities in 2 of 4 participants (89). However results released more recently from a Phase 1/2 trial of 3HP and dolutegravir in adults with HIV reported good tolerance and viral load suppression, no adverse events of Grade >3 related to the HP, and did not indicate that rifapentine reduced dolutegravir levels sufficiently to require dose adjustment (90). The GDG stressed however the continued need for studies of the pharmacokinetics of 3HP concomitantly with other medicines, particularly ART.

Concurrent use of alcohol needs to be avoided with TB preventive treatment.

Pregnancy

In preparation for the current update, a systematic review was conducted in 2019 to assess evidence in support or against recent reports from one RCT of adverse pregnancy outcomes associated with the use of IPT (91),(92). In addition to this RCT, three non-randomized, comparative observational studies provided data on at least one of the pregnancy outcomes in women with HIV (93),(94),(95) (see PICO 9 in **Annex 2**). While the RCT showed a higher risk of adverse pregnancy outcomes in women who initiated IPT during pregnancy (Mantel-Haenszel OR stratified by gestational age, 1.51 95%CI 1.09; 2.10), all three other studies reported an overall OR <1 suggesting the opposite (I^2=80%, p=0.002). A meta-analysis from two observational studies that cited adjusted estimates and whose data could be pooled suggested lower risk for composite adverse pregnancy outcomes (OR 0.40, 95%CI 0.20; 0.74) (93),(94). The observational studies did not reproduce the associations with IPT reported by the RCT for *individual* adverse outcomes such as foetal/neonatal death, prematurity, low birth weight, and congenital anomaly. No statistically significant risks for maternal hepatotoxicity, Grade 3 or 4 events or death were reported by any of the four studies. Based upon these findings the GDG concluded that there were insufficient grounds to change previous guidance or to develop a separate recommendation for the use of IPT in pregnant women with HIV. The GDG considered that systematic deferral of IPT to the postpartum would deprive women from its protective effect at a point when they are more vulnerable to TB. Appropriate care during the antenatal and postnatal periods and during delivery may reduce risk of adverse pregnancy outcome. While obtaining baseline liver function tests when IPT is given in pregnancy is strongly encouraged when feasible, it is not required, and routine liver function testing when IPT is given in pregnancy is not indicated unless there are other risk factors for liver toxicity are present. Vitamin B6 supplementation should however be considered. The GDG agreed that this is an area requiring more research, such as on pharmacokinetics and pharmacovigilance of IPT and other preventive treatment regimens. Rifampicin is generally considered safe in pregnancy. There are limited data on the pharmacokinetics and safety of rifapentine in pregnancy and therefore the use of 1HP in pregnancy would best await more data to ensure appropriate dosing and at least preliminary safety data for this regimen in pregnant women.

Table 3. Recommended dosages of medicines for TB preventive treatment

Regimen	Dose by weight band
6 or 9 months of daily isoniazid monotherapy (6H, 9H)	Age 10 years & older: 5 mg/kg/day Age <10 years: 10 mg/kg/day (range, 7–15 mg)
Four months of daily rifampicin (4R)	Age 10 years & older: 10 mg/kg/day Age <10 years: 15 mg/kg/day (range, 10–20 mg)
Three months of daily rifampicin plus isoniazid (3HR)	Isoniazid: Age 10 years & older: 5 mg/kg/day Age <10 years: 10 mg/kg/day (range, 7–15 mg) Rifampicin: Age 10 years & older: 10 mg/kg/day Age <10 years: 15 mg/kg/day (range, 10–20 mg)

Three months of rifapentine plus isoniazid weekly (12 doses) (3HP)

Age 2–14 years

Medicine, formulation	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg
Isoniazid, 100 mg*	3	5	6	7	7
Rifapentine, 150 mg	2	3	4	5	5

Age >14 years

Medicine, formulation	30–35 kg	36–45 kg	46–55 kg	56–70 kg	>70 kg
Isoniazid, 300 mg	3	3	3	3	3
Rifapentine, 150 mg	6	6	6	6	6

* 300mg formulation can be used to reduce pill burden

One month of rifapentine plus isoniazid daily (28 doses) (1HP)	Age ≥13 years (regardless of weight band) Isoniazid, 300 mg/day Rifapentine, 600 mg/day
Six months of levofloxacin daily (preventive treatment of MDR-TB)	Age >14 years, by body weight: < 46 kg, 750 mg/day; >45 kg, 1g/day Age <15 years (range, approx. 15–20 mg/kg/day), by body weight: 5–9 kg: 150 mg/day; 10–15 kg: 200–300mg/day; 16–23 kg: 300–400mg/day; 24–34 kg: 500–750mg/day

Other subgroups and settings

The recommended dosages for TB preventive treatment regimens in adults and children are shown in **Table 3**. Regimens based on isoniazid and rifampicin can be used in individuals of all ages. There are no or very limited data on the efficacy and safety of rifapentine in children < 2 years and the 3HP regimen is only recommended for use in children aged 2 years and more. The data from the 1HP trial relates only to individuals aged 13 years and more. The GDG considered that extrapolation of effects to children aged 2–12 years is reasonable, although the dosage of *daily* rifapentine in this age group has yet to be established. The suitability of this regimen in people <13 years needs to be

reviewed once results from studies of pharmacokinetics and safety in children of all ages become available in a near future.

In candidates for transplantation or anti-TNF treatment it may be particularly important to complete TB preventive treatment fast and therefore shorter regimens like 1HP and 3HP could have an advantage over longer treatments. Likewise, in homeless people and in people being released from prison, in whom there is limited opportunity for repeated encounters during treatment, shorter treatment could be more suitable than longer regimens.

In addition to PLHIV on ART, other populations who may be more commonly at risk of drug-drug interactions from rifampicin include women of childbearing age on contraceptive medicines (who need to be counselled about potential interactions and consider nonhormonal birth control while receiving rifampicin) and opiate users on substitution therapy with methadone.

Contacts of patients with laboratory confirmed isoniazid-resistant, rifampicin-susceptible TB (Hr-TB) may be offered a four-month regimen of daily rifampicin.

Other considerations

Given the widespread use of rifampicin-containing fixed dose combinations to treat drug-susceptible TB, single dose rifampicin has become less available to disease programmes. If the 4R regimen will be used more often the demand for loose tablets of rifampicin will increase and programmes would need to procure it. Quality-assured supplies of rifampicin should be used. The provision of 4R outside the TB programme centres (e.g. primary care facilities, HIV programmes) should be accompanied by stepwise guidance on how to maximise the effect of rifampicin and avoid it being diverted for use as a broad-spectrum antibiotic.

Fixed-dose combinations (FDC) of HR should be used where possible to reduce the number of pills to be taken. FDCs of 3HP are expected to be released in a near future and will facilitate administration. Shorter regimens are also more likely to be completed. Concerns about adherence should not be a barrier to starting TB preventive treatment and support provided to enable better person-centred care. No data-supported recommendations exist on how to handle interruptions of TB preventive treatment, i.e. how many missed doses can be made up for by prolonging treatment without compromising efficacy?

Individuals at risk for peripheral neuropathy, such as those with malnutrition, chronic alcohol dependence, HIV infection, renal failure or diabetes, or who are pregnant or breastfeeding, should receive pyridoxine (vitamin B6) when taking isoniazid-containing regimens. A lowering of isoniazid dosage from the one proposed may be required to avoid toxicity if there is a high population prevalence of "slow acetylators". Combination tablets of co-trimoxazole, isoniazid and pyridoxine could be helpful in PLHIV. However, unavailability of pyridoxine should not be a reason to withhold TB preventive treatment.

Interventions to enhance adherence and completion of treatment should be tailored to the specific needs of risk groups and the local context. A systematic review conducted for the WHO 2015 LTBI guidelines provided heterogeneous results for interventions to improve treatment adherence and completion, and the evidence was considered inconclusive (14). The WHO guidelines for treatment of drug-susceptible active TB propose several interventions to support adherence, which could also be applied to TB preventive treatment (96).

In areas with high background resistance to rifampicin, such as countries in eastern Europe, it is particularly important to try to get the strain from the presumed source tested for drug susceptibility so that treatment given is more likely to work. If there is rifampicin monoresistance or other contraindications to rifampicin, then an isoniazid regimen of 6 or more months may be the most appropriate option. Unfortunately, in many settings, rifampicin resistance is often accompanied by isoniazid resistance – multidrug-resistant TB (MDR-TB) – requiring different preventive medication (see below).

Preventive treatment for MDR-TB

Justification and evidence

Evidence for effectiveness and safety of MDR-TB preventive treatment was reviewed and summarised in **Section 1.1**. The medicines used in these studies were mainly fluoroquinolones (e.g. moxifloxacin, levofloxacin) with or without other agents (e.g. ethambutol, ethionamide). The median proportion of participants who discontinued treatment because of adverse events in all the studies was 5.1% (interquartile range, 1.9–30.2%).

While ethambutol is considered safe in pregnancy, ethionamide was associated with teratogenic potential at high doses in preclinical animal studies, with minimal data in human pregnancy. Although there has been concern about the use of fluoroquinolones in children because of retardation of cartilage development shown in animals (97), similar effects have not been demonstrated in humans (98),(99). While the effects of fluoroquinolones on bone and cartilage in animals have not been observed in humans, available data and infant follow-up times are limited. One meta-analysis of observational studies including 2800 pregnant women exposed to fluoroquinolones found no differences in birth defects, spontaneous abortion or prematurity compared to unexposed pregnant women (100). Recent alerts have however highlighted the safety concerns associated with prolonged use of fluoroquinolones in humans (101),(102).

There is limited evidence for the optimal duration of MDR-TB preventive treatment, and this should be based on clinical judgement. Regimens used in the studies conducted so far were given for 6, 9 and 12 months. None of studies included data on pharmacokinetics and safety in pregnancy or a comparison of the risk for adverse events, although one reported that no serious adverse events could be attributed to fluoroquinolone-based preventive treatment (36).

Implementation considerations

The regimen of preventive treatment of MDR-TB contacts should be individualized and based on reliable information on the drug resistance profile of the presumed source. Later-generation fluoroquinolones (e.g. levofloxacin or moxifloxacin) may be used unless the strain of the presumed source shows resistance to these medicines. A dosing schedule for levofloxacin in children and adults is proposed in **Table 3**. Paediatric formulations of levofloxacin can be used for this purpose. For strains showing additional resistance other treatment regimens used in some of the studies may be used (37).

Contacts of people with rifampicin-resistant TB (RR-TB) are usually treated as for MDR-TB unless isoniazid-susceptibility in the index case is reliably confirmed, in which case IPT may be effective.

As the recommendation for preventive treatment in MDR-TB exposure is based on very low-quality evidence, people must be given detailed information about the potential benefits and harms of giving fluoroquinolones or other regimens. In view of uncertainties about the balance of benefit to harm, informed consent, preferably in writing, is required, based on the local context and practices in similar situations.

2. Monitoring and evaluation

Coverage of contact investigation and TB preventive treatment among child contacts and PLHIV are among the top 10 core indicators for monitoring implementation of the End TB Strategy (8). National TB and HIV programmes report data yearly to WHO and UNAIDS on progress in LTBI care in target populations. PMTPT should include monitoring and evaluation systems that are aligned with national patient monitoring and surveillance systems (103),(104). Appropriate recording and reporting tools should be developed and electronic case-based monitoring will facilitate LTBI management and individual care[10]. Standardized indicators should be measured to regularly inform decision-making for programme implementation. Some may require changes to national regulations or health policies (e.g. making LTBI a notifiable condition or mandating a reporting framework), which should be addressed according to the local and national context. It is important to engage the private health sector and to ensure proper recording and reporting from both the private and public sectors.

Most individuals who receive TB preventive treatment are healthy and adverse reactions to treatment are likely to influence their likelihood of completing it. Drug-related toxicity should therefore be minimized. Medicines used for TB preventive treatment regimens are generally safe and well tolerated but adverse reactions have been associated with isoniazid (asymptomatic elevation of serum liver enzyme concentrations, peripheral neuropathy and hepatotoxicity) and rifampicin and rifapentine (cutaneous reactions, hypersensitivity reactions, gastrointestinal intolerance and hepatotoxicity). While most of these reactions are minor and occur rarely, specific attention should be paid to preventing drug-induced hepatotoxicity.

Individuals on TB preventive treatment should be monitored routinely at monthly encounters with healthcare providers, who should explain the disease process and the rationale of the treatment and emphasize the importance of completing it. They should also be advised to contact their healthcare provider at any time if they become aware of symptoms such as anorexia, nausea, vomiting, abdominal discomfort, persistent fatigue or weakness, dark-coloured urine, pale stools, jaundice, confusion or drowsiness. If a healthcare provider cannot be consulted at the onset of such symptoms, the patient should stop treatment immediately. This is one of the critical areas for frontline healthcare workers and students to receive training on.

There is insufficient evidence to support testing of baseline liver function (105). It is, however, strongly encouraged, where feasible, for individuals with the following risk factors: history of liver disease, harmful use of alcohol, chronic liver disease, HIV infection, age > 35 years, pregnancy or in the immediate postpartum period (within 3 months of delivery). For individuals with abnormal baseline test results, sound clinical judgement is required to ensure that the benefit of TB preventive treatment outweighs the risks, and they should be tested routinely at subsequent visits. Appropriate laboratory testing should also be performed for patients who become symptomatic while on treatment (e.g. liver function tests for those with symptoms of hepatotoxicity). Trial criteria for when to stop a medicine – e.g. an increase in transaminases to 5 times the upper limit of normal or to 3 times plus symptoms in people on rifampicin – will need to be adapted to something more practical under field conditions.

There is no evidence of a significant association between anti-TB drug resistance and use of isoniazid or rifamycins for the treatment of LTBI (106),(107). Nonetheless, active TB disease must be excluded before TB preventive treatment is initiated (**Section 1.2**), and regular follow-up is required to ensure

[10] More detail will be provided in the practical operational guide that WHO is releasing with these guidelines.

early identification of people who develop active TB while receiving TB preventive treatment. National surveillance systems for anti-TB drug resistance may need to be strengthened in countries scaling up PMTPT.

Monitoring the adherence to TB preventive treatment and ensuring its completion are conducive to clinical benefit. An electronic application for mobile phones has been created by WHO to guide national programmes on critical data to collect along the LTBI care pathway, as an accessory to monitoring and evaluation (103). It could also be helpful to collect information about the occurrence of active TB in people who have received TB preventive treatment. This can be done by asking patients registered for TB treatment about any history of starting or completing TB preventive treatment or the cross linkage of registers (e.g. LTBI registers compared with TB treatment or mortality registers). In people who develop TB after or well into a TB preventive treatment it would be important to test for emergence of resistance.

In people on MDR-TB preventive treatment the close monitoring for adverse events and adherence to treatment is essential. The types of adverse reactions depend on the medicines used (for more details see (101),(102),(108)). Adverse events should be monitored according to the WHO framework for monitoring and managing the safety of medicines against active TB (109). Evidence for the effectiveness and safety of MDR-TB preventive treatment is urgently needed (see also **Section 3**). The GDG reiterated that strict clinical observation and close monitoring for active TB disease based on sound clinical practice and national guidelines is required for at least 2 years after MDR-TB exposure, regardless of whether preventive treatment was given or not. Consideration should also be given to interactions with ART, immunosuppressants and other medicines when providing MDR-TB preventive treatment.

3. Research gaps

The evidence reviewed ahead of the current update exposed additional knowledge gaps to the ones reported in other recent updates of the guidelines. Continued research on development and on implementation science remain critical for many aspects of the PMTPT. Some of this information may be collected as part of user feedback put in place by the implementing programme.

Risks for progression to active TB

Evidence on the likelihood of progression from infection to active TB in different at-risk populations will help determine the potential benefits of TB preventive treatment and for the design of appropriate public health interventions. In particular, strong evidence from clinical trials is lacking particularly for indigenous populations and people under the following circumstances: diabetes, harmful use of alcohol, tobacco smoking, underweight, silica exposure, on steroid treatment, rheumatological diseases, and cancer. Both direct measurement of the incidence of active TB and methods for measuring the risk for active TB disease could be explored, such as use of genotyping to investigate reactivation. Evidence is also required on differential harm and the acceptability of LTBI testing and TB preventive treatment in specific risk groups, including socially adverse effects such as stigmatization.

Defining the best algorithm for ruling out active TB

Operational and clinical studies should be conducted to exclude active TB before preventive treatment is given. The performance and feasibility of the algorithms proposed in these guidelines should be assessed. Data on children and pregnant women are particularly limited. Better evidence is needed to identify the best strategies to trace contacts and to save cost and improve feasibility (e.g. use of mobile chest radiography).

Improved diagnostic tests and performance of LTBI tests in at-risk populations

Diagnostic tests with improved performance and predictive value for progression to active TB are critically needed. In addition, the performance of LTBI tests should be evaluated in various risk groups, to assess reinfection, and to understand how best to use available tools in each population (e.g. combination or sequential use of TST and IGRA).

Treatment options for LTBI

Research to find shorter, better-tolerated TB preventive treatment regimens than those currently recommended remains a priority. Studies of efficacy and adverse events in certain risk groups (e.g. people who use drugs, people who engage in the harmful use of alcohol and older persons) are essential. There remain very limited data on the use of rifapentine in children < 2 years and in pregnant women. Trial data on 1HP in children and adults not infected with HIV and in PLHIV with low CD4 counts, under different settings, would also be desirable. A direct comparison of 1HP vs. 3HP for safety, effectiveness, and cost-effectiveness will be useful. Pharmacokinetics studies could help establish an

optimal daily dosage of rifapentine in children under 13 years, and interactions between rifamycin-containing regimens and other medicines, particularly ART in both adults and children. In addition, the durability of protection of different preventive treatment regimens, including long-acting injectables, need to be evaluated in settings in which TB is endemic, including the efficacy of repeated courses of preventive treatment. Studies of the preference of different stakeholders for different regimen characteristics would be helpful.

Monitoring of adverse events

Prospective randomized studies are required to determine the incremental benefits of routine monitoring of liver enzyme levels over education and clinical observation alone for preventing severe clinical adverse events, with stratification of the evidence by at-risk population. Programmatic data on maternal and pregnancy outcomes, inclusive of post-natal follow-up of the child, could supplement current knowledge about the safety of different LTBI regimens when used in pregnancy.

Drug resistance and TB preventive treatment

Programme-based surveillance systems and clinical studies are needed to monitor the risk for resistance to the medicines used in TB preventive treatment. Particular consideration should be given to rifamycin-containing regimens because of the dearth of data. Conversely the impact on preventive treatment efforts of high levels of resistance to isoniazid and/or rifamycins among prevalent TB strains would be useful to study.

Adherence to and completion of treatment

Carefully designed studies, including RCTs, are required to generate evidence on the effectiveness of context-specific interventions to enhance adherence and completion of treatment. The studies should include specific risk groups, depending on the available resources and the health system infrastructure and address questions about how to integrate TB preventive treatment into differentiated models of HIV service delivery. Use of digital technologies to improve adherence is an important area. Further research is required on the effectiveness of self-administration of the 3-month regimen of weekly rifapentine plus isoniazid.

Cost–effectiveness

Although a number of studies of the cost-effectiveness of TB preventive treatment are available, their wide heterogeneity obviates a comprehensive appraisal of the cost-effectiveness of LTBI management stratified by population group, and type of regimen or intervention. Cost-effectiveness analysis using parameters from different resource settings could allow better planning for the extension of a PMTPT strategy at national or local level.

Preventive treatment for contacts of people with MDR-TB

The WHO recommendation on MDR-TB preventive treatment should not signal a lesser need for continued studies or create ethical impediments. RCTs with adequate power are urgently needed to update the recommendation on preventive treatment for contacts of people with MDR/RR-TB. Trials should be performed with both adult and paediatric populations and with at-risk populations such as PLHIV. The composition, dosage and duration of preventive treatment regimens for MDR-TB should be optimized, and the potential role of newer agents with good sterilization properties should be

investigated. The effectiveness and safety of preventive treatment for contacts of people with MDR-TB should be evaluated under operational conditions. Further evidence on the risk of contacts of people with MDR-TB for progression to active TB will be important to understand the benefits of preventive treatment.

Programme management

Continued epidemiological research should be conducted to determine the burden of LTBI in various geographical settings and risk groups and as a basis for nationally and locally tailored interventions, including integrated community-based approaches. Implementation research on context-specific barriers and facilitators is needed for different LTBI regimens, to explore dimensions for which evidence is often sparse, such as acceptability, feasibility, equity and resource use. Research is also needed on service delivery models to improve management including the provision of additional interventions for smokers, harm reduction services for people who use drugs or who engage in the harmful use of alcohol and in prison. Household implementation models could increase the effectiveness and efficiency of delivery of interventions. Future trial evidence could guide better how to optimise contact tracing strategies in households and elsewhere. Tools should be developed and assessed to facilitate monitoring and evaluation of PMTPT efforts as an accessory to improving future global guidance.

4. References

1. Getahun H, Matteelli A, Chaisson RE, Raviglione M. Latent Mycobacterium tuberculosis Infection. N Engl J Med. 2015 May 28;372(22):2127–35.
2. Dodd PJ, Gardiner E, Coghlan R, Seddon JA. Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. Lancet Glob Health. 2014 Aug;2(8):e453–9.
3. Houben RMGJ, Dodd PJ. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. PLOS Medicine. 2016 Oct 25;13(10):e1002152.
4. Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. Am J Epidemiol. 1974 Feb;99(2):131–8.
5. Vynnycky E. Lifetime Risks, Incubation Period, and Serial Interval of Tuberculosis. Am J Epidemiol. 2000 Aug 1;152(3):247–63.
6. United Nations General Assembly. Resolution A/RES/73.3. Political declaration of the high-level meeting of the General Assembly on the fight against tuberculosis. In 2018. Available from: http://www.un.org/en/ga/search/view_doc.asp?symbol=A/RES/73/3
7. Uplekar M, Weil D, Lönnroth K, Jaramillo E, Lienhardt C, Dias HM, et al. WHO's new end TB strategy. Lancet. 2015 May 2;385(9979):1799–801.
8. Implementing the End TB Strategy: the essentials (WHO/HTM/TB/2015.31). Geneva, World Health Organization. 2015. Available from: http://www.who.int/tb/publications/2015/end_tb_essential.pdf
9. Lönnroth K, Migliori GB, Abubakar I, D'Ambrosio L, de Vries G, Diel R, et al. Towards tuberculosis elimination: an action framework for low-incidence countries. Eur Respir J. 2015 Apr;45(4):928–52.
10. Global tuberculosis report 2019 (WHO/CDS/TB/2019.15). Geneva, World Health Organization; 2019. Available from: https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf
11. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva, World Health Organization. 2011. Available from: https://apps.who.int/iris/bitstream/handle/10665/44472/9789241500708_eng.pdf
12. Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2nd ed. (WHO/TB/2014.03). Geneva, World Health Organization; 2014. Available from: http://apps.who.int/iris/bitstream/10665/112360/1/9789241548748_eng.pdf
13. Guidelines on the management of latent tuberculosis infection (WHO/HTM/TB/2015.01). Geneva, World Health Organization. 2015. Available from: http://apps.who.int/iris/bitstream/10665/136471/1/9789241548908_eng.pdf
14. Getahun H, Matteelli A, Abubakar I, Aziz MA, Baddeley A, Barreira D, et al. Management of latent *Mycobacterium tuberculosis* infection: WHO guidelines for low tuberculosis burden countries. Eur Respir J. 2015 Dec;46(6):1563–76.
15. Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries (WHO/HTM/TB/2012.9). Geneva, World Health Organization; 2012. Available from: http://www.who.int/tb/publications/2012/contact_investigation2012/en/

16. Latent TB Infection: Updated and consolidated guidelines for programmatic management (WHO/CDS/TB/2018.4). Geneva, World Health Organization. 2018. Available from: http://apps.who.int/iris/bitstream/handle/10665/260233/9789241550239-eng.pdf
17. Ford N, Matteelli A, Shubber Z, Hermans S, Meintjes G, Grinsztejn B, et al. TB as a cause of hospitalization and in-hospital mortality among people living with HIV worldwide: a systematic review and meta-analysis. Journal of the International AIDS Society. 2016 Jan;19(1):20714.
18. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane HIV/AIDS Group, editor. Cochrane Database of Systematic Reviews. 2010 Jan 20 [cited 2019 Jul 29]; Available from: http://doi.wiley.com/10.1002/14651858.CD000171.pub3
19. Chaisson L, Saraceni V, Cohn S, Cavalcante S, Chaisson RE, Golub J, et al. CD4 count-based guidelines for tuberculin skin testing and tuberculosis preventive therapy in people living with HIV. In Mexico; 2019 [cited 2019 Oct 4]. Available from: http://programme.ias2019.org/Abstract/Abstract/3724
20. Rangaka MX, Wilkinson RJ, Boulle A, Glynn JR, Fielding K, van Cutsem G, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. The Lancet. 2014 Aug;384(9944):682–90.
21. The TEMPRANO ANRS 12136 Study Group. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. N Engl J Med. 2015 Aug 27;373(9):808–22.
22. Badje A, Moh R, Gabillard D, Guéhi C, Kabran M, Ntakpé J-B, et al. Effect of isoniazid preventive therapy on risk of death in west African, HIV-infected adults with high CD4 cell counts: long-term follow-up of the Temprano ANRS 12136 trial. Lancet Glob Health. 2017 Nov;5(11):e1080–9.
23. Bruins WS, van Leth F. Effect of secondary preventive therapy on recurrence of tuberculosis in HIV-infected individuals: a systematic review. Infect Dis. 2017 Mar 4;49(3):161–9.
24. Evaluation of the Effect of 3HP vs Periodic 3HP vs 6H in HIV-Positive Individuals (WHIP3TB). 2016. Available from: https://clinicaltrials.gov/ct2/show/NCT02980016
25. Recommendation on 36 months isoniazid preventive therapy to adults and adolescents living with HIV in resource-constrained and high TB- and HIV-prevalence settings – 2015 update (WHO/HTM/TB/2015.15 / WHO/HIV/2015.13). Geneva, World Health Organization. 2015. Available from: https://apps.who.int/iris/bitstream/handle/10665/174052/9789241508872_eng.pdf
26. WHO Guidelines on tuberculosis infection prevention and control, 2019 update (WHO/CDS/TB/2019.1). Geneva, World Health Organization. 2019. Available from: https://apps.who.int/iris/bitstream/handle/10665/311259/9789241550512-eng.pdf
27. Getahun H, Sculier D, Sismanidis C, Grzemska M, Raviglione M. Prevention, Diagnosis, and Treatment of Tuberculosis in Children and Mothers: Evidence for Action for Maternal, Neonatal, and Child Health Services. J Infect Dis. 2012 May 15;205(suppl 2):S216–27.
28. US FDA. Isoniazid Tablets, USP. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/008678s028lbl.pdf
29. US FDA. RIFADIN® (rifampin capsules USP) and RIFADIN ® IV (rifampin for injection USP). Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/050420s073,050627s012lbl.pdf
30. Zar HJ, Cotton MF, Strauss S, Karpakis J, Hussey G, Schaaf HS, et al. Effect of isoniazid prophylaxis on mortality and incidence of tuberculosis in children with HIV: randomised controlled trial. BMJ. 2007 Jan 20;334(7585):136.
31. Madhi SA, Nachman S, Violari A, Kim S, Cotton MF, Bobat R, et al. Primary Isoniazid Prophylaxis against Tuberculosis in HIV-Exposed Children. N Engl J Med. 2011 Jul 7;365(1):21–31.
32. Gray DM, Workman LJ, Lombard CJ, Jennings T, Innes S, Grobbelaar CJ, et al. Isoniazid preventive therapy in HIV-infected children on antiretroviral therapy: a pilot study. Int J Tuberc Lung Dis. 2014 Mar;18(3):322–7.

33. Frigati LJ, Kranzer K, Cotton MF, Schaaf HS, Lombard CJ, Zar HJ. The impact of isoniazid preventive therapy and antiretroviral therapy on tuberculosis in children infected with HIV in a high tuberculosis incidence setting. Thorax. 2011 Jun 1;66(6):496–501.

34. Garcia-Prats AJ, Zimri K, Mramba Z, Schaaf HS, Hesseling AC. Children exposed to multidrug-resistant tuberculosis at a home-based day care centre: a contact investigation. Int J Tuberc Lung Dis. 2014 Nov 1;18(11):1292–8.

35. Trieu L, Proops DC, Ahuja SD. Moxifloxacin Prophylaxis against MDR TB, New York, New York, USA. Emerg Infect Dis. 2015 Mar;21(3):500–3.

36. Bamrah S, Brostrom R, Dorina F, Setik L, Song R, Kawamura LM, et al. Treatment for LTBI in contacts of MDR-TB patients, Federated States of Micronesia, 2009–2012. Int J Tuberc Lung Dis. 2014 Aug 1;18(8):912–8.

37. Schaaf HS, Gie RP, Kennedy M, Beyers N, Hesseling PB, Donald PR. Evaluation of young children in contact with adult multidrug-resistant pulmonary tuberculosis: a 30-month follow-up. Pediatrics. 2002 May;109(5):765–71.

38. Knight GM, McQuaid CF, Dodd PJ, Houben RMGJ. Global burden of latent multidrug-resistant tuberculosis: trends and estimates based on mathematical modelling. Lancet Infect Dis. 2019 Aug;19(8):903–12.

39. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. 2nd edition. Geneva, World Health Organization; 2016. Available from: http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf

40. Consolidated guideline on sexual and reproductive health and rights of women living with HIV (WHO/CDS/TB/2019.1). Geneva, World Health Organization. 2017.

41. Denholm JT, Matteelli A, Reis A. Latent tuberculous infection: ethical considerations in formulating public health policy. Int J Tuberc Lung Dis. 2015 Feb;19(2):137–40.

42. Ethics guidance for the implementation of the End TB Strategy (WHO/HTM/TB/2017.07). Geneva, World Health Organization. 2017. Available from: http://apps.who.int/iris/bitstream/10665/254820/1/9789241512114-eng.pdf

43. Resolution WHA61.17. Health of Migrants. In: Sixty-first World Health Assembly, Geneva, 19–24 May 2008, Resolutions and decisions; annexes. Geneva, World Health Organization, 2008 (WHA61/2008/REC/1):23–25. Available from: http://apps.who.int/gb/ebwha/pdf_files/WHA62-REC1/WHA62_REC1-en.pdf

44. Kass NE. An ethics framework for public health. Am J Public Health. 2001 Nov;91(11):1776–82.

45. Getahun H, Kittikraisak W, Heilig CM, Corbett EL, Ayles H, Cain KP, et al. Development of a Standardized Screening Rule for Tuberculosis in People Living with HIV in Resource-Constrained Settings: Individual Participant Data Meta-analysis of Observational Studies. Murray M, editor. PLoS Med. 2011 Jan 18;8(1):e1000391.

46. Hamada Y, Lujan J, Schenkel K, Ford N, Getahun H. Sensitivity and specificity of WHO's recommended four-symptom screening rule for tuberculosis in people living with HIV: a systematic review and meta-analysis. The Lancet HIV. 2018 Sep;5(9):e515–23.

47. Ahmad Khan F, Verkuijl S, Parrish A, Chikwava F, Ntumy R, El-Sadr W, et al. Performance of symptom-based tuberculosis screening among people living with HIV: not as great as hoped. AIDS. 2014 Jun;28(10):1463–72.

48. Nguyen DTM, Bang ND, Hung NQ, Beasley RP, Hwang L-Y, Graviss EA. Yield of chest radiograph in tuberculosis screening for HIV-infected persons at a district-level HIV clinic. Int J Tuberc Lung Dis. 2016 Feb;20(2):211–7.

49. Cranmer. L, Pavlinac. P, Njuguna. I, Otieno. V, Maleche-Obimbo. E, Moraa. H, et al. Performance of WHO TB symptom screen in hospitalized HIV-positive Kenyan children. 47th World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease; 2016; Liverpool, United Kingdom.

50. Chest radiography in tuberculosis detection-Summary of current WHO recommendations and guidance on programmatic approaches. (WHO/HTM/TB/2016.20). Geneva, World Health Organization. 2016. Available from: https://apps.who.int/iris/bitstream/handle/10665/252424/9789241511506-eng.pdf

51. van't Hoog A, Langendam MW, Cobelens FGJ, Sinclair D, Leeflang M, Lönnroth K. A systematic review of the sensitivity and specificity of symptom- and chest-radiography screening for active pulmonary tuberculosis in HIV-negative persons and persons with unknown HIV status. 2013. Available from: https://www.who.int/tb/Review2Accuracyofscreeningtests.pdf

52. Mulenga H, Tameris MD, Luabeya KKA, Geldenhuys H, Scriba TJ, Hussey GD, et al. The Role of Clinical Symptoms in the Diagnosis of Intrathoracic Tuberculosis in Young Children: Pediatr Infect Dis J. 2015 Nov;34(11):1157–62.

53. Kruk A, Gie RP, Schaaf HS, Marais BJ. Symptom-based screening of child tuberculosis contacts: improved feasibility in resource-limited settings. Pediatrics. 2008 Jun 1;121(6):e1646–52.

54. Triasih R, Robertson CF, Duke T, Graham SM. A Prospective Evaluation of the Symptom-Based Screening Approach to the Management of Children Who Are Contacts of Tuberculosis Cases. Clin Infect Dis. 2015 Jan 1;60(1):12–8.

55. Mandalakas AM, Hesseling AC, Gie RP, Schaaf HS, Marais BJ, Sinanovic E. Modelling the cost-effectiveness of strategies to prevent tuberculosis in child contacts in a high-burden setting. Thorax. 2013 Mar;68(3):247–55.

56. Assefa Y, Woldeyohannes S, Gelaw YA, Hamada Y, Getahun H. Screening tools to exclude active pulmonary TB in high TB burden countries: systematic review and meta-analysis. Int J Tuberc Lung Dis. 2019 Jun 1;23(6):728–34.

57. Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis. A general review. Bibl Tuberc. 1970;26:28–106.

58. Gao L, Li X, Liu J, Wang X, Lu W, Bai L, et al. Incidence of active tuberculosis in individuals with latent tuberculosis infection in rural China: follow-up results of a population-based, multicentre, prospective cohort study. Lancet Infect Dis. 2017 Oct;17(10):1053–61.

59. Rangaka MX, Wilkinson KA, Glynn JR, Ling D, Menzies D, Mwansa-Kambafwile J, et al. Predictive value of interferon-γ release assays for incident active tuberculosis: a systematic review and meta-analysis. The Lancet Infect Dis. 2012 Jan;12(1):45–55.

60. Mahomed H, Hawkridge T, Verver S, Abrahams D, Geiter L, Hatherill M, et al. The Tuberculin Skin Test versus QuantiFERON TB Gold® in Predicting Tuberculosis Disease in an Adolescent Cohort Study in South Africa. Pai M, editor. PLoS ONE. 2011 Mar 29;6(3):e17984.

61. Mathad JS, Bhosale R, Balasubramanian U, Kanade S, Mave V, Suryavanshi N, et al. Quantitative IFN-γ and IL-2 Response Associated with Latent Tuberculosis Test Discordance in HIV-infected Pregnant Women. Am J Respir Crit Care Med. 2016 Jun 15;193(12):1421–8.

62. McCarthy KM, Scott LE, Gous N, Tellie M, Venter WDF, Stevens WS, et al. High incidence of latent tuberculous infection among South African health workers: an urgent call for action. Int J Tuberc Lung Dis. 2015 Jun;19(6):647–53.

63. Sharma SK, Vashishtha R, Chauhan LS, Sreenivas V, Seth D. Comparison of TST and IGRA in Diagnosis of Latent Tuberculosis Infection in a High TB-Burden Setting. PLoS ONE. 2017 Jan 6;12(1):e0169539.

64. Dorman SE, Belknap R, Graviss EA, Reves R, Schluger N, Weinfurter P, et al. Interferon-γ Release Assays and Tuberculin Skin Testing for Diagnosis of Latent Tuberculosis Infection in Healthcare Workers in the United States. Am J Respir Crit Care Med. 2013 Dec 3;131203133239003.

65. Zwerling A, Behr MA, Verma A, Brewer TF, Menzies D, Pai M. The BCG World Atlas: A Database of Global BCG Vaccination Policies and Practices. PLoS Med. 2011 Mar 22;8(3):e1001012.

66. Zunza M, Gray DM, Young T, Cotton M, Zar HJ. Isoniazid for preventing tuberculosis in HIV-infected children. Cochrane Infectious Diseases Group, editor. Cochrane Database of Systematic Reviews. 2017 Aug 29 [cited 2019 Aug 28]; Available from: http://doi.wiley.com/10.1002/14651858.CD006418.pub3

67. Smieja M, Marchetti C, Cook D, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. Cochrane Infectious Diseases Group, editor. Cochrane Database of Systematic Reviews. 1999 Jan 25 [cited 2019 Aug 28]; Available from: http://doi.wiley.com/10.1002/14651858.CD001363

68. Zenner D, Beer N, Harris RJ, Lipman MC, Stagg HR, van der Werf MJ. Treatment of Latent Tuberculosis Infection: An Updated Network Meta-analysis. Ann Intern Med. 2017 Aug 15;167(4):248.

69. Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? Int J Tuberc Lung Dis. 1999 Oct;3(10):847–50.

70. Den Boon S, Matteelli A, Ford N, Getahun H. Continuous isoniazid for the treatment of latent tuberculosis infection in people living with HIV: AIDS. 2016 Mar;30(5):797–801.

71. Stagg HR, Zenner D, Harris RJ, Muñoz L, Lipman MC, Abubakar I. Treatment of Latent Tuberculosis Infection: A Network Meta-analysis. Ann Intern Med. 2014 Sep 16;161(6):419.

72. Galli L, Lancella L, Tersigni C, Venturini E, Chiappini E, Bergamini B, et al. Pediatric Tuberculosis in Italian Children: Epidemiological and Clinical Data from the Italian Register of Pediatric Tuberculosis. IJMS. 2016 Jun 17;17(6):960.

73. Spyridis NP, Spyridis PG, Gelesme A, Sypsa V, Valianatou M, Metsou F, et al. The effectiveness of a 9-month regimen of isoniazid alone versus 3- and 4-month regimens of isoniazid plus rifampin for treatment of latent tuberculosis infection in children: results of an 11-year randomized study. Clin Infect Dis. 2007 Sep 15;45(6):715–22.

74. van Zyl S, Marais BJ, Hesseling AC, Gie RP, Beyers N, Schaaf HS. Adherence to anti-tuberculosis chemoprophylaxis and treatment in children. Int J Tuberc Lung Dis. 2006 Jan;10(1):13–8.

75. Menzies D, Adjobimey M, Ruslami R, Trajman A, Sow O, Kim H, et al. Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults. N Engl J Med. 2018 Aug 2;379(5):440–53.

76. Diallo T, Adjobimey M, Ruslami R, Trajman A, Sow O, Obeng Baah J, et al. Safety and Side Effects of Rifampin versus Isoniazid in Children. N Engl J Med. 2018 Aug 2;379(5):454–63.

77. Menzies D, Long R, Trajman A, Dion M-J, Yang J, Al Jahdali H, et al. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: a randomized trial. Ann Intern Med. 2008 Nov 18;149(10):689–97.

78. Menzies D, Dion M-J, Rabinovitch B, Mannix S, Brassard P, Schwartzman K. Treatment Completion and Costs of a Randomized Trial of Rifampin for 4 Months versus Isoniazid for 9 Months. Am J Respir Crit Care Med. 2004 Aug 15;170(4):445–9.

79. Swindells S, Ramchandani R, Gupta A, Benson CA, Leon-Cruz J, Mwelase N, et al. One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis. N Engl J Med. 2019 Mar 14;380(11):1001–11.

80. Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, et al. New Regimens to Prevent Tuberculosis in Adults with HIV Infection. N Engl J Med. 2011 Jul 7;365(1):11–20.

81. Sterling TR, Scott NA, Miro JM, Calvet G, La Rosa A, Infante R, et al. Three months of weekly rifapentine and isoniazid for treatment of Mycobacterium tuberculosis infection in HIV-coinfected persons: AIDS. 2016 Jun;30(10):1607–15.

82. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al. Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection. N Engl J Med. 2011 Dec 8;365(23):2155–66.

83. Villarino ME, Scott NA, Weis SE, Weiner M, Conde MB, Jones B, et al. Treatment for Preventing Tuberculosis in Children and Adolescents: A Randomized Clinical Trial of a 3-Month, 12-Dose Regimen of a Combination of Rifapentine and Isoniazid. JAMA Pediatr. 2015 Mar 1;169(3):247.

84. Moro RN, Scott NA, Vernon A, Tepper NK, Goldberg SV, Schwartzman K, et al. Exposure to Latent Tuberculosis Treatment during Pregnancy. The PREVENT TB and the iAdhere Trials. Annals ATS. 2018 May;15(5):570–80.

85. Belknap R, Holland D, Feng P-J, Millet J-P, Caylà JA, Martinson NA, et al. Self-administered Versus Directly Observed Once-Weekly Isoniazid and Rifapentine Treatment of Latent Tuberculosis Infection: A Randomized Trial. Ann Intern Med. 2017 Nov 21;167(10):689.

86. Dolutegravir (DTG) and the fixed dose combination (FDC) of tenofovir/lamivudine/dolutegravir (TLD). Geneva, World Health Organization; 2018. Available from: https://www.who.int/hiv/pub/arv/DTG-TLD-arv_briefing_2018.pdf

87. Podany AT, Bao Y, Swindells S, Chaisson RE, Andersen JW, Mwelase T, et al. Efavirenz Pharmacokinetics and Pharmacodynamics in HIV-Infected Persons Receiving Rifapentine and Isoniazid for Tuberculosis Prevention. Clin Infect Dis. 2015 Oct 15;61(8):1322–7.

88. Weiner M, Egelund EF, Engle M, Kiser M, Prihoda TJ, Gelfond JAL, et al. Pharmacokinetic interaction of rifapentine and raltegravir in healthy volunteers. J Antimicrob Chemother. 2014 Apr 1;69(4):1079–85.

89. Brooks KM, George JM, Pau AK, Rupert A, Mehaffy C, De P, et al. Cytokine-Mediated Systemic Adverse Drug Reactions in a Drug–Drug Interaction Study of Dolutegravir With Once-Weekly Isoniazid and Rifapentine. Clin Infect Dis. 2018 Jul 2;67(2):193–201.

90. Dooley KE, Churchyard G, Savic RM, Gupte A, Marzinke MA, Zhang N, et al. Safety & PK of weekly rifapentine/isoniazid (3HP) in adults with HIV on dolutegravir. In: TB: FROM CONTACT TO CURE AND BEYOND (Abstract Number: 80). Seattle, Washington, USA; 2019 [cited 2019 Apr 25]. Available from: http://www.croiconference.org/sessions/safety-pk-weekly-rifapentineisoniazid-3hp-adults-hiv-dolutegravir

91. Gupta A, Montepiedra G, Aaron L, Theron G, McCarthy K, Onyango-Makumbi C et al. Randomized trial of safety of isoniazid preventive therapy during or after pregnancy. In: CRITICAL ISSUES IN WOMEN'S HEALTH AND EARLY TREATMENT OF PEDIATRIC HIV INFECTION (Abstract Number: 142LB). Boston, Massachusetts, USA; 2018 [cited 2019 Apr 25]. Available from: http://www.croiconference.org/sessions/randomized-trial-safety-isoniazid-preventive-therapy-during-or-after-pregnancy

92. Gupta A, Montepiedra G, Aaron L, Theron G, McCarthy K, Bradford S, et al. Isoniazid Preventive Therapy in HIV-Infected Pregnant and Postpartum Women. N Engl J Med. 2019 Oct 3;381(14):1333–46.

93. Taylor AW, Mosimaneotsile B, Mathebula U, Mathoma A, Moathlodi R, Theebetsile I, et al. Pregnancy Outcomes in HIV-Infected Women Receiving Long-Term Isoniazid Prophylaxis for Tuberculosis and Antiretroviral Therapy. Infect Dis Obstet Gynecol. 2013;2013:1–5.

94. Salazar-Austin N, Cohn S, Lala S, Waja Z, Dooley KE, Hoffmann CJ, et al. Isoniazid Preventive Therapy and Pregnancy Outcomes In HIV-Infected Women in the Tshepiso Cohort. Clin Infect Dis. 2019 Oct 21;ciz1024.

95. Kalk EK, Heekes A, Mehta U, de Waal R, Jacob N, Cohen K, et al. Programmatic review of safety and effectiveness of isoniazid preventive therapy in HIV-infected pregnant women on ART in routine care. Reproductive Toxicology. 2018 Sep;80:155.

96. Guidelines for the treatment of drug-susceptible tuberculosis and patient care, 2017 update. (WHO/HTM/TB/2017.05). Geneva, World Health Organization. 2017. Available from: http://apps.who.int/iris/bitstream/10665/255052/1/9789241550000-eng.pdf

97. Takizawa T, Hashimoto K, Minami T, Yamashita S, Owen K. The comparative arthropathy of fluoroquinolones in dogs. Hum Exp Toxicol. 1999 Jun;18(6):392–9.

98. Hampel B, Hullmann R, Schmidt H. Ciprofloxacin in pediatrics: worldwide clinical experience based on compassionate use--safety report. Pediatr Infect Dis J. 1997 Jan;16(1):127–9; discussion 160–162.

99. Warren RW. Rheumatologic aspects of pediatric cystic fibrosis patients treated with fluoroquinolones. Pediatr Infect Dis J. 1997 Jan;16(1):118–22; discussion 123–126.

100. Acar S, Keskin-Arslan E, Erol-Coskun H, Kaya-Temiz T, Kaplan YC. Pregnancy outcomes following quinolone and fluoroquinolone exposure during pregnancy: A systematic review and meta-analysis. Reproductive Toxicology. 2019 Apr;85:65–74.

101. Safety announcement -> FDA reinforces safety information about serious low blood sugar levels and mental health side effects with fluoroquinolone antibiotics; requires label changes. 2018. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-reinforces-safety-information-about-serious-low-blood-sugar-levels-and-mental-health-side

102. Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics. European Medicines Agency; 2019. Available from: https://www.ema.europa.eu/en/documents/referral/quinolone-fluoroquinolone-article-31-referral-disabling-potentially-permanent-side-effects-lead_en.pdf

103. WHO | LTBI care: a mobile app to support programmatic management of LTBI. WHO. 2017. Available from: https://www.who.int/tb/areas-of-work/preventive-care/ltbi/ltbi_app/en/

104. Getahun H, Matteelli A, Abubakar I, Hauer B, Pontali E, Migliori GB. Advancing global programmatic management of latent tuberculosis infection for at risk populations. Eur Respir J. 2016 May;47(5):1327–30.

105. Sotgiu G, Matteelli A, Getahun H, Girardi E, Sañé Schepisi M, Centis R, et al. Monitoring toxicity in individuals receiving treatment for latent tuberculosis infection: a systematic review *versus* expert opinion. Eur Respir J. 2015 Apr;45(4):1170–3.

106. Balcells ME, Thomas SL, Godfrey-Faussett P, Grant AD. Isoniazid Preventive Therapy and Risk for Resistant Tuberculosis. Emerg Infect Dis. 2006 May;12(5):744–51.

107. Den Boon S, Matteelli A, Getahun H. Rifampicin resistance after treatment for latent tuberculous infection: a systematic review and meta-analysis. Int J Tuberc Lung Dis. 2016;20(8):1065–71.

108. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. (WHO/HTM/TB/2014.11). Geneva, World Health Organization; 2015. Available from: http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf

109. Active tuberculosis drug-safety monitoring and management (aDSM). Framework for implementation (WHO/HTM/TB/2015.28). Geneva, World Health Organization; 2015. Available from: http://apps.who.int/iris/bitstream/10665/204465/1/WHO_HTM_TB_2015.28_eng.pdf

Supplementary Table

Summary of changes to the WHO TB preventive treatment recommendations between 2018 and current updates

Note: In the current update, two of the 2018 recommendations on LTBI testing (Section C) were incorporated into the remarks as implementation considerations; four recommendations on individual TB preventive treatment options have been merged into one recommendation (Recommendation 17). Recommendations 3, 6, 9, 17 and 18 may apply to specific settings in a country regardless of the overall national TB incidence (see text and Annexes for further explanation of the changes). Other recommendations from the 2018 update remain unchanged or else underwent language editing to enhance clarity (Recommendations 1, 2, 4, 5, 7, 8, 10–16).

Recommendations in the 2018 update	***Recommendations in the current update***
A. Identifying at-risk populations for LTBI testing and treatment	**1.1. Identifying populations for LTBI testing and TB preventive treatment**
People living with HIV	*People living with HIV*
Adults and adolescents living with HIV, with unknown or a positive tuberculin skin test (TST) and who are unlikely to have active TB should receive preventive treatment of TB as part of a comprehensive package of HIV care. Treatment should be given to these individuals irrespective of the degree of immunosuppression and also to those on antiretroviral treatment (ART), those who have previously been treated for TB and pregnant women.	1. Adults and adolescents living with HIV who are unlikely to have active TB should receive TB preventive treatment as part of a comprehensive package of HIV care. Treatment should also be given to those on antiretroviral treatment, to pregnant women and to those who have previously been treated for TB, irrespective of the degree of immunosuppression and even if LTBI testing is unavailable. *(language editing)*
Infants aged < 12 months living with HIV who are in contact with a case of TB and are investigated for TB should receive 6 months of isoniazid preventive treatment (IPT) if the investigation shows no TB disease.	2. Infants aged < 12 months living with HIV who are in contact with a person with TB and who are unlikely to have active TB on an appropriate clinical evaluation or according to national guidelines should receive TB preventive treatment. *(language editing)*
Children aged ≥ 12 months living with HIV who are considered unlikely to have TB disease on the basis of screening for symptoms and who have no contact with a case of TB should be offered 6 months of IPT as part of a comprehensive package of HIV prevention and care if they live in a setting with a high prevalence of TB.	3. Children aged ≥ 12 months living with HIV who are considered unlikely to have active TB on an appropriate clinical evaluation or according to national guidelines should be offered TB preventive treatment as part of a comprehensive package of HIV prevention and care if they live in a setting with high TB transmission, regardless of contact with TB. *(refers to setting with high TB transmission rather than prevalence)*

Recommendations in the 2018 update	***Recommendations in the current update***
All children living with HIV who have successfully completed treatment for TB disease may receive isoniazid for an additional 6 months.	4. All children living with HIV who have successfully completed treatment for TB disease may receive TB preventive treatment. *(language editing)*
HIV-negative household contacts	*Household contacts (regardless of HIV status)*
HIV-negative children aged < 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have active TB on an appropriate clinical evaluation or according to national guidelines should be given TB preventive treatment.	5. Children aged < 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have active TB on an appropriate clinical evaluation or according to national guidelines should be given TB preventive treatment even if LTBI testing is unavailable. *(language editing)*
In countries with a low TB incidence, children, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB should be systematically tested and treated for LTBI.	*Incorporated into the following recommendation and its accompanying commentary* 6. Children aged ≥ 5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have active TB by an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment.
In countries with a high TB incidence, children aged ≥ 5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have active TB by an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment.	
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.	7. In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualized risk assessment and a sound clinical justification. *(no change)*
Other at-risk groups	*Other people at risk*
Patients initiating anti-TNF treatment, patients receiving dialysis, patients preparing for an organ or haematological transplant and patients with silicosis should be systematically tested and treated for LTBI.	8. People who are initiating anti-TNF treatment, or receiving dialysis, or preparing for an organ or haematological transplant, or who have silicosis should be systematically tested and treated for LTBI. *(language editing)*
In countries with a low TB incidence, systematic testing for and treatment of LTBI may be considered for prisoners, health workers, immigrants from countries with a high TB burden, homeless people and people who use illicit drugs.	9. Systematic LTBI testing and treatment may be considered for prisoners, health workers, immigrants from countries with a higher TB burden, homeless people and people who use drugs. *(language editing; restriction by TB burden setting removed)*
Systematic testing for LTBI is not recommended for people with diabetes, people with harmful alcohol use, tobacco smokers and underweight people unless they are already included in the above recommendations.	10. Systematic LTBI testing and treatment is not recommended for people with diabetes, people who engage in the harmful use of alcohol, tobacco smokers and underweight people unless they also belong to other risk groups included in the above recommendations. *(language editing)*

Recommendations in the 2018 update	***Recommendations in the current update***
B. Algorithms to rule out active TB disease	**1.2. Algorithms to rule out active TB disease**
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.	11. 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. *(no change)*
Adults and adolescents living with HIV who are screened for TB according to a clinical algorithm and who report any 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 that cause such symptoms.	12. Adults and adolescents living with HIV who are screened for TB according to a clinical algorithm and who report any 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 and offered preventive treatment if active TB is excluded. *(language editing)*
Chest radiography may be offered to people living with HIV and on ART and preventive treatment given to those with no abnormal radiographic findings.	13. Chest radiography may be offered to people living with HIV on ART and preventive treatment given to those with no abnormal radiographic findings. *(no change)*
Infants and children living with HIV who have poor weight gain, fever or current cough or who have a history of contact with a case of TB should be evaluated for TB and other diseases that cause such symptoms. If the evaluation shows no TB, these children should be offered preventive treatment, regardless of their age.	14. Infants and children living with HIV who have poor weight gain, fever or current cough or who have a history of contact with a person with TB should be evaluated for TB and other diseases that cause such symptoms. If TB disease is excluded after an appropriate clinical evaluation or according to national guidelines, these children should be offered TB preventive treatment, regardless of their age. *(language editing)*
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.	15. 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 risk groups before preventive treatment. *(no change)*
C. Testing for LTBI	**1.3. Testing for LTBI**
Either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) can be used to test for LTBI.	16. Either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) can be used to test for LTBI. *(no change)*
People living with HIV who have a positive test for LTBI benefit more from preventive treatment than those who have a negative LTBI test; LTBI testing can be used, where feasible, to identify such individuals.	*Incorporated into the implementation considerations*
LTBI testing by TST or IGRA is not a requirement for initiating preventive treatment in people living with HIV or child household contacts aged < 5 years.	

Recommendations in the 2018 update	***Recommendations in the current update***
D. Treatment options for LTBI	**1.4. TB preventive treatment options**
Isoniazid monotherapy for 6 months is recommended for treatment of LTBI in both adults and children in countries with high and low TB incidence.	*Incorporated into a single recommendation, applicable to all settings* 17. The following options are recommended for the treatment of LTBI regardless of HIV status : 6 or 9 months of daily isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or a 3 month regimen of daily isoniazid plus rifampicin. A 1-month regimen of daily rifapentine plus isoniazid or 4 months of daily rifampicin alone may also be offered as alternatives.
Rifampicin plus isoniazid daily for 3 months should be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for children and adolescents aged < 15 years in countries with a high TB incidence.	
Rifapentine and isoniazid weekly for 3 months may be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for both adults and children in countries with a high TB incidence.	
The following options are recommended for treatment of LTBI in countries with a low TB incidence as alternatives to 6 months of isoniazid monotherapy: 9 months of daily isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or a 1-month regimen of daily rifapentine plus isoniazid, or 3–4 months of daily isoniazid plus rifampicin, or 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.	18. In settings with high TB transmission, adults and adolescents living with HIV who have an unknown or a positive LTBI test and are unlikely to have active TB disease should receive at least 36 months of daily isoniazid preventive therapy (IPT). Daily IPT for 36 months should be given whether or not the person is on ART, and irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy in settings considered to have a high TB transmission as defined by national authorities. *(refers to setting with high TB transmission only)*

For further information, please contact:

World Health Organization
20, Avenue Appia CH-1211 Geneva 27 Switzerland
Global TB Programme
Web site: www.who.int/tb

World Health Organization

9789240001503