

WHO operational handbook on tuberculosis

Module 1: Prevention

Tuberculosis preventive treatment

Second edition



World Health
Organization

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Page iv, lines 11-12

Delete: The Technical Advisory Group on dosing of TB medicines for adults and children for advice on the dosing of TPT regimens in section 5.

Insert: Tiziana Masini (WHO Global Tuberculosis Programme) and the Technical Advisory Group on dosing of TB medicines for adults and children for advice on the dosing of TPT regimens in section 5.

Page iv, lines 24- 25

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Insert: Ahmad Khawaja (WHO Pakistan) and Nazis Arefin Saki (WHO Bangladesh), Fernanda Dockhorn Costa Johansen and

Table 3 page 45, footnote C

Delete: reference 69

Insert: reference 61, subsequent references in the document were adjusted taking into account the updated reference numbers mentioned on page 45 and page 74 below where reference 145 was added.

Second part of Table 4 page 47, row 5

Insert: Results for Row 5 (Rifapentine 300 mg and isoniazid 300 mg FDC tab) and a footnote

Page 74, line 4: One reference and associated text erroneously omitted.

Delete: Most adverse drug reactions associated with HP regimens are mild, self-resolving and without sequelae (145). The following specific actions may be considered during management of potential adverse drug reactions after treatment with 3HP and 1HP.

Insert: The HP regimens have several advantages and most adverse drug reactions associated with them are mild, self-resolving and without sequelae. However, systemic drug reactions like hypotension, dizziness, bronchospasm may lead to TPT discontinuation. Toxicity may be particularly pronounced among slow acetylators of isoniazid (see section 5.2) (145). The use of pyridoxine to prevent and treat isoniazid toxicity is described elsewhere in this handbook (see section 5.2.2). The following specific actions may be considered during management of potential adverse drug reactions after treatment with 3HP and 1HP.

These corrections have been incorporated into the electronic file.

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Abbreviations and acronyms

1HP	1 month of daily rifapentine plus isoniazid
3HP	3 months of weekly rifapentine plus isoniazid
3HR	3 months of daily rifampicin plus isoniazid
4R	4 months of daily rifampicin monotherapy
6H	6 months of daily isoniazid monotherapy
6Lfx	6 months of daily levofloxacin monotherapy
9H	9 months of daily isoniazid monotherapy
ACF	active case finding
ART	antiretroviral therapy
ARV	antiretroviral drugs
BCG	bacille Calmette-Guérin
CAD	computer aided detection
CRP	C-reactive protein
CXR	chest radiography
DSD	differentiated HIV service delivery
ELISA	enzyme-linked immunosorbent assay
FDC	fixed-dose combination
GDG	Guideline Development Group
HMIS	health management information system
IFN-γ	interferon- γ
IGRA	interferon- γ release assay
IPT	isoniazid preventive treatment
LFT	liver function test
Lfx	levofloxacin
MDR-TB	multidrug-resistant tuberculosis
M&E	monitoring and evaluation
mWRD	molecular WHO-recommended rapid diagnostic test
NGO	nongovernmental organization
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleotide reverse transcriptase inhibitor
NTP	national TB programme
PI	protease inhibitor
PMTPT	programmatic management of tuberculosis preventive treatment
PPD	purified protein derivative

RCT	randomized controlled trial
RR	relative risk
RR-TB	rifampicin-resistant TB
SOP	standard operating procedure
TB	tuberculosis
TB-KSP	TB Knowledge Sharing Platform
TBST	<i>Mycobacterium tuberculosis</i> antigen-based skin test
TDF	tenofovir-disoproxil fumarate
TNF	tumour necrosis factor
TPT	tuberculosis preventive treatment
TST	tuberculin skin test
UNHLM	United Nations High-level Meeting
WHO	World Health Organization

Definitions

Note: Unless otherwise specified, the definitions listed below apply to the terms as used in this handbook. They may have different meanings in other contexts.

Active case finding (ACF): is synonymous with systematic screening for tuberculosis (TB) disease, although usually implemented outside a health facility.

Adolescent: is a person aged 10–19 years.

Adult: is a person aged > 19 years.

At-risk group: is any group of people in which the prevalence or incidence of TB is significantly higher than in the general population.

Bacteriologically confirmed TB: refers to TB diagnosed in a biological specimen by smear microscopy, culture or a WHO-approved rapid diagnostic test such as Xpert® MTB/RIF or a urinary lipoarabinomannan assay.

Child: is a person aged < 10 years.

Contact: is any person who has been exposed to a person with TB disease.

Contact investigation: refers to systematic identification of previously undiagnosed TB disease and TB infection (TBI) among the contacts of an index person and/or settings where transmission occurs. Includes clinical evaluation and/or testing and provision of appropriate anti-TB therapy (for people with confirmed TB) or TB preventive treatment (TPT) (for those without TB disease).

Close contact: is a person who is not in the same household but shared an enclosed space, such as at a social gathering, workplace or facility, for extended periods during the day with an index person with TB during the 3 months before commencement of the current TB treatment episode.

Differentiated HIV service delivery mode: is a person-centred approach to simplify the provision of HIV services along the cascade, in ways that both serve the needs of people with HIV better and reduce unnecessary burdens on the health system.

High TB transmission setting: refers to a setting with a high frequency of individuals with undetected or undiagnosed TB disease, 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. Transmission will be increased by aerosol-generating procedures and by the presence of highly susceptible individuals.

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

Index person with TB: is 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 person is the one on whom a contact investigation is centred but is not necessarily the source.

Infant: is a child aged < 1 year (12 months).

Latent tuberculosis infection: is a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of clinically manifest TB disease. Most infected people have no signs or symptoms of TB but are at risk for TB disease. As infection cannot always be considered latent, however, the term “TB infection” is now used. There is no gold standard test for direct identification of *M. tuberculosis* infection in humans.

People who use drugs: are those who engage in harmful or hazardous use of psychoactive substances, which could negatively affect their health, social life, resources and legal situation.

Programmatic management of TB preventive treatment (PMTPT): refers to all coordinated activities by public and private health caregivers and the community for providing TPT to people who need it.

Skin test: refers to intradermal inoculation of either tuberculin (TST) or *M. tuberculosis* antigen (TBST) to elicit a response indicative of TBI.

Systematic screening for TB disease: refers to the systematic identification of people at risk of TB disease in a predetermined target group by assessing symptoms and using tests, examinations and other procedures that can be applied rapidly. For those who screen positive, the diagnosis must be established by one or several diagnostic tests and additional clinical assessments, which are together highly accurate. This term is sometimes used interchangeably with active TB case finding. It should be distinguished from testing for TB infection with a TB skin test or interferon- γ release assay.

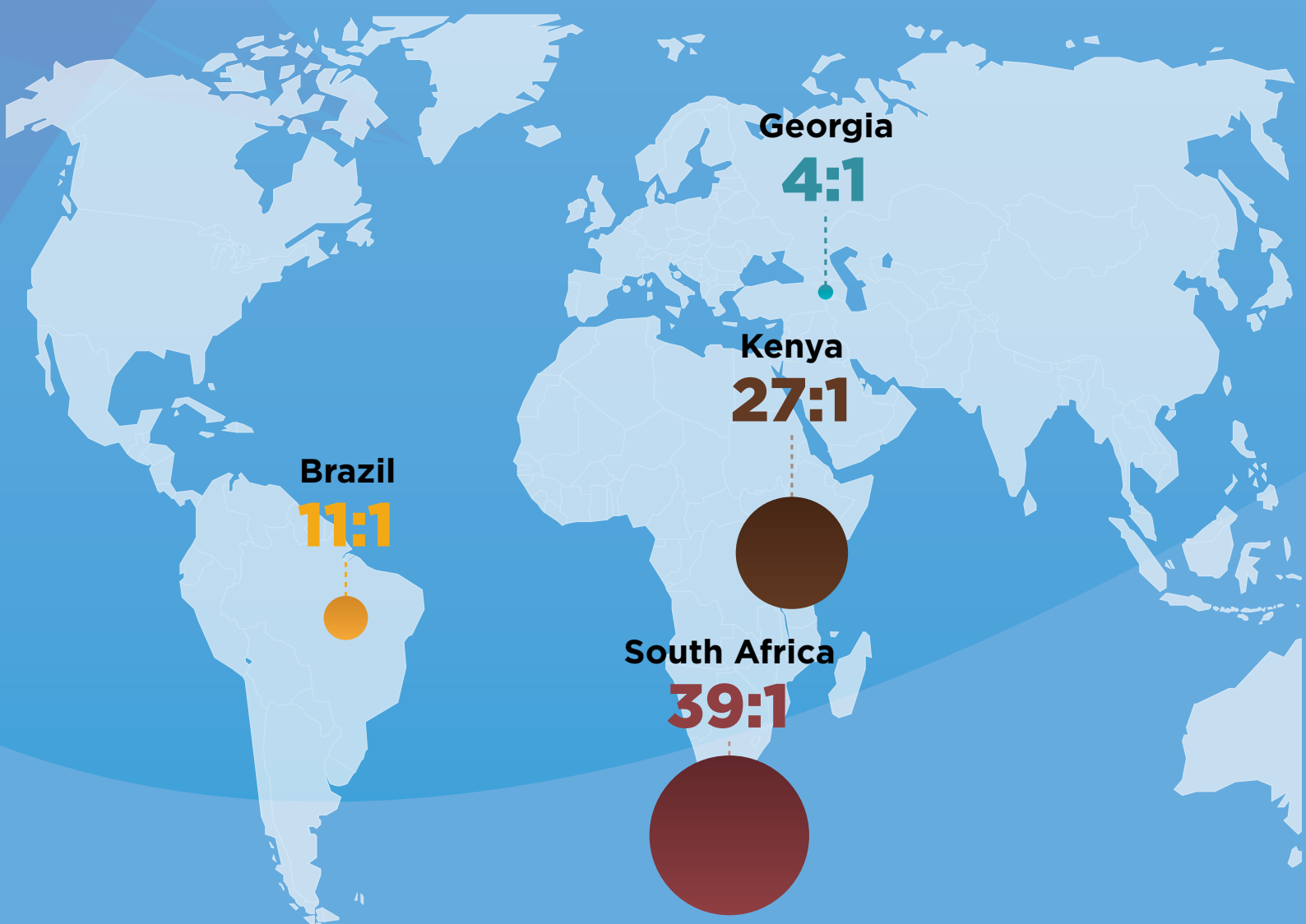
TB preventive treatment (TPT): is treatment offered to individuals who are considered to be harbouring TBI and to be at risk of developing TB disease in order to reduce that risk. Also referred to as treatment of LTBI or TB infection, or TB preventive therapy.

Tuberculosis (TB): is the disease state due to *M. tuberculosis*. In this document, it is referred to as “TB disease” in order to distinguish it from “TB infection”. In some sources, it is referred to as active TB.

Tuberculosis infection (TBI): is a state of persistent immune response to stimulation by *M. tuberculosis* antigens with no clinically manifest TB disease. Most infected people have no signs or symptoms of TB but are at risk of TB disease. TBI was previously referred to as “latent TB infection” or LTBI, but, as infection cannot always be considered latent, the term TBI (TBI) is preferred. There is no gold standard test for direct identification of *M. tuberculosis* infection in humans.

Underweight: in people ≥ 19 years, usually refers to a body mass index < 18.5 kg/m²; in people aged < 19 years, refers to a weight-for-age < -2 z-scores.

TPT along with TB screening offer a substantial societal return on investment, from US\$ 4 to US\$ 39 gained for every dollar invested, and reduce the cost of TB to society (Annex 1).



1. Introduction

Key points

- Tuberculosis (TB) preventive treatment (or TPT) is considered one of the most critical public health measures for protecting individuals who are infected with *M. tuberculosis*, those who have been exposed to it and are at higher risk of developing TB disease and communities.
- Achieving the new targets set by the United Nations High-level Meeting (UNHLM) on Tuberculosis will require a massive expansion of TPT services along the cascade of care to reach all those who need TPT. Large investments in health system strengthening and mobilization of commensurate human and financial resources are necessary for programmatic management of TPT (PMTPT).
- Scaling-up TPT for target populations is likely to generate significant dividends and returns on investment for communities.
- Ministries of health and other stakeholders should commit adequate funding and resources to build the capacity of programmes for effective contact investigation.
- The cascade of care approach for PMTPT involves four steps in which individuals move through the health system to receive care for TB infection, namely: (i) identification of people eligible for TPT, (ii) screening for and excluding TB disease, (iii) testing for TB infection, and (iv) initiating and completing TPT. This handbook is organized along the cascade of care and highlights elements for programmatic prioritization and investment at each stage.

1.1 Background

About one fourth of the world's population is estimated to have been infected with *M. tuberculosis* (1,2). The risk of TB disease after infection depends on several factors, the most important being weakened immunological status (3). The vast majority of infected individuals show no signs or symptoms of TB and are not infectious, although they are at increased risk of progressing to TB disease and becoming infectious. On average, 5–10% of those who are infected will develop TB disease during their lives, most within the first 5 years after initial infection (4). About 75% of people who develop TB disease after coming into contact with someone with TB do so within 1 year of the TB diagnosis of the index patient, and 97% develop TB within 2 years (5). Molecular typing studies in low-burden settings have also found that, among those who develop disease within 15 years of exposure, the probabilities of developing disease within 1, 2 and 5 years were 45%, 62% and 83%, respectively (6). Therefore, people living with HIV, individuals in contact with TB patients, people in congregate settings such as prisons and those with immunodeficiency conditions are at high risk of TB and are hence priority groups for receiving TPT. Unfortunately, currently available biomarkers and tests for TB infection do not differentiate between recent and past infection, and eligibility for TPT relies on ruling out TB disease clinically and radiologically among individuals and groups who are known to be at high risk of acquiring TB, with use of tests to aid decision-making, when they are available.

The WHO End TB Strategy (7) prioritizes TPT among people at high risk, as a key component of pillar 1. PMTPT fits into a larger framework of preventive action envisaged under pillars 1 and 2 of the End TB Strategy. It includes screening for TB disease, infection control, prevention and care of HIV

and other comorbidities, access to universal health care, social protection and poverty alleviation. The Strategy includes indicators of progress and sets a global target of 90% coverage of TPT among people with HIV and household contacts of TB patients by 2025. PMTPT is also considered a key intervention for low TB burden countries that are pursuing TB elimination (8). While TPT services are gradually increasing globally, access by many people at risk remains low, and the targets set at the 2018 UNHLM on TB have not been met, except for the sub-target of people living with HIV. Between 2018 and 2022, 15.5 million people were provided with TPT (52% of the target of 30 million), of whom 11.3 million people had HIV (> 100% of the target), 2.2 million children under 5 years of age (55% of the target of 4 million) and 2 million people aged ≥ 5 years (10% of the target of 20 million) (9). Coverage of contacts in particular remains very low and should be a priority for scaling up.

In September 2023, at the second UNHLM on Tuberculosis, Member States endorsed a political declaration committing them to the diagnosis and treatment of 45 million people with TB by the end of 2027 and to providing 45 million individuals with TPT to protect them from developing TB disease during this period (10). The TPT target in the declaration includes 15 million people with HIV and 30 million household contacts of TB patients including children. Achievement of these targets will entail massive extension of TPT services through health system strengthening and mobilization of commensurate human and financial resources. While the investments required may be substantial, large societal returns on investment can be expected from scaling up an intensified approach to TB screening combined with TPT ([Annex 1](#)) (11,12). In this context, ministries of health should take urgent action to redesign PMTPT and mobilize resources to support rapid scaling-up of TPT, aligned with the latest (2024) guidelines from WHO (13). [Table 1](#) lists the latest WHO recommendations on TPT, which are discussed further in this handbook.

In support of these guidelines, this operational handbook lays down key implementation considerations and steps in programmatic scaling up of TPT and provides implementation tools and job-aids for adaptation to local contexts and indicators for monitoring and evaluating PMTPT. It highlights elements to be considered in patient care, national strategic planning and resource mobilization. The handbook provides practical advice to facilitate the implementation of the evidence-based recommendations in [Table 1](#) and does not make additional recommendations. Although the handbook focuses on settings with a high TB and HIV burden, the considerations may also apply to low TB burden settings. This handbook is intended to guide policy-makers within ministries of health and other institutions and stakeholders who are involved in health, including national, subnational and district HIV and TB programme managers; health-care workers and staff of development and technical agencies, nongovernmental organizations (NGOs) as well as civil society and community-based organizations involved in supporting TPT services.

The contents of the handbook were updated from the first edition released in 2020. The WHO secretariat oversaw the update of the text and invited experts involved in the production of the respective guidelines to review the content. (See also [Annex 2](#) of (13)). In addition, WHO invited countries to submit examples of successful scale up of different elements of PMTPT and redacted the content to fit the style. The update of drug dosages in [section 5](#) was developed with the input of Technical Advisory Group on dosing of TB medicines for adults and children as well as academic groups involved in the pharmacokinetic modelling of the two TPT regimens concerned. (See also [Web Annex A](#).) Declarations of interest were sought for contributors to this handbook and were assessed by the WHO secretariat. (See also [Web Annex B](#).)

Table 1. Recommendations in the WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment (13)^a

1.1. Identifying populations for TB preventive treatment
People with HIV
1. Adults and adolescents living with HIV who are unlikely to have TB disease on an appropriate clinical evaluation or according to national guidelines 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 testing for TB infection 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 TB disease 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 TB disease 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 of people with TB (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 TB disease on an appropriate clinical evaluation or according to national guidelines should be given TB preventive treatment even if testing for TB infection 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 TB disease on an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment.
Other people at risk
7. People who are initiating anti-tumour-necrosis factor treatment, receiving dialysis, preparing for an organ or haematological transplant or have silicosis should be systematically tested and treated for TB infection.
8. Systematic testing and treatment for TB infection may be considered for prisoners, health workers, immigrants from countries with a high TB burden, homeless people and people who use drugs.
1.2. TB screening and ruling out TB disease
9. 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.
10. 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 TB disease. Those who report any of these symptoms may have TB, should be evaluated for TB disease and other diseases and should be offered TB preventive treatment if TB disease is excluded, regardless of their antiretroviral treatment status.

11. Among adults and adolescents living with HIV, chest X-ray may be used to screen for TB disease.

12. Among adults and adolescents living with HIV, C-reactive protein at a cut-off of > 5 mg/L may be used to screen for TB disease.

13. Among adults and adolescents living with HIV, molecular WHO-recommended rapid diagnostic tests may be used to screen for TB disease.

14. Among HIV-negative household contacts aged ≥ 5 years and other risk groups, the absence of any symptoms of TB and the absence of abnormal chest radiographic findings may be used to rule out TB disease before TB preventive treatment.

15. Among individuals aged ≥ 15 years in populations in which TB screening is recommended, systematic screening for TB disease may be conducted with a symptom screen, chest X-ray or molecular WHO-recommended rapid diagnostic tests, alone or in combination.

16. Among individuals < 15 years who are close contacts of a person with TB, systematic screening for TB disease should be conducted with a symptom screen of any one of cough, fever or poor weight gain; or chest radiography; or both.

1.3. Testing for TB infection

17. Either a tuberculin skin test (TST) or interferon- γ release assay (IGRA) can be used to test for TB infection.

18. *Mycobacterium tuberculosis* antigen-based skin tests (TBST) may be used to test for TB infection.

1.4. TB preventive treatment options

TB preventive treatment with isoniazid or rifamycins

19. The following TB preventive treatment options are recommended 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.

20. The following alternative TB preventive treatment options may be used regardless of HIV status: a 1-month regimen of daily rifapentine plus isoniazid or 4 months of daily rifampicin.

TB preventive treatment with levofloxacin

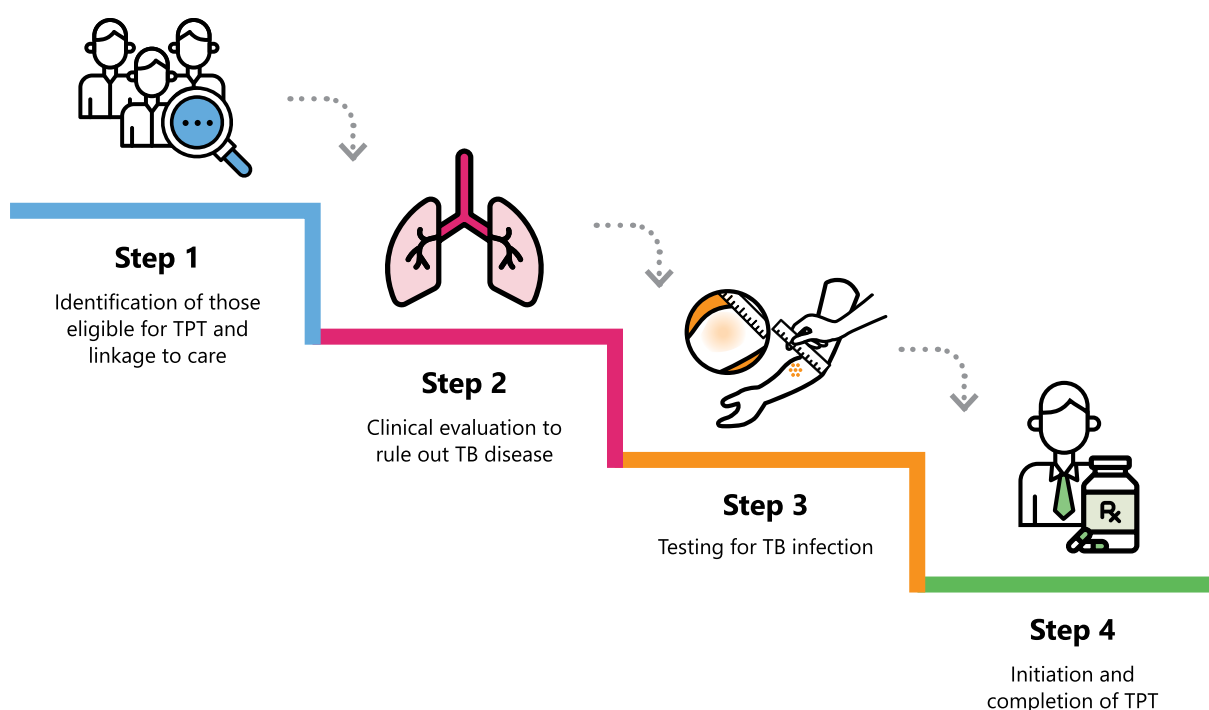
21. In contacts exposed to multidrug- or rifampicin-resistant tuberculosis, 6 months of daily levofloxacin should be used as TB preventive treatment.

^a The conditions under which these recommendations apply, and more details of their implementation are discussed in the following chapters

1.2 Cascade of care approach

PMTPT has long been a low-priority intervention for national programmes due to competing priorities. As Member States have committed themselves to take urgent steps to end the TB epidemic (10), however, major investments should be made in health systems strengthening and a comprehensive “cascade of care” approach adopted to scale up PMTPT (Fig. 1) (14–16). This approach for PMTPT involves four steps in which individuals move through the health system to receive care for TB infection: (i) identification of people eligible for TPT, (ii) screening for and excluding TB disease, (iii) testing for TB infection, and (iv) initiation and completion of TPT. This handbook is organized according to this cascade of care and highlights elements for programmatic prioritization and investment at each stage.

Fig. 1. Cascade of care approach to scaling TB, tuberculosis; TPT, TB preventive treatment



TB, tuberculosis; TPT, TB preventive treatment

Source: Oxlade et al. (15). Modified and used with permission of the copyright holder, The International Union Against Tuberculosis and Lung Disease.

Programmatic implementation and scaling up of TPT services require strengthening of each element in the cascade of care, starting from identification of the target population to provision of preventive treatment (Fig. 1). This will help to ensure that individuals at greatest risk of developing TB are systematically identified, evaluated and given access to a full course of TPT to improve individual health and reduce the risk for ongoing TB transmission. A systematic review and meta-analysis have shown that there are substantial gaps in the cascade of care and that people drop out at every step, with the greatest losses at the stages of initial testing of those intended for TB screening, completing medical evaluation if the test was positive, provider recommendation of treatment and completing therapy when started (16). Overall, among those estimated to be eligible for TPT, less than 20% complete the entire cascade of care (16). It should be noted that these data are from research conducted in developed countries, and losses may be even higher under programmatic conditions in resource-constrained settings.

Annexes 2–5 present lists and other suggestions for coordinating activities in countries, costing for budgeting and planning and reviewing the PMTPT component of their health services. TPT services should be integrated into TB screening and case-finding among target populations (17). People with a positive screening result, such as symptoms of TB or abnormalities on chest radiography (CXR), should receive diagnostic testing for TB with rapid molecular tests and TB treatment if found to be positive. When TB disease is ruled out, the individual should be evaluated for TB infection and receive TPT (see also algorithm in Fig. 6 in section 4). Better retention and referral of individuals evaluated for TB, identification of those eligible for TPT and development of person-friendly, accessible services will ensure that a substantial proportion of people with TB infection are initiated on TPT and complete the treatment, thereby reducing the reservoir of TB infection from which TB disease develops (18). Advocacy at various levels is critically important. This handbook includes messages on TPT for ministries of health, health-care workers, people with HIV and other individuals offered TPT, as well as community members (Annex 2).

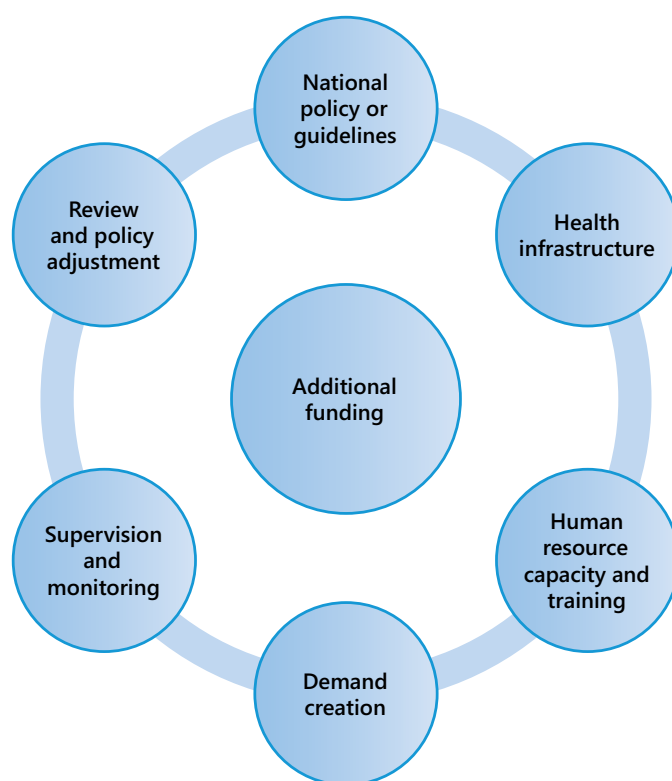
1.3 Components of a system for delivering TPT

Country-specific priorities, interventions and targets should be shaped by national stakeholders according to local requirements and available resources. Fig. 2 illustrates key considerations for PMTPT.

- **National policy or guidelines** specify the interventions and actions to be taken by all. These should be developed through broad consultation and be based on the TPT cascade of care and the needs of at-risk populations in the framework of national TB strategic planning.
- **Health infrastructure** must be available to provide access to services at delivery points for TB screening, radiography, tests for TB infection and TPT. Health infrastructure includes the procurement and supply system, information technology and digital tools, and systems for community outreach.
- **Human resource capacity and training** are required for correct, consistent implementation of TPT guidelines. A standard curriculum and training materials and continuing education and skills-building increase the quality of the performance of care providers.
- **Demand creation** is essential to address the unmet need for TPT. It requires engagement of health-care providers, people eligible for TPT, people with TB and their families.
- **Supervision and monitoring** are indispensable for high-quality service delivery, at every level of the health system, and should complement routine monitoring, evaluation and health information activities.
- **Review and policy adjustment** should be conducted by a technical working group that assesses the progress of implementation and scaling-up of TPT, sets priorities for resource allocation and refines policies and practice.
- **Additional funding** and sustained financial investment for all components are essential for successful implementation. To ensure sustainability, TPT services could be integrated into other programmes, such as for HIV, TB case finding and methadone maintenance services. Health-care workers and communities should be adequately enabled, compensated and incentivized to scale up TPT.

Items that require costing for budgeting and planning programmatic management of TPT are listed in Annex 4. The Integrated Health Tool for planning and costing TB services is a web-based tool designed to support national strategic health planning during the medium term and can also be used for costing TPT service delivery and associated programme and health systems costs (19). Annex 5 provides a checklist (A5.1) of PMTPT components that should be considered during development of a national strategic plan and during review of national TB and/or HIV programmes.

Fig. 2. Considerations in implementing PMTPT



1.4 Objectives and structure of the operational handbook

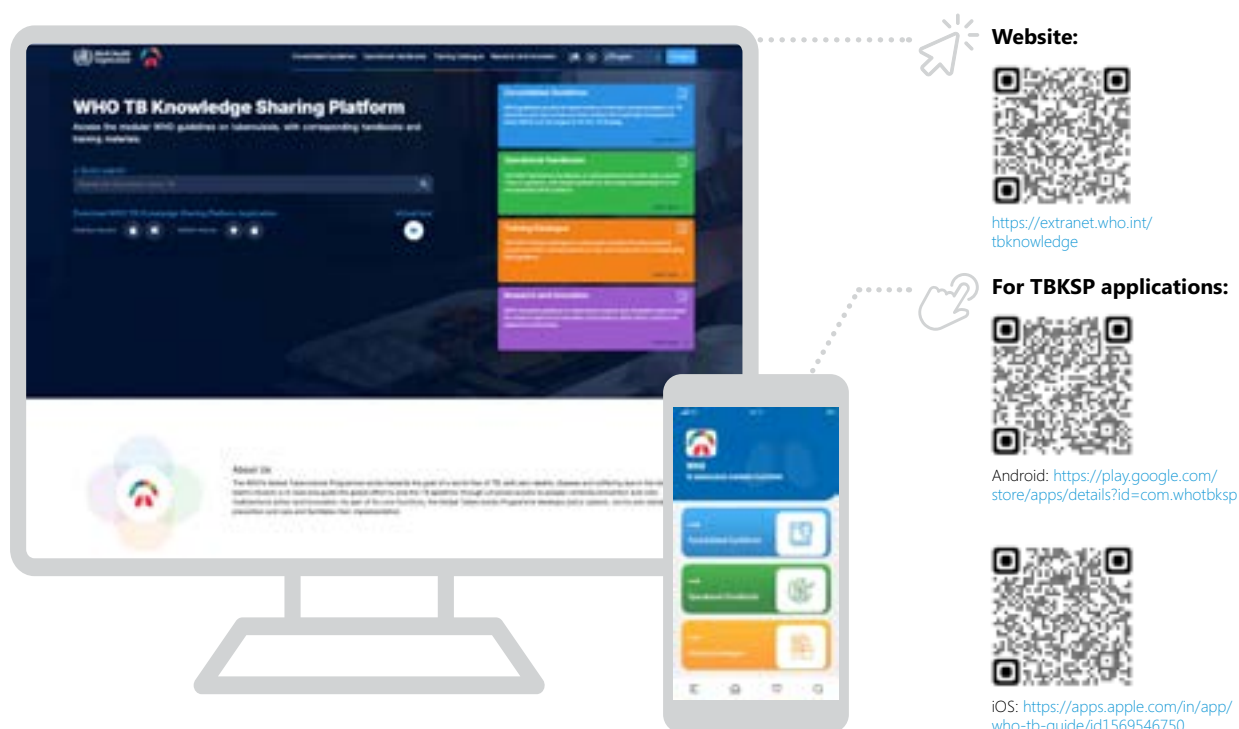
The aim of this operational handbook is to support countries in contributing to the global targets for TPT. The policy considerations suggested are aligned with the latest WHO guidelines ([Table 1](#)). The document outlines considerations for implementation at each step in the cascade of care. Identifying and reaching populations for TPT – people with HIV and household contacts – and how to reach them are addressed in [section 2](#), which also provides advice on establishing a system for contact investigations and integrating PMTPT into systematic screening for TB disease. [Section 3](#) addresses the second step in the cascade of care: screening for TB and ruling out TB disease before TPT. It presents the various tools and tests that can be used to screen for TB and the stages at which they are used in the cascade of PMTPT. The third step, testing for TB infection, is addressed in [section 4](#), including the reasons for testing for TB infection, the populations that benefit most from testing, the tests currently available, their characteristics, and arguments for and against their use. [Section 5](#) provides an overview of the TPT regimens and dosages of TPT medication that are recommended by WHO. The section includes provision of TPT for special populations and differentiated services and implementation. [Section 6](#) provides more details on the safety of TPT medications and on the management of adverse reactions and drug–drug interactions for people with co-morbidities who are also taking other treatments. Common questions and concerns in relation to TPT are also addressed in this section, including the duration of protection, when TPT should be repeated or reinitiated and whether TPT causes drug resistance. The importance of adherence to and completion of TPT is emphasized in [section 7](#), which provides guidance on person-centred interventions and strategies to improve adherence, such as differentiated service delivery and nutritional support, how barriers to adherence can be addressed effectively and concrete advice on management of missed doses or interruptions of TPT. Monitoring and evaluation (M&E) are essential for PMTPT, as shown in [section 8](#), and standard indicators for monitoring and evaluating TPT services are provided, with suggestions for

data variables to be captured in a national health management information system (HMIS), preferably with digital tools to minimize the reporting burden on health-care workers. [Section 9](#) discusses the ethics of TPT. It provides information on the requirements for obtaining informed consent and proposes ways to address issues of equity, stigmatization and human rights.

Since 2020, the WHO Global TB Programme has consolidated its normative material on all aspects of TB prevention and care into six modules: prevention, screening, diagnosis, treatment, children and adolescents and co-morbidities. The first set of guidelines and handbooks in the series was issued on World TB Day 2020, with the updated guidelines and operational handbook on TB preventive treatment, under Module 1.

In June 2021, the Global Tuberculosis Programme launched the WHO TB Knowledge Sharing Platform (TB-KSP) to enhance access to the latest WHO recommendations and resources on TB. The TB-KSP provides a “one-stop shop” for recommendations, guidelines, operational handbooks, training modules and tools to enhance research and evidence collection for policy-making, such as target product profiles. The TB-KSP may be accessed online, as an application for smartphones and tablets and on desktop and laptop computers.

The TB-KSP is constantly updated to provide users with the latest content in various languages. Users are welcome to send suggestions for continued improvement.



Tuberculosis is one of the topmost infectious killers worldwide. TPT preserves health, reduces the numbers of deaths and transmission and saves families from catastrophic costs.

It's time for governments and donors to be more proactive in helping all people at high risk of TB to access TPT.



2. Identifying populations for TB preventive treatment

Key points

- The largest component of UNHLM targets for prevention is provision of TPT to at least 30 million household contacts of people with TB between 2023 and 2027. Investments are critical to strengthen national programme capacity for contact investigation.
- National programmes should consider integrating TPT services with finding and notifying people with TB disease who have been missed and systematic linkage of individuals who are eligible for TPT to TB diagnosis and treatment services.
- Countries should attempt to achieve universal coverage with TPT for people with HIV and household contacts of TB patients aged < 5 years.
- TPT policies should be developed for other populations at risk, including those most likely to be exposed to TB disease and those at high risk of progression from infection to disease.
- A national technical working group should be established, or an existing equivalent mechanism mandated to advise the ministry of health and the national TB and HIV programmes on identification of target populations and strategies for reaching them.

The first step in scaling up PMTPT is identification of populations eligible for TPT. The WHO guidelines on TPT recommend (73) that the target populations are those that fulfil one or more of the following criteria:

- high prevalence of TB infection;
- high risk of progression to TB disease; and
- higher incidence of TB disease than in the general population, indicating high TB transmission.

The benefits of TPT outweigh the potential risk of acquiring TB or drug toxicity. WHO thus recommends two broad groups at risk for systematic assessment of eligibility and provision of TPT:

1. People at elevated risk of progression from infection to TB disease:
 - people with HIV and
 - patients with silicosis, starting or preparing for tumour-necrosis factor (TNF) treatment, receiving dialysis or preparing for an organ or haematological transplant.
2. People at increased likelihood of exposure to TB disease:
 - household contacts of people with bacteriologically confirmed TB, usually subdivided into:
 - children < 5 years and
 - children ≥ 5 years, adolescents and adults; and
 - people who live or work in institutional or crowded settings, such as prisoners, health workers, recent immigrants from countries with a high TB burden, homeless people and people who use drugs.

2.1 Populations eligible for TPT

2.1.1 People with HIV

People with HIV are about 18 times more likely to develop TB disease than those without HIV infection and should be prioritized for systematic evaluation and TPT in all settings (9). Despite major progress in access to and the effectiveness of antiretroviral treatment (ART), TB is the most frequent cause of AIDS-related deaths worldwide (20). In 2022, TB caused over 167 000 deaths among people with HIV, representing about one fourth of all HIV deaths (9). TPT increases the survival of people with HIV even when they are on ART (27). TPT also provides additional protection when given immediately after successful completion of treatment for TB disease in people with HIV (27–23).

While TPT should be considered for infants aged < 12 months living with HIV who have a history of contact with a person with TB, children with HIV aged ≥ 12 months should be considered for TPT irrespective of contact with a person with TB. TPT is recommended for children with HIV, regardless of whether they are on ART or not. The evidence for an additive benefit of TPT among children with HIV on ART is limited, but it is plausible, given the efficacy observed among adults with HIV receiving ART plus TPT. Similarly, the effect of TPT in children with HIV after successful completion of TB treatment is largely extrapolated from benefits observed in adults exposed to reinfection and recurrence of TB.

Infants born to HIV-infected mothers are vulnerable to early TB infection due to the mother's risk of contracting TB disease (24,25). Given the poor outcomes of TB disease in exposed infants, it is important to consider TPT for infants who show no signs of TB disease. Excluding TB disease before starting TPT in infants who are low birth weight or malnourished requires very careful evaluation. Prevention of mother-to-child transmission of HIV is an important platform for screening these infants for TB disease. A strong link should therefore be established between mother-and-child health services and national TB programmes (NTPs) (26).

WHO also recommends provision of TPT to children with HIV who successfully complete treatment for TB disease. People with HIV face a higher risk of recurrence of TB disease than HIV-negative individuals. While a complete course of TB treatment with a four-drug regimen has a very high success rate and a very low incidence (2–3%) of recurrence, the risk is several times higher in people with HIV, which can be due to treatment failure, emergence of drug resistance during therapy or reinfection with a new strain of *M. tuberculosis* (27–30). In a study of people with HIV whose initial episode of TB was considered to have been cured, 14% experienced a recurrence of TB, in nearly 90% of whom was due to reinfection with a different strain of *M. tuberculosis* (31). Interventions to minimize recurrence of TB include: ensuring completion of the initial course of TB treatment, effective infection control measures in clinics and communities frequented by people with HIV, and TPT in former TB patients who completed treatment successfully (secondary TPT) (32,33).

2.1.2 Household contacts (regardless of HIV status)

Household contacts of people with TB are well recognized as being at risk for TB infection and TB disease, including prevalent TB detected at the time of initial contact and incident TB occurring within the subsequent 2–5 years. The prevalence of TB infection among household contacts exceeds 50% in many low- and middle-income countries, while the prevalence of TB disease among household contacts in those countries was 3–5% (34,35). The results of the PHOENIX feasibility study in eight high TB burden countries showed that, of 1007 household contacts of 284 multidrug-resistant TB (MDR-TB) patients, 12% had TB disease and 72% were infected with TB (defined as either TST- or interferon-γ release assay (IGRA)-positivity) (36). Children < 5 years who are household contacts of people with TB are at significantly higher risk of acquiring TB infection and progressing rapidly to TB disease. A systematic review and meta-analysis were conducted to estimate the risk of children (defined as people aged < 19 years) for TB disease after close exposure and the effect on risk of TPT, bacille Calmette-Guérin (BCG) vaccination and time since TB exposure (37). It was found that the risk

of exposed infants with evidence of TB infection for TB disease within 2 years of being evaluated as a contact and did not receive TPT was 18%. In contrast to previous estimates that suggested a lower risk for children aged 2–5 years, this study found that children in this age group had an equally high risk of developing TB within 2 years (19%). The effectiveness of TPT in preventing development of TB disease was estimated to be 91% for children and adolescents with TB infection. Another important finding was that 61% of children and adolescents and 83% of all children aged < 5 years with TB infection who developed TB disease did so within weeks of the initial contact investigation.

Children < 2 years of age are also at greater risk for severe and disseminated forms of TB and at very high risk of morbidity and mortality. Therefore, TPT is strongly recommended once TB disease has been ruled out. Screening of household contacts for TB disease is a high priority for all TB control programmes because it has a high yield and is a cost-effective active case-finding (ACF) strategy (38).

Household contact investigation ensures timely treatment for TB disease and TPT and thereby reduces transmission and improves TB-related outcomes. It is also an opportunity to improve infection control in a household and can result in important financial benefits for the entire family. The occurrence of TB in a family has serious social and economic effects, including catastrophic costs due to loss of income or the cost of health care. By investigating, detecting and treating both TB disease and TB infection, transmission in a household can be stopped and the catastrophic costs and dire health outcomes due to TB prevented. This holistic “family health” approach offers more efficient TB care to all members. Providing TPT to all family members at the same time and while the index TB patient is still receiving treatment and care can increase understanding of the impact of TPT and increase the cost–effectiveness ratio of interventions such as home visits. Nutritional assessment and support for contacts further protect them from progression of disease (see also [section 7](#)).

2.2 Integrating systematic screening for TB disease

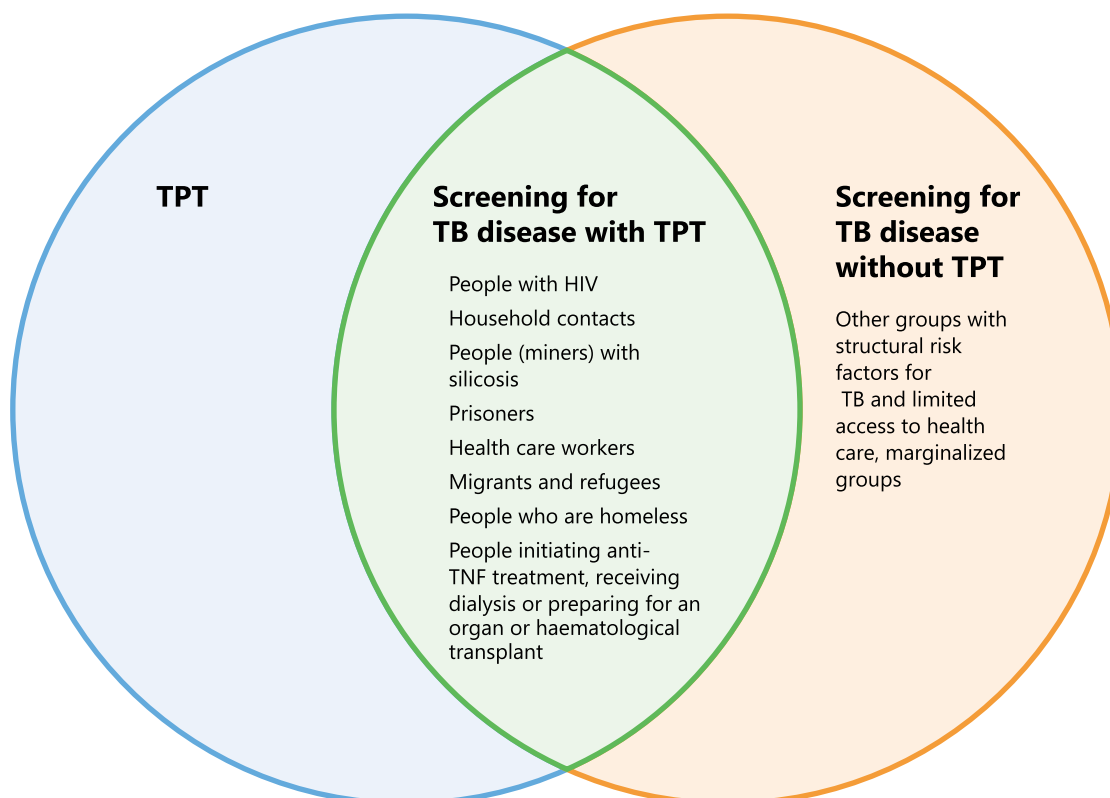
WHO recommends systematic screening for TB disease among at-risk populations that are also eligible for TPT ([Fig. 3](#)). These groups are people with HIV, household and close contacts of people with TB, miners exposed to silica dust and prisoners (strong recommendation for screening for TB disease). In addition, screening for TB disease is conditionally recommended for people with structural risk factors for TB and limited access to health care, such as urban poor, homeless people, refugees, migrants and other vulnerable or marginalized groups.

Integration of TPT services into systematic screening for TB disease in these populations allows NTPs to progress towards the UNHLM targets of reaching 90% of people with TB prevention and care, contributes to person-centred care and ensures efficient use of resources (13,17).

National programmes may integrate systematic evaluation for TPT eligibility in these populations, depending on individual risk in terms of recent exposure to a TB patient, immune status and other comorbidities, and provide access to TPT once TB disease has been ruled out. National programmes may adapt the algorithm for other risk groups (see [Fig. 6](#) in [section 4](#)) when integrating ACF and TPT for populations at risk.

The scope of activities during contact investigations can be extended beyond TB services, depending on the country. For example, when the index TB patient is HIV positive, household contacts should systematically also be offered HIV counselling and testing, and, if malnutrition is noted during contact investigation, all contacts should be screened and assessed for nutritional factors.

Fig. 3. Populations for which PMTPT and screening for TB disease are recommended



TB, tuberculosis; TNF, tumour necrosis factor; TPT, TB preventive treatment

2.3 National policy for identifying TPT target populations

A national policy for identifying TPT target populations should be established through the following steps.

1. **Establish a national technical working group** or extend the mandate of an existing technical working group or equivalent to advise the ministry of health and the national TB and HIV programmes. The technical working group may consist of national experts, stakeholders in national TB, HIV, maternal and child health and other relevant programmes, representatives of patient groups, civil society, front-line health providers, national research institutes, technical partners and WHO.
2. **Review national policies and guidelines.** The national technical working group may review current national policies and guidelines for PMTPT and lead updating and alignment with the latest global guidelines. The group may be mandated to lead identification of target populations and strategies for reaching those populations within PMTPT ([Annex 3](#)).
3. **Assess the situation.** The technical working group and/or national programme may review the following to guide decisions on identifying target populations for PMTPT:
 - the burden of TB disease (and TB infection) in various at-risk populations;
 - capacity of the health system (staff, skills and equipment) to assess the intensity and risk of TB exposure and exclude TB disease;

- the availability of financial resources and identification of gaps in nationwide scaling up of TPT services and opportunities to mobilize additional resources; and
 - opportunities to integrate PMTPT into systematic screening for TB disease.
4. **Other target populations** for PMTPT may be identified by a small-scale demonstration or phased implementation of PMTPT among target populations to identify operational issues and inform strategies to reach them with TPT services. Extensive research to review the efficacy of the TPT regimen is not required, as the WHO guidelines are based on in-depth reviews of evidence from the latest clinical trials. Moreover, any country-specific or population-specific study might result in delay in scaling-up TPT services, thereby denying the benefits of TPT to vulnerable populations.
 5. As a minimum aim, all countries should achieve **universal coverage of TPT** for people with HIV and household contacts of TB patients aged < 5 years.
 6. **Prioritize individuals who are likely to have acquired TB infection recently**, such as children, recent immigrants from countries with a high TB burden, recent contact with a TB patient or documented conversion of a TB infection test from negative to positive.

Particularly for populations in congregate settings, surveillance and treatment of TB disease and infection control measures must be implemented effectively (13,39). These are essential prerequisites for deciding to provide TPT services to such populations. Without good measures for control of airborne infection, the sustained benefits of TPT may be compromised by a high risk for reinfection. Therefore, once target populations for TPT are identified, ministries of health, donors and stakeholders should support capacity-building in programmes to strengthen infection control and ensure access to rapid TB diagnosis and treatment.

2.4 Reaching TPT target populations

2.4.1 Reaching people with HIV and other target populations

All HIV testing and treatment facilities, including community HIV care and support, should systematically intensify TB case finding, TPT and TB infection control. These require good collaboration between national TB and HIV programmes (40).

All people with HIV should be screened for TB symptoms at every opportunity or contact with a health worker. CXR screening increases sensitivity for detecting TB disease in people with HIV in regular care, and annual screening with CXR might be a good strategy for finding additional people with TB in this population (17). People with TB symptoms or TB-related abnormalities on CXR should be referred for diagnostic testing, and those without symptoms and a normal CXR should be evaluated for eligibility and started on TPT, as appropriate.

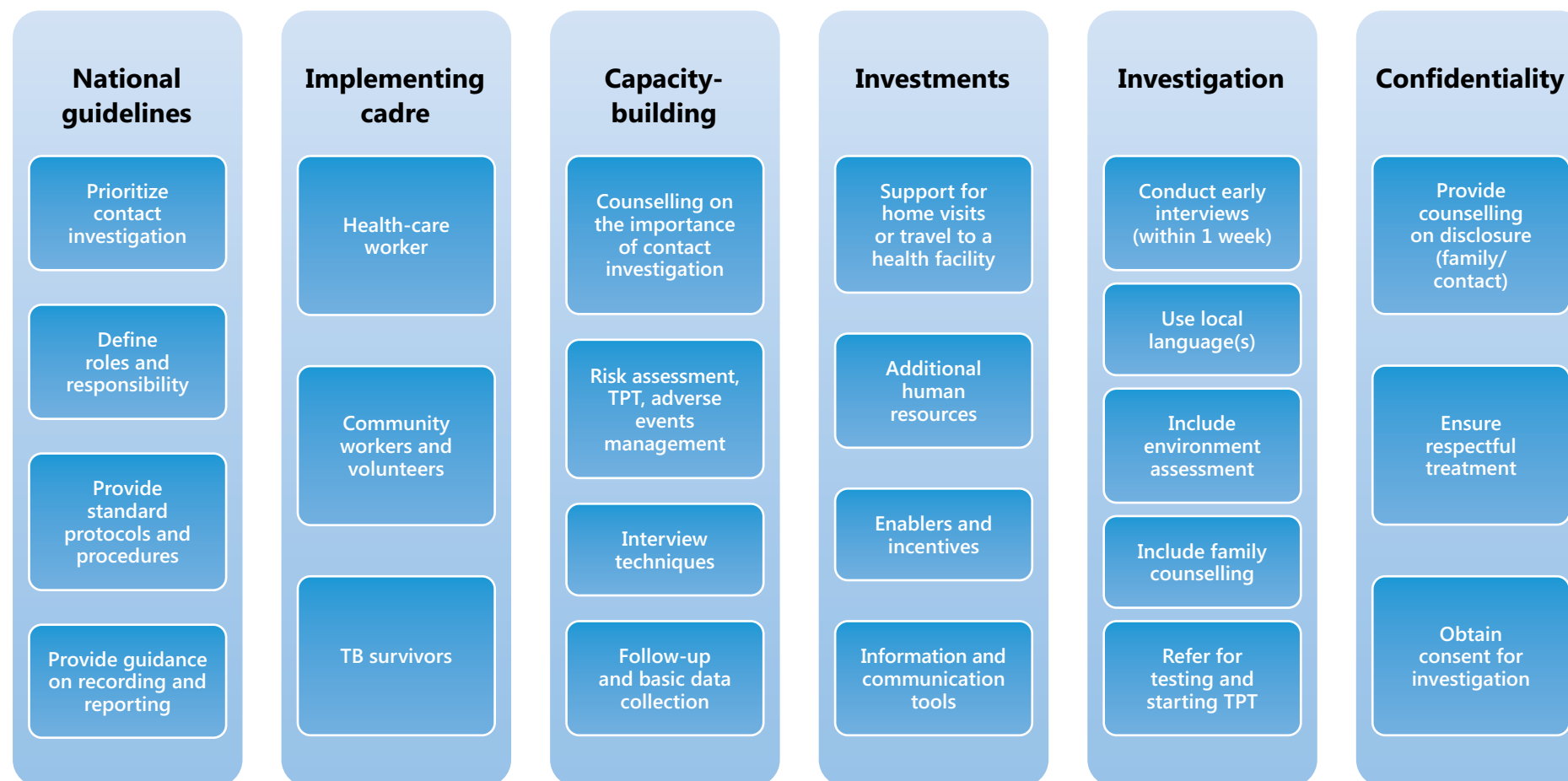
Adults and adolescents with newly diagnosed HIV should always be screened for TB. CRP is more specific than symptom screening alone and could be considered an additional screening test for this group (17). People with TB symptoms or CRP values > 5 mg/L should be referred for diagnostic testing, and those without symptoms or CRP values of ≤ 5 mg/L should be evaluated for eligibility and started on TPT, as appropriate.

National TB and HIV programmes should provide resources and monitor sites to ensure implementation and quality improvement measures when gaps are noted (such as lack of screening, cursory screening, lack of linkage to TPT).

For other target populations, the national programme should tailor TB screening and TPT services to the needs and capacities of the existing health infrastructure. The approach should optimize and synergize delivery of TPT services with other health and social welfare services. Target populations and screening approaches should be monitored regularly to ensure their efficiency and to improve services.

2.4.2 Strengthening investigation of household contacts

Contact investigation is an important first step for both ACF and TPT. It consists of systematic identification of people with TB disease and contacts of index TB patients who should receive TPT. After identification, clinical evaluation and/or testing and provision of access to appropriate TB treatment should be provided for people with confirmed TB or TPT for those without TB disease. It should be a standard component of all national TB control programmes. Moreover, contact investigation is good public health practice and is essential for tracking several infectious diseases (such as coronavirus disease 2019). Therefore, ministries of health should invest in strengthening health system capacity. If mechanisms for contact investigation are in place, national programmes should strengthen them to ensure that all contacts aged ≥ 5 years are also covered. If such a mechanism is lacking, the ministry of health should dedicate the necessary human and financial resources to establish effective mechanisms for contact investigation. An indicative list of items to be considered for determining appropriate unit costs for budgeting and planning to strengthen contact investigations is provided in [Annex 4](#). In addition to extra funding, NTPs should ensure effective contact investigation ([Fig. 4](#))

Fig. 4. Building blocks for strong contact investigation

TB, tuberculosis; TPT, TB preventive treatment

To ensure efficient contact investigation, the following elements should be included.

1. Provide national guidelines that:
 - define priority populations for contact investigation (household and beyond);
 - define the model of care, facility, community or a combination;
 - define the roles and responsibilities of programme personnel, health-care workers and community health workers in reaching contacts, screening for TB disease by symptoms and other tests such as CRP and CXR, and referral for clinical evaluation and diagnostic testing; include responsibilities in job descriptions;
 - provide standard guidance and approaches for reaching contacts, and conduct investigations to ensure uniform implementation;
 - define the data elements to be captured in the index patient's record and/or digital tools for contact investigations (see also [section 7](#));
 - in a community model, include tools or referral slips for recording data on TB screening and referral of identified contacts; and
 - define the level of service delivery points for systematic recording and reporting and frequency; and
 - provide locally tested messages to generate demand and to educate patients.
2. Use human resources and mechanisms in other disease programmes (such as the public health response model promoted by the US President's Emergency Plan for AIDS Relief for people with HIV) for contact investigation, and ensure sustainability and efficiency. TB and HIV screening could be integrated.
3. Train health workers and community workers in conducting a contact investigation, including the following (41):
 - The index person with TB should be interviewed as soon as possible after diagnosis, preferably within 7 days, to elicit details about household and other close contacts (see Box 1 for information on measuring timeliness) (42). Health providers should clearly and sensitively explain the urgency of initiating contact investigations to the index patient in view of the increased risk of progression to TB disease after recent exposure. A second interview may be required to elicit additional contacts and any missing information.
 - While the focus of the contact investigation should be household members, additional contacts should be considered as per the national guideline for evaluation, including contacts at the workplace, residential care facilities, residential schools, long-term care facilities, prisons, other correctional facilities and acute medical care facilities. This is especially important when exposure is likely to have been prolonged and the index person is likely to be highly infectious (e.g. with prolonged cough or extensive cavitory disease on CXR).
 - Ideally, interviews should be conducted by a person who speaks the same language as the index person and is familiar with his or her social and cultural context.
 - Education of the index person and household members on the benefits of taking TPT and the risks of not taking it should be central to contact investigation. The aim should be to enable an informed decision to receive a complete course of a TPT regimen.
 - Counselling of index people should also help them to appreciate the importance of identifying all close contacts. This will make it possible to reach more people at risk.
 - In the community model, approval should be sought from the index person for a home visit. In addition to counselling the index person, arrangements should be made to counsel contacts before starting TPT.
 - Preferably, health-care workers who conduct contact investigations should visit the home or workplace of the index person, conduct interviews and emphasize the importance of identifying and evaluating contacts, conduct screening for TB disease, collect accurate information about the intensity and duration of exposure, and ensure that all relevant contacts are referred for further evaluation and treatment decisions ([Boxes 2 and 3](#)) (43). Information to be documented during a contact investigation includes the name of the person who identified the contact, the

person who identified the index person with TB, the demographics of the contact, the results of TB screening tests and tests for TB infection (if done), the date on which eligibility for TPT was determined and the decision to prescribe TPT. Visits might have to be made outside normal working hours, as contacts may be at work or school during those hours.

- Home visits also provide an opportunity to identify any requirement for social or nutrition support or education on infection control measures, and the health provider may subsequently link the index person and contacts to relevant social and nutritional support programmes. During the home visit, the health provider should assess the residence and provide counselling and education to family members on symptoms of TB. A recent cluster-randomized, controlled trial in India showed that provision of nutritional supplementation to households of people with microbiologically confirmed pulmonary TB prevented further TB cases among contacts (44). (Nutritional interventions for TB prevention are to be evaluated by a WHO Guideline Development Group on undernutrition (45).) If required, prompt medical attention and referrals should be made, especially for child contacts and people with HIV, in whom TB can progress rapidly. HIV testing and counselling should also be offered, including to the biological children of any adults with HIV.
 - If the home or workplace cannot be visited, the index person may be interviewed at a health facility and contacts listed. The complete address and modality for future communication should be mutually agreed with the index person (such as phone numbers, email, contact of an intermediary or treatment provider). Responsible people or health-care workers should then systematically follow up the index person.
 - After contact investigation, health-care workers should refer relevant contacts to a health facility for symptom screening, possible screening with CXR, diagnostic testing for TB and TB infection when indicated, and evaluation for eligibility for TPT.
 - Information from the interviews should be recorded maintaining confidentiality.
4. Budget and cost implementation of contact investigation. (See [Annex 4](#) for further details.)
- Ensure that all enablers and incentives are costed, including travel costs.
 - Health workers who conduct home visits and/or families might require support for travel to a facility; the costs should not be borne by affected families.
 - Information and communication tools should also be costed.
5. Provide guidance on M&E (see also [section 8](#)):
- Use standard tools and a protocol for data collection for contact investigation, data entry and analysis.
 - Monitor the yield of contact investigations and the proportions of TB disease and TB infection detected.
6. Provide guidance on confidentiality and informed consent (see also [section 9](#)):
- Maintaining confidentiality during contact investigation may be difficult because of social connections between index people and their contacts. All people should be treated with respect and confidentiality maintained. National programme guidelines on data protection, confidentiality and consent should be adhered to.
 - When the index person is reluctant to provide information on household and social contacts, counselling should continue to gain the trust of the person with TB. The index person should not be coerced, nor should her/his TB treatment or services be made conditional on cooperation with contact investigation.

[Annex 6](#) provides an example of data collection form for use during household contact evaluation.

Box 1. Use of measures of timeliness for screening and implementing TPT for household contacts of index patients with pulmonary TB (42).

Household contacts of patients with pulmonary TB are at high risk of developing TB, which can be prevented or significantly reduced by timely initiation of TPT. Unfortunately, at global level, uptake of TPT by household contacts remains sub-optimal, and timely initiation of TPT is poor.

In 2021, a “7–1–7” metric was proposed to improve early detection and rapid control of health threats due to outbreaks and pandemics of suspected infectious disease. The metric is defined as follows: detection of an outbreak within 7 days of emergence; notification of the outbreak to public health authorities within 1 day of detection; and completion of early response within 7 days of notification. This metric was adapted for screening and managing household contacts as follows: First, “7” – line-listing of household contacts within 7 days of initiation of the index pulmonary TB patient on TB treatment; next, “1” – line-listed household contacts complete symptom screening within the next 1 day; third, “7” – eligible household contacts start TB treatment or TPT or a decision is taken to receive no drugs within the next 7 days.

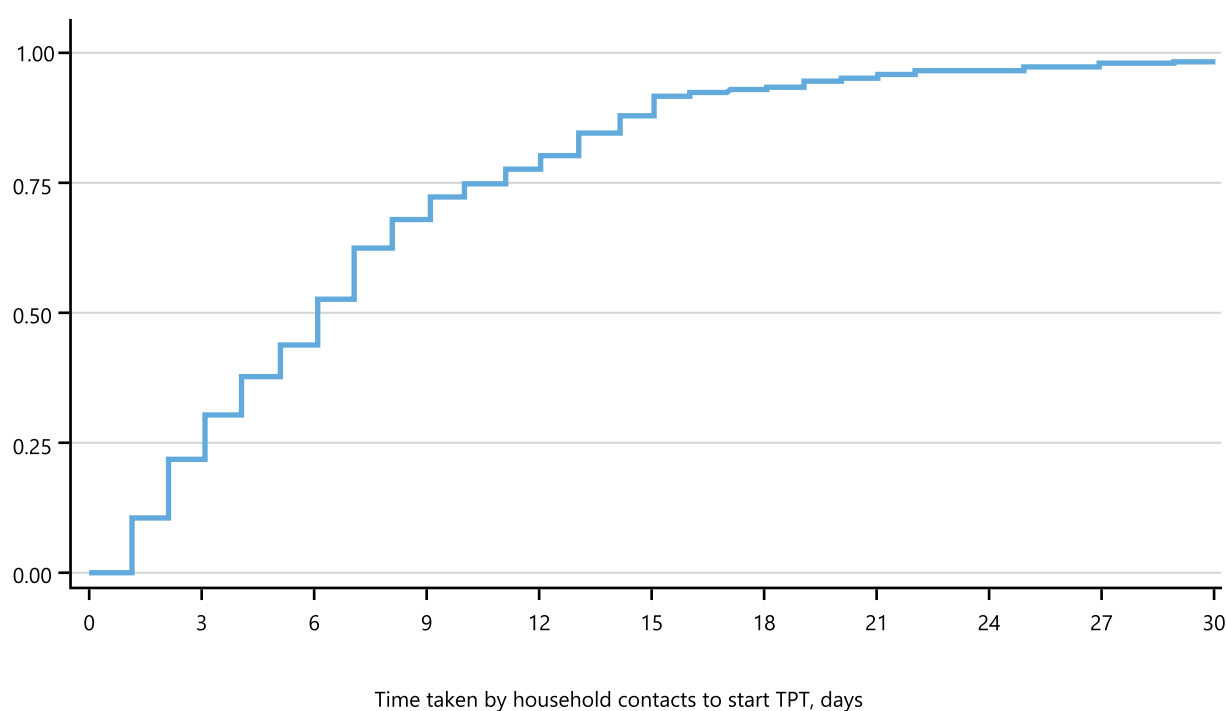
The feasibility and usefulness of “7–1–7” was assessed in 37 selected health facilities in the private sector and in the NTP in India; in the private and public sector in Pakistan; and in the NTP in Kenya. When possible, the findings were compared with those of a control group assessed 3 months before the “7–1–7” metric was implemented.

Altogether, 1816 index patients started TB treatment, and 5166 household contacts were line-listed. Achievement of the first “7” was 91% (the household contacts of 1661/1816 index patients were line-listed within 7 days). Achievement of the “1” was 79% (in 4074/5166 household contacts, symptom screening outcomes were available within 1 day). Achievement of the second “7” was 50% (in 1944/3888 eligible household contacts, a decision for TB treatment, TPT or no drugs was taken within the next 7 days). The main reasons for not achieving the second “7” were household contacts not presenting to health facilities due to costs, fear and stigmatization of TB, health-care worker hesitancy to provide TPT and drug shortages.

When past data were available, 49% of household contacts were initiated on TPT at any time after screening during the “7–1–7” period compared with 28% of household contacts 3 months before the “7–1–7” period was started. Altogether, 1635 household contacts started TPT within the times shown in [Fig. 5](#). The median time to TPT initiation was 6 days (interquartile range, 3–10 days); 98% of household contacts cumulatively initiated TPT within 30 days.

At all sites, field staff found the timeliness metrics feasible and useful for improving management of household contacts. The clear steps and explicit timelines gave structure to the various steps in household contact management. NTPs could consider including timeliness metrics in screening and managing household contacts to ensure timely TPT uptake (see also [section 8](#)).

Fig. 5. Time to initiation of TPT in household contacts



Time is measured from the start of TB treatment of index patients with pulmonary TB in selected sites in India, Kenya and Pakistan. Overall, only 25 of 1635 household contacts were initiated on TPT after 30 days.

Source: Harries et al. (42)

Box 2. 10 steps in conducting a contact investigation (46)

1. Review information on the index person.
2. Determine the duration and degree of infectiousness of the index person with TB.
3. Counsel the index person, and elicit household and close contacts.
4. Develop a plan for contact investigation in consultation with the index person and the head of the household.
5. Consider other contacts for investigation (such as in the workplace).
6. Conduct home visits, or invite contacts to a health centre for evaluation.
7. Conduct a clinical assessment, and refer for testing as appropriate.
8. Provide treatment for TB disease or TPT according to eligibility.
9. Review the completeness of the contact investigation.
10. Ensure systematic recording and reporting,

The steps may not always be taken in sequence.

Box 3 provides an example of contact investigation by nurse-led outreach teams in Mozambique.

Box 3. Nurse-led outreach for contact investigation in Mozambique (47)

In Mozambique, the US Agency for International Development (USAID) and partners supported a demonstration project in which five nurse-led outreach teams were recruited, trained and deployed to five mostly rural districts in Nampula Province. Between July 2022 and September 2022, the teams of two nurses each conducted comprehensive investigations of community TB contacts, locating and screening household and other close contacts exposed to TB patients. Starting in November 2022, all eligible contacts aged ≤ 15 years were offered and started on TPT. Between November 2022 and March 2023, 584 people with TB (572 drug-susceptible and 12 drug-resistant TB) reported 3224 (3149 drug-susceptible TB and 75 drug-resistant TB) household or other close contacts, for an average of 5.5 per index case. Overall, 81/3224 (2.5%) of contacts were diagnosed with TB, 70% of whom were < 15 years old; 1928/2022 (95%) were eligible for TPT. Among eligible contacts aged < 15 years, 1911/1928 (99%) were started on TPT (1870 for drug-susceptible TB and 41 for drug-resistant TB). This project demonstrated that nurse-led TB contact investigation teams can be recruited, trained and deployed rapidly and are highly effective in identifying close contacts, finding cases of TB disease and starting TPT, with a high rate of acceptance among eligible people.

People in close contact with TB patients are at high risk of developing TB. Governments and donors should commit resources to strengthen contact investigation to reach individuals who need TPT.

It's time to invest in health systems for effective contact investigation.



3. Screening for TB and ruling out TB disease before TB preventive treatment

Key points

- The process for ruling out TB disease before starting TPT has much in common with screening for TB disease. It involves largely the same risk groups, the same tests and adherence to the same monitoring principles.
- CXR can be important in ruling out TB before TPT and increase the confidence of the provider and the person radiographed that they do not have TB disease. Governments and donors should invest in increasing access to CXR.
- Decentralization and provision of family-centred, integrated care ensure consistent, systematic removal of gaps and bottlenecks along the pathway of care and can facilitate rapid expansion of TPT and early TB diagnosis and treatment.

The second step in the cascade of care for PMTPT is to rule out TB disease before offering TPT. The ministry of health should choose screening and diagnostic approaches appropriate for the target population.

Provision of TPT to someone with TB disease can delay resolution of disease and lead to emergence of drug resistance. Thus, exclusion of TB disease before initiating TPT is a critical step in the preventive care pathway. This section includes WHO recommendations and key policy and implementation considerations in development of national algorithms to rule out TB disease, keeping in mind the barriers that additional steps could create to successful implementation of TPT. The same tests are often used to screen for TB disease, the risk groups are often similar, and same monitoring principles are used. The activities at this step include determining HIV status, eliciting a history of household or other close contacts, determining the presence of other risk factors, eliciting suggestive signs and symptoms according to the person's age, abnormality on CXR and the results of other screening tests. The introduction of systematic screening for TB disease in target populations requires assessment of health system capacity and the availability of human and financial resources. The programme must mobilize funds from domestic and external sources to address these needs adequately.

3.1 Screening for TB disease using signs and symptoms

Using a standard set of signs and symptoms to screen for TB disease has multiple advantages. First, in many settings, this is highly sensitive and has a high negative predictive value, such that it can reliably rule out TB if none of the clinical manifestations are present. Secondly, it is a straightforward intervention that can be conducted at any clinical encounter and can be repeated as often as necessary without special equipment or associated cost. Additional tests such as CXR can be combined with symptom screening to improve its accuracy.

Evidence reviewed by WHO during the past decade, before updates to the guidelines, showed the following.

- For adults and adolescents with HIV, a symptom screening rule of a combination of current cough, fever, weight loss or night sweats has a negative predictive value of $\geq 99\%$ when conducted in populations with a TB prevalence of 0.5–2% (73). It is therefore suggested that, for people with HIV aged ≥ 10 years, the WHO four-symptom screen (any one of cough, fever, night sweats or weight loss) be applied.
- For infants and children with HIV, a symptom screen (any one of current cough, fever, poor weight gain or close contact with someone with TB) had a pooled sensitivity of 61% (95% CI 58% ; 64%) and a pooled specificity of 94% (95% CI 86% ; 98%) (17). In children < 10 years, a broader set of clinical manifestations may be used to exclude TB disease, including cough, fever, weight loss or lack of weight gain and reduced playfulness.
- For children and adolescents < 15 years who are close contacts of someone with TB, symptom screening (any one of cough, fever or poor weight gain) has a pooled sensitivity of 89% (95% CI 52% ; 98%) and a pooled specificity of 69% (95% CI 51% ; 83%) (17).
- Among individuals aged ≥ 15 years with negative or unknown HIV status, screening for cough has low sensitivity (51%) but higher specificity (88%), while screening for any TB symptom improves sensitivity (71%) but reduces specificity (64%). In this group, CXR has high sensitivity (94%) and specificity (89%) for any abnormality (13). A parallel screening algorithm consisting of any symptom of TB and any abnormal CXR findings is likely to be highly sensitive and may be the best tool for excluding pulmonary TB disease before initiating TPT among HIV-negative household contacts aged ≥ 5 years and other risk groups. Symptom screening without the addition of CXR should nevertheless be acceptable for individuals and programme managers.

3.2 Screening for TB with CXR and computer aided detection (CAD) software

A key policy decision with financial implications is whether to consider systematic use of CXR with TB symptom screening to rule out TB disease. CXR is a rapid imaging technique for identifying lung abnormalities. It is a good screening tool for pulmonary TB because of its high estimated accuracy for detecting TB disease, especially before the onset of symptoms. From the perspective of the person being screened, CXR is valuable because it can also detect medical conditions other than TB, such as other pulmonary and thoracic conditions (17).

In contacts aged ≥ 5 years, screening for TB with CXR is more sensitive than screening for symptoms (48). A combined screen comprising any abnormalities on CXR with any TB symptom had a negative predictive value of 1 (48) and was thus the most accurate means for excluding TB disease before TPT. Although CXR is the preferred screening tool from the viewpoint of test accuracy, it can be expensive and logistically challenging to use, especially when screening is done outside health services. It is important to keep in mind that people may have to travel from their usual facility for a CXR and pay for it out of pocket (17). The availability of mobile X-ray technology offers the opportunity for community CXR screening.

WHO recommends that CXR be offered to people with HIV. A combined strategy of the WHO-recommended four symptom screen (cough, fever, weight loss or night sweats) and CXR is significantly more sensitive than symptom screening alone, particularly for outpatients enrolled in ART care, although with less specificity (33% compared with 70% for symptoms alone) and sensitivity (85% compared with 53% for symptoms alone (17). If there are no abnormal radiographic findings, TPT should be considered; however, CXR should not be considered a mandatory requirement, and lack of CXR should not be a barrier to starting TPT for people with HIV.

Use of CXR with TB symptom screening is likely to increase the confidence of health providers, given the very high sensitivity of the combination. This could reduce the concern of providers about development of drug-resistant TB resulting from inadvertent treatment of TB disease with a TPT regimen. This consideration is particularly important for HIV-negative household contacts who are adolescents and adults, other close contacts and clinically at-risk populations. Similarly, use of CXR may increase the confidence of care providers of people with HIV who are receiving ART.

In 2021, WHO first recommended use of CAD software in place of human readers for interpreting digital CXR for screening and triage for TB disease (17). This recommendation is currently limited to individuals aged ≥ 15 years in whom TB screening is recommended, while more evidence is being generated in the age group <15 years. Use of CAD requires thorough consideration of the infrastructure requirements, including digital radiography equipment, reliable electricity, computer availability, Internet access, fees for use and the cost of the license for CAD products. The resources required and cost-effectiveness will depend on the setting, including the current availability and salaries of human readers (49).

When any abnormal CXR findings are seen (not just those suggestive of TB), detailed investigation for TB disease, including confirmatory testing with a molecular WHO-recommended rapid diagnostic test (mWRD), and other diseases should be undertaken in accordance with national guidelines and sound clinical practice.

The increased availability of digital radiography, use of CAD to interpret films and engagement by private health facilities to purchase radiographic services is expected to increase access to radiography in TB screening and diagnostic algorithms.

3.3 Screening for TB disease with other tests

3.3.1 C-reactive protein

CRP may be used to screen for TB in people with HIV (17). CRP is an indicator of systemic inflammation that can be measured with a blood test. It is a point-of-care test that is performed on capillary blood collected from a finger-prick, making it simple, affordable and feasible in primary care. WHO recommends use of the cut-off value of > 5 mg/L, the lowest threshold that indicates abnormality in many clinical settings and because it is the most sensitive (49). This test may have a specific role in screening for TB among outpatients living with HIV who are not on ART, as it has clinically significantly greater sensitivity and specificity than screening for symptoms (CRP, sensitivity 89% and specificity 54%; symptom screen, sensitivity 84% and specificity 37%) in this group (49). CRP can also be used in combination with symptom screening.

3.3.2 Molecular WHO-recommended rapid diagnostics

mWRDs are not only diagnostic tests for TB but may also be used as screening tests in both people with and without HIV (17). It should be noted that the accuracy of a test for screening is different from that for diagnosis. The sensitivity of mWRDs for screening high-risk populations (non-HIV-infected) is estimated to be 69% and the specificity 99% (49). People who screen positive for TB with an mWRD should always be followed up with a thorough clinical evaluation, including symptom screening and further tests, such as CXR or repeat mWRDs on additional sputum samples, to establish a definitive diagnosis of TB. Use of mWRD for screening will require significant resources, including more capacity and expansion of diagnostic and sample transport networks. There has been limited experience in widescale use of mWRDs for screening under programmatic conditions. Priority should be given to ensuring universal access to mWRDs as diagnostic tests for TB and drug-resistant TB before extending their use to screening (49).

3.4 Screening algorithms

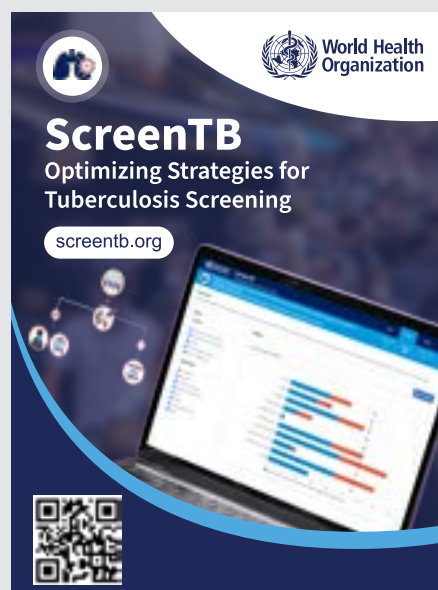
The screening tests described above can be used on their own or in combination with other screening tests. The WHO Operational Handbook on Tuberculosis. Module 2: Screening – systematic screening for TB disease (49) contains a number of algorithms in which screening tests are combined in different ways. A positive symptom screen or screening test (CXR, CRP or mWRD) should always be followed by a confirmatory diagnostic test. In most algorithms, the diagnostic confirmatory test is an mWRD. If an mWRD is used for screening, a thorough clinical evaluation should be conducted to confirm TB (see also [section 3.3.2](#)). WHO has developed the ScreenTB tool to help users choose the most suitable screening algorithms for different populations (50) ([Box 4](#)).

Box 4. The ScreenTB tool for prioritizing and planning systematic TB screening in selected risk groups

The ScreenTB tool (screentb.org) is designed to aid in the design and prioritization of systematic TB screening programmes for populations and groups of people at higher risk for TB. The tool incorporates the best available data to generate estimates of the size, yield and cost of screening programmes specific to the group targeted for screening and the testing algorithm used. The tool also provides estimates of the number of people screened who, according to the chosen algorithm, should be evaluated and considered for TPT.

The tool is meant to be used for preliminary prioritization rather than for detailed planning. Users should repeat the exercise several times, varying some or all of the inputs and the risk groups, in order to understand how variation in the targeted populations and the screening parameters affect the estimated size, yield and cost.

The average costs per test in this tool are derived with the Integrated Health Tool for TB (<https://tb.integratedhealthtool.org/>). The unit costs comprise the average costs of drugs and supplies per test plus the estimated costs of using general health systems. The cost per person tested of using general health systems was estimated from WHO modelled unit costs of visits in US\$ 2022, multiplied by assumed standard use quantities.



3.5 Considerations for ruling out TB disease

Health ministries should coordinate implementation of the activities outlined below to screen for and exclude TB disease before providing TPT.

- Make screening of at-risk populations for TB an integral part of the overall package of health care for these populations (such as an HIV care package for people with HIV). In principle, the overall responsibility for planning, resource allocation, service delivery (TB screening and activities to rule out TB disease) and M&E should be vested in the national authority responsible for services to the respective populations. The NTP, in collaboration with primary care and maternal and child health services, should assume responsibility for TB screening among contacts of index people with TB; the national HIV programme should organize services for people with HIV in collaboration with the national TB control programme; the clinical services in the ministry of health should support TB screening and linkages to treatment and care for other clinical at-risk populations; and, likewise, state agencies should be responsible for prisons, occupational health and migrant care.
- Solicit advice from a national coordinating body, technical expert group or similar body for each national programme in developing a national plan for scaling up programmatic implementation of TB screening and services to rule out TB disease in various target populations and locations. The coordinating body or group may also advise on standard operating procedures (SOPs) and a plan for building the capacity of various types of providers and coordinate procurement and supplies of commodities for interventions in various programmes.
- Develop a standard implementation guide, including roles and responsibilities, operating procedures, implementation tools, job aids and recording and reporting tools (integrated for HIV, TB and maternal and child health services), for ruling out TB disease in at-risk populations.
- Develop communication materials for display and use at all sites at which intensified TB screening is provided.
- Identify a cadre of health-care workers at various levels of the health-care system to perform clinical screening and referral for further testing for TB disease, infection and evaluation, as per national guidelines.
- Conduct training and on-the-job capacity-building for health-care workers, community health workers and other service providers in systematic screening for TB.
- Conduct regular supportive supervision at national, provincial and district levels of TB screening activities, especially those conducted by community health workers, to ensure good-quality screening and adherence to national algorithms.
- Develop job-aids highlighting the steps in ruling out TB disease.
- Organize access to CXR in public or private health facilities or mobile vans, as required by national policy, memoranda of understanding with private hospitals and radiologists and vouchers to ensure free access to X-ray services in the private sector.
- Develop standard tools for data capture or update existing tools (such as patient files and electronic records) with relevant data elements on ACF and activities to rule out TB disease. The national HMIS should summarize data at each step in the cascade and report indicators of programme performance to national level (see also [section 8](#)).

[Table A2.1](#) in [Annex 2](#) provides an overview of considerations for ruling out TB disease in various target populations before starting TPT. While effective TB symptom screening is the backbone of TPT services, CXR and other tests may be used to exclude TB disease

3.5.1 Models of care for TB in children

WHO guidelines on the management of TB in children and adolescents contain recommendation on models of care to improve detection of people with TB and provision of TPT that are applicable to TB screening and TPT (17):

- In high TB burden settings, decentralized models of care may be used to deliver TB services to children and adolescents with signs and symptoms of TB and/or those exposed to TB (conditional recommendation, very low certainty of evidence).
- Family-centred, integrated models of care to deliver TB services may be used in children and adolescents with signs and symptoms of TB and/or those exposed to TB, in addition to standard models of care (conditional recommendation, very low certainty of evidence).

Decentralization and provision of family-centred, integrated care allow for consistent, systematic action to fill gaps and remove bottlenecks along the pathway of care and can reduce transmission of TB, prevent TB infection and result in earlier TB diagnoses, with better outcomes. This continuum of care requires collaboration among service areas, disciplines and sectors, community engagement and decentralization and integration of service delivery at primary health-care level (51,52). The road map for ending TB among children and adolescents, third edition (52), proposes action to strengthen implementation of integrated people, family and community-centred strategies as part of primary health care. These activities are equally valid for adult populations: (i) integrated, family-centred, community-based models of care for contact investigation and TPT; (ii) differentiated HIV service delivery (DSD) models designed and used to improve access to and retention in TB care for children and adolescents; (iii) outreach programmes for special populations, such as children and adolescents who are abused or neglected; (iv) investing in education and sensitization of communities, with a focus on young generations, to create awareness, generate knowledge and understanding of TB and to destigmatize the disease; and (v) promoting decentralized models of TB care with diagnostic capacity available and accessible at primary health care level as part of comprehensive, integrated primary health care (52).

Increased investment in diagnostic services will target TPT better to people who need it most by confirming TB infection.

It's time to invest in systems for testing for TB infection.



4. Testing for TB infection

Key points

- A positive test for TB infection increases the probability that individuals targeted for TPT will benefit from it.
- The decision on whether to test for TB infection before TPT is based on the expected prevalence of TB infection in the at-risk population, the risk of progression to TB disease and the risk of harm due to unnecessary TPT.
- The currently recommended tests for TB infection – TST, *Mycobacterium tuberculosis* antigen-based skin test (TBST) and IGRA – are all indirect and measure immune sensitization (type IV or delayed-type hypersensitivity) to mycobacterial protein antigens that occurs after infection by *M. tuberculosis*.

The third step in the cascade of care for PMTPT is testing for TB infection. Confirmation of TB infection increases the probability that individuals targeted for TPT will benefit from it. There is, however, no gold standard test for diagnosing TB infection. The tests currently available are indirect and require the person to mount an immune response. A positive test result is not by itself a reliable indicator that the infection will progress to TB disease, while a negative test result does not rule out TB infection, given the possibility of false-negative test results among at-risk groups such as young children and people who were recently infected. National health authorities should decide how to use tests for TB infection within PMTPT in view of the uncertainty of test results, the balance of benefit to harm of testing before starting TPT and the logistics of procurement and testing in the context of the programme.

4.1 Tests for TB infection

The currently recommended tests for TB infection are TST, TBSTs and IGRA. These tests detect immune sensitization (type IV or delayed-type hypersensitivity) to mycobacterial protein antigens that occur after infection by *M. tuberculosis*. A test for TB infection cannot on its own differentiate between TB infection and TB disease. A diagnosis of TB infection must be complemented by a negative test for TB disease, through clinical evaluation, CXR and examination of sputum or another suitable specimen if the person is symptomatic, as per national policy.

A brief description is given below of the different tests for TB infection. Details of WHO-recommended assays are available in the WHO operational handbook on tuberculosis. Module 3: diagnosis; tests for tuberculosis infection (53).

4.1.1 Skin tests

The TST measures delayed hypersensitivity reaction to exposure to purified protein derivative (PPD) of the mycobacterium. TBST is an in-vivo skin test for detection of TB infection with *M. tuberculosis*-specific antigens, early secretory antigenic target 6 kDa protein and culture filtrate protein 10. Intradermal injection of PPD causes a delayed hypersensitivity reaction if a person has TB infection. The T cells in such individuals are sensitized by prior *M. tuberculosis* infection, and the injected agent recruits these immune cells to the skin test site, causing a local inflammatory reaction. Nurses and

other health-care workers with the right training and skills can administer and read a TST or TBST. They should also be able to explain to the people tested what the result of the test implies in their case. There is no need for complex laboratory equipment or procedures or trained technicians to implement TST/TBST.

4.1.2 IGRAs

IGRAs are in-vitro blood tests for measuring interferon- γ released by circulating lymphocytes when mixed with *M. tuberculosis* antigens in an enzyme-linked immunosorbent assay (ELISA) or from the number of T-lymphocytes that produce interferon- γ (ELISPOT). IGRAs detect sensitization to *M. tuberculosis* by measuring interferon- γ release in response to antigens representing *M. tuberculosis*. IGRAs assess responses to synthetic overlapping peptides that represent specific *M. tuberculosis* proteins, such as early secretory antigenic target-6 and culture filtrate protein 10. These proteins are present in all *M. tuberculosis* complex species and stimulate measurable release of interferon- γ in most infected people but are absent from BCG vaccine strains and from most nontuberculous mycobacteria. For accurate measurement of an interferon- γ response, a fresh blood specimen that contains viable white blood cells is required.

4.1.3 Selecting a test for TB infection for programme use

TST, TBST or IGRA can be used to test for TB infection. There is no strong evidence that one test should be preferred over the others in terms of predicting progression from TB infection to TB disease. None of the tests should be used in people with low risks of TB infection and disease.

The choice of test for programmatic use depends on cost, availability, human resources and infrastructure to provide testing services. [Table 2](#) summarizes the characteristic features and the advantages and disadvantages of currently available tests for TB infection.

Table 2. Characteristic features of TST, TBST and IGRA

Characteristic	TST	TBST	IGRA
Test requirements	<ul style="list-style-type: none"> • A valid TST requires proper intradermal administration of 0.1 mL tuberculin-PPD into the volar surface of the forearm. • PPD requires a cold chain. • Trained staff are required to administer and read skin induration. • Must be read within 48–72 h 	<ul style="list-style-type: none"> • A valid TBST requires proper intradermal administration of recombinant antigen into the volar surface of the forearm. • Requires a cold chain. • Trained staff are required to administer and read skin induration. • Must be read within 48–72 h. 	<ul style="list-style-type: none"> • IGRAs are in-vitro blood tests that detect interferon-γ in blood with an ELISA. • Requires fresh blood specimens to mix with antigens and controls, to be processed within 8–30 h after collection while white blood cells are still viable • Requires efficient sample transport • Different blood collection tubes are necessary for different altitudes.

Characteristic	TST	TBST	IGRA
Potential inaccuracy	<ul style="list-style-type: none"> False-positive TSTs can result from contact with nontuberculous mycobacteria or vaccination with BCG. Potential inaccuracies and bias in reading skin induration False negatives in people with immunodeficiency conditions 	<ul style="list-style-type: none"> Potential inaccuracy and bias in reading skin induration 	<ul style="list-style-type: none"> Delay in transport of blood specimen Errors in processing blood specimen Wrong interpretation of assay False-negative results likely in people with immunodeficiency conditions, faded immune memory, technical-operational variation and in children < 2 years
Advantages	<ul style="list-style-type: none"> Can be performed in the field Significantly fewer resources required than for IGRA No laboratory set-up required More familiar to practitioners in resource-constrained settings 	<ul style="list-style-type: none"> Can be performed in the field No laboratory set-up required No false-positive results due to BCG 	<ul style="list-style-type: none"> Single visit required to conduct test; however, test result may be communicated on a second visit, when, as for the TST, clinical management decisions are made Results possible within 24 h No booster effect No false-positive results due to BCG For serial and periodic screening of people who might have occupational exposure to TB (such as surveillance programmes for health-care workers), IGRAs offer technical, logistic and possible economic advantages over TSTs. Two-step testing is not required for IGRAs, because IGRA testing does not boost subsequent test results.

Characteristic	TST	TBST	IGRA
Challenges	<ul style="list-style-type: none"> • Training in intradermal injection, reading and interpretation required • Second visit by individual or health-care worker required for test reading • Recurrent global shortages and stock-outs of quality-assured PPD • Requires a cold chain • Repeat test (two-step testing) for individuals whose immunity may have waned 	<ul style="list-style-type: none"> • Training in intradermal injection, reading and interpretation • Second visit by individual or health-care worker required for test reading • Requires a cold chain 	<ul style="list-style-type: none"> • Higher test cost • Phlebotomy necessary • Sophisticated laboratory equipment and highly skilled laboratory personnel necessary to perform and interpret test results • Potential delays in sample transport over long distances to laboratories that offer IGRA testing • Processing and results require at least 1 day (often longer), so that the person might have to return to collect results. • If the laboratory standard operating procedure requires batching of tests to reduce costs, delays in reporting results may be > 1 week. • Blood samples must be processed within 8–30 h of collection while white blood cells are still viable. • Errors in collection or transport of blood specimens or in conducting the test can decrease accuracy. • Limited data on use of IGRAs to predict who will progress to TB disease
Preferred test	<ul style="list-style-type: none"> • Children < 2 years • Settings with poor laboratory infrastructure 	<ul style="list-style-type: none"> • Settings with poor laboratory infrastructure 	<ul style="list-style-type: none"> • People who have received BCG (either as a vaccine or for cancer therapy); less applicable for adults who received BCG as infants due to waning of effect • Groups that are unlikely or unable to return for TST reading, such as homeless people and people who use drugs or for reasons such as long distance, job security and other pressing commitments

BCG, bacille Calmette-Guérin; ELISA, enzyme-linked immunosorbent assay; IGRA, interferon- γ release assay; mWRD, molecular WHO-recommended rapid diagnostic test; PPD, purified protein derivative; TB, tuberculosis; TBST, *Mycobacterium tuberculosis* antigen-based skin test; TPT, TB preventive treatment; TST, tuberculin skin test

4.2 Role of testing for TB infection

A decision on whether to test for TB infection before TPT is based on the expected prevalence of TB infection in the at-risk population, the risk of progression to TB disease and the risk of harm due to unnecessary TPT (Fig. 6). For individuals or populations at higher risk of harm due to TPT or a (relatively) lower risk of progression to TB disease, confirmation of TB infection may be preferred. For individuals or populations that are more likely to be infected and are at risk for progression to TB disease and adverse outcomes if TB disease develops, TPT is justified without testing.

People with HIV who are on ART benefit from TPT regardless of whether they test positive or negative for TB infection. WHO therefore recommends that testing for TB infection not be a requirement for initiating TPT among people with HIV and child contacts < 5 years, particularly in countries with a high TB incidence, given that the benefits of treatment (even without testing) clearly outweigh the risks (13). Furthermore, these tests are insensitive and may provide a false-negative result, particularly among immunocompromised hosts who are at a greater risk for severe forms of disease and death if they develop TB. The immune response to TB antigens varies, and tests for TB infection could be positive even after successful completion of TPT. Therefore, results of tests for TB infection should not be used to assess the efficacy of TPT. Overall, testing for TB infection should not be considered mandatory before starting TPT (especially when access to testing remains limited), given that the benefits of treatment (without testing) still outweigh the risks.

When national programmes recommend testing for TB infection before providing TPT, tests should be used only for at-risk groups (such as clinical risk groups, contacts of TB patients, prisoners and health-care workers). Targeted testing allows identification, evaluation and treatment of people who are at high risk for TB infection or for developing TB disease when infected with *M. tuberculosis*. A positive test for TB infection among HIV-negative contacts or individuals in other clinical risk groups (patients initiating anti-TNF treatment, receiving dialysis, preparing for organ or haematological transplantation) may reassure clinicians and health-care workers that TB infection is likely, so that they can start TPT. A positive test of TB infection may motivate the person at risk to start and complete TPT.

4.3 Considerations for testing services for TB infection

The choice of a test for TB infection in a country might depend on the availability and affordability of the tests, the structure of the health system, the feasibility of implementation and infrastructure requirements. Considerations for testing for TB infection in general and for specific tests are described below. Details of how the tests work, test procedures and result interpretation can be found in the WHO operational handbook on tuberculosis. Module 3: diagnosis – tests for tuberculosis infection (53).

4.3.1 General requirements

- Define the target population for testing, and specify the choice of test in the national guidelines.
- Build the capacity of the health-care workers responsible for testing for TB infection, such as in administration of TST or TBST reading, collection and processing of blood specimens for IGRAs, specimen collection and transport.
- Develop SOPs for administration of TST or TBST, collection and processing of blood specimens for IGRA and interpretation of test results.
- Develop SOPs for appropriate follow-up after testing, including access to clinical evaluation, CXR and other TB investigations to decide on the eligibility of individuals for TPT.
- Develop job-aids to assist providers in informing the test recipient and responding to frequently asked questions on the utility and procedure of TST, TBST or IGRA.
- Develop tools for systematic recording and reporting of test results and linkage to care and treatment, such as the *Prevent TB* mobile application (54).
- Strengthen mechanisms for supportive supervision and monitoring of accurate implementation.

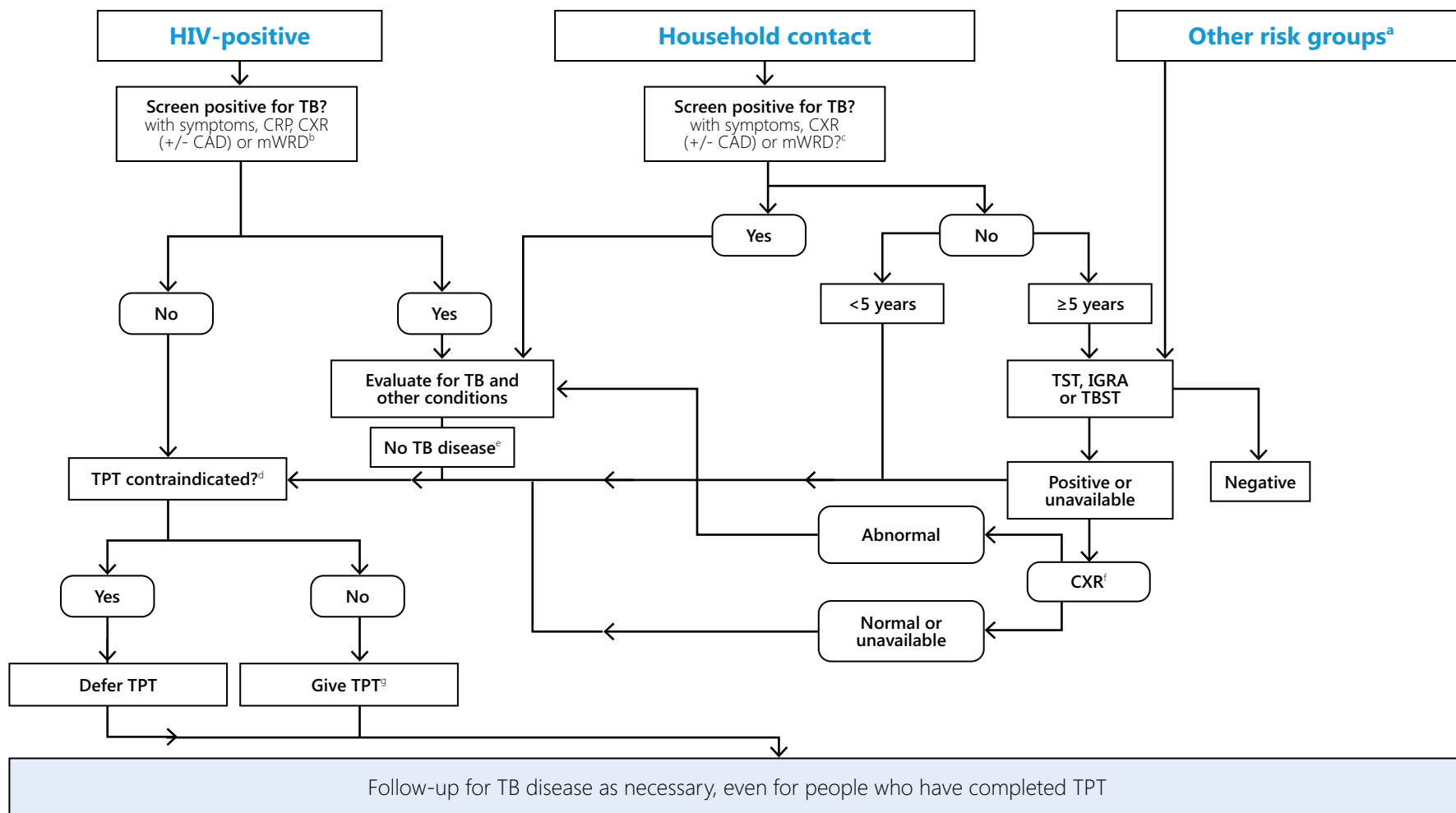
4.3.2 Programmatic implementation of TST and TBST

- Ensure the availability and supply of tuberculin or *M. tuberculosis*-specific antigens in the cold chain and of syringes, needles and other consumables.
- Train personnel in intradermal injection and in reading and interpreting tests, and provide ongoing capacity-building and supportive supervision to maintain skills. Ensure that staff can explain to the people they test what the result of the test implies in their case.
- Ensure standardized application of test procedures, mentoring, supervision and periodic standardized reliability testing for quality assurance.
- Develop and provide job-aids for health-care workers showing the correct techniques for TST and TBST administration and measurement of induration.
- Establish mechanisms to contact people who have been tested to return for the test reading within 48–72 h of administration of tuberculin or *M. tuberculosis*-specific antigens, or, alternatively, ensure test reading at the person's residence.
- Provide funding for people to travel for testing or for health-care workers to administer and read test results.
- Develop and supply TST or TBST request forms, and update the HMIS to ensure documentation and reporting of TST and TBST results.
- As there is less experience in use of the new TBST, its safety is less well understood than that of TST. Therefore, surveillance of adverse events should be organized in countries that are initiating use of the new TBST.

4.3.3 Programmatic implementation of IGRA

- Develop the capacity of the laboratory system to conduct IGRA (phlebotomy, processing of blood specimens, incubation and ELISA reading). National programmes may collaborate with other, non-TB-specific laboratories that have the capacity for drawing blood and ELISA testing or private institutions and laboratories through memoranda of understanding or free vouchers for individuals who require testing.
- Ensure the availability of trained laboratory technicians in laboratories in which IGRA tests are performed.
- Establish mechanisms to ensure rapid transport of blood specimens from peripheral centres to an IGRA testing laboratory (within 8–30 h) to allow incubation, depending on the type of IGRA.
- Ensure the functioning of laboratory equipment, and establish a mechanism for regular equipment maintenance for optimal functioning.
- Ensure a supply of appropriate reagents and testing tubes for IGRA, suitable for use at different altitudes (e.g. Johannesburg, South Africa, which is nearly 1700 m above sea level, requires different reagents or tubes from a place closer to sea level) (55).
- Ensure a supply of updated laboratory request forms and registers, and update laboratory information systems to document and report IGRA test results.

Fig. 6. Combined algorithm for screening and testing of individuals at risk before starting TB preventive treatment



CAD, computer aided detection of TB; CRP, C-reactive protein; CXR, chest radiography; IGRA, interferon- γ release assay; mWRD, molecular WHO-recommended rapid diagnostic test; TB, tuberculosis; TBST, *Mycobacterium tuberculosis* antigen-based skin test; TPT, TB preventive treatment; TST, tuberculin skin test

^a Including miners with silicosis, people on dialysis or anti-TNF agent treatment, preparation for transplantation or other risks in national guidelines. TB disease should be ruled out for people in this category.

^b For children aged ≥ 10 years, a four-symptom screen is used (current cough or fever or weight loss or night sweats). For children aged < 10 years, consider their history of contact with TB or reported or confirmed weight loss or growth curve flattening or weight for age < -2 Z-scores. Asymptomatic infants aged < 1 year with HIV are given TPT only if they are household contacts of people with TB. For other screening options, see the latest [WHO guidance \(TB-KSP\)](#).

^c 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, poor weight gain (plateau on growth chart), reduced playfulness or lethargy should also be included in symptom screening; cough may be absent. For other screening options see the latest [WHO guidance \(TB-KSP\)](#).

^d 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. The person is counselled about the benefits and potential risks of TPT.

^e In household contacts aged ≥ 5 years, TST, IGRA or TBST is recommended before consideration of TPT.

^f CXR is required only if it was not conducted at a previous step.

^g Regimen chosen according to age, strain (drug susceptible or otherwise), risk of toxicity, availability and preference. Adherence supported until completion as prescribed.

Shorter, safer and affordable TPT options are now also recommended. Government and donors should support access to an uninterrupted supply of these new regimens.

It's time to invest in shorter TPT regimens for adults and children.



5. TB preventive treatment

Key points

- WHO recommends several TPT options, which range in duration from 1 to 9 months. National programmes should progressively change to shorter rifamycin-based regimens, which are safer and more likely to be completed.
- It is now possible to offer the regimen of 3 months of weekly rifapentine plus isoniazid (3HP) to all age groups, including children < 2 years. Insufficient data on safety currently preclude its use in pregnancy.
- Six months of daily levofloxacin monotherapy (6Lfx) is now the recommended TPT regimen for contacts of people with MDR/RR-TB.
- The drug dosage schedule by weight band, for both solid and dispersible formulations, has been revised for all TPT regimens.
- The isoniazid + cotrimoxazole + B6 triple pill combination may be preferred for pregnant and postpartum women with HIV until more data on the safety of rifapentine-based shorter regimens become available.
- The choice of TPT regimen depends on the availability of appropriate formulations and considerations of a person's age, safety, drug–drug interactions and adherence.
- Available evidence does not support the common concern that large-scale use of TPT will result in drug resistance.
- Differentiated ARV service delivery is being scaled up globally. This will provide an opportunity to increase TB case finding and to integrate TPT into these care models.

The fourth step in the cascade of care for PMTPT is the choice of TPT regimen and providing support to people on TPT in completing their treatment.

5.1 Recommended TPT regimens

TPT falls broadly into three categories: (i) isoniazid monotherapy for 6 or 9 months (6H or 9H), (ii) rifamycin-based shorter treatment and (iii) Lfx for 6 months (6Lfx) for people exposed to MDR/RR-TB. Isoniazid preventive treatment (IPT) for 6 months was the mainstay of TPT until recently, for both adults and children, HIV-positive and HIV-negative, and in high and low TB incidence countries. Several systematic reviews have consistently demonstrated the efficacy of IPT in preventing TB disease among people infected with *M. tuberculosis*. A systematic review of randomized control trials (RCTs) with people with HIV in 2009 showed that IPT reduces their overall risk for TB by 33% (RR 0.67; 95% CI 0.51 ; 0.87), and the preventive efficacy reached 64% for people with a positive TST (RR 0.36; 95% CI 0.22 ; 0.61) (56). This review also demonstrated that the efficacy of the 6-month regimen was not significantly different from that of 12-month daily isoniazid monotherapy (RR 0.58; 95% CI 0.3 ; 1.12). A 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 0.65; 95% CI 0.50 ; 0.83) (57).

Evidence from clinical trials over the past two decades shows a similar preventive efficacy of a shorter rifamycin-based TPT regimen, in both HIV-positive and HIV-negative individuals, as monotherapy or

in combination with isoniazid (56–60). The clear advantages of these regimens are better adherence due to the shorter duration and fewer adverse events. Use of the shorter rifamycin-based regimens is associated with at least 20% better treatment completion rate (82% vs 61%) (76). WHO has assessed and recommended several shorter rifamycin-based regimens as alternatives to 6H.

The external experts convened by WHO in GDGs to advise on treatment policies have assessed the evidence for the various TPT options, including the values and preferences of the beneficiaries and other considerations, such as regimen acceptability, feasibility, resource implications and likely impact on health equity. With these elements, the GDGs recommended various regimens with which the benefits are likely to outweigh potential harms of acquiring TB disease or drug toxicity. When choosing a regimen, health caregivers and the person taking the treatment should consider circumstances that would increase the likelihood of it being completed. The choice may also depend on the availability of resources, fixed-dose combinations (FDCs), child-friendly formulations, concomitant medication (such as antiretroviral drugs, ARVs), opioid substitution therapy, oral contraception), as well as its acceptability to recipients in the country context. [Table 3](#) summarizes the characteristics of all currently recommended TPT options. The GDGs recommend that cost considerations not be a barrier to the provision of advantageous interventions such as dispersible drug formulations and tests of TB infection.

The 2020 guidelines broadened the applicability of a number of previous recommendations on testing for TB infection and TPT treatment regimen options from low-TB burden settings to any TB burden setting, on the condition that the country or treatment site has the capacity to rule out TB disease reliably before starting TPT, resources are available to implement TPT properly and measures are in place to limit the risks of TB infection and reinfection.

Since 2011, WHO has recommended IPT and other alternative regimens for people with HIV and other at-risk populations. In 2018, WHO recommended weekly rifapentine plus isoniazid for 3 months (3HP) and 3 months of daily isoniazid plus rifampicin (3HR) as options for TPT. In the 2020 update of the WHO guidance, two new regimens were added: (i) daily rifapentine plus isoniazid for 1 month (1HP), and (ii) daily rifampicin monotherapy for 4 months (4R). These, with 6H, are proposed as equivalent alternatives to TPT for individuals exposed to drug-susceptible TB in all settings. In 2024, a recommendation was added for use of 6Lfx in individuals exposed to MDR/RR-TB.

Table 3. Key characteristics of currently recommended TPT options

Characteristic	6H	3HP	3HR	4R	1HP	H + CPT + B6 (Q-TIB)	6Lfx
Drugs(s)	Isoniazid	Isoniazid + rifapentine	Isoniazid + rifampicin	Rifampicin	Isoniazid + rifapentine	Isoniazid + cotrimoxazole + pyridoxine	Lfx
Duration (months)	6	3	3	4	1	6	6
Frequency	Daily	Weekly	Daily	Daily	Daily	Daily	Daily
Total no. of doses	182	12	84	120	28	182	182
Pill burden per dose (total per regimen), person weighing 50 kg using adult formulations^a	1 (182)	6 singles (72) or 3 with FDC (36)	3 (252)	3 (360)	3 (84)	1 (182)	1 (182)
Cost of a full treatment^b	Adult: US\$ 3 Child: US\$ 3 (non-dispersible); US\$ 25 (dispersible)	Adult: US\$ 10 (P-300 mg / H-300 mg FDC) Child: US\$ 7 (P-150 mg / H-100 mg singles)	Adult: US\$ 12 (2FDC); US\$ 28 (R-150 mg / 300 mg; H-300 mg singles) Child: US\$ 19 (FDC)	Adult: US\$ 47 (R-300 mg singles)	≥ 13 years: US\$ 17 (FDC+P-300 mg single); US\$ 19 (P-300 mg / H-300 mg singles)	Adult: US\$ 14	Adult: US\$ 9 (Lfx-500 mg) Child: US\$ 5 (Lfx-250 mg non-dispersible); US\$ 44 (Lfx-100 mg dispersible)
Children	All ages; child-friendly (dispersible) formulation available; preferred for children with HIV on LPV/r or NVP	All ages; child-friendly (dispersible) formulation available	All ages; child-friendly (dispersible) formulation available	All ages; no child-friendly formulation available, not generally feasible for children < 25 kg	≥ 13 years	Adults and adolescents; no child-friendly formulations available	All ages; child-friendly (dispersible) formulation available

Characteristic	6H	3HP	3HR	4R	1HP	H + CPT + B6 (Q-TIB)	6Lfx
Pregnant women	Safe for use ^c	Not known	Safe for use ^{c,d}	May be safe, although no safety or efficacy data available for this population ^d	Not known	Safe for use ^c	May be safe, although no safety or efficacy data available specifically in this population
Interactions with ART^e	No restriction	Contraindicated: All protease inhibitors (PIs), nevirapine (NVP), doravirine and etravirine, tenofovir alafenamide (TAF) Use: tenofovir-disoproxil fumarate (TDF), EFV, DTG, RAL	Contraindicated: All PIs, NVP, doravirine and etravirine Use with caution: TAF Adjust dose: DTG, RAL Use: TDF, EFV	Contraindicated: All PIs, NVP, doravirine and etravirine, TAF Adjust dose: DTG, RAL Use: TDF, EFV	Contraindicated: All PIs, NVP, doravirine and etravirine, TAF Use: TDF, EFV, DTG, RAL	No restriction	No restriction (may interfere with lamivudine clearance)
Toxicity	Hepatotoxicity (more), peripheral neuropathy, rash, gastrointestinal upset	Flu-like syndrome, hypersensitivity reactions, gastrointestinal upset, orange discolouration of body fluids, rash, hepatotoxicity (less)	Hypersensitivity reactions, hepatotoxicity (less), rash, gastrointestinal upset, hypoproteinaemia, orange discolouration of body fluids	Rash, gastrointestinal upset, hepatotoxicity (less), hypoproteinaemia, orange discolouration of body fluids	Hepatotoxicity (more), hypersensitivity reaction, rash, gastrointestinal upset, orange discolouration of body fluids	Hepatotoxicity, rash, gastrointestinal upset	Diarrhoea, nausea and bloating, arthralgia, inflamed or torn tendons, muscle pain or weakness, prolonged QTc interval, mood or behaviour changes, insomnia
Absorption	Best absorbed on an empty stomach; up to 50% reduction in peak concentration with a fatty meal	Oral rifapentine bioavailability is 70%; peak concentration increased if given with a meal	Rifampicin absorption is rapid but may be delayed or decreased by high-fat meals.		Same as 3HP	Same as 6H	Absorption is not influenced by food. Concomitant steroid use may increase risk of tendon rupture. Multivalent cation-containing products including antacids (may contain aluminium), mineral supplements (e.g. iron or magnesium) or multivitamins may decrease absorption. Effect of warfarin may be enhanced.

1HP, 1 month of daily rifapentine plus isoniazid; 3HP, 3 months of weekly rifapentine plus isoniazid; 3HR, 3 months of daily rifampicin plus isoniazid; 4R, 4 months of daily rifampicin monotherapy; 6H, 6 months of daily isoniazid monotherapy; 6Lfx, 6 months of daily levofloxacin monotherapy; B6, pyridoxine; CPT, cotrimoxazole; DTG, dolutegravir; EFV, efavirenz; FDC, fixed-dose combination; H, isoniazid; LPV/r, lopinavir–ritonavir; NVP, nevirapine; P, rifapentine; PI, protease inhibitor; H + CPT + B6 (Q-TIB), isoniazid–cotrimoxazole–pyridoxine combination; R, rifampicin; RAL, raltegravir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate

^a H-300 mg; P-300 mg; H-300 mg/P-300 mg FDC; R-150 mg/H-75 mg FDC; R-300 mg/150 mg; Lfx-500 mg

^b Approximate pricing for child (~12 kg) or average adult provided by the Stop TB Partnership Global Drug Facility (May 2024)

- ^c One RCT has shown increased risk of poor birth outcomes for mothers taking isoniazid during pregnancy (61); however, other studies have shown benefits of IPT (73).
- ^d Bleeding attributed to hypoprothrombinaemia has been reported in infants and mothers after use of rifampicin in late pregnancy. Vitamin K is recommended for both mother and infant postpartum if rifampicin is used in the last few weeks of pregnancy.
- ^e In women receiving rifamycin-based TPT and oral contraceptives, consider additional barrier contraception methods to prevent pregnancy.

5.1.1 Isoniazid monotherapy

6H or 9H has been used most often for TPT worldwide. Isoniazid is, however, increasingly being replaced by rifamycin regimens, which are becoming more affordable and feasible and with more evidence on their efficacy and safety in different populations. It is likely that 6H or 9H will continue to be an important choice for TPT, particularly in situations in which rifamycin-based regimens cannot be used. In such situations, national programmes may consider use of a triple-pill combination of isoniazid, cotrimoxazole and vitamin B6 for people with HIV, which is available at a discounted price through the Stop TB Partnership's Global Drug Facility, instead of an isoniazid-only regimen (62). Isoniazid may remain the preferred regimen for HIV-infected children on a protease inhibitor-based regimen (lopinavir–ritonavir), nevirapine or integrase inhibitors (dolutegravir) because of potential drug–drug interactions, until more evidence becomes available. Isoniazid monotherapy should also protect contacts of TB patients with laboratory confirmed isoniazid-susceptible, rifampicin-resistant disease (mono RR-TB).

In the second edition of the WHO TPT guidelines in 2024 (73), the conditional recommendation for ≥ 36 months of daily IPT for adults and adolescents with HIV in settings with high TB transmission has been withdrawn. The recommendation was based on low-certainty evidence from a systematic review and meta-analysis of three RCTs (63). 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. Since the first release of the recommendation in 2011, country uptake has been poor, while access to ART has increased substantially worldwide. Shorter TPT options are preferred to IPT.

5.1.2 Three months of weekly rifapentine plus isoniazid and one month of daily rifapentine plus isoniazid

National programmes may consider either of these two rifapentine-containing regimens. The efficacy of both has been shown to be similar to that of isoniazid for TB prevention, but there is currently no direct evidence of efficacy from a comparison of 1HP and 3HP, although results from ongoing comparative studies are expected shortly.

WHO first recommended use of 3HP in 2018. At the time, however, the cost of rifapentine was a major barrier to uptake of 3HP. Large-scale interventions by global partners to shape the market for rifapentine resulted in introduction of generic products, which reduced the price of the 3HP regimen significantly, and it is now one of the preferred shorter TPT options throughout the world. It is recommended for use in people of all ages, including children < 2 years. Table 4 provides the recommended weight-band dosage down to 3 kg. (See also section 5.2.) The availability of child-friendly rifapentine and isoniazid formulations and an adult FDC make programmatic use of 3HP even more feasible. Further data on its use in pregnancy and with dolutegravir are expected shortly.

WHO first recommended use of 1HP in 2020. This regimen can be used in people aged ≥ 13 years, which was the age limit for the study population in the single RCT of the regimen for which results have been published to date (64–67). Further data are expected that could help to establish the appropriate dose of daily rifapentine for children < 13 years (67). The 1HP regimen may be used when a shorter duration is preferred, even if the total number of doses increases from 12 in 3HP to 28. The latter duration is used for prisoners incarcerated for a short term, patients awaiting anti-TNF treatment or preparing for a transplant, and people who must complete TPT before migration.

Table 4. Drug dosage schedule for TPT regimens according to body weight band

TPT regimens and drug formulations	No. of tablets or quantity of suspension by body weight band								
	4–7.9 kg	8–11.9 kg	12–15.9 kg	16–24.9 kg	25–29.9 kg	30–34.9 kg	35–49.9 kg	50–64.9 kg	≥ 65 kg
Six or nine months of daily isoniazid monotherapy (6H or 9H)									
Isoniazid 100 mg dt	0.5 (0.5 mL ^a)	1	1.5	2	–	–	–	–	–
Isoniazid 300 mg tab ^b	–	–	–	–	0.5	1	1	1	1.25
Four months of daily rifampicin monotherapy (4R)									
Rifampicin 150 mg cap	–	–	–	–	2	3	4	4	5
Rifampicin 300 mg cap ^c	–	–	–	–	1	1.5	2	2	2.5
Three months of daily rifampicin plus isoniazid (3HR)									
Isoniazid 300 mg tab	–	–	–	–	0.5	1	1	1	1.25
Rifampicin 300 mg cap ^c	–	–	–	–	1	1.5	2	2	2.5
Rifampicin 75 mg and isoniazid 50 mg FDC dt	1	2	3	4	–	–	–	–	–
Rifampicin 150 mg and isoniazid 75 mg FDC tab	–	–	–	–	2	3	4	4	5

TPT regimens and drug formulations	No. of tablets or quantity of suspension by body weight band												
	3–5.9 kg (< 3 months)	3–5.9 kg (≥ 3 months)	6–9.9 kg (< 6 months)	6–9.9 kg (≥ 6 months)	10–14.9 kg	15–19.9 kg	20–24.9 kg	25–29.9 kg	30–34.9 kg	35–39.9 kg	40–44.9 kg	45–49.9 kg	≥ 50 kg
Three months of weekly rifapentine plus isoniazid (3HP)													
Isoniazid 100 mg dt	0.6 (6 mL ^a)	0.7 (7 mL ^a)	1	1.5	2.5	3	4.5	4.5	6	6	7.5	7.5	9
Isoniazid 300 mg tab	–	–	–	–	–	1	1.5	1.5	2	2	2.5	2.5	3
Rifapentine 150 mg dt	0.5 (5 mL ^d)	0.7 (7 mL ^d)	1.5	1.5	2	3	4	4	5	6	6	6	6
Rifapentine 300 mg tab	–	–	–	–	–	1.5	2	2	2.5	3	3	3	3
Rifapentine 300 mg and isoniazid 300 mg FDC tab ^e	–	–	–	–	–	1	1.5	2	2.5	3	3	3	3
One month of daily rifapentine plus isoniazid (1HP) ^f													
Isoniazid 300 mg tab	–	–	–	–	–	–	–	1	1	1	1	1	1
Rifapentine 300 mg tab	–	–	–	–	–	–	–	2	2	2	2	2	2
Six months of daily levofloxacin (6Lfx)													
Lfx 100 mg dt	0.5	1	1	1.5	2	2.5	3	3.5	–	–	–	–	–
Lfx 250 mg tab	0.25 (2.5 mL ^d)	0.5 (5 mL ^d)	0.5 (5 mL ^d)	1 (10 mL ^d)	1	1.5	1.5	2	2	2	2	2	3
Lfx 500 mg tab	–	–	–	–	–	–	–	1	1	1	1	1	1.5

1HP, 1 month of daily rifapentine plus isoniazid; 3HP, 3 months of weekly rifapentine plus isoniazid; 3HR, 3 months of daily rifampicin plus isoniazid; 4R, 4 months of daily rifampicin monotherapy; 6H or 9H, 6 or 9 months of daily isoniazid monotherapy; 6Lfx, 6 months of daily levofloxacin monotherapy; dt, dispersible tablet; FDC, fixed-dose combination; kg, kilogramme; mg, milligramme; mL, milliliter; tab, tablet

Please note different weight bands are used in the two parts of this table; a process of weight-band harmonization is ongoing.

^a Suspension with a concentration of 10 mg/mL (one 100 mg isoniazid dispersible tablet in 10 mL water).

^b A triple pill combination of isoniazid 300 mg + pyridoxine 25 mg + sulfamethoxazole 800 mg + trimethoprim 160 mg (scored) can be used for people with HIV.

^c A quantity of 0.5 can be achieved by adding a 150-mg capsule of rifampicin.

^d Suspension with a concentration of 15 mg/mL (one 150-mg rifapentine dispersible tablet in 10 mL water).

^e For individuals < 50kg on FDC, close monitoring for isoniazid toxicity is advised and pyridoxine added as needed. Optimized dosing using single-dose formulations of the two drugs is shown elsewhere in the Table.

^f For individuals aged ≥ 13 years.

5.1.3 Three months of daily rifampicin plus isoniazid

Children < 5 years are particularly vulnerable because of increased risks of progression to TB disease and of developing severe forms of TB, such as TB meningitis and disseminated TB. In addition, it is difficult to confirm TB disease, given its paucibacillary nature. Therefore, averting paediatric TB by delivering preventive treatment is strategically important. For TPT among children, the 3HR regimen is better tolerated and more child-friendly than isoniazid, as dispersible FDC formulations are available. Until access to the child-friendly rifapentine formulations (which became available only in November 2023) is enhanced, national programmes could consider 3HR as an option for TB prevention among children of all ages. Those weighing < 25 kg (including children < 2 years) may receive the RH formulation used for the continuation phase of TB treatment (R/H, 75/50 mg), while children weighing > 25 kg may receive either 3HP or 3HR as adult FDCs of RH. Child-friendly FDCs of RH have the added benefit that they are already in the national supply chain for TB treatment of children weighing < 25 kg. In adults, however, the risk of hepatotoxicity with use of 3HR is expected to be as high as with 6H or 9H, and 3HP may be the preferred option.

In the medium to long term, 3HP (or 1HP) may become the preferred regimen for all ages. This document provides updated information on the dosage of 3HP for children, including those < 2 years. Dispersible formulations of rifapentine (150 mg scored) and isoniazid (100 mg) are increasingly becoming available. The shorter duration of treatment with 3HP and the higher rates of treatment completion will probably make it more cost-effective in the long term.

5.1.4 Four months of daily rifampicin monotherapy

Rifampicin has a long history of use in TB treatment, and national procurement systems have experience in acquiring it, usually with other TB medicines in FDC tablets. Rifampicin has a much better safety profile than isoniazid, and its cost is lower than that of rifapentine. WHO recommends daily rifampicin for 4 months as one TPT option, which may also be given to contacts of people with confirmed isoniazid-resistant, rifampicin-susceptible TB disease. Some of the main challenges with 4R, however, are the perception that rifampicin should be protected for use as first-line TB medicine and concern that its use in TPT may increase rifampicin resistance in the community or promote misuse of the agent as monotherapy for TB disease. There is, however, no evidence of a significant increase in rifampicin resistance due to scaling up of TPT services. Other possible challenges are drug–drug interactions with ARVs (see [section 6](#)), the current lack of child-friendly formulations and the limited supply of single-dose formulations due to the widespread availability of FDCs of first-line TB treatment.

5.1.5 Levofloxacin and other TPT regimens for drug-resistant TB

The second edition of the *WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment*, published in 2024 (13), contains an updated recommendation on TPT for individuals exposed to MDR/RR-TB. WHO now recommends 6Lfx as a TPT option for people exposed to MDR/RR-TB in all settings, subject to specific conditions. Lfx is the preferred choice of fluoroquinolone for TPT, and the recommendation is based on evidence from two randomized controlled trials with this drug – TB CHAMP and V-QUIN, a systematic review of studies on use of TPT for MDR/RR-TB and studies on the programmatic feasibility and acceptability of 6Lfx (13).

Confirmation of infection by TST, TBST or IGRA before starting TPT for MDR/RR-TB is not required for child contacts and people with HIV or other immunocompromising conditions. In other populations, this is desirable but not mandatory, and the lack of availability of testing should not be a barrier to providing TPT to individuals at risk of MDR/RR-TB. If Lfx is used for TPT of MDR-TB, TB disease must be carefully excluded to limit the risk of emergence of resistance to fluoroquinolones – key components of second-line TB treatment regimens – should the person subsequently require treatment for MDR-TB disease. TB disease should be ruled out by an appropriate clinical evaluation or according to national guidelines. Provision of TPT with Lfx should also account for factors such as age, risk of toxicity or interaction, co-morbidity, drug susceptibility of the strain of the most likely source case, background resistance to fluoroquinolones in MDR/RR-TB strains, availability and the individual's preferences.

While there are no comparable data to support use of alternatives, moxifloxacin can be used if Lfx is not available, and the dosage proposed for treatment of MDR/RR-TB can be used (68). Drug-susceptibility testing of the strain from the presumed source patient would be important additional information, especially in situations where fluoroquinolone resistance is known to be high. If the strain of the source patient shows resistance to these medicines, other TB drugs (e.g. ethionamide, ethambutol) can be used for TPT, with the best available information on the drug susceptibility profile of the presumed strain. In this case, the certainty of the effectiveness of TPT is much lower than with Lfx. Results from the PHOENIX trial, in which 26 weeks of delamanid are compared with isoniazid for household contacts (all ages) of MDR-TB patients in 11 countries are expected in mid-2025 (69).

Contacts of individuals with rifampicin-resistant TB may be treated similarly to those with MDR-TB; if susceptibility to isoniazid is confirmed in the presumed source patient, contacts may be given IPT.

5.2 Recommended dosage of TPT medication

Table 4 presents an updated dosing scheme for all recommended TPT regimens by standardized body weight-bands. In 2024, the Technical Advisory Group on dosing of TB medicines for adults and children (70) reviewed questions relating to the dosage of TPT regimens. They considered published evidence and the results of pharmacokinetics modelling and simulation in studies of 6Lfx and 3HP. (See details in [Web Annex A](#).) Dosing of smaller children is adjusted for differences in the rate at which drugs are metabolized. For infants and young children, age cut-offs are given in the first two weight bands for 6Lfx and 3HP. It is important to note that infants in these two weight bands may be malnourished, a condition that warrants particular care to exclude TB disease before TPT is considered. A specialist should be consulted for dosing of TPT regimens for infants who weigh ≤ 3 kg.

Weight-band dosing facilitates administration of medication by front-line staff. The doses shown in Table 4 also take into account the most common drug formulations available on the market. When more than one formulation of the same medicine is commonly available, doses are shown for each option. For three regimens, the weight bands used adhere to the harmonized approach recommended by WHO for dosing schedules. (The weight bands in the first part of Table 4 do not adhere to the harmonized approach.) The recommended dosing is designed to avoid splitting of non-dispersible tablets into fractions smaller than one half. When administering treatment, factors should be considered that may increase the risk of drug toxicity, such as malnutrition, co-morbidity and drug–drug interactions. These factors should also be reflected in job aids for health-care providers. In settings in which many people are known to be slow acetylators (mutation in the NAT2 genotype leading to persistence of isoniazid),¹ national programmes may consider pyridoxine supplementation for all individuals receiving isoniazid-containing TPT (68). (See also [section 5.2.2](#).) More empirical data should be made available for settings with different distributions of slow and fast isoniazid acetylators in order to develop better guidance on the selection of doses that ensures therapeutic exposure to isoniazid-based TPT without reaching toxic levels.

5.2.1 Availability of appropriate formulations

Rifampicin: The most widespread use of rifampicin is in rifampicin-containing FDCs to treat drug-susceptible TB, and single-dose rifampicin is less commonly procured. It is therefore likely to be available in only limited quantities to national programmes. Additionally, child-friendly dispersible formulations of single-dose rifampicin are not currently available. The development of a 100-mg scored, dispersible rifampicin tablet may be useful for rifampicin-containing TPT in children. If the demand for the 4R regimen increases, programmes will have to increase their orders for single-dose rifampicin capsules. In this case, use of rifampicin should be regulated and limited for use as part of

¹ Isoniazid is metabolized by *N*-acetyltransferase 2 (NAT2), and a mutation in the NAT2 genotype leads to persistence of isoniazid in the body, predisposing to toxicity. The prevalence of NAT2 mutations differs geographically, with slow acetylators (known to be at risk of most drug-induced toxicity) very common in some settings (83% in Egypt and 67% in the USA) but rare elsewhere (12% in China).

the TPT regimen, to avoid it being diverted for use as a broad-spectrum antibiotic. The supplies of 4R to peripheral centres (primary-care facilities, HIV programmes) should be accompanied by specific guidance on use of rifampicin.

Isoniazid plus rifampicin FDC: Child-friendly dispersible FDC of HR are available and are already used in many countries for treatment of TB disease in children. The same formulations can be used for TPT. Child-friendly FDCs of HR should be preferred over single-dose formulations, to reduce the pill burden. Similarly, FDCs used for treatment of adult TB disease may be used for TPT among adults. The dispersible formulation is currently more expensive than solid formulations.

Isoniazid plus rifapentine (weekly or daily): Regimens based on these two drugs are now more feasible for use by people of all ages, in view of the formulations available, such as child-friendly tablets of isoniazid and rifapentine that are dispersible in water and have a fruity flavour. While they are currently more expensive than solid formulations, they allow more precise, reliable dosing of children than crushing of adult tablets (71). 3HP or 1HP can be given in different combinations of single-dose isoniazid (100-mg scored dispersible paediatric and 100-mg or 300-mg solid formulations), single-dose rifapentine (150-mg scored dispersible paediatric and 300-mg solid formulation) or as an FDC of isoniazid 300 mg and rifapentine 300 mg (72). The 300-mg rifapentine formulation reduces the pill burden of both 3HP and 1HP for adults. The FDC will further reduce the weekly pill burden for 3HP in adults weighing ≥ 50 kg from nine to three pills and the daily pill burden for 1HP to just one FDC plus one rifapentine 300-mg capsule. The child-friendly rifapentine and isoniazid formulations will increase the flexibility and ease of administration of 3HP to young children, including those aged < 2 years. Functional scoring of rifapentine tablets allows use of 75-mg dose increments for different weight bands. The generic product of the 150-mg rifapentine scored dispersible tablet that is on the market has been approved by the Global Fund Expert Review Panel and can be ordered from the Stop TB Partnership Global Drug Facility (62). The tablet has a raspberry–mint flavour when dispersed in water. A small volume of about 10 mL is required to disperse a tablet (it might have to be increased if several dispersible tablets are taken at once) (71). It has a shelf-life of about 24 months. In addition, WHO has prequalified a 100-mg scored dispersible tablet formulation of isoniazid, which is fruit flavoured for greater palatability. The FDC containing 300 mg isoniazid and 300 mg rifapentine is also available from generic manufacturers, and access to child-friendly formulations is being facilitated by the Unitaaid-funded IMPAACT4TB Consortium (73). The Treatment Action Group is campaigning for access to rifapentine-containing regimens through the 1/4/6x24 campaign (74).

Isoniazid + cotrimoxazole + pyridoxine combination: This combination is available at a discounted price through the Stop TB Partnership Global Drug Facility and the Global Fund Pooled Procurement Mechanism. These combination pills may be considered alternatives for people with HIV when shorter rifamycin-containing regimens are not available or drug–drug interactions occur. They are single-scored tablets and cannot be used for children aged < 5 years.

Levofloxacin is available as 100-mg scored dispersible paediatric tablets and as 250-, 500- or 750-mg solid formulation tablets. The dispersible formulation is currently more expensive than the solid formulations.

5.2.2 Role of pyridoxine and its availability

Pyridoxine (vitamin B6) in the diet is converted into coenzymes that play an essential role in the metabolism of protein, carbohydrates, fatty acids and several other substances, including brain amines. Isoniazid apparently competitively inhibits the action of pyridoxine in these metabolic functions (75) and is associated with neurotoxicity and peripheral neuropathy.

Individuals at risk for isoniazid-induced peripheral neuropathy include those with malnutrition, chronic alcohol dependence, HIV infection, renal failure and diabetes, as well as pregnant and breastfeeding women and infants who are exclusively breastfed by mothers on isoniazid. The earliest symptom of isoniazid-induced neurotoxicity is usually paraesthesia, followed by pricking pain and a burning

sensation in the feet and later in the hands (symmetrical numbness and tingling). If untreated, the symptoms worsen and cause distress. These symptoms are easily recognized and are usually easily reversed upon withdrawal of isoniazid and institution of pyridoxine therapy.

The incidence of peripheral neuropathy is closely correlated with the dose of isoniazid used. Studies conducted mainly in the 1950s (76–79) reported that, while > 40% of people receiving high-dose isoniazid (16–24 mg/kg per day) developed signs and symptoms of peripheral neuropathy, only 2% of those receiving a standard dose of 4–6 mg/kg/day did so. The incidence of neuropathy was, however, observed to be higher at a standard isoniazid dosage in malnourished patients (up to 20%) (77) and among slow acetylators of isoniazid, reaching 20%. (See also [section 5.2](#)) Signs of toxicity tend to appear later among those taking standard doses of isoniazid.

Pyridoxine supplementation may be required to prevent or treat isoniazid-associated neurotoxicity. While a standard dose of isoniazid is used in IPT, the weekly dose of isoniazid in 3HP is higher. Routine administration of pyridoxine supplements to otherwise healthy individuals on a standard dose of isoniazid is not usually required (76). An adequate human diet containing 1–2 mg of vitamin B6 compounds daily may protect against isoniazid toxicity. Good dietary sources of vitamin B6 include carrots, spinach, peas, potatoes, milk, cheese, eggs, fish, meat and fortified flour. Concurrent administration of pyridoxine with isoniazid protects individuals at risk from the development of peripheral neuropathy; the recommended dose is 10–25 mg/day. For established isoniazid-induced peripheral neuropathy, pyridoxine should be given at a higher dose of 50–75 mg daily and even up to 100–200 mg per day (78). It is important to maintain pyridoxine supplementation at the right dose, as higher levels may interfere with the antibacterial activity of isoniazid. Moreover, excessively high doses of pyridoxine (≥ 2000 mg/day) have been reported to cause toxicity, including peripheral neuropathy (79–83).

The pyridoxine formulation currently available in the Global Fund's Pooled Procurement Mechanism and the Global Drug Facility products list are 10-mg film-coated tablets, 50-mg uncoated tablets and 100-mg film-coated tablets (62). The latter formulations are suitable primarily for therapeutic use and are difficult to fraction into the doses recommended for prophylactic supplementation. National programmes may consider local procurement of a quality-assured product of lower-dose pyridoxine (10–25 mg) for use in high-risk individuals or, alternatively, procure vitamin B complex. Use of isoniazid–B6–cotrimoxazole combination tablets may be considered for people with HIV. Programmes are nonetheless advised to stock higher-dose pyridoxine for treatment of peripheral neuropathy. It is important that programmes do not delay initiation of TPT if procurement of pyridoxine is difficult.

5.3 Provision of TPT for special populations

5.3.1 Pregnancy and postpartum period

Pregnancy increases the risk of progression from TB infection to disease and the risk of poor maternal and fetal outcomes should TB disease occur. Women with HIV are at higher risk for TB during pregnancy and the postpartum period, which can have severe consequences for both the mother and the infant (84,85). Pregnancy should therefore not disqualify women from receiving TPT if they are eligible for it, regardless of their HIV status. Isoniazid and rifampicin, the medicines commonly used in preventive treatment, are considered safe for use in pregnancy (classified as Pregnancy Category C by the US Food and Drug Administration) (86,87).

Preventive treatment with isoniazid and/or rifampicin can be safely given to breastfeeding women (88). One trial showed an increased risk of adverse pregnancy outcomes with IPT (88); however, no other studies have shown an association of IPT with fetal or neonatal death, prematurity, low birth weight or congenital anomaly. Similarly, no statistically significant risks for maternal hepatotoxicity, grade 3 or 4 events or death were reported. A study published in 2023 showed no difference in infant acquisition of TB between mothers with HIV who received IPT during pregnancy or post partum (89). Therefore,

systematic deferral of TPT to the post-partum period is not necessary. When indicated, IPT should be started during the antenatal and postnatal periods, with due care. The triple-pill combination of isoniazid + cotrimoxazole + B6 may be used for TPT among pregnant and breastfeeding women with HIV. Rifampicin is generally considered safe for use during pregnancy, and no dose adjustment is necessary, although no data are available on its safety or efficacy in pregnant and post-partum women on 4R as TPT (90).

Few data were available on the efficacy and safety of rifapentine in pregnancy. Programmatic use of 1HP and 3HP in pregnancy is thus cautioned until more data become available. One clinical trial (WHIP3TB) of the outcomes of women who initiated 3HP and became pregnant showed a similar frequency of spontaneous abortion and adverse pregnancy outcomes (when analysed as a composite outcome) in the exposed and unexposed groups (91). A study of the pharmacokinetics and safety of 3HP in pregnant women showed that dose adjustment would not be required to achieve therapeutic levels in pregnancy. Although rifapentine clearance was higher among women with HIV, their exposure was considered sufficient for TB prevention (92).

The risks and benefits of TPT with Lfx in pregnancy should be assessed, and pregnant women should be enabled to make an informed choice about whether to take TPT or to defer TPT to the end of pregnancy. The advice given should be adapted to the circumstances (e.g. use in the first trimester or later). MDR/RR-TB in pregnancy is a serious condition, and some of the drugs used to treat MDR-TB may be toxic to the fetus. Observations from studies in animals exposed to Lfx have limited its use in pregnancy; however, one meta-analysis of observational studies of 2800 pregnant women given fluoroquinolones for any indication (e.g. urinary tract infection) found no difference in the incidence of birth defects, spontaneous abortion or prematurity from that in unexposed pregnant women (93). Lfx concentrations in breastmilk appear to be far lower than the infant dose and would not be expected to cause adverse effects in breastfed infants (94); therefore, Lfx should not be suspended during breastfeeding. While the effects of fluoroquinolones on bone and cartilage in animals have not been reproduced in humans, data and infant follow-up are limited. Recent alerts have raised safety concerns associated with prolonged use of fluoroquinolones in humans (95–97).

Routine liver function testing is not indicated when TPT is given during pregnancy, unless other hazards are present. Pyridoxine (vitamin B6) supplementation should be given routinely to all pregnant and breastfeeding women on isoniazid-containing TPT. Pyridoxine should be given to infants who are taking isoniazid or whose breastfeeding mothers are taking isoniazid.

5.3.2 Infants born to mothers with TB disease

- Assess the newborn. If the newborn is unwell, refer him or her to a specialist or a paediatrician. It is important that the mother receives effective TB treatment so that she is no longer infectious. Ensure that infection control measures are in place in the nursery, especially in an inpatient facility for the care of preterm or small-at-birth infants.
- If the newborn is well (with no signs or symptoms suggestive of TB), provide TPT and delay BCG vaccination until two weeks after TPT is complete. Administer pyridoxine at 5–10 mg/day. Exclusion of TB disease is particularly critical in infants who are malnourished before starting TPT.
- Infants born to mothers who are HIV-positive and are on nevirapine should also receive IPT. Rifamycin-based TPT cannot be given with nevirapine prophylaxis, as rifampicin and rifapentine decrease nevirapine levels and may thus increase the risk of mother-to-child transmission of HIV (98).
- At the end of TPT, perform a TST or IGRA test. If the test for TB infection is negative or not available, give BCG (unless the infant is HIV-positive).
- If the mother is taking anti-TB drugs, she can safely continue to breastfeed. The mother and infant should stay together, and the infant may be breastfed while on TPT. Infants being breastfed by a mother who is on TPT should receive pyridoxine for the duration of the mother's treatment.

5.3.3 Women taking oral or hormonal contraceptives

Rifampicin and rifapentine interact with oral and hormonal contraceptive medications, with a potential risk of decreased contraceptive efficacy. Women who are taking oral contraceptives while on rifampicin or rifapentine should either:

- change the oral contraceptive pill and use an alternative, such as depot medroxyprogesterone acetate every eighth week (99) or higher-dose oestrogen (50 µg) in consultation with a clinician; or
- use another form of contraception, a barrier contraceptive or an intrauterine device.

In women with hormonal contraceptive implants, the interval for replacing the implants might have to be shortened from 12 to 8 weeks (99).

5.3.4 People with hepatitis or liver disease

Isoniazid, rifampicin and rifapentine are associated with liver dysfunction. TPT should be initiated with caution among individuals whose baseline liver transaminase values are found to be more than three times the upper limit of normal. TPT should not be given to individuals with end-stage liver disease. IPT is, however, well tolerated by individuals with chronic hepatitis B or hepatitis C infections (100,101). In people with acute hepatitis due to infection or another cause, TPT should be deferred until the condition has resolved. Rifampicin and rifapentine can decrease the concentration of direct-acting ARV used to treat hepatitis C infection to subtherapeutic levels, and their use together is therefore not recommended (102–105). People with hepatitis C should consult their health-care providers and start rifamycin-based TPT either before or after completing treatment for hepatitis C.

5.3.5 People with renal failure

Isoniazid, rifampicin and rifapentine are eliminated by biliary excretion and can therefore be given in standard dosages to patients with renal failure. Patients with severe renal failure should receive isoniazid with pyridoxine to prevent peripheral neuropathy.

5.3.6 People with HIV

A key challenge in TPT with rifamycin-based regimens for people with HIV is drug–drug interaction between rifamycin and antiretroviral drugs. No dose adjustment is required when rifapentine or rifampicin is co-administered with efavirenz. The dose of dolutegravir should be increased to 50 mg twice daily when given with rifampicin; no dose adjustments are necessary when rifapentine is used. Rifampicin or rifapentine TPT regimens should not be co-administered with protease inhibitors or nevirapine (for details, see [section 6.3](#)).

5.3.7 People who use drugs

The prevalence of TB infection and incidence of TB disease is higher among people who use drugs (105). IPT is safe for these people, although careful monitoring for liver toxicity is important. No systematic study of use of rifapentine by people who use drugs has been conducted; however, rifampicin is known to reduce exposure to opioid substitution therapy such as methadone and buprenorphine (106). In some people, this results in opiate withdrawal. For this reason, people taking 3HP, 3HR or 4R with opiate substitution therapy should be closely monitored for signs of opiate withdrawal and other adverse events. Increasing the dose of methadone or buprenorphine for people taking rifamycins can lessen the risk of withdrawal. Drug use should never be considered a blanket reason for denying someone TPT. It is the responsibility of health-care providers to proactively manage drug–drug interactions for people who use drugs safely (107).

5.3.8 TB among older adults

Many countries are experiencing demographic shifts as average life expectancy increases, with larger numbers and proportions of older adults in their populations (708). TB remains one of the foremost infectious causes of disease and death among ageing adults. About 12% of all notified TB patients worldwide today are over 64 years of age, although the proportion is much higher in some countries (e.g. 30% in China, 70% in Japan). In settings with a lower TB burden and limited community transmission, the TB epidemic is driven by TB reactivation in older adults as their immunity wanes; however, TB reactivation in older adults is also relevant in high-burden settings and contributes to ongoing community transmission.

WHO recommends screening, testing for TB infection and provision of TPT to people exposed to TB, regardless of age, and to people with clinical conditions due to immune suppression. These recommendations must also be implemented for older people. National programmes should: promote the acquisition of local evidence on gaps in preventive care for older adults; invest in enhancing access to testing for TB infection and to shorter rifamycin-containing TPT; provide guidance on risks and benefits before TPT is initiated in older adults; and monitor adverse events in people on TPT. Routine TB screening and care of people living in homes for the elderly, provision of age-friendly infrastructure and services, awareness of atypical TB features, integration of TB and noncommunicable disease services, and person-centred approaches to treatment support could enhance access to TPT and improve TB management among older adults.

5.4 Duration of protection

The durability of protection from TB is a function of both the potency of the TPT regimen to sterilize TB infection and the risk of re-infection after treatment. TB infection that is not adequately treated because of an inadequately potent regimen or poor adherence to treatment may result in reactivation of TB infection, leading to TB disease.

People with HIV are at high risk of reactivation of TB infection and of progressing to TB disease when infected. Studies conducted before ART found an escalating risk for TB after a course of TPT in high-TB burden countries, while more lasting protection was observed in countries with a low or medium burden of TB in terms of reduced mortality and incident TB. Recent trials conducted since widescale access to ART, however, suggest that the protection offered by TPT, even in high TB burden settings, can last as long as in countries with a low or medium TB burden.

- In Côte d'Ivoire, where TB incidence was reported in 2017 as 159 per 100 000 people, 6 months of IPT had a strongly protective effect against mortality among HIV-infected people who had started ART, even in those with a high CD4 cell count, and the protective effect lasted for up to 6 years (27).
- In Brazil, which has a medium prevalence of TB, IPT significantly reduced the risk for TB of HIV-infected patients with a positive TST. A 6-month course of isoniazid reduced the TB risk for > 7 years. In studies in high-burden settings in Africa, however, the TB incidence increased immediately after IPT (109,110).
- Recent studies in Indonesia and Myanmar, which are high TB burden countries, reaffirm the durability of protection after 6 months of IPT among people with HIV. In Indonesia, the protective benefit lasted > 5 years (111). In Myanmar, completing a course of IPT significantly reduced the risk of TB disease and death for as long as 8 years (112).
- In the BRIEF-TB trial, in which 97% of participants were in high TB burden countries, the TB incidence after a complete course of TPT with either 1-month isoniazid and rifapentine or a 9-month isoniazid regimen remained stable throughout the 3-year follow-up period. Almost all people with HIV in this trial were receiving ART (64). Among household contacts of TB patients receiving TPT in the pre-HIV era, IPT had a long-lasting benefit, even in settings with very high rates of TB disease.
- The US Public Health Services sponsored several studies to assess the efficacy of IPT in the 1960s. A large group of individuals at risk for TB due to recent or remote contact with a pulmonary TB

patient in Alaska were studied (113). In 1958, 2% of the population in this area was reported to have TB, and a tuberculin survey revealed an average annual rate of TB infection of 8%. These levels were among the highest ever reported, even higher than those in the highest-transmission settings, such as mines in South Africa, where an occurrence of 4.2% was estimated in 2005 (114). Participants received isoniazid at 300 mg daily or 5 mg/kg for children or a matching placebo for 1 year and were followed up actively for 2 years and passively for the next 10 years. Follow-up data from a study that started in 1958 of 28 villages and two boarding-schools in Alaska showed that the protective effect of isoniazid persisted for up to 19 years (115). The conclusion that 6–9 months of preventive therapy was optimal is based on follow-up data for this study and a study by the International Union Against Tuberculosis and Lung Disease that found that provision of isoniazid for more than 9 months does not increase its effectiveness (116,117).

- A systematic review published in 1999 (118) reaffirmed the effectiveness of isoniazid in preventing development of TB disease in approximately 60% of individuals in various at-risk groups, including family contacts. For every 35 recent household contacts with a positive TST who were prescribed isoniazid for 6 months, one case of TB disease was prevented during the next 5 years.
- A trial conducted in 2021 (119) clearly demonstrated that TPT was more likely to be completed if it included 3HP rather than 6H, and the protection provided by a single round of 3HP lasted as long as with isoniazid.

5.5 Repeating or re-starting TPT

No evidence is available on the utility of repeated courses of TPT, and WHO does not specifically recommend a repeated course of TPT. A randomized pragmatic trial (WHIP3TB) of people with HIV on ART in Ethiopia, Mozambique and South Africa, completed in late 2019, compared the effectiveness of 3HP given once (N=1802) or twice (N=1808) within 14 months versus one course of 6H (N=404) (119). Treatment completion was better with 3HP than 6H. Follow-up for 24 months after randomization showed similar rates of TB incidence, the incidence of rifampicin-resistant TB, and mortality in participants who received 3HP once or twice, suggesting that 3HP for people with HIV on ART in high TB transmission settings provides protection. An additional round of 3HP given approximately 1 year after the first did not provide additional benefit in preventing TB among people receiving ART, indicating that a single course of 3HP provides lasting protection. Longer follow-up of this trial will be important.

A repeated course of TPT should, however, be considered for people who previously completed a course of TPT but were subsequently in a household or in close contact with a TB patient. As the currently available tests (TST, TBST and IGRA) are not negative after a complete course of TPT, they cannot be used to determine eligibility for a repeated course in the case of a new exposure or reinfection. Careful assessment of the intensity of exposure and the balance between benefits and harm should guide a decision to administer a repeated course of TPT. TPT should also be considered for people with HIV who were previously treated for TB disease, especially infants and children. The risk of recurrence is likely to be determined by the extent of initial TB disease and the efficacy of previous TB treatment, which is substantially reduced by ART.

Re-starting TPT may be necessary if there has been a significant interruption. [Section 7](#) proposes thresholds for determining whether to continue a regimen after interruption and how, largely based on criteria used in trials of different regimens. Reliable evidence on regimen interruption is lacking.

5.6 Does TPT cause drug resistance?

A common concern about wide-scale use of TPT is its potential to propagate drug resistance. While there is ample evidence that suboptimal treatment of TB disease favours the emergence of drug-resistant TB strains, no convincing data are available of an association with TPT. A number of trials have failed to find evidence of a significant association between TB drug resistance and widescale use of

isoniazid or rifamycin for TPT (120,121). Concerns such as these have deprived countless populations of the benefit of a potentially life-saving intervention.

An increase in drug resistance is unlikely if good TPT practices are observed by programmes, namely, that TPT is used for people without TB disease, the appropriate dosage is respected, and treatment is completed as prescribed. As individuals with TB infection have a small number of slowly replicating bacteria in their body, there is a low risk that TPT will select drug-resistant strains (120). It is in fact conceivable that TPT actually lowers the overall burden of TB disease and thus reduces the number of people among whom drug-resistant strains can emerge and spread.

TB disease should be excluded with all available tools before TPT is initiated, and regular follow-up done to ensure adherence to TPT and early identification of TB symptoms while on treatment. Drug susceptibility testing should be prioritized in individuals who develop microbiologically confirmed TB during or after TPT.

5.6.1 Isoniazid resistance after IPT

In a systematic review of 13 studies published between 1951 and 2006, which included 18 095 people on IPT and 17 985 controls, there was no suggestion of an increased risk of isoniazid-resistant TB after IPT (120). The results were similar when stratified for HIV. In addition, in the Thibela study cohort in South Africa, the proportions of TB episodes with drug resistance among patients who had received IPT did not significantly differ from those in comparison groups (122).

5.6.2 Rifamycin resistance after TPT

In an analysis of six RCTs of rifamycin-containing regimens for TPT versus active control or placebo, the occurrence of rifampicin resistance was 0.09% in 6808 individuals receiving rifamycin-based TPT vs 0.01% in 7415 individuals receiving alternative regimens (RR = 3.45, 95% CI 0.72 ; 16.56; $P = 0.12$) (120). In three of the studies in which intermittent rifamycin-based TPT was used, there were two cases of rifampicin resistance among 4673 individuals on an intermittent rifamycin-containing regimen and one case of rifampicin resistance among 4427 individuals on control regimens (RR = 3.89; 95% CI 0.44 ; 34.56; $P = 0.22$). In placebo-controlled trials, no cases of rifampicin resistance were found among participants receiving rifamycin-containing regimens, whereas several cases occurred in people on placebo (RR 0.20, 95% CI 0.02 ; 1.66) (121).

5.6.3 Resistance to levofloxacin after TPT

Microbiological sub-studies conducted within the V-QUIN and TB CHAMP trials provided no conclusive evidence of emergence of additional fluoroquinolone resistance in TB strains at the time of analysis in late 2023 (Annex 5 of (13)).

5.7 Introducing and scaling-up TPT

This section provides a stepwise approach to the introduction and extension of TPT in countries. [Annex 3](#) provides additional details on coordination mechanisms for PMTPT. [Box 5](#) provides an example from Brazil, where nurses have been entrusted with TPT administration through skill extension, and [Box 6](#) illustrates actions taken by national programmes in high TB burden countries that have reported substantial increases in the use of shorter rifamycin-based TPT.

5.7.1 Considerations for programmatic implementation of TPT

- Define the roles, responsibilities and cadres of health-care workers in prescribing TPT. Trained doctors, nurses and peripheral health-care workers can evaluate and start TPT once TB disease has been reliably ruled out according to a national protocol. Nurses and front-line health-care workers

can also be trained to monitor TPT and make decisions about whether TPT should be started, suspended, changed or re-started. This includes management of adverse events and treatment interruption. In most instances, it is unnecessary to seek the opinion of a medical doctor or a specialist for such decisions; however, provision for soliciting such support if it becomes necessary should be made.

- Define the levels of the health-care system at which TPT can be started and where refills of medicines can be accessed.
- Develop SOPs for TPT initiation and follow up to:
 - maintain the flow of people identified for TPT among health facilities and service points in the facilities;
 - ascertain the roles and responsibilities of health providers, community health workers and other stakeholders (such as nutrition care services, prisons and other correctional facilities, refugee camps, mining communities) in evaluation of eligibility and initiation of TPT;
 - provide support for adherence to TPT;
 - manage TPT interruptions; and
 - identify, document and manage adverse drug events.
- Establish TPT services in all relevant delivery sites, such as TB treatment sites, ART centres, maternal and child health services and community health centres.
- Decentralize TPT to health facilities that initiate and continue TB treatment, to ART centres or to the facility closest to the person's residence to minimize travel to receive TPT.
- Use existing TB, HIV and general health services to provide any specialized care required by people receiving TPT, such as management of severe or serious adverse events, drug–drug interactions, pregnancy and other special situations.
- Evaluate the capacity and availability of health-care workers, and assess additional requirements for nationwide scaling-up of TPT services.
- Evaluate the availability and capacity of community health workers and other networks. Former TB patients can contribute to TPT service delivery and support individuals and families in taking TPT.
- Build capacity through initial training, sensitization and mentoring of:
 - primary care doctors, nurses and other health-care workers in taking a history, screening for symptoms, assessing eligibility for TPT, referral for investigations, conducting tests for TB infection and starting TPT; and
 - community health workers in the provision of TPT and follow-up.
- Undertake phase-in/phase-out planning for TPT medications from a procurement perspective as the national programme changes to shorter TPT regimens. This is important during introduction of a new regimen.
- Review and strengthen the mechanism for quantification, ordering and an uninterrupted supply of TPT medications, pyridoxine and other commodities.
- Address specific issues regarding TPT for children, such as:
 - coordinating TPT with several family members, including parents and grandparents, and target the many service delivery sites at which children receive care, such as maternal and child health services and TB and HIV centres;
 - building capacity on managing vomiting of medication and indications for redosing; and
 - providing information on foods that can mask the taste of medication.
- Strengthen systematic recording and reporting, including information from case forms, or capture data on electronic platforms. Data variables should be integrated into the HMIS for M&E of performance.

Box 5. Nurses play a leading role in programmatic management of TPT in Brazil

In Brazil, nursing professionals are responsible for many public health actions in primary health care, including implementing strategies to improve TB prevention and care. Nurses also play an essential role in identifying individuals with TB infection and providing TPT. An important milestone in definition of the role of the nursing cadre in PMTPT was publication of a protocol by the Ministry of Health in 2011, which facilitated establishment of the role of nurses in TB prevention and care, including local health facility protocols for TPT, training and monitoring. The Ministry of Health collaborated proactively with the Brazilian Federal Nursing Council and issued a resolution that entrusted nurses with consultation, diagnosis and treatment of TB and requesting the TST, among other tests. In 2023, a new Resolution was issued by the Council, authorizing nurses to request IGRA tests and start TPT at all levels of care (123). This gave nurses autonomy for PMTPT. The Ministry of Health and the Council also developed job aids for interpreting IGRA results (124) and algorithms for TB screening and prescription of TPT.

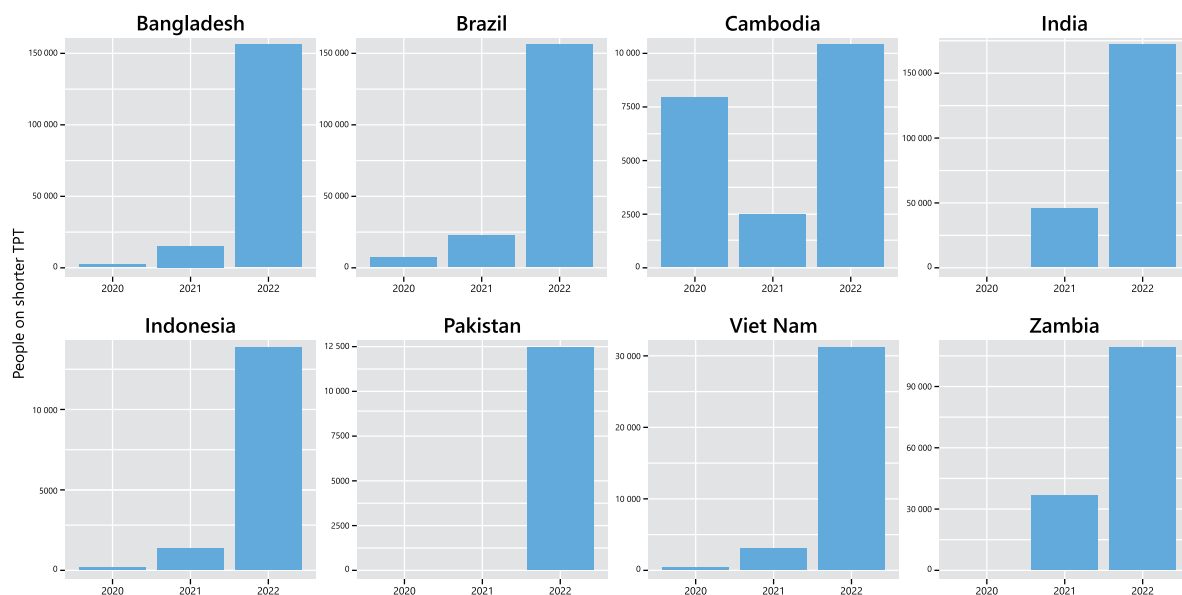
In 2017, Brazil developed a national plan to end TB aligned with the WHO End TB Strategy, which included intensified TB screening, diagnosis, TPT and surveillance of TB infection. It has been updated to cover the period 2021–2025. Nurses are central to this plan, for development of work plans at state and municipal levels, facilitating programmatic implementation and M&E along the cascade of TB care. In 2018, Brazil issued a protocol for digital case-based system for notification of people on TPT, which allows nurses to notify and monitor progress in achieving key performance indicators.

Organization of TB public policies within Brazil's Unified Health System and inclusion of public services, schools and professional institutions in the nursing category are the basis for integrating PMTPT activities into the professional functions of nurses.

Box 6. Actions taken by high TB burden countries for recent scaling up of shorter TPT for contacts of TB patients

Several countries have recently introduced shorter TPT regimens (Fig. 7). The work in eight countries is described under the Figure.

Fig. 7. Individuals given shorter rifamycin-based TPT regimens, selected high TB burden countries, 2020–2022



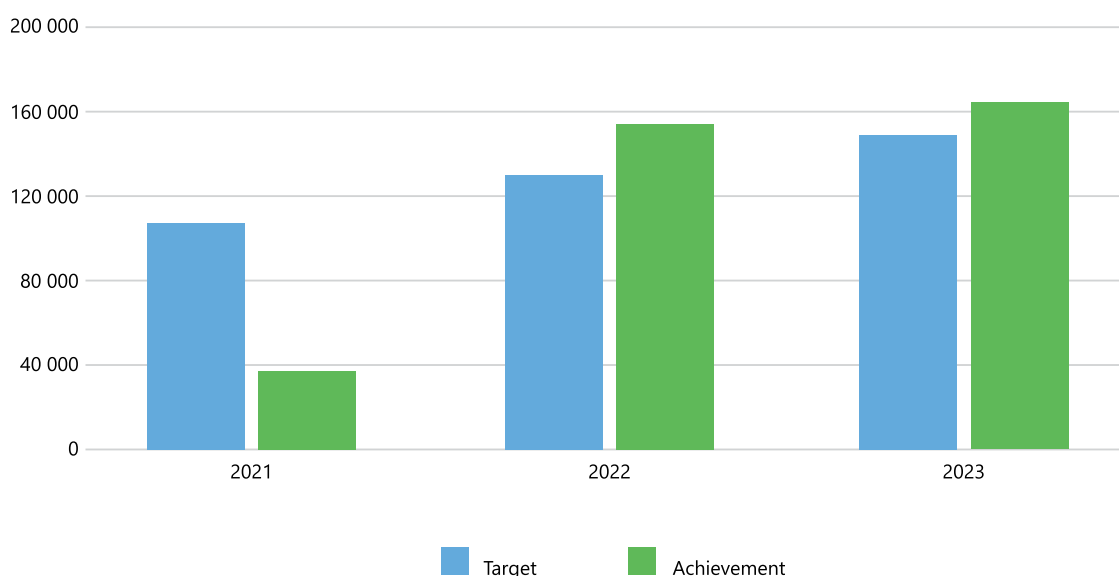
TPT, TB preventive treatment.

Source: National data reported to WHO (as of 8 May 2024)

Bangladesh: Innovations for extending use of shorter TPT in Bangladesh (Fig. 8) include:

- a rapid feasibility study for programmatic use of shorter 3HR in 2021 among 10 000 contacts of TB patients, which demonstrated a high level of acceptance, few adverse events and > 95% treatment completion. A similar study was conducted for 3HP in 2021 in one region. Lessons from these studies enabled the Ministry of Health to scale up 3HP and 3HR in 2022.
- creation by the Ministry of Health of a pool of primary-care doctors as trainers for health workers and community volunteers for TPT;
- a large network of community workers, supported by the Ministry of Health and an NGO, who engaged systematically in contact evaluation and TPT initiation;
- entrustment of community TB treatment providers by the Ministry of Health with provision of medication for prompt initiation and support of TPT; and
- systematic organization of workshops by the Ministry of Health to familiarize health workers at sub-national and district levels and raise awareness and acceptability of TPT.

Fig. 8. TPT enrolments supported by Global Fund grants, Bangladesh, 2021–2023

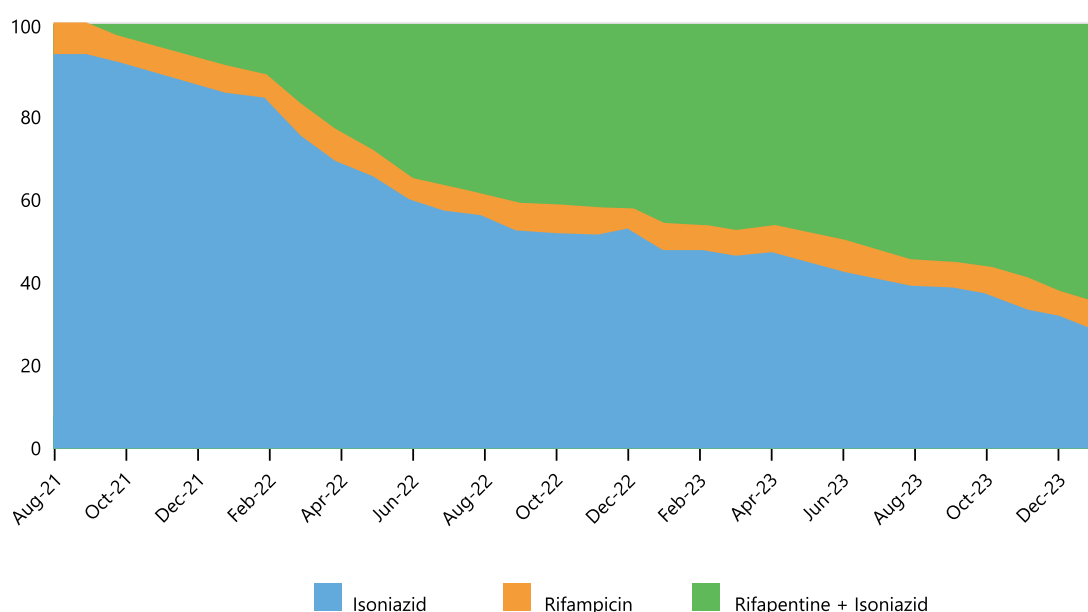


Brazil: 3HP is progressively replacing the 6H regimen for contacts of TB patients in Brazil (Fig. 9) through the following actions:

- a digital case-based surveillance system for notification of individuals starting TPT established in 2018 by the NTP and gradually scaled up nationwide;
- monthly digital reporting of data for analysis of the cascade of care, TPT uptake and identification of implementation gaps; and
- job aids for health-care professionals and managers developed by the NTP; webinars and workshops on clinical management of TB infection and training in application and reading of skin tests organized.

The NTP extended access to IGRAs by ensuring their availability in laboratory networks and also extended the populations eligible for IGRA testing to include immunocompromised individuals, children aged 2–10 years and people with HIV.

Fig. 9. Percentages of individuals placed on TPT by regimen type, Brazil, August 2021–January 2024



Source: Information System for Notifying People Under TPT (Ministry of Health; Information System for LTBI (SILT) (Secretariat of Health of Goiás State); Information System Vigilantes (Secretariat of Health of Santa Catarina State, Brazil).

Cambodia: The total number of people on shorter regimens (3HP and 3RH) has increased substantially since 2020. The following actions facilitated this expansion:

- strong commitment from the Ministry of Health and national technical partners to scale up shorter TPT;
- a technical working group established for regular monitoring and timely action to overcome bottlenecks;
- systematic creation of demand in communities and health facilities and investment to strengthen contact evaluation;
- systematic dissemination of national guidelines and capacity-building of health-care workers and NGO staff with support from partners; and
- uninterrupted availability of 3HP and 3RH with funding from partners.

India: India adopted use of 3HP for TPT in the following steps,

- Nationwide scaling up of shorter TPT was announced by the Prime Minister, resulting in strong political commitment.
- The National TB Elimination Programme (NTEP)
 - held a broad consultation on inclusion of 3HP in the national TPT guidelines (July 2021);
 - organized national online and offline training for health-care workers at all levels;
 - facilitated planning in districts;
 - mobilized about 125 000 courses of 3HP for use in contacts of TB patients from the WHO Country Office in India, the Global Fund and Unitaids, and ensured local procurement in some states during 2021–2022; and
 - developed a TPT module in the national case-based online TB information system (Ni-kshay) to strengthen monitoring and evaluation.

- In August 2022, a national workshop was held to share experience in use of 3HP in feasibility studies and programmatic implementation. The challenges highlighted during the consultation included concern about adherence to TPT, apprehension about the use of TPT from private providers and medical college experts and reports of adverse drug reactions. The steps taken to overcome these concerns were:
 - introduction of dedicated “treatment supporters”, who were given an incentive of INR 250/– per course of TPT completed;
 - continuing education sessions for private doctors and evidence sessions with medical college faculties; and
 - development of an adverse drug reaction module on the *Ni-kshay* platform to record and report adverse events.
- Since January 2022, about 100 000 contacts of TB patients have started 3HP. A completion rate of 90% was reported in the 2022 cohort (n = 14 310), with 1% loss to follow-up, 0.6% failure and four deaths.
- In early 2024, India used domestic funds to complete procurement of approximately 5 million courses of 3HP.



Photo credits: National TB Elimination Programme, India

Indonesia: 3HP was introduced through the Unitaid-supported IMPAACT4TB project in 2021 in Jakarta. The actions that enabled national scaling up were:

- high-level commitment by the Government to scale up TPT and include TPT coverage as one of the three main indicators in the national road map to End TB by 2030 and a Presidential decree on TB elimination in 2021;
- extension of 3HP to six high-burden provinces in 2022 and to all 34 provinces in 2023. In 2023, about 50% of 35 649 household contacts received 3HP as TPT.
- significantly increased domestic funding for training health-care workers through district health offices;
- domestic procurement of 3HP, with over 910 000 courses of 3HP procured in 2023;
- facilitation by the Ministry of Health of intrasectoral collaboration among health facilities, community leaders and territorial defence management for contact evaluation, TPT and monitoring of TPT implementation;
- facilitation by the Ministry of Health engagement of professional organizations, such as of pulmonologists and paediatricians, to facilitate training and as champions for TPT; and
- regular monthly meetings among district health offices, involving all health facilities and organization of information, education and communication campaigns on TPT.

Pakistan: The following were key enablers for implementation of shorter TPT, including 3HP:

- PMTPT a key priority in the National Strategic Plan (2024–2026);
- ambitious targets for TPT (151 000 in 2024) by the Ministry of Health;
- a consensus-building workshop involving all stakeholders and implementing partners organized by the Ministry of Health; and
- the first national guidelines and operational guidance developed through broad consultation with implementers and partners.

Viet Nam: The following were key enablers for implementing 3HP:

- combining active TB case-finding and TPT by systematic listing of TB contacts and implementation of the “double X strategy” (CXR and Xpert MTB/Rif®);
- promotion of testing for TB infection with TST or QuantiFERON before TPT, except in contacts aged < 5 years and people with HIV;

- integration of reporting of TB infection and TPT into the national HMIS;
- use of social media for monitoring TPT by health-care workers and home visits for children;
- updating and training in new guidelines for screening and TPT for health workers in communes; and
- a strategy for communication and education on TPT, especially for parents of children, with the support of civil society and local authorities.

Zambia: In 2022, over 100 000 individuals were started on shorter TPT regimens, facilitated by:

- rapid adoption of the latest WHO guidelines, including shorter TPT, into national guidelines, which increased acceptance by health-care workers;
- inclusion of TPT in a comprehensive care package for both HIV and contacts of TB patients;
- clear training and a plan for introducing shorter TPT in NTP plans;
- strong collaboration between TB and HIV programmes and stakeholders, including civil society and affected communities, for consensus building; and
- close coordination to ensure uninterrupted supplies of TPT products by the NTP with the Ministry of Health and national and international organizations.

5.7.2 TPT initiation and pre-TPT baseline assessment

Once TB disease has been ruled out and a decision made to consider TPT, a baseline assessment should be made to determine the eligibility of an individual. In addition to testing for TB infection (as indicated), the baseline assessment includes a personal and medical history and investigations according to national guidelines.

- Personal history: elicit information relevant for TPT initiation and continuation, such as
 - allergy or known hypersensitivity to TB drugs (isoniazid, rifampicin, rifabutin or rifapentine);
 - HIV status and ART regimen;
 - pregnancy status or birth control method used;
 - comorbidity: presence of comorbidities (such as malnutrition, diabetes, viral hepatitis) and medications being taken;
 - contacts of patients with drug-resistant TB (isoniazid, rifampicin only or MDR-TB); and
 - potential contraindications to TPT: active hepatitis (acute or chronic) or known elevation in transaminases (more than three times the upper limit of normal), regular or heavy alcohol consumption and symptoms of peripheral neuropathy. These conditions should prompt detailed investigations and application of clinical judgement to weigh the harms against the benefits of TPT, and timing of the start of TPT if the benefits outweigh the harm. A history of TB treatment or current pregnancy should not be considered contraindications to starting TPT.
- History of medication: elicit a history of medication to guide the choice of TPT regimen or determine whether treatment of comorbid conditions should be modified. Certain drug classes – ARVs, opioids, antimalarials – often affect TPT.
- Liver function test (LFT): There is insufficient evidence to support a mandatory or routine LFT at baseline (125) or whether the benefit of TPT without LFT would outweigh the harm, particularly with a less hepatotoxic regimen. When feasible, however, baseline testing is strongly encouraged for individuals with risk factors such as a history of liver disease, regular use of alcohol, chronic liver disease, HIV infection, age \geq 35 years and pregnancy or immediately post partum (within 3 months of delivery). In individuals with abnormal baseline LFT results, sound clinical judgement is required to determine whether the benefit of TPT would outweigh the risk of adverse events. These individuals should be tested routinely at subsequent visits.

- The social and financial situation of the person and the family should be assessed and support provided to overcome barriers to TPT completion.
- **Counselling:** Explain to the individual that (s)he is eligible for TPT, and provide information to the individual, family and treatment supporter on the:
 - rationale for TPT and the benefits to the individual, the household and the wider community;
 - the availability of TPT free of charge through national programmes;
 - the TPT regimen prescribed, including the duration, directions for intake of medicines and follow-up schedule;
 - potential side-effects and adverse events and what to do if they occur;
 - the importance of completing the full course of TPT;
 - the reasons and schedule of regular clinical and laboratory follow-up for monitoring; and
 - signs and symptoms of TB and advice on what to do if they occur.

Agree on the best approach to support treatment adherence, including the most suitable location for taking the drug and support according to each individual's preference, such as:

- location: home, community or health facility (with counselling);
- treatment supporter: if required, could be an oriented family member, community volunteer, workplace colleague or health-care worker; in a weekly regimen, it is preferable that intake of each dose is directly observed by the supporter (either in person or with a digital tool); and
- digital tools: include video-supported treatment, electronic medication monitors and use of phone or text messaging to maintain contact with the individual or household.

Table A2.1 in Annex 2 summarizes the issues to be considered when deciding to start TPT.

5.7.3 Monitoring of adherence and treatment completion

Adherence to medication and treatment completion are important determinants of the clinical benefit of TPT. Individuals receiving TPT should therefore be well informed at every contact with health-care providers. These elements are discussed further in section 7. Section 8 describes methods for monitoring and evaluating PMTPT in health services.

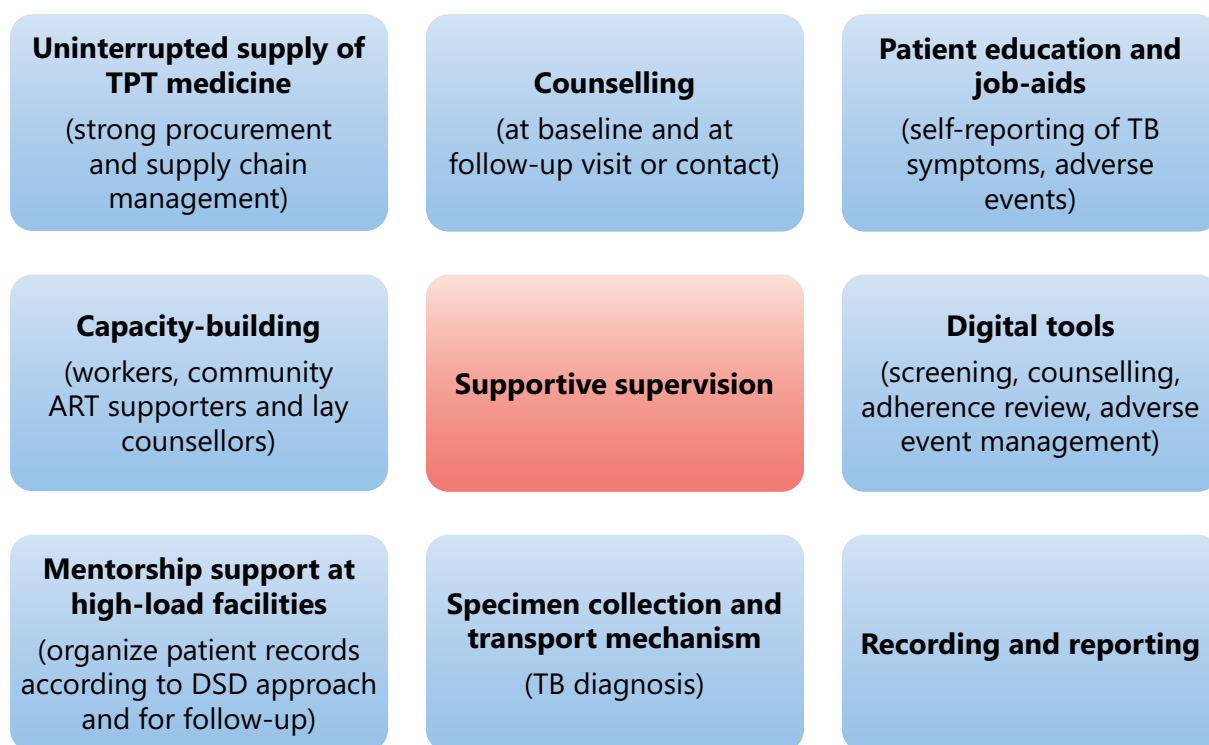
5.8 Differentiated HIV service delivery and implications for scaling up TPT

High HIV burden countries, particularly in sub-Saharan Africa, are increasingly scaling up differentiated HIV service delivery (DSD). DSD models for people with HIV who are stable on ART are person-centred, with the aim of changing treatment for people who are doing well to less intensive models, requiring fewer visits to health facilities. DSD is expected to reduce overcrowding at ART clinics, increase the quality of care, improve adherence and viral suppression rates and increase convenience. DSD includes appropriate support and education about potential adverse events, tolerability and the importance of treatment completion.

In principle, all TB services recommended for people with HIV, including regular TB screening, referral for diagnosis when TB symptoms are seen and TPT if TB disease is ruled out, should be included in DSD, and mechanisms for reviewing the quality of ART services should be used to monitor intensified TB case-finding and TPT services.

TPT may be started during an evaluation for ART or before starting spaced appointments under DSD, particularly for shorter regimens (1HP) or at the time of a follow-up visit to a health centre for longer regimens (6H, 6LFx, 4R, 3HR, 3HP) as per national guidelines. While TPT regimens of any length can be provided under DSD, it is critical to establish a mechanism for identifying and managing any adverse event, in view of the duration of TPT regimens, and to document TPT indicators systematically (see section 8). Fig. 10 illustrates the key elements of TPT to be integrated into DSD initiatives.

Fig. 10. Key elements of integration of TPT services into DSD models for ART



ART, antiretroviral treatment; DSD, differentiated HIV service delivery; TB, tuberculosis; TPT, TB preventive treatment

Various models of differentiated ART delivery have been tested, including health-care worker-managed group models; models used by people taking TPT; individual facility models; and community-based individual models. A few examples of implemented DSD models (126,127) are listed below.

- appointment spacing (facility and individual model): multi-month prescriptions and rapid circuit established at high-volume facilities to enable quick check-ups for stable patients and direct access to the pharmacy to collect medication;
- community points for ART distribution (community individual models): screening and drug distribution provided by lay health workers;
- adherence clubs (in facilities and communities): treatment distribution during support group meetings (every 3–6 months);
- specialized child-friendly clinics that provide 2–8 weeks of TPT and ART, depending on the travel schedule of each recipient; and
- remote access from commercial pharmacies or “pill boxes” (“medication ATMs”) without involvement of a community health-care worker.

As more countries implement DSD, a key opportunity for scaling up TPT services is a country’s decision to change to new regimens, such as dolutegravir ART. Countries in eastern and southern Africa have decided to align their transition to a regimen comprising tenofovir, lamivudine and dolutegravir with scaling up of 3HP. As a transition to new ART requires more frequent clinical follow-up, national programmes are also using the opportunity to start TPT and to use the experience to guide national scaling up.

DSD models could also be used for household contacts of TB patients and other people without HIV who are nonetheless at increased risk of TB disease.

Governments and donors should advocate and campaign to raise awareness among health care providers and populations at risk to generate demand for TPT.

It's time to allay concerns and expand TPT services in all settings.



6. Safety and management of adverse drug reactions in TB preventive treatment

Key points

- Severe or serious adverse events that require withdrawal of TPT are uncommon. As TPT is usually given to people who are otherwise healthy, it is all the more important to identify and manage any drug toxicity promptly.
- National programmes should establish mechanisms to record and manage adverse events systematically and to report adverse drug reactions to the national authority responsible for pharmacovigilance as per local regulations and requirements.
- Liver function testing before initiation of TPT is not routinely indicated. These tests are necessary only when there is a defined risk, such as pre-existing liver dysfunction or liver cirrhosis.
- ART can be used safely with shorter TPT regimens, and ARV options that limit the risk of drug–drug interaction are available. Possible interactions between rifamycins and other medications that a person may be taking should be anticipated and mitigated.
- Women on oral contraceptives should use an additional barrier contraceptive to avoid pregnancy while using rifamycin-based TPT.

WHO has long recommended use of TPT for populations at risk of TB, particularly those with HIV and child household contacts of TB patients. Programmatic scaling up of TPT has nevertheless been limited in most high TB and HIV burden countries due to competing priorities. Concern about the efficacy and safety of TPT and interactions with other medicines, particularly ARVs, may also be barriers. Frequently raised questions include whether TPT will increase TB drug resistance in a community (see also [section 5.6](#)) and the durability of TPT (see also [section 5.4](#)) to protect against disease or mortality. This section presents the available evidence on some of these important issues to facilitate TPT uptake and programmatic scaling up.

6.1 Drug safety and adverse drug reactions

Overall, serious adverse events leading to death or requiring withdrawal of TPT occur rarely. It is nevertheless critical to identify any sign of drug toxicity as soon as possible and to manage it immediately, particularly because people on TPT are usually healthy. Unmanaged drug toxicity may not only harm individuals but can also damage the reputation of a programme and result in widescale suspension of TPT due to loss of public confidence. As in any preventive action, health-care providers must weigh the risks and benefits of TPT for each individual. Obtaining a detailed, accurate medical history (including medicines being taken and past adverse drug reactions) and keeping up-to-date information at every contact with a person on TPT can help to identify people who should be closely monitored and the most

appropriate course of action if an adverse event occurs. Individuals on TPT should also be monitored at regular scheduled visits (monthly if feasible or as required for individual care or national programmes). [Table 5](#) summarizes adverse events associated with currently used TPT drugs.

Table 5. Documented adverse events with drugs used for TPT

Drug	Known adverse events	Uncommon adverse events
Isoniazid	Asymptomatic elevation of serum liver enzyme titres Hepatitis Peripheral neuropathy (paraesthesia, numbness, limb pain) Skin rash Sleepiness and lethargy	Convulsions Pellagra Arthralgia Anaemia Lupoid reactions
Rifampicin	Gastrointestinal reactions (abdominal pain, nausea, vomiting) Hepatitis Generalized cutaneous reactions Thrombocytopenic purpura Discolouration of body fluids	Osteomalacia Pseudomembranous colitis Pseudo adrenal crisis Acute renal failure Shock Haemolytic anaemia Influenza-like syndrome Hypoprothrombinaemia
Rifapentine	Gastrointestinal reactions (abdominal pain, nausea, vomiting) Hypersensitivity reactions (influenza-like symptoms) Hepatitis Discolouration of body fluids	Hypotension or syncope Decrease in white and red blood cell counts Decreased appetite Hyperbilirubinaemia Hypoprothrombinaemia
Levofloxacin	Diarrhoea Nausea and bloating Arthralgia	Inflamed or torn tendons Muscle pain or weakness Peripheral neuropathy Mood or behaviour changes Insomnia Prolongation of the QTc interval Altered taste and smell

In a network meta-analysis conducted in 2014 (updated in 2017), adverse events associated with the use of standard isoniazid regimen were compared with those associated with 3 or 4R and 3 or 4HR (57,128). The regimen with rifampicin only and that with rifampicin plus isoniazid were reported to be associated with a lower risk for hepatotoxicity than isoniazid monotherapy. Another systematic review, which included data from 23 randomized and 55 nonrandomized studies, reported high hepatotoxicity rates with 6H or 9H (2–6%) and the lowest rates with 3HP (1%) and 3R or 4R (0.01–2%) (129). The review, however, clearly stated the overall weak documentation of adverse events, heterogeneity in the data (different definitions of hepatotoxicity) and a high risk of bias in the studies. The data do provide indications of the frequency of adverse events and events that eventually require stopping preventive

treatment. The highest median rates of withdrawal due to adverse events were associated with 6H, followed by 9H, and the lowest rates with 3HP. Possible hypersensitivity reactions were reported in up to 4% of individuals on 3HP and 2% on 3HR. Few deaths due to any cause during TPT have been reported. In the studies included in the analysis, no deaths were reported among participants on 9H, 3HP or 3–4R, while a few deaths occurred in those on 6H and 3–4HR, largely among people with HIV who were not on ART and people with other comorbid conditions. Reassuringly, anaphylaxis was rarely reported with any regimen.

A systematic review and meta-analysis published in 2023 estimated the cumulative incidence of all types of adverse events and of hepatotoxicity associated with TPT regimens containing isoniazid and/or rifamycins (130). Children had a very low incidence of adverse events with all TPT regimens, including hepatotoxic adverse events of any severity and grade 3 and 4 severity or that resulted in drug discontinuation. Studies in which more than 50% of people had HIV had lower rates of adverse events of any type and severity and lower rates of adverse events leading to drug discontinuation. The incidence of adverse events leading to TPT discontinuation in pregnancy was 0.8% (95% CI 0.2% ; 3.3%). One death was related to TPT with rifamycin-based regimens and several related to IPT regimens, but no TPT-related deaths were identified in the studies in children. Pooled analysis of the studies in this review show a rate of any adverse events related to the study drug of about 7% (95% CI 5.3% ; 9.3%), with 16.4% (8.7% ; 28.7%) grades 1 and 2 and 2.4% (1.7% ; 3.5%) grades 3 and 4. The cumulative incidence of TPT discontinuation due to adverse events was 3.7% (95% CI 3.1% ; 4.5%). Adverse events leading to permanent drug discontinuation among children was < 1%. Table 6 shows the frequency of grades 3 and 4 events and discontinuation of TPT due to adverse events in recent studies and from two unpublished studies of Lfx use as TPT for MDR-TB (see Annex 5 of the second edition of WHO TPT guidelines, 2024) (64,119,130). The frequency of drug discontinuation due to adverse events varied from 0.6% with 3HP to 3.8% with the 3HR regimen. Several studies in high-burden countries (131,132) align with the discontinuation rate reported in the systematic review of 1.7% (0.5% ; 4.9%) and for 4R and 1HP of < 3% (133).

Table 6. Grade 3–4 adverse events and discontinuation of treatment due to adverse events in people on TPT

Regimen	No. of participants	Frequency % (95% CI) (reference)
Grade 3–4 adverse events^a		
6H or 9H	13 532	2.7% (1.3% ; 5.2%) (130)
1HP	1 488	16% (NA) (64)
3HP	9 867	3.6% (2.2% ; 6%) (129)
4R	3 865	0.6% (0.1% ; 3.6%) (130)
3 HR or 4HR	1 553	0.9% (0.3% to 3%) (130)
6Lfx (< 18 years)	452	0.9% (NA) ^b
6Lfx (≥ 14 years)	960	1.0% (0.3% ; 2.4%) ^b
Discontinued TPT because of adverse events		
6H or 9H	102 213	4.1% (3.2% ; 5.2%) (130)
1HP	1 488	1.1% (NA) (64)
3HP	1 802	0.6% (0.3% ; 10.2%) (110)

Regimen	No. of participants	Frequency % (95% CI) (reference)
4R	11 171	2.9% (1.8% ; 4.6%) (130)
3HR or 4HR	8 458	3.8% (3.4% ; 4.3%) (130)
6Lfx (< 18 years)	453	1.3% (NA) ^b
6Lfx (≥ 14 years)	1 412	5.5% (NA) ^b

1HR, 1 month of daily rifapentine plus isoniazid; 3HR, 3 months of weekly rifapentine plus isoniazid; 3HR or 4HR, 3 or 4 months of daily rifampicin plus isoniazid; 4R, 4 months of daily rifampicin monotherapy; 6H or 9H, 6 or 9 months of daily isoniazid monotherapy; 6Lfx, 6 months of daily levofloxacin monotherapy; NA, not available; TPT, TB preventive treatment.

^a Grade-3 adverse event: medically significant but not an imminently life-threatening; Grade-4 adverse event: life-threatening

^b Unpublished data from TB CHAMP and V-QUIN trials (see Annex 5 of (13))

The following sections provide further details on of the adverse events associated with specific drugs.

6.1.1 Isoniazid

- Asymptomatic elevation of serum liver enzyme concentrations occurs in 10–20% of people taking isoniazid, which usually return to normal even if treatment is continued.
- Clinical hepatitis leading to death occurs in about 0.1% of people taking isoniazid and is more common when the drug is combined with other hepatotoxic agents. Factors that may increase either the rate or severity of hepatitis include daily alcohol consumption, underlying liver disease or risk for liver disease, age > 65 years, and concurrent use of other medications that are metabolized in the liver. Symptomatic hepatitis is rare among people < 20 years, although severe and fatal cases have been reported.
- Peripheral neuropathy (paraesthesia, numbness and limb pain) occurs in < 0.2% of people taking isoniazid at normal doses. It is more likely in the presence of other conditions associated with neuropathy, such as diabetes, malnutrition, HIV, renal failure and problem alcohol use.
- Isoniazid is recognized as a secondary cause of pellagra, as it interrupts cellular niacin (vitamin B3) production in people with underlying nutritional deficiency. Niacin plays a vital role in numerous metabolic processes. Pellagra is clinically diagnosed by its characteristic skin rash; other symptoms include diarrhoea and neuropsychiatric changes. Populations at increased risk for pellagra include people who consume alcohol in excess and those with an undiversified reliance on unfortified maize staples.
- Other known adverse drug reactions due to isoniazid are skin rash, sleepiness and lethargy.

6.1.2 Rifampicin

- Gastrointestinal symptoms, such as nausea, anorexia and abdominal pain, are rarely severe enough to discontinue treatment.
- Hepatotoxicity, evidenced by transient asymptomatic hyperbilirubinaemia, occurs in 0.6% of people taking rifampicin. Hepatitis is more likely when rifampicin is combined with isoniazid.
- Cutaneous reactions, such as itching (pruritus), with or without a rash, may occur in about 6% of people taking rifampicin. They are generally self-limiting and may not be true hypersensitivity reactions. Continuation of treatment may be possible.
- Rifamycin hypersensitivity syndrome has been reported with use of rifampicin, characterized by influenza-like symptoms. The syndrome, when it occurs, typically develops a few weeks after the start, and, in most instances, TPT can be tolerated subsequently (131,132). Rarely, rifamycins are associated with hypersensitivity reactions, including hypotension, nephritis or thrombocytopenia manifested by symptoms such as fever, headache, dizziness or light-headedness, musculoskeletal pain, petechiae and pruritus.

- Orange discolouration of body fluids is expected and is harmless.

6.1.3 Rifapentine

- Overall, rifapentine in TPT is associated with fewer adverse events and is well tolerated, even by people with various degrees of hepatic dysfunction (133).
- Clinically significant systemic drug reactions, most of which are influenza-like, are reported in up to 3.5% individuals receiving 3HP, most cases being mild and resolving within 24 h (134). Clinical monitoring and continued vigilance for systemic drug reactions are nevertheless warranted in PMTPT. While there have been reports of hypotension or syncope after taking 3HP, hypersensitivity is uncommon.
- Other common adverse reactions include a change in the colour of body fluids to orange–red (benign), gastrointestinal side-effects (such as nausea, vomiting, loss of appetite), decreased white and red blood cell counts, skin rash or itching, joint pain and red eyes (135).

Recently, concern has been raised about reports of nitrosamine impurities in rifamycins. [Box 7](#) summarizes the context and measures being implemented to mitigate any potential risk.

Box 7. Nitrosamine contamination of rifamycins

In October 2020, WHO announced that nitrosamine impurities had been identified in rifampicin and rifapentine products after a review earlier that year of all applications for active pharmaceutical ingredients and medicines. Some nitrosamines have been classified by WHO as probable or possible causes of cancer in humans. They are widespread in foodstuffs, tobacco, cosmetics, drinking-water and elsewhere in the environment. Nitrosamines can be introduced into pharmaceutical products during manufacture, degradation or through cross-contamination. The degree of exposure to nitrosamines from medicines is usually similar to that in the environment. Furthermore, the duration of rifamycin use for TPT or TB treatment is relatively short – 1–6 months.

Health authorities in Canada, the European Union and the USA have assessed the risk of health effects of nitrosamines in medicines and have reported a very low risk that nitrosamine impurities at the levels found in TB drugs could cause cancer in humans. An initial benefit–risk assessment was conducted as soon as the WHO Prequalification Unit became aware of the presence of nitrosamine impurities in rifapentine and rifampicin products (136–139). The consensus has been that the risk to patients associated with interruption of treatment after product recall or suspension of distribution far outweighs any potential future cancer risk associated with any nitrosamine impurity present in the products. In 2020, the US Food and Drug Administration stated that it would not object to temporary distribution of rifapentine containing 1-cyclopentyl-4-nitrosopiperazine at a level < 20 parts per million and of rifampicin containing 1-methyl-4-nitrosopiperazine at a level < 5 parts per million (139).

Drug manufacturers are working with WHO and health regulators to reduce the level of nitrosamines in rifampicin and rifapentine.

6.1.4 Levofloxacin

Results from the TB CHAMP and V-QUIN studies were reviewed by the WHO GDG that developed the second edition of the TPT guidelines in 2024. These showed an important difference in the risks for adverse events between children and adults, with very good tolerance in children but less tolerability with increasing age. One or more adverse events of any grade was reported in about 32% of adolescents and adults taking Lfx in the V-QUIN trial, most being grade 1 or 2. Serious adverse events were infrequent, about 1% of participants developing grade 3 or 4 events, the occurrence of

which was not statistically significantly different from that in the placebo arm (Table 6). Pooled analysis of data from the two trials shows that Lfx was associated with more musculoskeletal events (arthritis, arthralgia or tendonitis) in adolescents and adults, mostly grade 1 or 2. Treatment discontinuation for adverse events, although uncommon, occurred more frequently among adolescents and adults than among children, which may have implications for adherence by adolescents and adults.

A systematic review conducted to inform the 2022 update of the consolidated guidelines on treatment of DR-TB showed that Lfx is generally safe, with some mild or moderate drug-related adverse events in children but no grade 3 or 4 or serious adverse events (140). Recent alerts highlight the safety concerns associated with prolonged use of fluoroquinolones in humans (96,97,141). The most commonly reported adverse events are dizziness, headache, nausea and abdominal pain (142). Although the adverse events may be mild, they might still require discontinuation of therapy. Fluoroquinolones increase the risk of tendon injuries, and older age and concomitant use of corticosteroids may be additional risk factors for tendinopathy (143).

6.2 Management of adverse events

As individuals who receive TPT are otherwise healthy, adverse events during TPT must be minimized. Most adverse events in people on TPT are mild and self-limiting. Conservative management and continuation under observation can be considered by the health-care provider if there are mild-to-moderate adverse events; however, if a severe adverse reaction occurs, TPT must be discontinued immediately and supportive medical care provided.

As a part of initial counselling, health workers should stress the importance and rationale for TPT and of completing the course and re-emphasize the risk associated with TB disease. A person on TPT should also be told about likely adverse events and be urged to contact their health-care provider if they develop events between visits that suggest drug toxicity (such as loss of appetite, persistent fatigue or weakness, abdominal discomfort, nausea, vomiting, dark-coloured urine, pale stools, rash or itching, yellow skin or eyes, tingling or numbness in the hands or feet). If a health worker cannot be consulted at the onset of such symptoms, the person on TPT should immediately stop treatment. People treated with rifamycins should be warned about pink discolouration of secretions due to this medicine, and people on Lfx should be informed of the rare occurrence of musculoskeletal symptoms such as tendonitis.

Clinician discretion should be exercised, and a complete history, including concomitant medications and supplements, must be taken. The following steps may help in assessing management of adverse events.

- How severe is the adverse event (mild, moderate, severe)?
- How serious is the event (likely to lead to death or life-threatening; hospitalization or prolongation of hospitalization required; persistent significant disability; congenital anomaly)?
- What should immediate management consist of (reassurance, symptomatic relief, discontinuation of TPT or requires an intervention to avert a severe outcome)?
- What is the underlying cause (the drug, other factors)?
- How will the adverse event affect future adherence (tolerability, consideration of substitution with an alternative regimen)?
- What is the next step (continue or restart, substitute, follow up and reassess, definitive halt)?

Once a person is started on TPT, routine monitoring should include evaluation of tolerability and adherence. The following should be checked at every contact:

- signs or symptoms of TB disease (“breakthrough” disease or missed diagnosis at start of TPT). If the person starts a cough, unexplained weight loss, fever or night sweats, they should immediately let the provider know and undergo testing. In younger children other, non-specific features such as failure to thrive, lack of playfulness and reduced appetite should be carefully monitored as they may be early signs to TB disease.

- pregnancy: continue TPT; if on 1HP or 3HP monitor closely or consider switching to an alternative TPT regimen such as 3HR;
- adverse event: type, onset and duration, severity, seriousness;
- assessment of adherence and provision of necessary support: any interruption to treatment should be discussed with the person on treatment and her or his treatment supporter, and interventions instituted to address problems in adherence;
- occurrence of another disease, such as malaria or diabetes;
- relevant physical examination;
- any medication (including traditional cures) that may interact with TPT; and
- liver function tests for individuals who had raised levels at baseline or at a previous visit, or with a history of regular use of alcohol. (See also [section 5](#).)

National programmes should establish a mechanism for systematic recording and management of any adverse event reported by people on TPT. In addition to prompt management, suspected or confirmed adverse drug reactions should be reported to the national authority responsible for pharmacovigilance as per local regulations. Patient files should be reviewed regularly to assess the most frequent types of adverse events and programme implementation adjusted to minimize them.

The following section provides guidance on management of the most common adverse drug reactions related to TPT drugs and regimens.

6.2.1 Isoniazid and rifampicin

Drug-induced hepatitis

- Features that indicate stopping medication: Transient, asymptomatic increases in serum liver transaminases during the early weeks of treatment. Treatment need not be interrupted or changed unless there is anorexia, malaise, vomiting or clinically evident jaundice. Clinical features of concern include protracted vomiting, mental changes and signs of bleeding, all of which suggest impending acute liver failure and require immediate discontinuation of medication.
- Management of jaundice and other severe features: If jaundice or any of the clinical features that suggest acute liver failure develop, all drugs must be stopped until jaundice or hepatic symptoms have resolved and liver enzymes have returned to baseline levels. If liver enzymes cannot be measured, it is advisable to wait 2 weeks after jaundice has disappeared before starting TPT. Other causes of hepatitis should be explored. Younger people with underlying risk factors for liver disease should be monitored clinically with the same precautions as older people.
- Reintroduction: Once hepatitis has resolved, the same drug regimen can be reintroduced, either gradually or all at once (“rechallenge”). If hepatitis was life-threatening and was unlikely to have been caused by something else (such as alcohol or viral infection), it is safer to switch to an alternative regimen.

Skin reactions

- Itching with no or a mild rash: Symptomatic treatment with antihistamines may be tried and TPT continued.
- Itching with moderate or severe rash: If the rash is severe or if there is evidence of mucosal involvement, hypotension or severe illness, corticosteroid treatment should be considered. Oral prednisolone (40–60 mg) should be given daily until there is a response; the dose should then be reduced gradually over the following days according to the clinical response. TPT should be withheld until the reaction has completely subsided. If the initial cutaneous reaction was severe, the full dose may be increased with smaller initial challenge doses. If a severe reaction occurs, the suspected medicine should not be given again, and an alternative regimen may be considered.
- People who develop isoniazid-associated pellagra should discontinue isoniazid and take high-dose nicotinamide (a form of vitamin B3). Full recovery is possible. Pellagra may result in severe illness or death if untreated (144). The recommended treatment for pellagra is 300 mg of nicotinamide

daily for 3–4 weeks. Good dietary sources of vitamin B3 are similar to those of vitamin B6 (see [section 5.2.2](#)).

Peripheral neuropathy

- To prevent peripheral neuropathy, administer 10–25 mg of vitamin B6 (pyridoxine) daily.
- For established peripheral neuropathy, give pyridoxine at a higher dose of 100–200 mg daily. (See [section 5](#) for more details.)
- Routine pyridoxine supplementation is recommended only in such conditions or when there is another risk of isoniazid toxicity (e.g. individuals who are slow acetylators or in a setting with known high levels of slow acetylators).

Gastrointestinal reactions

- Abdominal pain, nausea or vomiting may be associated with rifampicin use. If the symptoms are mild, the episode is usually self-limiting, and reassurance may suffice. If gastrointestinal upset is severe enough to risk interruption of treatment, suspend rifampicin for three or four doses, use medications that provide symptomatic relief (such as metoclopramide to counteract nausea and vomiting), or, as a last resort, give rifampicin with small amounts of food to allow continued use of the medicine. Although concomitant ingestion of food reduces the absorption of rifampicin slightly, this is preferable to complete discontinuation of TPT.

Lethargy: reassurance.

Discolouration of body secretions: red or orange urine, tears, semen and sweat are normal in people taking rifamycins. They should be reassured that the condition is innocuous and reversible.

6.2.2 Isoniazid and rifapentine

The HP regimens have several advantages and most adverse drug reactions associated with them are mild, self-resolving and without sequelae. However, systemic drug reactions like hypotension, dizziness, bronchospasm may lead to TPT discontinuation. Toxicity may be particularly pronounced among slow acetylators of isoniazid (see [section 5.2](#)) (145). The use of pyridoxine to prevent and treat isoniazid toxicity is described elsewhere in this handbook (see [section 5.2.2](#)). The following specific actions may be considered during management of potential adverse drug reactions after treatment with 3HP and 1HP.

- **Influenza-like syndrome** (attacks of fever, chills and malaise, sometimes with headache, dizziness or bone pain)
 - Influenza-like and other acute symptoms appear shortly after taking a dose of rifapentine-containing TPT, most commonly with the third dose.
 - If the symptoms are mild and not increasing, continue treatment and observe closely.
 - If the symptoms are moderate to severe, consider alternative TPT options without rifamycin (such as 6H).
- **Drug-associated fever**
 - Consider reintroduction of TPT if body temperature stays below 39 °C, but stop TPT permanently if fever recurs.
 - If body temperature is > 39 °C after a previous episode of drug-associated fever, stop TPT, and do not reintroduce HP.
- **Gastrointestinal reactions** (persistent nausea, frequent vomiting and/or persistent episodes of unformed watery stools)
 - Administer antiemetic or anti-diarrhoeal medication, and consider reintroducing HP with caution once the symptoms have resolved,
 - If the nausea, vomiting or diarrhoea requires aggressive rehydration, stop TPT, and do not reintroduce HP.

- **Cutaneous reactions**
 - In the case of diffuse rash (no vesicles) or diffuse rash with limited vesicles, stop, and consider reintroduction with caution.
 - If there are extensive bullous lesions, ulceration of mucous membranes or Stevens Johnson or toxic epidermal necrolysis, contact a specialist and administer steroids.
- **Other hypersensitivity reactions** (hypotension, acute bronchospasm, conjunctivitis, thrombocytopenia)
 - Assess the clinical severity of the symptoms, and, if they are severe, consider an alternative TPT option without rifamycin (6H).
 - Hypersensitivity usually resolves quickly after medication is stopped, with no long-term consequences.
- **Hepatitis**
 - Early signs of hepatotoxicity include weakness, fatigue, loss of appetite and persistent nausea. They should be identified early, as hepatotoxicity is reversible without permanent sequelae. Late signs of hepatotoxicity include liver tenderness, liver enlargement (hepatomegaly) and jaundice.
 - Stop HP, and consider reintroduction with caution if alanine and aspartate aminotransferase levels are less than five times the upper limits of normal in the absence of symptoms.
 - Stop and do not reintroduce HP if alanine and aspartate aminotransferase levels are five or more times the upper limit of normal in the absence of symptoms or three or more times the upper limit of normal in the presence of symptoms.
- **Psychosis**
 - Undertake a psychiatric evaluation, consider antipsychotic therapy, and provide pyridoxine supplementation. Stop, and do not reintroduce isoniazid if the psychosis is attributable to isoniazid.
- **Seizures**
 - Withhold isoniazid pending resolution of seizures, and evaluate the possible causes (146); stop and do not reintroduce isoniazid if the seizures are attributable to isoniazid.

Rifamycins are potent enzyme inducers and may induce drug–drug interactions. (See also [section 6.3.](#))

6.2.3 Levofloxacin

Patients should be advised to inform their health-care provider immediately if any of the following occurs:

- pain, swelling or tearing of a tendon (such as the back of the ankle or elbow) or muscle or joint pain;
- severe diarrhoea (watery or bloody);
- paraesthesiae (tingling or burning sensations in the peripheries);
- seizures, epilepsy, change in mood or behaviour; or
- low blood sugar symptom (headache, hunger, sweating, irritability, dizziness, nausea, fast heart rate or feeling anxious or shaky).

The specific course of action will depend on the adverse event reported, such as use of pain medication and pyridoxine for neuropathy. It is important to note whether the adverse events are worsening, in which case, a doctor should be consulted. Sunscreen lotions should be used for Lfx-induced sun sensitivity. Some of the adverse events may take time to resolve, and the person should be counselled to exercise patience.

6.3 Drug–drug interactions

6.3.1 Rifamycins and ARV

When rifamycins and ARVs are given together, the effect of either drug on the body may be changed. A drug–drug interaction can increase or decrease the action of either or both drugs, reduce efficacy or cause adverse events. Rifamycins are potent inducers of metabolizing enzymes, including cytochrome

P450 enzymes, and may therefore interfere with medicines that depend on this metabolic pathway, accelerating their elimination. Rifampicin in particular is a potent inducer of hepatic CYP 450 (mostly 3A and 2C sub-families), P-glycoprotein and uridine diphosphate glucuronosyltransferase 1A enzymes. Similarly, rifapentine induces P450 enzymes, specifically the CYP3A4, CYP2C8 and CYP2C9 isoenzymes (147). Rifampicin and rifapentine are similarly potent inducers, while rifabutin is less powerful.

In general, care should be taken when prescribing regimens containing rifampicin and rifapentine to people with HIV who are on ART. Rifamycins accelerate the metabolism of some ARV drugs; thus, co-administration of these ARVs with rifamycins may cause HIV treatment failure or resistance. The ARVs most affected by CYP 450 induction due to rifamycin include all PIs, non-nucleoside reverse transcriptase inhibitor (NNRTIs), integrase strand transfer inhibitors (such as dolutegravir) and CCR5 antagonists (such as maraviroc). These regimens can significantly decrease the concentrations of boosted protease inhibitors or nevirapine and should not be co-administered, including to HIV-exposed infants on TPT. While dose adjustment is not required when rifampicin is co-administered with efavirenz, the dose of dolutegravir should be increased to 50 mg twice daily for adults when given with rifampicin (148). This dose is well tolerated and is of equivalent efficacy to efavirenz in viral suppression and recovery of CD4 cell count (149). 3HP can be administered to people receiving efavirenz-based ARV regimens without dose adjustment (150). Administration of rifapentine with raltegravir is also safe and well tolerated (151).

Rifamycins also interact with many other medicines (see Table 6). Sound clinical judgement is therefore required when these medicines are to be co-administered with rifamycin-based TPT, either by avoiding them or adjusting their dose (152).

6.3.2 Co-administration of rifapentine and dolutegravir

While once-weekly rifapentine is known to reduce exposure to dolutegravir, the blood levels of dolutegravir remain above the target concentrations for viral suppression in adults taking both medicines. One study showed that a reduction in dolutegravir concentration – even by 75–80% – is unlikely to be clinically significant, as even a dose of 10 mg dolutegravir once daily (with nucleotide reverse transcriptase inhibitor backbone) results in high rates of virological suppression over 96 weeks, similar to those with an efavirenz-containing regimen (153). Dolutegravir can therefore be given with weekly rifapentine without modifying the dose.

The results of a phase 1/2 clinical trial of 3HP and dolutegravir in adults with HIV showed good tolerance and viral load suppression, no adverse events related to 3HP higher than grade 3 and no reduction of dolutegravir levels sufficient to require dose adjustment (154). Recent work continues to support this position (155,156). Preliminary evidence from a phase 1/2 trial (DOLPHIN TOO) (157) also supports the immediate start of TPT among ART-naïve people starting a dolutegravir based regimen. When 3HP was administered to 50 people with HIV who were ART-naïve and were started on dolutegravir-containing ART, high rates of viral suppression, comparable to those with 6H, were achieved, and no difference in Grade 3 or 4 adverse events was observed (157). Administration of rifapentine with raltegravir was also found to be safe and well tolerated (151). The 3HP regimen can be administered to patients receiving efavirenz-based antiretroviral regimens without dose adjustment, according to a study of their pharmacokinetics (152).

No dose adjustment is required when rifampicin is co-administered with efavirenz, and the two drugs can be used together safely. The dose of dolutegravir, however, should be increased to 50 mg twice daily when given with rifampicin. This dose is usually well tolerated and is of equivalent efficacy to efavirenz in viral suppression and recovery of the CD4 cell count.

More studies should be conducted on the pharmacokinetics of concomitant administration of 3HP with other medicines, particularly boosted PIs and tenofovir alafenamide, and should include both pregnant women and children. Studies of the doses of dolutegravir with daily rifapentine and whether the dose of dolutegravir should be adjusted with 1HP for adults and children are under way (ACTG 5372).

6.3.3 ARV options for concomitant administration with rifamycin-based TPT

ART should be changed to accommodate a certain TPT regimen with the utmost caution. The clinician should seriously weigh the risks versus the benefit of such a change, as frequent changes of ART are associated with loss of virological control and should hence be avoided to the extent possible, particularly when the person is virologically suppressed by current ART. In addition, changing to efavirenz-based ART in areas with high rates of NNRTI resistance (including many areas in sub-Saharan Africa) is not ideal. Overall, successful ART should have primacy in a decision over choice of TPT regimen. If changing the ART regimen is being considered for compatibility with rifamycin-containing TPT the following should be considered.

- Most nucleotide reverse transcriptase inhibitors and fusion inhibitors do not interact significantly with rifamycins.
- Pharmacokinetics data show no significant drug–drug interactions between rifapentine and the NNRTI efavirenz (158–160) or the integrase strand transfer inhibitor raltegravir (151).
- No significant drug–drug interactions have been reported with use of rifapentine and an ART regimen containing abacavir, emtricitabine, TDF, lamivudine or zidovudine. Regimens with efavirenz or raltegravir used in combination with either abacavir/lamivudine or TDF/emtricitabine can be used with 3HP.

Tenofovir alafenamide is a notable exception, as it is a P-glycoprotein substrate and may result in unacceptably low exposure to a rifamycin such as rifapentine. Concomitant administration of tenofovir alafenamide and a rifapentine should therefore be avoided until further data are available to support their concurrent use (161). Of note, tenofovir alafenamide given with rifampicin results in intracellular levels of the active drug tenofovir diphosphate similar to those with TDF alone, suggesting that this combination could be used; however, clinical data are limited (162).

6.3.4 Isoniazid

Isoniazid is known to inhibit certain cytochrome P-450 enzymes. Therefore, co-administration of isoniazid with drugs that undergo biotransformation through these metabolic pathways may decrease their elimination, thereby increasing exposure. Consequently, dosages of drugs metabolized by these enzymes might have to be adjusted when starting or stopping to maintain optimal therapeutic blood levels. Isoniazid has been reported to inhibit the metabolism of efavirenz, anticonvulsants, benzodiazepines, haloperidol, ketoconazole, theophylline and warfarin. The impact of the competing effects of rifampicin and isoniazid on the metabolism of these drugs is unknown, but the inducing effects of rifampicin tend to be more prominent (Table 7).

Table 7. Common drug–drug interactions of isoniazid and rifamycins

Medication class	Examples	Isoniazid inhibits metabolism and increases blood levels	Rifamycins accelerate metabolism and decrease blood levels ^a
Antiarrhythmics	Disopyramide, mexiletine, quinidine, tocainide		↓
Antibiotics	Chloramphenicol, clarithromycin, dapsone, doxycycline, fluoroquinolones		↓
Anticoagulants	Warfarin	↑	↓
Anticonvulsants	Phenytoin	↑ (Phenytoin, carbamazepine, primidone, valproic acid)	↓
Antidepressants	Amitriptyline, nortriptyline	↑ Some selective serotonin reuptake inhibitors	↓
Antimalarials		↑ Halofantrine	↓ Quinine
Antipsychotics	Haloperidol	↑	↓
Antivirals		↑ Ritonavir, efavirenz	↓ Protease inhibitors, integrase strand transfer inhibitor ↓ Nevirapine with rifampicin
Azole antifungals	Fluconazole, itraconazole, ketoconazole	↑	↓
Barbiturates	Phenobarbital		↓
Benzodiazepines	Diazepam	↑ Diazepam, triazolam	↓
Beta-blockers	Propranolol		↓
Calcium channel blockers	Diltiazem, nifedipine, verapamil		↓
Cardiac glycoside preparations	Digoxin		↓

Medication class	Examples	Isoniazid inhibits metabolism and increases blood levels	Rifamycins accelerate metabolism and decrease blood levels ^a
Corticosteroids	Prednisone		↓
Fibrates	Clofibrate		↓
Oral hypoglycaemic agents	Sulfonylureas		↓
Hormonal contraceptives/progestins	Ethinyl oestradiol, levonorgestrel		↓(Rifapentine)
Immunosuppressants	Cyclosporine, tacrolimus		↓
Methylxanthines	Theophylline	↑	↓
Narcotic analgesics	Methadone	↑ Levomethylate acetate	↓
Phosphodiesterase-5 Inhibitors	Sildenafil		↓(Rifapentine)
Thyroid preparations	Levothyroxine		↓

^a For many agents, the magnitude of effect may depend on daily dosing of rifamycins versus a once-weekly dose (rifapentine).

6.3.5 Rifamycin-based TPT and antimalaria treatment

As rifampicin and other rifamycins are potent CYP3A4 inducers, they decrease exposure to quinine in adults on malaria treatment, leading to a five-times increase in the rate of recrudescence (79). Similarly, concomitant administration with mefloquine reduces exposure to mefloquine by three times. A similar decrease in exposure was reported with co-administration of rifampicin and artemether, dihydroartemisinin and lumefantrine (decreases of nine, six and three times, respectively). There is insufficient evidence to change the current recommendations for dosing by body weight of these antimalarial agents, and close monitoring for recrudescence is advised. The following guidance may be applied until clear evidence becomes available on ways to increase exposure to antimalarial drugs.

- If a person has diagnosed malaria but is not yet on rifamycin-containing TPT, the episode of malaria should be prioritized and treated first.
- If a person has diagnosed malaria while on rifamycin-based TPT, malaria treatment should be started concomitantly and monitored clinically according to national guidelines to ensure that the malaria is cured. There is insufficient evidence to indicate that the doses of either TPT or artemisinin-based combination therapy should be adjusted.
- If malaria recurs in a person on TPT, they should be retreated for malaria according to national guidelines. Preventive treatment should be withheld only if the new malaria treatment also includes drugs that are known to interact with rifamycins. TPT may be resumed once the episode of malaria is resolved.
- If a person meets the diagnostic criteria for severe malaria (impaired consciousness, low blood glucose, high bilirubin, jaundice, bleeding, anaemia, kidney failure and parasitaemia > 10%), TPT

should be withheld, and the person treated urgently according to national guidelines. TPT should be recommenced only when the episode of malaria is fully resolved.

6.3.6 Levofloxacin

The absorption of Lfx is not influenced by food. There are no major interactions between milk or dairy products and third-generation fluoroquinolones. Concomitant steroid use may increase the risk of tendon rupture. Antacids (especially those containing aluminium), mineral supplements (e.g. iron or magnesium) or multivitamins may decrease absorption and should therefore be taken more than 2 h before or after this medication. The effect of warfarin may be enhanced by Lfx. Prothrombin time and international normalized ratio should be monitored, and the patient should be informed about the risk of bleeding. As Lfx may affect glucose metabolism, blood sugar levels should be monitored.

A complete course of TPT offers most benefit. Governments and donors should support patient and family education and treatment support during TPT.

It's time to invest and build patient support systems to ensure TPT completion.



7. Supporting people in adhering to and completing TB preventive treatment

Key points

- Adherence to treatment and completion of TPT are critical for maximum efficacy.
- Counselling, patient education and continuous support are essential for successful completion of TPT.
- National programmes should provide both an enabling environment and incentives to overcome barriers to TPT adherence.
- Efforts should be made to identify non-adherence early and an adherence plan be developed in consultation with the person receiving TPT and their family or other caregiver.

Adherence to treatment is critical for the efficacy of TPT. Adherence to medication is a complex behaviour that is influenced by many factors, such as personal motivation, beliefs about health, risks and benefits of treatment, comorbid conditions, competing demands, the family environment, the complexity of the drug regimen, drug toxicity, trust and relationships with health providers (163). [Section 7](#) discusses monitoring of adherence, determining TPT completion, analysing challenges and supporting people in completing their TPT.

7.1 Monitoring TPT

Individuals receiving TPT should be monitored at every contact with health-care providers. It is important to determine non-adherence as early as possible in order to take corrective action. Monitoring is particularly important at the beginning of treatment, when people are getting used to the routine and their medication. Afterwards, monitoring may be done monthly or more frequently as required for care of people on TPT or as per national policy. Nurses and other front-line health-care workers can be trained to monitor and to decide whether TPT should be changed because of adverse events or be re-started (e.g. after an interruption of treatment). Medical doctors or specialists are not required for such decisions, but their services should be available when required.

Alternatively, monitoring may be aligned with mechanisms in the DSD model for people with HIV, where implemented, or in a schedule for collection of other medication at a health facility (see also [section 5](#)). On principle, the schedule for follow-up visits or drug collection should be at the individual's convenience. It is important that an informed decision by a person offered TPT not to take the treatment or to stop it after having started it be respected; people should not feel coerced to take treatment. (See also ethical principles in [section 9](#).)

7.2 Management of missed doses

When people interrupt TPT, it is important to identify the reasons for the interruption. The person taking TPT and their caregiver should be counselled on the importance of adherence, and the health-care worker, with the person taking TPT and their caregiver, should review ways to improve adherence and agree on a way forward. There is little evidence on how many missed doses can be made up for by prolonging treatment without compromising efficacy. [Table 8](#) proposes means to manage interruptions in TPT, depending on the duration of non-adherence and the TPT regimen.

Table 8. Management of interruptions by duration for different TPT regimens

TPT regimen	Duration of treatment interruption	Next step
3HR, 4R, 6H, 6Lfx	< 2 weeks	<p>Resume TPT, and add the number of days of missed doses to the total treatment duration.</p> <p>Do not change the scheduled date of the next follow-up visit, but postpone the last follow-up visit by the number of extra days to compensate for missed doses. For example, if a child on 3HR misses 3 days of treatment, continue TPT for a total of 3 months + 3 days from the date of start.</p>
	≥ 2 weeks	<p>If treatment interruption occurred after more than 80% of doses in the regimen had been taken, continue and complete the remaining treatment as per the original plan.</p> <p>If less than 80% of doses in the regimen were taken, and the treatment course can still be completed within the expected treatment duration + 33% additional time, continue and complete the remaining treatment as per the original plan. For example, if an adult on 6H had taken only 120 doses by month 6, the remaining 62 doses can be taken in the next 2 months, without exceeding the 239-day limit.</p> <p>If < 80% of doses in the regimen were taken, and the treatment course cannot be completed within the expected time, consider re-starting the full TPT course. A shorter regimen would be preferable.</p>
3HP	1 weekly dose missed	<p>If the missed dose is remembered within the next 2 days, continue to take remaining doses according to the original schedule.</p> <p>If the missed dose is remembered > 2 days later, take the missed dose immediately, and change the schedule for weekly intake to the day the missed dose was taken, until treatment completion. This will avoid 2 weekly doses being taken fewer than 4 days apart.</p>

TPT regimen	Duration of treatment interruption	Next step
3HP	> 1 weekly dose missed	<p>If treatment interruption occurred after at least 9 doses were taken within 12 weeks of starting, continue and complete the remaining doses, thus prolonging the total treatment duration to a maximum of 112 days.</p> <p>If ≥ 4 weekly doses are missed, consider re-starting the full TPT course.</p> <p>If an individual has difficulty in adhering to a weekly routine, consider discontinuing 3HP and offering an alternative regimen with daily dosing.</p>
	> 7 doses missed	<p>If > 7 consecutive doses were missed, consider re-starting the complete course of 1HP regimen.</p> <p>If > 7 doses were missed intermittently, continue and complete the remaining doses, thus prolonging the total treatment duration to a maximum of 6 weeks (42 days from starting TPT).</p>
1HP	≤ 7 doses missed	Continue and complete the remaining doses, thus prolonging the total treatment duration to a maximum of 6 weeks (42 days from starting TPT).
	> 7 doses missed	<p>If > 7 consecutive doses were missed, consider re-starting the complete course of 1HP regimen.</p> <p>If > 7 doses were missed intermittently, continue and complete the remaining doses, thus prolonging the total treatment duration to a maximum of 6 weeks (42 days from starting TPT).</p>

1HP, 1 month of daily rifapentine plus isoniazid; 3HP, 3 months of weekly rifapentine plus isoniazid; 3HR, 3 months of daily rifampicin plus isoniazid; 4R, 4 months of daily rifampicin monotherapy; 6H, 6 months of daily isoniazid monotherapy; 6Lfx, 6 months of daily levofloxacin monotherapy; TPT, TB preventive treatment.

Interruptions may be consecutive or intermittent, unless otherwise indicated.

7.3 Determining TPT completion

The proportion of expected doses taken within the usual duration of the regimen and the total number of doses taken are considered to be key determinants of the efficacy of TPT (115,116). Various end-points have been used in trials to determine TPT completion, such as 80% of the doses consumed within 120% of the planned TPT duration (164) and 90% of recommended doses consumed within 133% of the planned TPT duration (165). The V-QUIN trial of 6Lfx considered a contact to have completed the study therapy if they completed $\geq 80\%$ of the total number of prescribed doses within a total of 30 weeks after randomization (166). In this handbook, we propose that programmes declare TPT to be completed when at least 80% of the expected doses are taken within the usual duration of the regimen and the remainder taken within an extended time equivalent to one third of the usual duration. Table 9 shows how these timings apply to all recommended regimens. The limits shown in this table are meant to guide classification of TPT completion; other considerations may apply for decisions on continuing or re-starting of TPT after an interruption (see Table 8).

Table 9. Criteria for determining completion of different TPT regimens

TPT regimen	Total duration (months)	Expected number of doses	80% of recommended doses (days)	Extended time for treatment completion (days) (treatment duration +33% additional time)
6H (daily)	6	182	146	239
3HR (daily)	3	84	68	120
3HP (weekly)	3	12	10	112
4R (daily)	4	120	96	160
1HP (daily)	1	28	23	40
6Lfx (daily)	6	182	146	239

In addition to the indicators for monitoring PMTPT proposed in [section 8](#), programmes may wish to consider unfavourable end-points of TPT for triggering a review of case management and, in some instances, changes to medication:

- failed: development of TB disease any time while on TPT;
- died: death from any cause while on TPT;
- lost to follow-up: interruption of TPT for a duration that precludes completion of treatment in the maximal time possible (at thresholds shown in [Table 9](#));
- TPT discontinued by a health-care worker: due to toxicity, other adverse events or drug–drug interactions, with or without re-starting or switching the regimen; and
- not evaluated: such as records lost, transfer to another health facility with record of TPT completion.

7.4 Potential barriers to adherence

Many factors may influence a person's decision to adhere to or interrupt a recommended treatment regimen. Non-adherence should be recognized and addressed as soon as possible. The following should be considered potential barriers to adherence to TPT among adults:

- competing priorities, such as work, travel, school, caring for children or the elderly;
- little conviction of the importance of TPT (TPT considered more of a nuisance than of use);
- treatment-related issues:
 - understanding how to take or administer TPT correctly and its duration;
 - adverse drug reactions associated with the medicines and personal history of reactions to medicines;
 - coexisting medical conditions;
 - onset or possibility of pregnancy;
 - concomitant use of other medicines, conventional or otherwise, or food supplements that could interfere with adherence to or the effectiveness of TPT medicines (e.g. oral contraceptives, ARVs);
 - alcohol intake during medication;
 - difficulty in remembering daily or weekly doses; and
 - religious practices such as fasting;
- health-care service issues: cost of clinic visits (transport, time, loss of work), clinic opening hours, conflict with a person's schedule, long waiting times at clinics;
- incorrect or insufficient information about TB infection and TB disease;
- real or perceived stigmatization of people with TB infection, disease and treatment; and
- health beliefs and practices.

7.5 Strategies to improve adherence and treatment completion

7.5.1 Supportive measures

National programmes should have mechanisms to improve adherence of specific risk groups in the local context. In general, all TPT options can be self-administered. Appropriate scaling-up of TPT is unlikely to increase the selection of drug-resistant TB strains. Modalities for treatment provision and adherence support should be determined primarily by the individual. Although several methods have been used to improve treatment adherence and completion, the evidence for their effectiveness remains inconclusive (167). Pill counting by providers at every contact with a person on TPT is inexpensive and feasible and was associated with a reduction in the risk for TB in a clinical trial (168). This practice can easily be included into TPT services. Adoption of blister-packaged products rather than pill bottles might also facilitate monitoring of adherence.

WHO guidelines for treatment, care and support propose several interventions for supporting adherence (169), which could also be applied to TPT. They include peer support networks, coaching and educational interventions, including counselling, use of electronic medication monitors and video-supported treatment. National programmes should dedicate the necessary financial and human resources to strengthening adherence to TPT and not allow concern about adherence or lack of tools for adherence to be a barrier to scaling up TPT services.

Acceptance of TPT by a person at risk is often influenced by information given by counsellors, nurses, doctors, pharmacists and other health-care staff. So that people can fully appreciate the rationale of TPT, the following benefits should be explained.

- TPT can prevent TB disease from occurring later. TB disease can lead to a long period of severe illness, permanent damage to organs and premature death if untreated.
- It is particularly important for people who have the following conditions to take TPT to reduce their risk of developing TB disease:
 - people with recent TB infection;
 - contacts of people with TB disease, especially children aged < 5 years;
 - people with HIV and other medical conditions that lower their immunity; and
 - people taking medication that lowers their immunity, such as anti-TNF and steroids.
- TPT with new medicines that shorten the treatment duration to ≤ 3 months is now recommended by WHO, whereas TB disease requires ≤ 4 –6 months of treatment, starting with four medicines.

Providers should also alert people about TPT-related adverse drug reactions and the likelihood of their occurrence (see [section 6](#)). Red discolouration of urine and other body fluids while taking 3HR, 3HP, 1HP or 4R is normal and is harmless and reversible.

7.5.2 Providing guidance to individuals receiving TPT

Interventions to ensure adherence and treatment completion should be tailored to the needs of each risk group and the local context. It should be emphasized that protection from TB by a course of TPT depends on the degree of adherence, although concern about perfect adherence should not be a barrier. The 2022 WHO guidelines on TB care and support propose digital and other interventions to support adherence by people on treatment for TB disease, which could also be used for TPT (169). Similarly, best practices for the care of TB patients include considerations that could be used for TPT (170).

The following should be considered when providing guidance to individuals receiving TPT.

- Ensure that the person prescribed TPT is committed to taking it properly and understands the importance of adherence and completion of treatment for maximum protection. Provide information in the first language and at the appropriate literacy level of the person concerned.

- Explore the person's understanding of TB and TPT, and elicit support from family members or a companion in a similar situation ("treatment buddy").
- Explain the importance of taking treatment on a fixed schedule, which makes it easier to remember to take the medication. A time of the day could be fixed for daily regimens and a time and day of the week for 3HP.
- Offer reminders and suggestions to help take medication regularly, including
 - electronic reminders on cell phones: bidirectional SMS and voice calls can improve communication with the caregiver, such as on suspected toxicity; or
 - a suggestion to take the medication with a specific meal or before sleeping (daily) or at the time of recurring activities, such as Friday, Saturday or Sunday prayers (weekly). (A television or radio programme should not be recommended as a reminder as it may be rescheduled or moved to a different time slot or there may be an electricity outage.)
- Explain that all medications should be taken together and the dose not be divided over a few hours or days. Pills can be taken separately, provided that the whole dose is taken within 30 min.
- Explain the importance of completing the full course of treatment for optimal protection from TB.
- Give clear information about adverse drug reactions ("side-effects") and signs that treatment should be stopped and a health-care worker contacted. Stress the importance of informing and seeking care from the provider in case of an adverse drug reaction, even if it is mild. In most cases, treatment of symptoms will suffice without having to stop or defer TPT.
- Involve family members and caregivers in health education when possible. Children often move between households and health facilities, and additional family members and caregivers could also be involved in support for adherence.
- Seek agreement with the person on TPT and their family, caregiver or health worker on a personal adherence plan, aligned to the treatment regimen. [Box 8](#) shows an example of a plan that could be adapted to each context. Informative materials (leaflets, posters, video clips) could be developed to reinforce messages.

At each contact with the person receiving TPT, the provider should:

- reinforce the person's understanding of symptoms of TB disease, reasons for TPT and the importance of completing the course;
- discuss the points on the adherence plan with the person on TPT at each visit, including the motivation of the person to remain TB free and strategies to optimize the best time to take the medicines;
- reinforce supportive educational messages at each contact during treatment;
- invite questions, provide clear, simple answers, and provide a telephone number for other queries or advice from health services;
- measure body weight, and adjust the TPT dosage accordingly, particularly for young children, as rapid weight gain is normal in growing infants and young children, thus requiring dosage adjustment;
- check for the presence of signs or symptoms of TB disease;
- ask about any adverse drug reactions, and manage any toxicity or refer to specialist care if necessary;
- elicit reasons for any missed dose, and extend the necessary support for adherence;
- continue management of comorbidities, and consult the treating doctor when necessary;
- ask about pregnancy, breastfeeding and contraceptive use;
- make a record of the visit, drug intake and findings from individual case files or forms prescribed by the national programme; and
- ensure confidentiality in all exchanges with the person on TPT and their entourage.

Box 8. Example of an adherence plan

- Review the understanding of people or caregivers on TB and TPT.
 - Ask them what they know about TB infection, TB disease and TPT.
 - Correct any false belief or wrong information about TB, as necessary.
- Understand the individual's motivation to start TPT.
 - What motivates them to stay healthy?
 - Find out whether the person is ready to start TPT, and, if not, provide appropriate advice.
 - Elicit their views on disclosure to others: Are they willing to disclose their treatment status to anyone? If yes, to whom?
- Discuss the medication
 - Explain the role of TPT and how the medicine should be taken (daily or weekly, within 30 min).
 - Ensure that the person understands possible adverse drug reactions and what to do if they occur.
 - Explain that concurrent intake of conventional and traditional medications may interact with TPT.
 - For children in their care:
 - Explain what to do after vomiting of a medication and when to repeat the dose of TPT; provide families with extra doses, or request that they report vomiting early if it occurs.
 - Explain the types of foods that can be used to mask the taste of crushed medication.
 - Discuss early signs of hepatotoxicity in children.
- Discuss the person's lifestyle, and provide advice on:
 - a time of day or a day in the week (3HP) for medication;
 - a routine for medication: before sleep, with a meal or every Sunday (weekly regimens);
 - reminders for medication, such as a cell phone alarm, a daily or weekly routine or a ritual;
 - choosing more than one strategy or reminder system; and
 - keeping alcohol consumption low.
- TPT planning for a family: If a medication box is used, discuss how to organize the medicines for each member.
- TPT support options:
 - preferred mode of contact with the health-care worker: telephone call, home visit, clinic visit, digital adherence technology;
 - preferred mode of contact when TPT doses are missed: cell phone call, home visit, contact family member or TPT buddy;
 - need for travel support for routine medicine collection;
 - details of contacts if adverse events are noted during TPT; and
 - links to other support, such as nutrition or other social support schemes in the country.
- Ongoing support: Reassure people that they may return at any time if they miss a TPT dose or face any other challenge to continuing their medication.

7.5.3 Creating an empowering environment to improve adherence

In addition to counselling people taking TPT and their families, the environment of the person on TPT should enhance the treatment experience.

- Align TPT delivery and follow-up with HIV or other services that the person may be receiving, including use of DSD models, and organize motivational counselling by trained providers.
- Identify an appropriate treatment supporter, such as a family member, neighbour or colleague. The treatment supporter should be counselled on providing care and support. Record the contact details (home address, home and work phone numbers, mobile phone number, e-mail address)

of the treatment supporter to minimize the risk of losing contact. It is important to maintain the confidentiality of this information.

- Schedule in-person meetings for individuals whose treatment has been interrupted or who missed appointments for medication refills. Digital adherence technologies, such as electronic medical monitors (pill boxes equipped with SIM cards) and video-supported therapy may help to ensure adherence when in-person visits are not feasible.
- If possible, encourage or motivate individuals, depending on the country context and availability of funds. Some countries provide mobile phone credit ("airtime"), grocery shop coupons or food parcels. While these are common, their role in improving adherence has not been clearly demonstrated (171).
- Provide incentives such as reimbursement of transport cost and phone calls to facilitate keeping appointments, depending on the availability of funds.

People on TPT should be seen by health-care workers at scheduled intervals appropriate to the country (every 2 weeks, monthly, quarterly). These encounters may take place in a clinic, in the community or in the household and serve to dispense medicines, assess progress and update records. Each such contact is an opportunity:

- to ask the individual about adherence and strategies used to ensure adherence (Show that you are also interested in helping them to adhere to treatment; discuss how many daily or weekly doses have been missed and how this can be avoided.);
- for adherence counselling, by
 - discussing any barriers and proposing joint solutions and
 - using motivational interviewing techniques to improve adherence (172) ("How do you feel when you have missed a dose?" "How do you want to change that?");
- for checking used blister packs and counting the remaining pills to determine whether the pill count corresponds to the expected consumption during the interval;
- to ask specifically about adverse events and TB symptoms;
- to check contact information against clinic records, including one verified cell phone number and the number of a close contact person; and
- to update the monitoring system and flag any person who misses a visit for a follow-up call within 1 week of missing the scheduled clinic visit, to enquire:
 - about adverse events, TB symptoms, pregnancy;
 - whether the person still has medicines; and
 - agree on the next clinic appointment as soon as possible.

7.5.4 Special considerations for adherence by children

As infants and children depend on caregivers for administration of medication, the barriers faced by their adult caregivers can result in missed doses for children. Other barriers that may apply include:

- lack of child-friendly, dispersible, palatable medication, which is easier to administer to children than solid tablets or even crushed pills dispersed in water;
- lack of conviction by the caregiver about the importance of TPT. Only if both caregivers and health-care workers are invested in successful completion of TPT will it be possible for the child to adhere to TPT;
- lack of one or more appropriate caregivers among relatives, as young children may move among different houses in the family; involvement of several caregivers (grandparents, father's family) may be necessary;
- lack of knowledge of caregivers about TB and TPT;
- changes in the routine of the family or child (such as school holidays) that disrupt the administration schedule; and
- lack of acceptance of the authority of a caregiver by older and more mature children and adolescents.

Strategies for managing and enhancing adherence among children are similar to those discussed above.

- Explain and emphasize to the caregiver and child why they must take the full course of TPT.
- Inform them about the availability of child-friendly formulations, and provide clear explanations and instructions to caregivers on dissolving dispersible tablets in water. Illustrative posters, handouts and videos may help.
- Provide a person-friendly schedule for appointments for drug refills.
- Take note of the reasons for poor adherence, and attempt to address them: such as long-distance transport, orphans, previous adverse reactions to medicines or the ill health of the primary caregiver.
- Provide adolescents directly with education and adherence support, especially if they are living with HIV.
- For young children who refuse to take medicine:
 - change the food type to better mask the taste, or place crushed medicines in the centre of solid food that is easy to swallow as alternatives to mixing with water; or
 - provide a small reward for taking medication completely.
- If a child vomits within 30 min of a dose, ensure that a new dose is given. Families should therefore be given a few extra doses every month. (The programme should estimate the extent of such losses and reflect it in procurement plans.)
- Prepare an adherence plan with the caregiver and ask that it be shared with other caregivers.
- Review the adherence plan at each encounter, especially if a new caregiver is present.
- Review the knowledge and barriers of the caregiver at each visit. Examples of questions to be asked are:
 - Who is the primary caregiver (parent, grandparent, aunt, uncle, another child)?
 - Does the child sometimes sleep in another family member's house?
 - Is the caregiver aware that the treatment is daily (isoniazid, 3HR) or weekly (3HP) for 3–6 months?
 - Is the caregiver aware of the number of pills to be given each time?
 - Is the caregiver aware of the procedure for administering child-friendly dispersible formulations?
 - Has the caregiver been counselled about the importance of adherence, adverse drug reactions, when to seek a health-care worker's advice and what to do when the child vomits medication?

Governments and donors should support the systematic monitoring and evaluation of programmatic management of TPT and generate strategic information.

It's time to invest in digital solutions for recording and reporting of TPT services.



8. Monitoring and evaluation

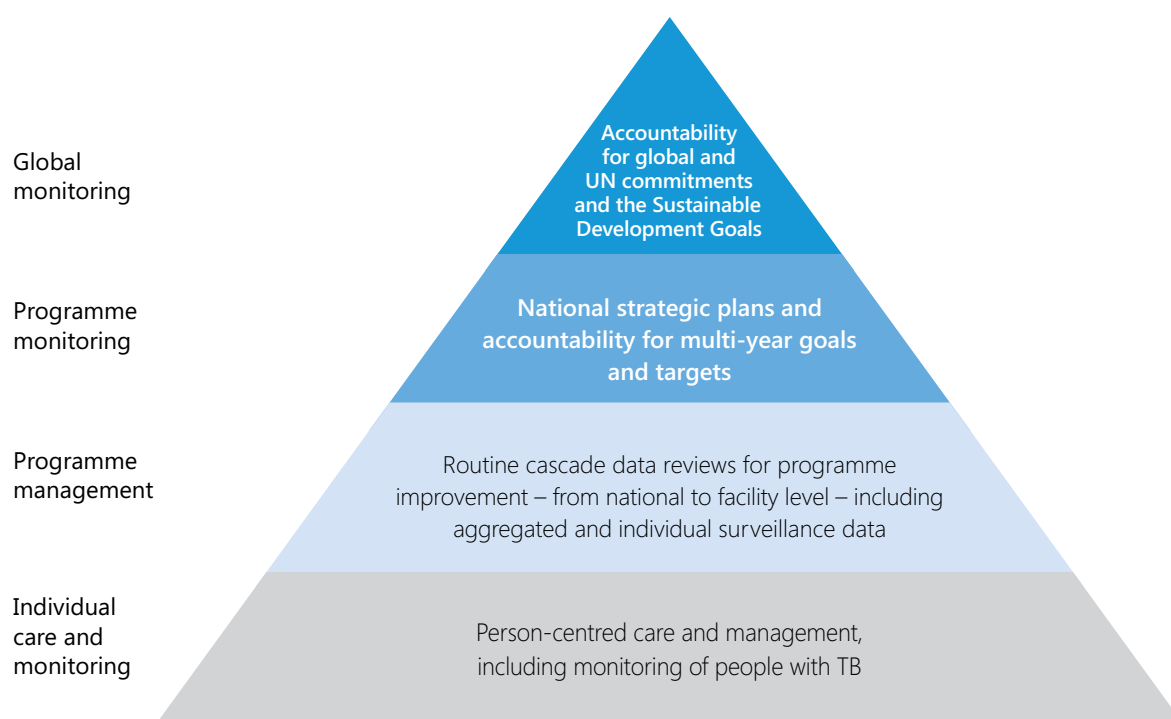
Key points

- Monitoring and evaluation (M&E) play an important role in patient care and in assessing national programmes and global response. Generation of indicators is a critical end-point for recording and reporting. This is usually done every quarter at regional and national levels, depending on the number of people being monitored.
- Supportive supervision involves checking the quality of data recording and reporting, including inspecting and validation of a person's case files and data collection tools for validity and completeness of recording.
- Ministries of health and national programmes should integrate M&E for TPT into the national health information system. Establishment of a parallel, separate data collection and reporting system for PMTPT is unnecessary. Digital tools such as the Prevent TB app can show the data necessary to monitor TPT and record adverse events.

8.1 The role of M&E

M&E play important roles in patient care and in assessing national programmes and the global response ([Fig. 11](#)). Accurate recording and reporting of programmatic data inform managers about the immediate outputs and outcomes of programme services as well as the larger impact of resources invested into a programme. If services are adequately accessed, activities are conducted in a timely manner, and expected results are achieved, it is likely that the overall goals will be met. When properly implemented, M&E should provide health-care providers and programme managers with information on how many contacts are in a TB patient's household and how many of them were effectively evaluated, or, how many people who were offered TPT in an ART clinic decided to take it and how many of those who started TPT continued it until the end.

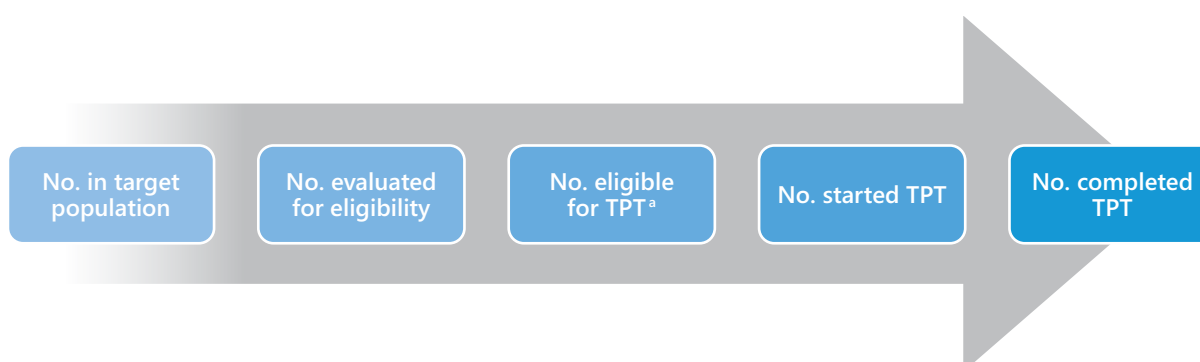
Fig. 11. Use of health data at different levels of the health system



8.2 Monitoring PMTPT

As several activities under PMTPT – such as contact investigation and preventive care of people with HIV – overlap with screening for TB disease and involve similar at-risk populations, M&E should be aligned to promote synergies and limit duplication. It is important to ensure that individuals who are at greatest risk of developing TB are systematically identified, and, once TB disease has been excluded, offered TPT to improve both their individual health and the community disease burden. Programmatic implementation and scaling up of TPT require strengthening of each element in the cascade of care, starting from identification of the target population to provision and continuation of TPT (Fig. 12).

Fig. 12. Critical numbers of people to be monitored at each step in the TPT pathway



No., number; TPT, TB preventive treatment.

^a if CXR and tests for TB infection are not used, this is the number of people with no clinical evidence of TB disease; if CXR and tests for TB infection are available, this is the number with no clinical or radiological evidence of disease and with a positive test for TB infection. In some individuals at risk TPT may be medically contraindicated.

8.2.1 Indicators for monitoring PMTPT

Generation of indicators is a critical outcome of recording and reporting. It is usually done every 3 months at regional and national levels, depending on the number of people being monitored. Data on TPT services are aggregated at regular intervals and reported for monitoring progress. If an electronic case-based data system is available, with nationwide coverage, data at lower levels may be aggregated at any required frequency to evaluate programme performance.

Principles for estimating the numbers eligible for TPT are listed in [Box 9](#).

Box 9. Calculation of the number of people eligible for TPT

The number of people eligible for TPT is strategic information for programme managers for judicious assignment of human resources, to order enough medicines and to assess other elements of logistics management. Most people eligible for TPT are in two groups – people with HIV and contacts of TB patients. Their numbers can be calculated as follows:

People with HIV: the number is derived from either the estimated number of people with HIV on ART or programme data on the following subpopulations:

- total number of people with HIV on ART at the end of the reporting period,
- [minus] total number of people with HIV currently on treatment for TB disease or being evaluated for TB disease,
- [minus, where possible] total number – or estimate – of people with HIV who previously completed TPT within the time as per national policy (or who are currently on TPT) and
- [minus, where possible] total number – or estimate – of people with HIV not eligible for TPT because of co-morbidity or contraindications (such as active hepatitis, chronic alcoholism, use of other medications that are potentially hepatotoxic such as nevirapine, neuropathy) or a decision to opt out.

If reliable data are not available, an estimate may be derived from discussions with clinical staff.

Contacts of people with TB: the number is based on the estimated number of household contacts of people with pulmonary TB in the country. The estimate also requires the following demographic data:

- the average size of a household and the proportion of the population in the age group 0–4 years (demographic indicators for countries, which are updated each year by the World Bank (173)). For example, if there were 20 000 people with pulmonary TB in the previous year, the average size of the household is 5, and 16% of the country population is < 5 years, an expected 100 000 contacts would be exposed, of whom 16 000 would be 0–4 years of age. This total might have to be adjusted downwards because some of the people notified with pulmonary TB would be in the same household, some of the contacts would require treatment for TB disease, and some of the contacts would be people with HIV on ART and therefore already included in the estimate.
- [minus, where possible] Total number – or estimate of the proportion – of people who would opt out or have a contraindication for TPT.

Individuals in other risk groups: these include clinical risk group, people in prisons, immigrants, health-care workers and other people eligible for TPT. Estimates should be collected from hospitals, prisons, testing centres and other sources.

Before placing an order for medicines, it is essential to consider feasibility. For example, if there is not yet a system for contact investigation, a realistic short-term target should be set while capacity is increased. It is important to know what proportion of people with HIV receiving ART can be reached in national HIV and TB programmes (especially if there is an active private sector). If more than one TPT regimen option is available, the programme should apportion the number of people to be assigned to the different treatments.

Table 10 lists the minimum indicators for PMTPT that should be measured. The programme may also decide to monitor other activities, such as the coverage of testing for TB infection among people targeted for testing during investigation of eligibility for TST. Use of metrics of the timeliness of screening and implementation of TPT in household contacts of people with pulmonary TB are discussed in section 2 (Box 1).

8.2.2 Data requirements for monitoring TPT at individual level

A minimum set of variables proposed to be collected at individual level is shown in Box 10. A more extensive list of variables is provided in Annex 6 to help programmes organize evaluation of the contacts of an index person with TB in a household or other setting.

Box 10. Variables to be collected at individual level

Assessment of people eligible for TPT

Contacts of people with TB

- identifier of contact (or name)
- identifier of index person with TB (name or TB registration number)
- demographics (age, sex)
- result of TB screening or infection test (if done)
- date when eligibility for TPT was determined
- decision to prescribe TPT (Yes; if No, why^a (opted out, medical contraindication))

People with HIV and other at-risk groups

- identifier of person at risk (or name)
- category of risk group (HIV, other)
- demographics (age, sex)
- result of TB screening or infection test (if done)
- date when eligibility for TPT was determined
- decision to prescribe TPT (Yes; if No, why^a (opted out, medical contraindication))

Initiation (start) and completion of TPT

- identifier of person on TPT (link to dataset for contacts and other risk groups)
- TPT regimen prescribed (e.g. 3HP, 3HR, 6H)
- TPT initiation (start) date
- TPT completion date

^a Registered only if standard coding is available and an electronic tool is used. See Annex 6 for a more complete data collection form for index people with TB and their contacts.

Table 10. Indicators for monitoring PMTPT

Indicator	Definition	Numerator	Denominator	Remarks
Contact investigation coverage	Number of contacts of people with bacteriologically confirmed TB evaluated for TB disease and TB infection of those eligible, expressed as a percentage	Total number of contacts of people with bacteriologically confirmed TB who completed evaluation for TB disease and TB infection during the reporting period	Total number of contacts of people with bacteriologically confirmed TB during the reporting period	Contact investigation identifies people recently exposed to TB with a high risk of developing TB disease. This activity is poorly implemented in many countries and should be improved urgently to achieve the UNHLM targets. It is also one of the first 10 indicators of the WHO End TB strategy. Contacts of people with MDR/RR-TB should be included.
TPT coverage	Number of individuals initiated on TPT of those eligible, expressed as a percentage	Total number of individuals eligible for TPT who initiated treatment during the reporting period	Total number of individuals eligible for TPT during the reporting period	<p>This indicator (also referred to as a <i>TPT initiation</i> indicator) should include all people considered to be at risk and eligible for TPT according to the national policy, including contacts of people with MDR/RR-TB. A time trend analysis of the numerator provides information on the trajectory of TPT scale-up and helps in assessing progress towards UNHLM targets.</p> <p>Disaggregation by people with HIV (newly or currently enrolled for ART), contacts < 5 years and ≥ 5 years allows reporting to WHO for monitoring of UNHLM targets. Disaggregation by TPT regimen (e.g. 3HP, 3HR, 6H, 6Lfx) helps to assess uptake of newer regimens and procurement and supply chain management.</p>
TPT completion	Number of individuals who complete TPT of those initiating treatment, expressed as a percentage	Total number of individuals who completed a course of TPT ^a that was initiated during the reporting period	Total number of individuals who initiated a course of TPT during the reporting period	<p>This indicator helps to assess the quality of implementation of PMTPT, as the effectiveness of TPT depends on its completion. For comparison of TPT completion indicators with coverage indicators, the period of reporting should cover the time necessary to complete treatment and to collect data.</p> <p>Disaggregation of regimens of ≥ 6 months from those of shorter duration to assess TPT completion in “cohorts” within a practical time window.</p>

3HP, 3 months of weekly rifapentine plus isoniazid; 3HR, 3 months of daily rifampicin plus isoniazid; 6H, 6 months of daily isoniazid monotherapy; 6Lfx, 6 months of daily levofloxacin monotherapy; ART, antiretroviral treatment; MDR/RR-TB; multidrug-/rifampicin-resistant TB; TPT, TB preventive treatment; UNHLM, United Nations High-level Meeting on TB

^a See text and Table 9 for proposed thresholds of completion by regimen.

Programmes may collect additional data to review certain programmatic aspects, such as adherence to medication. If drug safety cannot be monitored satisfactorily in routine pharmacovigilance systems, data on adverse drug reactions (frequency, organ class, severity and response to withdrawal and rechallenge) can also be included. Attention should be paid not to overburden the data collection system with details that are not used systematically for patient care and programme management. It may be tempting to do this when electronic data systems are installed, but it should be avoided, as it is a waste of resources and demotivates staff.

When capacity for routine M&E of minimum indicators is still being built, ministries of health and national programmes may consider periodic analyses of medical records, which can be done by simple sampling. Adherence to medication and drug safety may also be investigated in such a survey. In many settings, service data on people with HIV on ART are captured in electronic data systems, which allow a variety of analyses with unique personal identification in various data systems (such as a cohort analysis of people with HIV newly enrolled in HIV care who were screened for TB, evaluated for TPT eligibility, started on TPT and completed TPT). The availability of unique personal identification enables de-duplication of entries and increases the reliability of data for programme management.

8.3 Monitoring TPT completion

It is important to monitor TPT completion in individual care as well as for programme management. An electronic data capture tool should record details of treatment outcomes for everyone starting on TPT. TPT may be considered completed when an individual has taken at least 80% of doses within the expected duration of the regimen and the rest of the doses within an extended time equivalent to one third of the normal duration and remains well or asymptomatic during the entire period. [Table 10](#) shows how these timings apply to all recommended regimens. Other outcomes of TPT to help improve programmatic performance are proposed in [section 7](#).

8.3.1 Data recording tools

National TB and HIV programmes use patient cards, medical histories, case files or electronic medical records as sources of information on TPT services. Challenges to scaling up TPT services are the requirement for diverse data, which are often available only in paper-based records, and the involvement of many health-care service providers. Programmes for monitoring PMTPT usually capture data on paper, such as lists of contacts investigated in a household, or additional columns in an ART register to record TPT initiation among people with HIV. These tools are reviewed periodically to derive indicators, usually manually. Printing and updating of paper records adds to the burden of health-care workers.

Data from TB programmes on people with TB disease who require treatment, including ART, are increasingly being recorded electronically and are used to generate M&E indicators as well as to follow patient responses. Many programmes, however, are yet to develop systematic electronic data collection mechanisms to generate indicators. WHO promotes development of existing or new electronic systems to capture the data necessary for PMTPT care and monitoring to generate indicators automatically. Hand-held devices such as smartphones are particularly suitable because they can capture data from sites critical to PMTPT activities, such as the home of an index person, an ART clinic, a hospital, an occupational health centre or an immigration screening service (see [Box 11](#)).

Box 11. Prevent TB: a prototype mobile application to support PMTPT and screening

The Prevent TB mobile app was developed by WHO to capture the data required to monitor screening and TPT activities, including adherence to medication and adverse events (54). The app is available for use on iOS and Android phones and is compatible with District Health Information software 2 (<https://www.dhis2.org/>). It is designed to help health-care workers collect person-specific data and to visualize them on an online dashboard for real-time monitoring. The tool has been used in high TB-burden countries, either as a stand-alone system or as an integrated component of their TB information systems. While Prevent TB is available freely, any adaptation by a country requires support for building the capacity of staff and work on the software, including translation into the local language and data hosting arrangements.

With increasing numbers of people being evaluated for TPT, the many available TPT regimens and the importance of disaggregation of various subpopulations, it is important to invest in electronic recording systems for accurate quantification and procurement of consumables. The information is also useful for planning human and financial resources. As global access to affordable hardware, software and connectivity increases, real-time monitoring of the performance of PMTPT components becomes more feasible. Dedicated M&E staff should be assigned and trained to coordinate and build national and subnational capacity in use of data for decision-making. Countries should dedicate a budget for digitizing data collection and reporting and request funding from donors if necessary.

8.3.2 Data confidentiality

Optimal TPT and care involve disclosure of personal information to the health-care system. This sensitive information must be treated with the utmost confidentiality, in accordance with the professional code of conduct. It should be shared only with people who require it, who are usually those who are providing direct care. All documents containing confidential information must be securely stored. Duplicates and unnecessary documents should be discouraged and destroyed when no longer required. Computerized databases that contain sensitive information should be protected by coded passwords and encryption, and only certain users should be granted access. Entries should be immediately de-identified after data aggregation. Personal details should be removed as soon as possible from data collected and reported when they are no longer required. Care should be taken in making referrals to other services, such as when information on an individual is transferred from one care facility to another (either manually or electronically). Each programme should have a policy to ensure the confidentiality of personal data, and, if there is a national policy, it should be enforced in all parts of the health sector. Information on how their data are handled should be included in counselling provided to people who are offered TPT. Just as they are empowered to opt out of TPT, their decision about use of their personal information should also be respected.

8.4 Supportive supervision

Good supportive supervision is an essential element of routine M&E in both central and district health facilities. It includes checks on the quality of data recording and reporting, including inspection and validation of a person's medical files and data collection tools for the validity and completeness of recording. National programmes may provide a standard checklist for assessing data quality and use along the cascade of care, from identification of the target population for TPT initiation to completion. The frequency of supportive supervision depends on resources and requirements, and closer monitoring may be necessary to ensure data quality when PMTPT is relatively new. Supervisory visits may also be used to collect data for HMIS reporting. At least once a year, the supervision team should conduct an audit of data quality in routine monitoring systems. This should involve members of both TB and HIV programmes and possibly others, such as prison health and occupational health services.

National programmes have a duty to care for people at risk of TB by counselling them in making an informed choice on TPT, upholding their rights and striving to protect them from stigmatization.

It's time to stand up against stigmatization and discrimination.



9. Ethics and TB preventive treatment

Key points

- As TPT is given to people who do not experience symptoms and who are generally healthy, the balance between benefits and harms is different from that of people who take treatment for TB disease.
- Counselling and informed consent before administration of TPT are of paramount importance to safeguard human rights and to allow individuals eligible for TPT to make an informed choice, with clear understanding of the potential benefits and harms of taking treatment. Confidentiality and protection of personal data are essential.
- TPT services must respect human rights, with appropriate safeguards in law, policy and practice to minimize stigmatization, discrimination, violation of bodily integrity or restriction on freedom of movement.
- Interventions such as support to cover social and economic costs associated with TPT, minimizing the number of health-care visits, offering community care and providing access to shorter, safer TPT regimens can minimize the burden on a person taking TPT.

In general, only 5–10% of people infected with *M. tuberculosis* will develop TB disease at some time in their life, but the risk is much higher for some groups, such as people with HIV, very young contacts and people who have recently acquired infection. As treatment always carries some risk of adverse drug reactions, it is important that individual benefits and potential harms be evaluated before TPT is administered. Routine testing and treatment should be limited to groups with a demonstrated risk of progression from TB infection to TB disease. Indiscriminate population-wide TPT is not recommended.

TPT is given to people who are not ill and not infectious. This basic difference from treating TB disease alters the ethical obligations that are imposed when a condition threatens the health of an affected individual and their community (174). A decision to take TPT must therefore always be an individual choice, made with full information and without coercion. People offered TPT should feel empowered to opt out or to stop TPT once started. Provision of TPT must always be based on human rights and respect for people (107). The absence of an immediate risk of transmission makes it unethical to restrict the movements of someone with TB infection who refuses treatment.

WHO guidance on TB ethics clearly states that taking TPT should never be compulsory (174). National programmes should strengthen counselling services for eligible people to ensure effective, adequate communication on protective benefits, uncertainties and likely adverse events. The risks and uncertainties should be communicated in a culturally appropriate way. Regular feedback should be invited to guide programme implementation. Counselling and informed consent of TPT recipients should be documented and monitored systematically to ensure effective implementation. Proactive measures, including routine clinical and laboratory monitoring (when indicated), should be an integral part of PMTPT to ensure that those treated remain safe throughout TPT.

9.1 Informed consent

Explicit consent is generally required for TPT, as the person does not pose an immediate risk to others, and the potential benefits are highly context-specific and may be outweighed by a risk of harm for some individuals. The provider usually has a professional obligation to obtain consent. Whether this is documented in writing or not depends on local practice. Informed consent requires adequate, effective communication about the possibility of adverse drug reactions and the prospect of TB risk reduction. Key messages that should be conveyed to a person considering TPT are:

- In the absence of specific risk factors, most individuals with TB infection will not progress to TB disease.
- The poor predictive value of current tests in determining who will progress from TB infection to disease decreases the certainty of the effectiveness of TPT at individual level.
- There are currently no tests for establishing that TPT has been successful for an individual.
- There is a very low risk of emergence of drug resistance when TPT is given to people with TB disease.
- While TPT protects people from disease due to an existing TB infection, a person may be re-infected after completing TPT.

Nurses and other front-line health-care workers can be trained to counsel people on TPT and treatment options and to interpret the results of testing for TB infection or TB disease. The information should include not only the benefits and risks for individuals but also the implications of TPT for a person's family and community. All messages should be provided in a culturally and linguistically appropriate manner.

9.2 Equity, stigmatization and human rights

Person-centred TPT care must be provided in an equitable fashion, without disadvantage to marginalized and vulnerable populations. It should encompass the human rights aspects of TPT interventions, with appropriate safeguards in law, policy and practice to minimize additional stigmatization, discrimination, violation of bodily integrity or restrictions on freedom of movement. People who are offered testing and treatment should understand the uncertainties well enough to be able to participate in decisions on care options.

The risk of TB disease is higher among population groups who are marginalized and who are likely to live in crowded places with poor infection control. Access to TB screening and TPT for these groups should be prioritized to ensure equity, human rights and solidarity. Efforts must be made to address any 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.

TPT may increase the psychological burden and anxiety of a person taking the treatment. In addition, they might experience stigmatization or discrimination (175). TPT also has financial implications for households – for testing, adherence to treatment and care. Therefore, any TPT services, particularly those for vulnerable groups such as people in prisons, should include measures to minimize the risk of stigmatization, protect the confidentiality of personal data and ensure informed consent; support might also be required to cover social and economic costs associated with screening and treatment. Other interventions can contribute to minimizing the burden on a person on TPT, such as requiring only one visit to a health-care setting or community-based care and access to a shorter, safer TPT regimen.

9.2.1 Mandatory TB screening at borders

Migrants who are screened for TB disease may also be screened for TB infection. Screening for either should always be done with the intention to provide appropriate medical care and not to deport or

deny entry to the country. As TB infection indicates a potential future risk to a small number of people, denying or deferring immigration according to infection alone is unjustified and unethical. Whether the individual tests positive for TB infection or is receiving TPT should not affect the immigration procedure. This should be reflected in laws or other policy regulations. People should be tested for TB infection and receive TPT in strict adherence to human rights and ethical considerations.

9.2.2 Screening of health-care workers

Health-care workers are at increased risk of acquiring TB infection and/or disease when infection control measures are not effective. Health workers have the right to work in a safe work environment. They are also under a professional obligation to behave in such a way as to minimize the risk of harm to people in their care. Any consideration of mandatory screening should include both the burden on health-care workers and potential risks for others. Policies should be based on an evaluation of the likelihood of transmission (e.g. for health-care workers in a clinical or ambulatory setting with greater exposure of themselves or their patients) and the likelihood that patients will develop TB disease (e.g. for health-care workers who work with immunosuppressed patients who are at higher risk of developing TB disease after infection). If health-care workers are exposed occupationally to TB or undergo screening and TB treatment or TPT, the health system is obliged to alleviate their burdens as much as possible, such as by offering free screening and TPT. In addition, it is important to invest in infection control measures to reduce the risks of health-care workers, patients and the wider community. Any decision to implement periodic screening for TB infection and/or TB disease among health-care workers should be based on high-quality evidence of the risk of transmission and on the benefit to both health-care workers and others who may be affected.

9.2.3 Community engagement

Engaging affected communities in the development and evaluation of policy can ensure that their views and experiences are considered and that they are prepared for any unexpected effects of the policy. Affected communities, including people who have taken TPT and people who have had TB previously, can also contribute to TPT communication strategies and to disseminating knowledge about TPT. Policy should always be based on current and relevant evidence.

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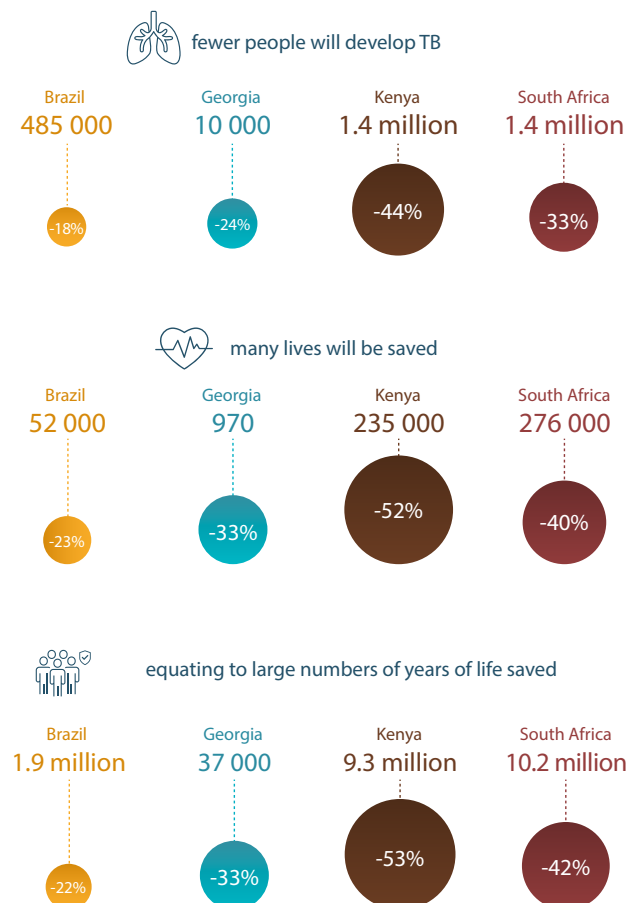
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Annex 1. Investment case for TB screening and preventive treatment

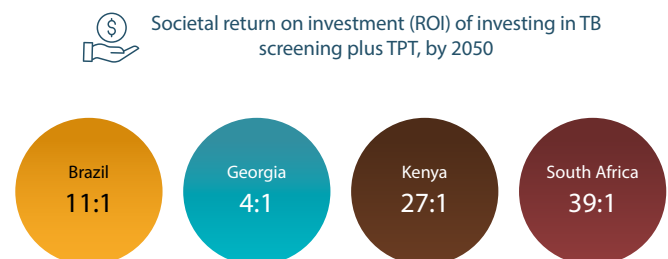
Investing now in screening and preventive treatment for TB means that by 2050



This requires investment to scale up TB screening and preventive treatment



Investing in TB screening and preventive treatment offers a substantial societal return for each dollar invested



View the document at <https://iris.who.int/handle/10665/376301>.

Annex 2. Messages for different stakeholders

Messages for ministries of health

- National governments renewed their commitments to fight TB at the second UN High-level Meeting on 22 September 2023 (1) and:

pledged to accelerate progress towards timely, quality universal access to tuberculosis services in both high and low burden countries, as outlined in the End TB Strategy, such that, by 2027, at least 90 per cent of people at high-risk of developing tuberculosis are provided with preventive treatment, which translates to providing up to approximately 45 million people with TB preventive treatment, including approximately 30 million household contacts of people with tuberculosis, including children and approximately 15 million people living with HIV, with the vision of reaching more people, including those who live in remote geographical regions or in areas difficult to access, taking into account World Health Organization guidance.

- In May 2014, national governments endorsed a World Health Assembly resolution for an End TB Strategy and its targets to end the global TB epidemic (2), with targets to reduce TB deaths by 95% and to reduce the number of new cases by 90% between 2015 and 2035. The strategy includes a target to provide TPT to 90% of those eligible by 2025.
- TPT is a proven, effective intervention for averting the development of TB disease; it reduces the risk to 60–90% of that of people who do not receive TPT (3).
- TPT given to people at the highest risk of progressing from TB infection to disease remains a critical intervention to end TB worldwide. TPT is part of a larger group of actions to eradicate poverty – from screening for TB disease, TB infection control, prevention and care of HIV, management of other comorbidities and health risks, better access to universal health care and social protection.
- Large numbers of deaths due to TB could have been avoided if TPT had been made available worldwide after recommendation for its programmatic use in 2008 (4). Urgent steps for nationwide implementation should therefore be taken to prevent massive suffering, catastrophic costs and deaths. In countries in which such programmes start now, achievement of the End TB targets will be accelerated.
- PMTPT is a key element of TB elimination in all settings and should be undertaken aggressively, particularly in settings with a low TB incidence.
- Shorter, rifamycin-based TPT (4R, 3HR, 3HP, 1HP) provides alternative options to IPT, which has been the main approach up until now. A shorter TPT regimen is more likely to be completed, as it is more tolerable and easier to manage programmatically; it may therefore have greater potential to save lives. Demand for access to TPT should be increased by raising awareness among people at risk for TB and TB-affected communities. National programmes should be mindful that they are accountable for delivering TPT.
- Access to rapid tests and investigations to diagnose TB disease and TB infection (such as Xpert MTB/Rif, CXR, urinary LAM, TST, TBST or IGRA) should be increased by investments in infrastructure, human resources and logistics for nationwide scaling up of TPT.

- Mechanisms and investment are required for building the capacity of nurses and other health-care workers in counselling people with HIV and people with TB and their families and contacts, to understand TPT, initiate TPT, follow-up treatment, identify and manage adverse events and signs of toxicity, and decide when to stop TPT.
- Investment in strengthening systematic recording and reporting for PMTPT with digital tools would improve monitoring of progress in programme management and resource allocation.
- Priority groups for TPT include household and other close contacts of people with TB, people with HIV and people with other immunodeficiency or predisposing clinical conditions (such as silicosis, dialysis, organ or blood transplant). National programmes may consider including TPT and TB screening activities for at-risk populations.

Messages for health-care workers

- TPT saves lives, prevents transmission of infection and illness and averts suffering due to TB. Strong proof comes is provided by the TEMPRANO trial, in which use of IPT for people with HIV in Côte d'Ivoire. A 37% reduction in mortality was observed among those who received IPT, independently of whether they were also on ART, and people on both IPT and ART had the greatest protection against severe disease and death (5).
- Currently recommended TPT regimens offer durable protection after one course in people with HIV, HIV-negative contacts and other at-risk populations. The protection lasts for 6–19 years.
- Some TPT regimens comprise two TB drugs – isoniazid and rifapentine or rifampicin – and are taken for only 1 or 3 months. They are as effective as IPT in preventing progression to TB disease and are easier to complete. While they may cost more in the short term, they provide more cost-effective protection, as people on shorter drug regimens are up to three times more likely to complete their course of TPT than those on longer regimens, leading to better outcomes and more lives saved.
- [Table A2.1](#) summarizes the steps to be considered by health-care workers in initiating TPT. Counselling of people at risk and their families enables an informed decision on whether to accept TPT and adhere to the treatment schedule. People on TPT should be educated about the signs and symptoms of serious adverse events, such as drug-induced hepatitis, and encouraged to report adverse events promptly.
- Explain to an individual that a course of medical treatment lasting weeks to several months is needed even if she or he is not sick. It is also important to support and ensure adherence to completion of the full course of TPT.
- There is no clear evidence that PMTPT increases resistance to TB drugs. Nevertheless, all efforts should be made to rule out TB disease with recommended procedures. If a screening test is negative, the likelihood of TB disease is minimal. In such cases, withholding TPT is a missed opportunity to protect individuals and communities from avoidable disease and death and could hence be viewed as unethical.
- Concern about harming otherwise healthy individuals must be addressed. A very small proportion of people on TPT develop adverse events, most of which are self-limiting and reversible. The shorter rifamycin-based regimens are safer than others. The availability of alternative options can help to minimize the risk.
- All people prescribed TPT should be informed clearly of the schedule of treatment, possible adverse events ("side-effects") and health alerts and to contact their health-care provider or stop TPT.
- Systematic recording and reporting are important both to inform individual care and to monitor indicators of programme performance.
- With appropriate training, nurses and other front-line health-care workers can undertake most of the clinical duties required in PMTPT. They include deciding on testing for TB infection and TB disease, interpretation of results, establishing eligibility for TPT, starting TPT and monitoring adherence, and deciding whether TPT should be suspended or changed (e.g. in the case of adverse events) or re-started (e.g. after an interruption by the person on treatment). There is usually no need to solicit the opinion of a medical doctor or a specialist for such decisions, although this should be available if necessary.

Table A2.1. Steps in starting TPT

Steps	Adults and adolescents with HIV ^b	Children with HIV ^a	HIV-negative household or other close contact of a person with TB
Clinical symptom-based screening^a	Current cough, fever, weight loss or night sweats	Absence of or poor weight gain, fever or current cough or history of contact with a person with TB, reduced playfulness, night sweats	Cough of any duration, haemoptysis, fever, night sweats, weight loss, chest pain, shortness of breath, fatigue
CXR	May be considered for people living with HIV on ART, asymptomatic adolescent and adult contacts and clinical risk groups. Not mandatory but desirable because it improves sensitivity to detect TB. Extra costs should not be shifted to the person being screened.		
Screening with other tests	CRP may be used to screen for TB in people with HIV, with a cut-off value of > 5 mg/L. CRP can be used in screening for TB among outpatients living with HIV who are not on ART, as it is significantly more sensitive and specific than symptom screening. It can be used in combination with symptom screening. mWRDs can be used to screen people with and without HIV. Those who screen positive should be followed up by clinical evaluation and further tests, such as CXR or repeated mWRDs on additional sputum samples, to establish a definitive diagnosis of TB.		
Diagnostic testing for TB if screening test is positive	mWRDs (such as Xpert MTB/Rif or urine lipoarabinomannan assay) among seriously ill people with HIV) or as per national guidelines		
Test for TB infection	Tests for TB infection (TST, TBST or IGRA) limit unnecessary treatment of uninfected individuals (such as in settings with a low prevalence of TB infection). Lack of availability of tests should not, however, be a barrier to provision of TPT to those who need it. TBI testing is not required in people with HIV and contacts < 5 years.		
Baseline assessment to determine the eligibility of an individual for TPT	Personal history relevant for TPT initiation and continuation, such as <ul style="list-style-type: none"> • allergy or known hypersensitivity to TB drugs • HIV status and ART regimen • pregnancy • contraception • comorbidity and medications • contact with drug-resistant TB • potential contraindications to TPT, such as active hepatitis (acute or chronic), regular and heavy alcohol consumption, symptoms of peripheral neuropathy and concurrent use of other medications subject to interaction (e.g. nevirapine) 		
Social and financial situation of patient and family	Assess whether support is required to overcome barriers for starting and completing TPT		
Counselling	Explain to the individual that (s)he is eligible for TPT, and provide the individual and her/his family/treatment supporter with information on TB infection, TPT, schedule of medication collection, medication adherence support and follow-up visits, benefits of completing the course, adverse events, response to development of TB symptoms or adverse events		

ART, antiretroviral therapy; CRP, C-reactive protein; CXR, chest radiography; HIV, human immunodeficiency virus; IGRA, interferon- γ release assay; mWRDs, molecular WHO-recommended rapid diagnostic tests; TB, tuberculosis; TBI, TB infection; TBST, *Mycobacterium tuberculosis* antigen-based skin test; TPT, TB preventive treatment; TST, tuberculin skin test

^a Screening of children and pregnant or breastfeeding women can be integrated into other care, such as for maternal and child health, vaccination, well-baby clinics, nutrition clinics.

^b Among people with HIV, all the above steps should be included if differentiated HIV service delivery models are used. Screening and TPT should be an integral part of the care package for people with HIV.

Messages for people with HIV and other people offered TPT

- You (your family members) do not have TB disease. You (your family members) may have an infection that could become TB disease. TB is a serious disease, could threaten your life and could spread to your family, neighbours and co-workers.
- Your doctor has determined that you would benefit from TPT (for you or your family members) although you and your family are currently healthy. TPT can reduce your risk of getting TB by 60–90%. In most individuals, TPT will not cause any discomfort or adverse events (“side-effects”); however, if adverse events occur, your caregiver will visit you regularly and provide care. Your health-care provider will inform you of the common adverse events of the TPT you are offered. You are free to take TPT, opt out or stop it after starting.
- The protection offered by TPT is optimal only when the prescribed course of TPT is completed as expected. If you decide to take TPT, please remember to take it as indicated by your health-care provider.
- If you (or your family members) notice any adverse event, consult your health-care worker as soon as possible. If danger signs are noted (such as signs of jaundice – yellowing of the skin and whites of the eyes), stop TPT, and seek care and support in a health facility.
- If you (or your family members) are on rifamycin-based TPT and wish to avoid pregnancy, please note that rifapentine (and other rifamycins) decrease the effectiveness of hormonal contraceptives (6). You (your family members) should consider using a different or barrier form of contraception when taking rifapentine or a rifampicin-based TPT.
- Parents and legal guardians: giving your children TPT will protect them from TB, which can be difficult to diagnose and could have long-lasting effects. Child-friendly medicines that dissolve in water and have a nice taste are now available to make it easier for your child to take treatment regularly.

Messages for communities

- TB is a contagious disease that is transmitted through air when a person with infectious TB coughs. TB is associated with considerable morbidity and mortality, even when treated. Even when people with TB complete treatment, some are left with considerable damage to their lungs or to other organs, which can seriously affect their quality of life.
- TB is preventable, and prevention is much better than cure. A number of options are available to prevent TB and to reduce the burden of TB in the community. They include early detection and treatment, BCG vaccination of infants and providing TPT to individuals who are currently well but have been exposed to TB or are at a high risk of developing TB disease.
- To reduce the number of individuals who develop TB each year, countries have committed themselves to providing TPT to people who have been exposed or already have TB infection in their bodies even if it has not yet progressed to TB disease, such as in people with HIV, and family members of people with TB, including children. Providing treatment to these individuals will prevent them from developing TB disease and result in a healthier community.
- TB infection is extremely common. Community members who require TPT are not sick, are not coughing and are at no risk of transmitting TB. TPT is prescribed to minimize an individual’s future risk of developing TB disease. This also protects the community, because TB is a contagious disease.
- The drugs used for TPT are generally very safe. Shorter TPT regimens with a combination of two TB drugs – isoniazid with rifapentine or rifampicin – are now available, which are effective in preventing progression to TB disease. These TPT regimens have fewer side-effects and are easier for people to take. It may, however, be difficult for people with TB infection who do not show symptoms to understand that they must take a medication to treat infection. Although treatment of TB disease lasts ≥ 6 months, shorter TPT regimens that can be completed in 4–12 weeks are now available. All TPT must be completed as prescribed in order to be effective.

- Individuals may find it difficult to complete a full course of TPT. Community health workers, affected communities, TB survivors, civil society organizations and nongovernmental organizations can support people who are taking TPT to finish it.
- By keeping adults free from TB, children will be able to avoid being exposed to TB and live healthier lives as they grow up. Keeping people with HIV free from TB reduces their suffering and help them live healthier, longer TB-free lives.
- People with HIV who are responding well to ART may still contract TB. Their TB infection may go unnoticed and untreated for long, until it is too late. Taking TPT will ensure that people with HIV will be protected from TB disease. Not taking TPT is a missed opportunity to prevent unnecessary sickness or even death.
- Most children who become infected with TB have been infected by an adult – whether a parent or another person in the household. They are also at higher risk of developing TB in the following years and would benefit from TPT. It is important that when someone in the family has been identified as having TB disease, family members, including children, are evaluated and encouraged to take TPT.
- Demand should be created by sharing information with communities about accessing TPT and by promoting TPT among people who should be protected from TB infection and disease.
- The HIV community, people affected by TB, TB survivors, civil society organizations working with children and civil society organizations and NGOs working on TB could advocate strongly for TPT. Their role is important for screening household and community contacts for symptoms, encouraging and referring people to access TPT, lobbying and advocating local and national health ministries for allocation of resources and increasing demand for TPT in their countries and localities.

An example of a community flyer promoting TPT is available in Annex 1 of the first edition of this operational handbook (pages 99–102) (7)

References

1. The second United Nations high-level meeting on TB: new global pledge to end the TB epidemic. declaration on TB. Geneva: World Health Organization; 2023 (<https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023/featured-topics/un-declaration-on-tb>).
2. The End TB Strategy. Geneva: World Health Organization; 2024 (<https://www.who.int/teams/global-tuberculosis-programme/the-end-tb-strategy>).
3. Lobue P, Menzies D. Treatment of latent tuberculosis infection: An update. *Respirology*. 2010;15(4):603–22. doi:10.1111/j.1440–1843.2010.01751.x.
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5. Badje A, Moh R, Gabillard D, Guéhi C, Kabran M, Ntakpé JB 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;5(11):e1080–9. doi:10.1016/S2214–109X(17)30372–8.
6. Borisov AS, Bamrah Morris S, Njie GJ, Winston CA, Burton D, Goldberg S et al. Update of recommendations for use of once-weekly isoniazid-rifapentine regimen to treat latent *Mycobacterium tuberculosis* infection. *Morb Mortal Wkly Rep*. 2018;67(25):723–6. doi:10.15585/mmwr.mm6725a5.
7. WHO operational handbook on tuberculosis; module 1; prevention; tuberculosis preventive treatment. Geneva: World Health Organization; 2020 (<https://apps.who.int/iris/bitstream/handle/10665/331525/9789240002906-eng.pdf>).

Annex 3. Coordination mechanisms to support PMTPT

Ministries of health should create a national coordinating body and/or national technical expert working group to support national scaling up of PMTPT according to the latest global guidelines. Alternatively, the mandate of an existing body that could serve both management and technical functions could be extended to advise the ministry of health and national TB, HIV and other programmes, thus guiding and supporting governments in fulfilling their national commitments to PMTPT. The technical expert group, although established at national level, should provide advice at all levels. The coordination body and technical working group should be chaired by the highest administrative heads in federal and local governments and have equal or reasonable representation of all relevant stakeholders.

Terms of reference

The national coordinating body should be responsible for the governance, planning, coordination and implementation of PMTPT, as well as mobilization of financial resources from the government and donors. It should establish or identify an existing technical working group to provide advice on technical matters in scaling up PMTPT.

The mandate of the national technical expert working group may be to:

- review emerging national and global evidence, review current national policies and guidelines for PMTPT and lead updating and alignment of local guidelines with the latest evidence and WHO guidelines;
- undertake situational assessments to guide policy decisions for PMTPT, such as:
 - estimates of the burden of TB disease (and TB infection) in various at-risk populations;
 - the capacity of the health system (staff, skills and equipment) to assess the intensity and risk of TB exposure and to exclude TB disease;
 - the available financial resources and gaps for nationwide scaling up of TPT services and the implications of different approaches for impact and cost (various regimens and tests of TB infection);
 - mobilization of additional resources as required; and
 - programme performance and implementation bottlenecks;
- provide a scientific basis for PMTPT components of national strategic plans and policy advice to the joint national coordinating body and/or national programmes;
- lead identification and prioritization of target populations for PMTPT and strategies to reach them;
- develop national implementation guidance, SOPs and job-aids (including for training modules) suitable to the country context; and
- develop tools to address the concerns of TPT providers and dispel myths about TPT to promote implementation and national scaling up.

Membership

A joint national coordinating body for implementation of TPT could consist of:

- a programme head in the ministry of health;
- programme heads in other relevant ministries according to the country context (such as those responsible for harm reduction, prisons or mining health services);
- members of the federal ministry responsible for public funding;
- national TB, HIV and other relevant programme managers (such as for reproductive, maternal, newborn, child and adolescent health services, prison health services);
- programme heads in implementing partners for TPT;
- representatives of civil society;
- people at risk of or affected by TB; and
- country leads in technical partner organizations and funding agencies.

The national technical expert working group for scaling up TPT might consist of:

- national TB and HIV experts;
- stakeholders from national TB, HIV, reproductive, maternal, newborn, child and adolescent health and other relevant programmes;
- clinicians, front-line health providers, nurses and community service providers;
- representatives of agencies responsible for drug procurement, regulation and safety;
- representatives of TB and HIV patient groups, civil society, people at risk of or affected by TB;
- representatives of national research institutes;
- local and/or international technical partners; and
- the WHO country officer.

Frequency of meetings: The national coordinating body and technical expert working group should meet regularly as deemed appropriate for current activities in the national context.

Secretariat: The national TB and HIV programmes could function as the secretariat for both the coordinating body and the technical expert working group and convene alternate meetings of the groups according to the priorities for discussion. Both programmes should allocate funding for regular meetings.

Annex 4. Costing considerations for PMTPT

When preparing a budget for PMTPT, for example as part of a National Strategic Plan, it is important to conduct systematic costing. The TB module of the integrated health tool for planning and costing is designed to support national strategic health planning over the medium term (7). The WHO costing guidelines for tuberculosis interventions explain how to cost TB interventions from the perspective of the providers of health services and include tools for data collection (2). Listed below are key items that require costing when developing a budget for PMTPT.

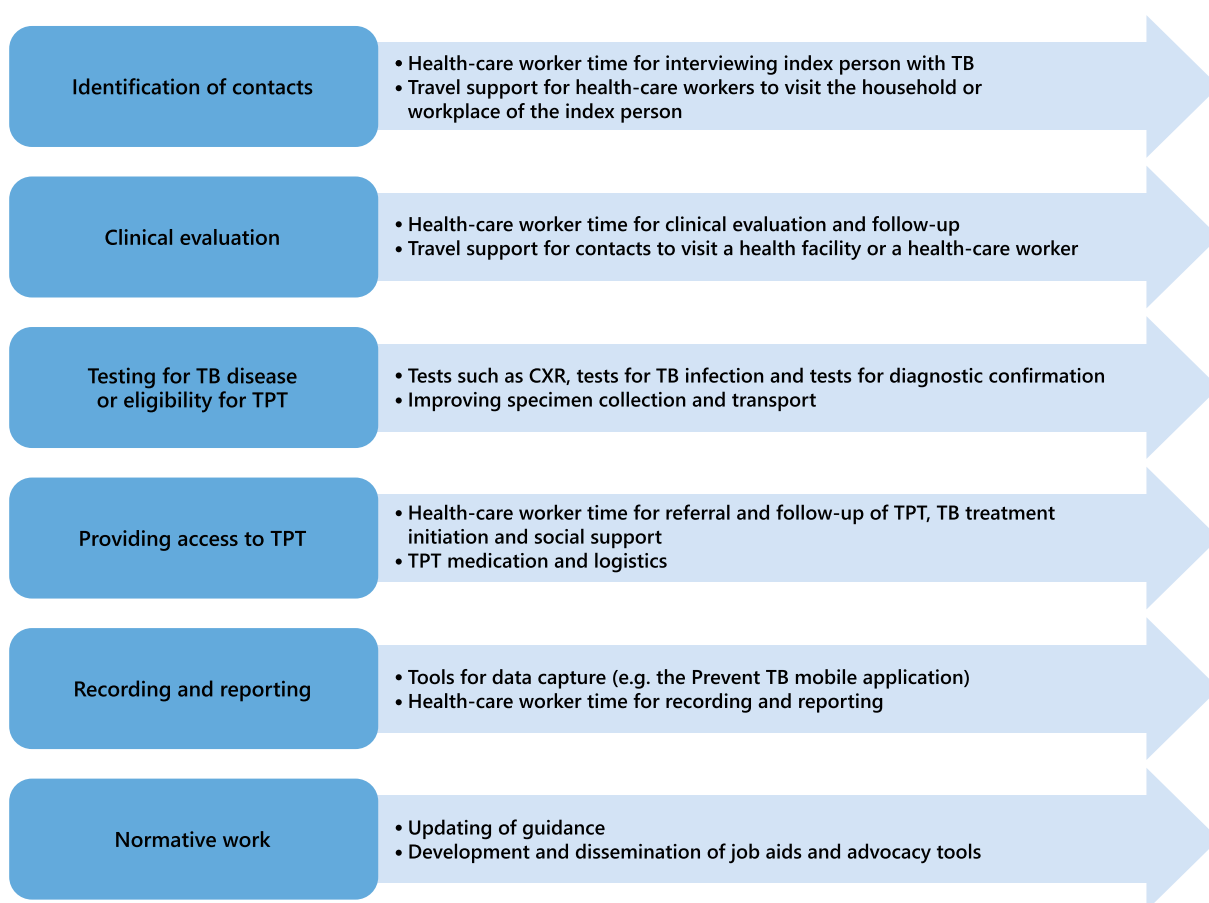
Estimate the burden

- Populations of each target group (people with HIV, contacts, clinical risk groups, other risk groups)
- Number of households and other sites (health facilities, ARV centres) to be covered for expansion of TPT activities

Investigating target populations

- Test for TB infection (TST/TBST/IGRA) as per national policy (such as test equipment general supplies, procurement fees for supplies, specimen collection and transport)
- Access to chest radiography services as per national policy (such as free vouchers for individuals, outsourcing chest radiography services to private providers)
- Referral for investigation (such as travel support for contacts, specimen collection and transportation)
- Integrate contact investigations into the roles and responsibilities of existing health and community workforce.
- Dedicate human resources as required to implement and to monitor implementation of contact investigations.
- Train and build capacity of health care workers, community workers and other implementers.
- Provide travel support or incentives for health care workers, community workers or other implementers of contact investigations.
- Provide travel support for index people with TB and contacts to reach facilities for screening, testing and continuation of TPT.
- Strengthen recording and reporting of data (updating existing electronic data systems with variables for PMTPT or adoption of digital tools such as the WHO Prevent TB mobile application (3)).
- Generate awareness among patients, contacts and communities.
- Cost items for the strengthening of contact investigation are included in [Fig. A3.1](#)

Fig. A3.1. Indicative costing of items to strengthen contact investigations



CXR, chest radiography; TPT, TB preventive treatment

Ruling out TB disease

- Support regular convening of and consultation with the national technical working group or a similar mechanism to review strategies for ruling out TB disease before TPT in target populations.
- Develop and implement a plan for human resource development, including hiring, training, mentoring and ongoing sensitization for TB screening, family counselling and evaluation of eligibility for TPT.
- If CXR is used for TB screening in national guidelines, funding will be required for
 - equipment (such as for digital radiography, CAD),
 - logistics,
 - maintenance of equipment,
 - training of clinicians and other health-care workers in reading CXRs, and/or
 - hiring radiography services from the private sector (such as vouchers for a free CXR for individuals receiving care in public or private facilities).
- Extend access to rapid TB diagnostics, such as mWRD and lateral flow urine lipoarabinomannan assays.
- Establish or strengthen specimen collection and transport according to the requirements of different target populations (including children).
- Print and disseminate SOPs and job-aids for TB screening.

Testing for TB infection

The following are required for testing for TB infection:

- cost per test and estimated number of target populations to be tested;
- travel support for individuals considered for TPT and health-care workers to access TST/TBST and IGRA testing and TST/TBST reading;

- incentives for health-care workers and laboratory technicians;
- maintenance of a cold chain for tuberculin;
- training, capacity-building and ongoing supportive supervision;
- maintenance of laboratory services for IGRA and specimen collection and transport;
- hiring of laboratory technicians or laboratory services as required, including from the private sector;
- strengthening supply chain management to ensure an uninterrupted supply of tuberculin or IGRA blood collection tubes and reagents; and
- tools for routine data capture, preferably electronic.

TPT

The following are required for TPT:

- medications for regimens for different at-risk populations;
- procurement (such as freight, procurement fees, warehousing, repacking);
- additional drugs (such as buffer stock, supporting medicines such as vitamin B6); and
- support for adherence (such as phone calls, SMS, video communication, additional home visits)

Human resources

The following are required for human resources for TPT:

- additional personnel and/or incentives for community workers or volunteers;
- contact investigation:
 - transport of health-care workers and
 - transport of contacts to facilities for TB screening, investigation and TPT;
- TPT provision and follow-up;
- laboratory work;
- supervision and monitoring;
- drug distribution and management; and
- capacity-building and support:
 - training for health-care workers and
 - job-aids

Demand creation

The following are required to create demand for TPT:

- advocacy with policy-makers and key stakeholders;
- sensitization of specialists and health-care workers;
- community sensitization of TB survivors, people with HIV networks and others;
- counselling of index patients and families; and
- health education material for at-risk populations and their families.

Monitoring and evaluation

M&E require:

- data systems: electronic tools for recording and reporting; and
- updating tools or creation of new ones for recording data elements for programme indicators and clinical management (such as adverse events) for TB and/or HIV.

References

1. TB module of the Integrated Health Tool for planning and costing. Geneva: World Health Organization; 2024 (<https://tb.integratedhealthtool.org>).
2. Costing guidelines for tuberculosis interventions. Geneva: World Health Organization; 2019 (<https://www.who.int/publications-detail-redirect/9789240000094>).
3. Prevent TB Digital Platform. Geneva: World Health Organization; 2024 (<https://www.who.int/activities/preventing-tb>).

Annex 5. Checklist for PMTPT components in reviews of national programmes

Background: A programme review is an integral part of the management cycle of a TB programme. It is a structured way of assessing the performance of the programme and for improving its quality; it is also the basis for developing or updating the national strategic plan. PMTPT is one of several preventive actions envisaged in the End TB Strategy, such as TB case-finding, infection control, prevention and care of comorbidities (e.g. HIV), access to universal health care, social protection and poverty alleviation.

Objectives: The review should determine how TPT is implemented in public and private health services, by ensuring that:

- national guidelines are updated in line with the latest global recommendations, and the national strategic plan provides adequate resources for implementation of the guidelines;
- appropriate staff, stakeholders and expert groups are engaged in implementing the guidelines;
- clear guidance is available on identifying target populations for TPT, ruling out TB disease, diagnosing TB infection or assessing patient eligibility for TPT, and providing TPT when necessary;
- medication support is available to help people start and complete TPT effectively;
- data are recorded systematically to monitor indicators in the cascade of care for TPT; and
- other implementation support is available, such as training, advocacy and management of commodities.

Various personnel play a role in TPT implementation. Staff to be interviewed include:

- managerial staff for the national and subnational TB programmes and the national HIV/AIDS programme;
- health workers and community health workers involved in TB and HIV care, household contact evaluations, diagnostic services in health-care facilities (in both the public and private sectors and at both primary and secondary levels of health care); and
- staff in other state sectors, such as primary care, hospitals, occupational health services (e.g. mining industry), prison health services and migrant screening facilities.

Table A5.1 provides a checklist of TPT components to be used in reviews of NTPs (1). The elements should be available in their NTP guidelines and national strategic plan (2).

Table A5.1 Checklist of TPT components for programme reviews

Activity	Current status	Next steps
Governance and policies		
National coordinating mechanism or national technical expert group to support PMTPT?		
TPT is part of national strategic plans for TB and HIV?		
Provision of incentives or support for travel to ensure systematic TB screening and evaluation of individuals targeted for provision of TPT?		
Diagnostic algorithms specifying the roles of testing for TB infection and CXR and alignment with algorithms for TB case finding or TB screening?		
Preventive treatment options and criteria for choice of TPT regimens for different populations?		
Support for people to take TPT?		
National TB strategic plan		
Estimates of cost of implementing PMTPT guidelines		
National PMTPT indicators agreed		
Revision of national TB strategic plan		
Guideline update		
National TB and HIV guidelines aligned with the latest WHO recommendations?		
National technical expert group meeting		
Identification of (priority) risk groups		
Diagnostic algorithm (role of testing for TB infection and CXR)		
Treatment options (regimens, criteria for choice)		
Dissemination of guidelines to key stakeholders		
PMTPT extension plan		
Multistakeholder group meeting to support scaling up of TPT (TB and HIV programme managers, representatives of ministries responsible for prisons, migrants, drug users, private or hospital providers)		
Plan to scale up a shorter rifamycin-containing TPT regimen?		
Plan to increase access to CXR and tests for TB infection; for example, to evaluate people living with HIV on ART or adult household contacts of TB patients?		
Coverage of people with HIV		

Activity	Current status	Next steps
Coverage of child household contacts < 5 years		
Coverage of household contacts ≥ 5 years		
Coverage of clinical risk groups and other contacts		
Support mechanisms for people taking TPT		
Training		
Needs assessment		
Training modules and public education materials (consider e-learning)		
Advocacy to key policy-makers		
Orientation of physicians, doctors, nurses, other health staff and community workers on regimens, treatment and management of adverse events		
Community outreach		
Mapping of community health facilities, community health workers and volunteers		
Mapping of community organizations		
Plan for engaging community stakeholders in raising awareness and implementation of TB screening, TPT and follow-up		
Monitoring and evaluation		
Recording and reporting tools updated with national TPT indicators		
Electronic tools for data collection and reporting		
Systems for monitoring and management of adverse events		
Review of implementation of TPT at all levels and supervisory visits		
Data collected on PMTPT for people with HIV, child household contacts and other contacts		
Data collected on other clinical risk groups (silicosis, dialysis, anti-TNF treatment, transplant patients)		

Activity	Current status	Next steps
Procurement and supply management		
Inclusion of rifapentine on the national essential medicines list		
Registration of rifapentine or waiver of importation fees to facilitate supply		
Forecasting requirements for medicines and diagnostics		
Placement of orders for medicines and diagnostics		
Packaging and supply		
Stock management		

ART, antiretroviral therapy; CXR, chest radiography; HIV, human immunodeficiency virus; PMTPT, programmatic management of TB preventive treatment; TB, tuberculosis; TNF, tumour necrosis factor; TPT, TB preventive treatment; WHO, World Health Organization

References

1. Guidance on conducting reviews of tuberculosis programmes. Geneva: World Health Organization; 2024 (<https://www.who.int/publications/i/item/9789240085817>).
2. Guidance for national strategic planning for tuberculosis. Geneva: World Health Organization; 2022 (<https://www.who.int/publications/i/item/9789240052055>).

Annex 6. Variables to be collected for TB contact evaluation

Table A6.1 proposes a list of variables on which data should be collected for index cases and their contacts in an evaluation of the contacts of a person with TB disease. The data may be collected at various stages of the investigation. Usually, demographic information and much of a person's medical history is available at the first visit, while other details, such as the results of tests for ruling out TB, confirming infection or starting TPT would be collected at subsequent encounters. Ideally, the data should be registered electronically to facilitate retrieval, storage and analysis.

Table A6.1 Suggested data variables for capture at different steps of contact evaluation

Index person			
Registration number			
Surname			
First name			
Interview date			
Clinic name			
District TB coordinator			
TB contact investigator			
Was the patient screened for TB in the household?			Yes/ No
Demographic information			
Date of birth			
Sex			
Address			
Occupation			
List of household contacts			
	Name	Age	Sex
1			
2			

Current TB episode	
Have you had cough?	Yes/No
If yes, for how long have you had cough?	
Are you coughing up blood or blood-stained sputum?	Yes/No
If yes, for how long?	
Have you had fever?	Yes/No
If yes, for how long?	
Have you had noticeable weight loss? (≥ 3 kg loss in a month)	Yes/No
Have you been sweating at night for ≥ 3 weeks in the past 4 weeks?	Yes/No
Have you noticed any swelling and/or lumps on your neck, arm pits or groin?	Yes/No
Previous episode of TB	
Have you ever been told that you had TB?	Yes/No
If so, did you take all the medication you were given?	Yes/No
Do you have contact with anyone with TB?	Yes/No
If so, is that person a household contact or a non-household contact?	
Medical history	
What type of TB does this patient have?	
What is this patient's HIV status?	
Was a chest X-ray done?	Yes/No
If a chest x-ray was done, what was the result?	
Was sputum examination done?	Yes/No
If yes, what are the results?	
Does the patient have extrapulmonary TB?	Yes/No

Contacts

(If the contact answers "Yes" to any of the symptom screening questions, refer them to a health facility for testing for TB disease. If the answer is "No", refer them for assessment of eligibility for TPT and or testing for TB infection.)

Contact and personal information

Index person ID

Index person surname

Index person first name

Contact number

1/2/3/4

Contact surname

Contact first name

Contact date of birth

Contact sex

What is the relation of the contact to the index person?

Address

Date of this interview

Which household visit is this?

1, 2, 3 or 4

Contact telephone

TB symptom screening

Do you have a cough?

Yes/No

If yes, how long have you had a cough?

Are you coughing up blood or blood-stained sputum?

Yes/No

If yes, for how long? (in weeks)

Have you had a fever?

Yes/No

If yes, for how long? (in weeks)

Have you had noticeable weight loss?

Yes/No

Have you been sweating at night for ≥ 3 weeks in the past 4 weeks?

Yes/No

Have you noticed any swelling and/or lumps on your neck, arm pits, or groin?

Yes/No

Medical history

Have you ever been told that you had TB?	Yes/No
--	--------

Have you ever been tested for HIV?	Yes/No
------------------------------------	--------

If yes, are you HIV-positive?	
-------------------------------	--

If yes, what medications are you taking? (ask for medication card)	
--	--

Do you have any other underlying medical conditions?	Yes/No
--	--------

If yes, please list them.	
---------------------------	--

Degree of exposure to the index person

How much time in one day do you spend in the same room as the index person?	
---	--

Do you share a bed with the index person?	Yes/No
---	--------

Do you sleep in the same room as the index person?	Yes/No
--	--------

How long have you lived in the same house as the index person?	
--	--

Medical examination results: to be filled in at the clinic by the clinician or district TB coordinator if the contact is being evaluated for TB	
---	--

Date of clinical examination	
------------------------------	--

Chest X-ray reading	
---------------------	--

Test of TB infection (TST, IGRA or TBST)	
--	--

Sputum examination results	
----------------------------	--

Outcome of medical evaluation	
-------------------------------	--

Was TPT started?	Yes / No / Unknown
------------------	--------------------

If yes, regimen used	
----------------------	--

Date of initiation of TPT	
---------------------------	--

Date of completion of TPT	
---------------------------	--

If TB treatment started, give the TB registry number of this patient.	
---	--

Preventive treatment for tuberculosis

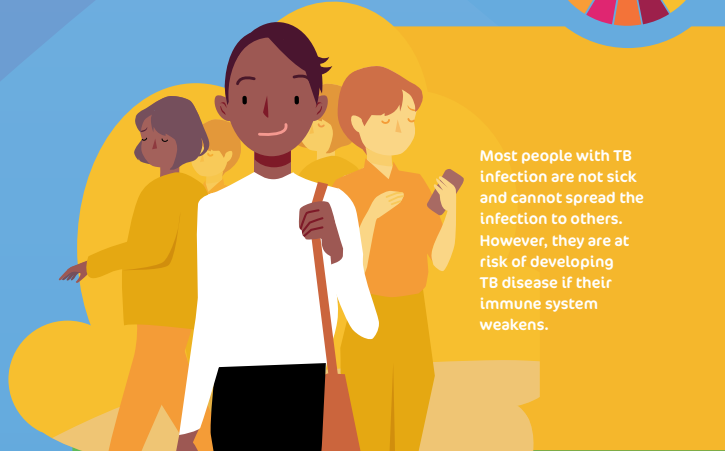
TB preventive treatment (TPT) can stop infection from turning into disease.



What is TB infection?

Tuberculosis (TB) is caused by bacteria that spreads through air and can infect anyone. Sometimes, a person gets infected with bacteria but they do not fall ill with TB immediately. In this case, the TB bacteria remain inactive in the body and the person is said to have TB infection.

People with TB infection do not show any signs or symptoms of TB.



Most people with TB infection are not sick and cannot spread the infection to others. However, they are at risk of developing TB disease if their immune system weakens.

Am I at risk?

You can be infected with TB bacteria even if you are not ill. In fact, as many as 1 in 4 people in the world are estimated to have been infected with TB bacteria, most of whom are well.

Some people who are infected will go on to develop TB disease.

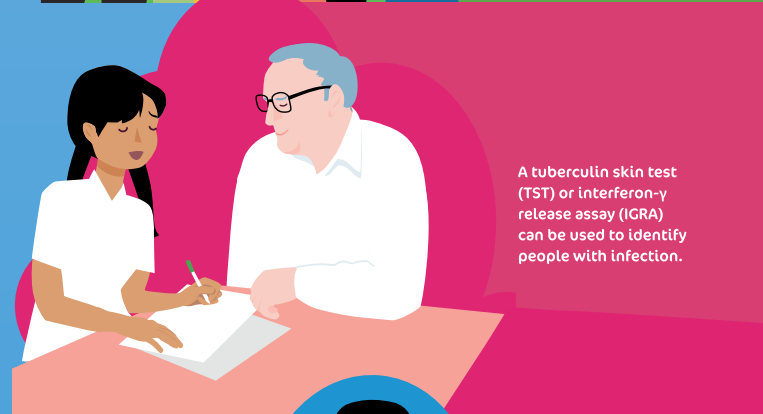


The chance of getting TB disease is higher if you:

- live in the same household or are in close contact with a TB patient
- are living with HIV
- belong to other high-risk groups including people who are initiating anti-TNF treatment or receiving dialysis, those preparing for an organ or haematological transplant, those who have silicosis, as well as prisoners, health workers, migrants from countries with a high TB burden, homeless people and people who use drugs.

Do I need TB preventive treatment?

If you are at risk then your health care provider will first rule out TB disease before assessing if you need TPT.



A tuberculin skin test (TST) or interferon- γ release assay (IGRA) can be used to identify people with infection.

What are the treatment options?

Today, there are multiple TPT options available. New, shorter treatment options mean that people can be protected from TB for many years with treatment lasting only 1 or 3 months instead of 6 months or more as in the past.



It is important to complete the full course of TB preventive treatment so that it is effective.

Protect yourself and your loved ones!



For further information, please contact:

Global Tuberculosis Programme

World Health Organization

20, Avenue Appia CH-1211 Geneva 27

Switzerland

Web site: www.who.int/tb