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Module 1: Prevention

Tuberculosis preventive treatment



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WHO operational handbook on tuberculosis

Module 1: Prevention

Tuberculosis preventive treatment



Contents

Acknowledgements.....	iv
Abbreviations & acronyms.....	vi
Definitions.....	viii
Chapter 1. Introduction and approach.....	2
Chapter 2. Identification of populations for TB preventive treatment.....	8
Chapter 3. Ruling out TB disease before TB preventive treatment.....	20
Chapter 4. Testing for TB infection.....	28
Chapter 5. TB preventive treatment.....	36
Chapter 6. Safety, management of adverse reactions and other drug-related issues in TB preventive treatment.....	56
Chapter 7. Adherence to TB preventive treatment.....	72
Chapter 8. Monitoring and evaluation.....	82
Chapter 9. Ethics and TB preventive treatment.....	92
Annexes	
Annex 1. List of key messages.....	95
Annex 2. Coordination mechanisms to support PMTPT.....	105
Annex 3. Costing considerations for programmatic management of TB preventive treatment.....	107
Annex 4. Planning checklist for PMTPT.....	109
Annex 5. Answers to frequently asked questions on TST.....	111
Annex 6. Answers to frequently asked questions on IGRAs.....	116
References.....	119

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Guideline Development Group of the 2020 guideline revision

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Observers of the 2020 guideline revision

Sevim Ahmedov (US Agency for International Development (USAID), USA); Draurio Barreira Cravo Neto (UNITAID, Switzerland); Anand Date (Centers for Disease Control and Prevention, USA); Suvanand Sahu (Stop TB Partnership, Switzerland); Surbhi Modi (Centers for Disease Control and Prevention, USA); Harry Hausler (TBHIV Care, South Africa); Lucia Gonzalez Fernandez (International AIDS Society, Switzerland); Anna Scardigli (Global Fund to Fight AIDS, TB and Malaria, Switzerland).

External Review

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Abbreviations & acronyms

1HP	one month of daily rifapentine plus isoniazid
3HP	three months of weekly rifapentine plus isoniazid
3HR	three months of daily rifampicin plus isoniazid
3TC	lamivudine
4R	four months of daily rifampicin monotherapy
6H	six months of daily isoniazid monotherapy
9H	nine months of daily isoniazid monotherapy
ABC	abacavir
ACF	active TB case finding
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral drugs
AST	aspartate aminotransferase
AZT	zidovudine
BCG	bacille Calmette-Guérin (vaccine)
CAD	computer aided detection
CFP-10	culture filtrate protein 10
CLHIV	children living with HIV
DDI	drug-drug interaction
DHIS2	District Health Information Software 2
DMPA	depot medroxyprogesterone acetate
DSD	differentiated HIV service delivery
ELISA	enzyme-linked immunosorbent assay
ESAT-6	early secretory antigenic target-6
EMR	electronic medical record
FDC	fixed-dose combination
FTC	emtricitabine
GDGs	Guideline Development Groups
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HMIS	health management information system
Hr-TB	isoniazid-resistant, rifampicin susceptible TB disease
ICF	intensified TB case finding
IFN-g	interferon-gamma
IGRA	interferon-gamma release assay

INSTIs	integrase strand transfer inhibitors
IPT	isoniazid preventive treatment
LF-LAM	lateral flow urine lipoarabinomannan assay
LFT	liver function test
Lfx	levofloxacin
LMICs	low and middle income countries
LTBI	latent tuberculosis infection
MDR-TB	multidrug-resistant tuberculosis
MoU	memorandum of understanding
NGO	nongovernmental organization
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleotide reverse transcriptase inhibitor
OST	opiate substitution therapy
P-gp	P-glycoprotein
PBMCs	peripheral blood mononuclear cells
PDE-5	phosphodiesterase-5
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
PIs	protease inhibitors
PLHIV	people living with HIV
PMTCT	prevention of mother-to-child transmission (of HIV)
PMTPT	programmatic management of tuberculosis preventive treatment
PPD	purified protein derivative
PWUD	people who use drugs
RCT	randomized controlled trial
RR	relative risk
SOP	standard operating procedure
SSRI	selective serotonin reuptake inhibitor
STBP/GDF	Stop TB Partnership's Global Drug Facility
TDF	tenofovir-disoproxil fumarate
TDF-DP	tenofovir diphosphate
TNF	tumour necrosis factor
TPT	tuberculosis preventive treatment
TST	tuberculin skin test
TB	tuberculosis
UGT	uridine diphosphate glucuronosyltransferase
UID	unique personal identifier
UNHLM	United Nations High Level Meeting on Tuberculosis (2018)
VOT	video supported treatment
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 TB disease, although it normally implies screening that is implemented outside of health facilities.

Adolescent: is a person aged 10–19 years.

Adult: is a person over 19 years of age.

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

Child: is a person under 10 years of age.

Contact: is any individual who was exposed to a person with TB disease.

Contact investigation: is a systematic process for identifying previously undiagnosed people with TB disease and TB infection among the contacts of an index TB patient and/or other comparable settings where transmission occurs. Contact investigation consists of identification, clinical evaluation and/or testing and provision of appropriate anti-TB therapy (for people with confirmed TB) or TB preventive treatment (for those without TB disease).

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

Differentiated HIV service delivery (DSD) models: is a person-centred approach to simplify the provision of HIV services across the cascade, in ways that both serve the needs of PLHIV better and reduce unnecessary burdens on the health system.

High TB transmission setting: is 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 susceptible individuals.

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

Index patient (index case) of 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 patient is the person on whom a contact investigation is centered but is not necessarily the source.

Infant: is a child under one year (12 months) of age.

Latent tuberculosis infection (LTBI): is a state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of clinically manifest TB disease. There is no gold standard

test for direct identification of *M. tuberculosis* infection in humans. Most infected people have no signs or symptoms of TB but are at risk for TB disease. Given that the main difference from active TB is the absence of disease and given that infection cannot always be considered latent, LTBI is sometimes referred to as just “TB infection”.

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

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

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

Systematic screening for TB disease: is a systematic identification of people with presumed TB disease, in a predetermined target group, using tests, examinations or other procedures that can be applied rapidly. Among those screened positive, the diagnosis needs to be established by one or several diagnostic tests and additional clinical assessments, which together have high accuracy.

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

Tuberculosis (TB): is the disease that occurs in someone infected with *M. tuberculosis*. It is characterized by signs or symptoms of TB disease, or both, and is distinct from TB infection, which occurs without signs or symptoms of TB. In this document, it is commonly referred to as “active” TB or TB “disease” to distinguish it from LTBI or TB infection.

Underweight: among adults this usually refers to a body mass index < 18.5 and among children < 10 years of age to a weight-for-age < -2 z-scores.

In September 2018, countries committed to provide tuberculosis preventive treatment to at least 30 million individuals by 2022, including 24 million household contacts of TB patients and 6 million people living with HIV.

It's time to act and fulfil commitments made at the UN high-level meeting on tuberculosis



Chapter 1.

Introduction and approach

Introduction

About one fourth of the world's population is estimated to be 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 have an increased risk of progressing to TB disease and becoming infectious. On average, about 5–10% of those infected will develop TB disease over the course of their lives, most of them within the first five years after initial infection (4). Studies have found that about 75% of people who develop active disease after coming into contact with someone with TB do so within one year of TB diagnosis of the index patient, and 97% develop TB within two years (5). Molecular typing studies in low-burden settings have also found that, among those who develop disease within 15 years of exposure probabilities of developing disease within one, two and five years were 45%, 62% and 83%, respectively (6). Therefore, people living with human immunodeficiency virus (PLHIV), individuals in contact with TB patients and those with immunodeficiency conditions are at high risk of TB and hence are priority groups to receive TB preventive treatment (TPT). Unfortunately, biomarkers and tests for TB infection available currently cannot differentiate between recent and remote infection. The 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, using the tests just as an aid in decision-making when available.

The WHO End TB Strategy prioritized TPT among persons at high risk, as a key component under Pillar 1. The programmatic management of TPT (PMTPT) fits within a larger framework of preventive actions envisaged under Pillars 1 and 2 of the End TB Strategy, and 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 (7). The End TB strategy provides indicators to monitor progress and set a global target to achieve 90% coverage of TPT among PLHIV and household contacts of TB patients by 2025 (8). PMTPT is also considered a key intervention for low TB burden countries that are pursuing TB elimination (9). While TPT services are gradually expanding globally, access among persons at risk remains low. In 2018, about 1.8 million PLHIV, 350 000 children under five years of age and nearly 80 000 people aged five years or above were reported by countries to have received TPT (10). Coverage of contacts thus remains very low with an absolute priority for the United Nations High-Level Meeting (UNHLM) targets to be met.

In September 2018, at the first ever UNHLM on Tuberculosis, Member States endorsed a political declaration committing to diagnose and treat 40 million people with TB by the end of 2022 and provide 30 million individuals with TPT to protect them from development of TB disease during this period (11). The TPT target in the declaration includes 6 million PLHIV, 4 million children under five years of age who are contacts of TB patients, and 20 million other household contacts of TB patients. Achievement of these targets entails a massive expansion of TPT services through health system strengthening and a mobilization of commensurate human and financial resources. In this context ministries of health need to take urgent actions to redesign PMTPT and mobilize resources to support rapid scale-up of TPT aligned with the latest (2020) guidelines from the World Health Organization (WHO) (12). Table 1.1 lists the latest WHO recommendations on TPT, that are discussed further in this handbook.

In support of these guidelines, this operational handbook lays down key implementation considerations and steps in the programmatic scale-up of TPT and provides implementation tools and job-aids for adaptation to the local context, and monitoring and evaluation indicators for PMTPT. It highlights key elements to consider in patient care, national strategic planning and resource mobilization. Although the handbook focuses on settings with a high TB and HIV burden, implementation considerations may apply also to low TB burden settings. This handbook is intended to guide policy-makers within the ministries of health and other institutions, and stakeholders that have an impact on health, including HIV and TB programme managers at national, subnational and district levels; 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.

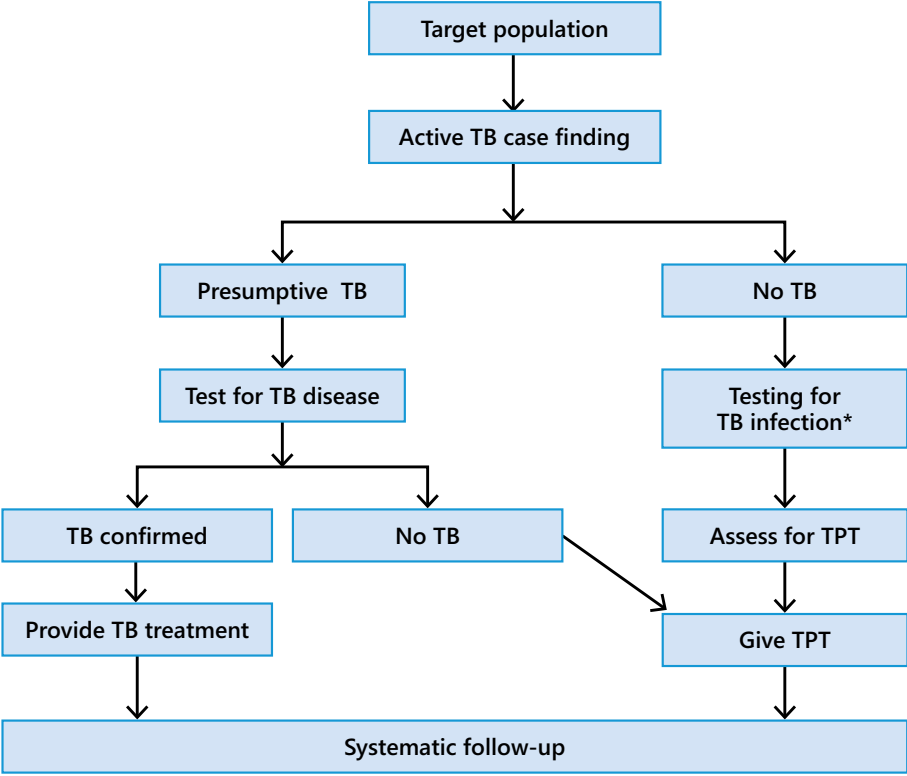
Cascade of care approach

PMTPT has long been a low priority intervention for national programmes due to other competing priorities. However, with Member States committed to take urgent steps towards ending the TB epidemic (71), major investments towards health systems strengthening should be made and a comprehensive 'cascade of care' approach adopted to scale up PMTPT (73). Advocacy efforts at different levels are critically important in the process and some key messages have been included in this handbook (see **Annex 1**; which includes an informative flyer developed by the WHO South-East Asia Region and the Global Coalition of TB Activists as an example that can be adapted elsewhere as well as a joint Call to Action to scale up TPT globally issued by partners in May 2020). It is important to ensure that all individuals most at risk of developing TB are systematically identified and provided access to a full course of TPT to improve individual health and reduce ongoing TB transmission. This is challenging as losses in the cascade of care prior to starting TPT are significant, even more than that from patient non-adherence to therapy after starting. A systematic review and meta-analysis in 2015 showed that the steps in the cascade of care associated with greatest losses were: 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. Overall, among those estimated to be eligible for TPT, less than 20% completed the entire cascade of care (74). It should be noted that these data were from research studies in developed countries, and losses under programmatic conditions in resource-constrained settings are expected to be even higher. Concerted efforts by national programmes and other stakeholders are necessary to enhance the reach of services for recommended target populations (74).

Programmatic implementation and scale-up of TPT services requires strengthening of each element in the cascade of care starting from identification of the target population to provision of preventive treatment (**Fig. 1.1**). **Annexes 2, 3** and **4** present suggestions for in-country structures to coordinate activities, costing considerations in budgeting as well as technical advice for PMTPT. TPT services should be integrated with efforts for TB case finding among target populations. Presumptive TB patients among target populations should receive diagnostic testing for TB with rapid molecular tests, and TB treatment if found positive. When TB disease is ruled out the individual should be evaluated for TB infection and receive TPT (see also algorithm in Fig. 4.1). Better retention and referral of individuals evaluated for TB, identification of those eligible for TPT and development of more person-friendly and 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 (75). This handbook is organized around the cascade of care and highlights elements that require programmatic prioritization and investment at each stage.

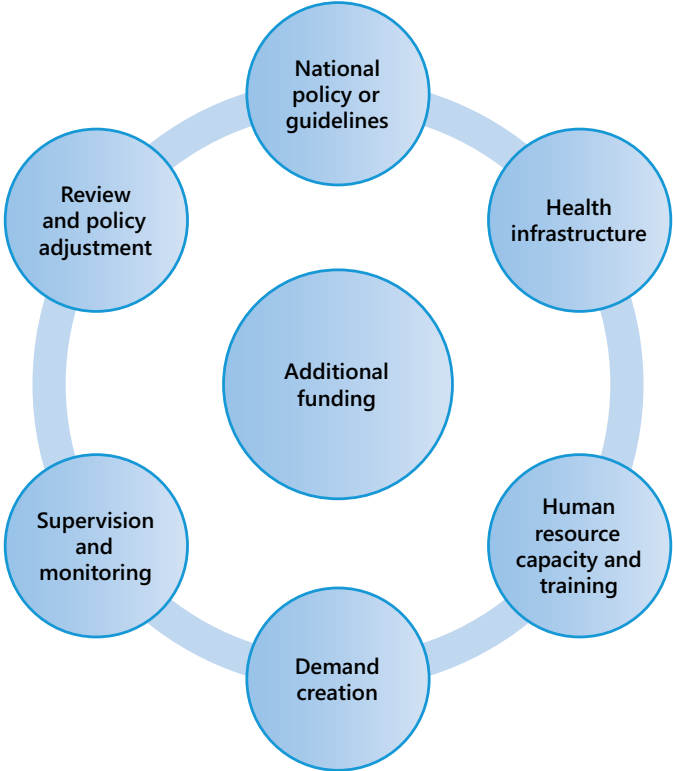
At each step of the cascade of care, national programmes and stakeholders should: prioritize the adoption of relevant national policy to facilitate implementation; earmark investment to strengthen health systems and enhance human resources; build capacity of providers; promote rapid scale-up of the latest diagnostic tools and shorter TPT regimens; generate demand for services; strengthen supervision and monitoring; and establish mechanisms for ongoing review and programme adjustments with the goal of national coverage of TPT services among all at-risk populations (**Fig. 1.2**).

Fig. 1.1: Cascade of TB case finding and preventive treatment



**Not required in PLHIV and child household contacts aged < 5 years*

Fig. 1.2: Implementation considerations in the programmatic management of TPT



This document outlines key decision points on policy considerations, health system requirements and areas for additional investment at each step in the cascade of care. A set of standard indicators for monitoring and evaluation of TPT services is also included along with suggested data variables to be captured in the national health management information system (HMIS) preferably using digital tools to minimize the reporting burden on health care workers. The policy considerations suggested are aligned with the latest WHO guidelines (**Table 1.1**). The overall aim is to support country efforts to achieve their individual contributions to the global targets for TPT.

Key point: Achievement of the UNHLM targets to provide TPT to at least 30 million individuals between 2018 and 2022, requires collective efforts and investments from governments, donors and other stakeholders to: strengthen health system across the cascade of care for TB, enhance provider and community awareness on importance of TPT, and ensure rapid access to latest tools for detection of TB infection and shorter TPT regimens.

Table 1.1: Recommendations in the WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment¹

1.1. Identifying populations for LTBI testing and TB preventive treatment

People living with HIV

1. Adults and adolescents living with HIV who are unlikely to have active TB should receive TB preventive treatment as part of a comprehensive package of HIV care. Treatment should also be given to those on antiretroviral treatment, to pregnant women and to those who have previously been treated for TB, irrespective of the degree of immunosuppression and even if LTBI testing is unavailable.
2. Infants aged < 12 months living with HIV who are in contact with a person with TB and who are unlikely to have active TB on an appropriate clinical evaluation or according to national guidelines should receive TB preventive treatment.
3. Children aged ≥ 12 months living with HIV who are considered unlikely to have active TB on an appropriate clinical evaluation or according to national guidelines should be offered TB preventive treatment as part of a comprehensive package of HIV prevention and care if they live in a setting with high TB transmission, regardless of contact with TB.
4. All children living with HIV who have successfully completed treatment for TB disease may receive TB preventive treatment.

Household contacts (regardless of HIV status)

5. Children aged < 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have active TB on an appropriate clinical evaluation or according to national guidelines should be given TB preventive treatment even if LTBI testing is unavailable.
6. Children aged ≥ 5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have active TB by an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment.
7. In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualized risk assessment and a sound clinical justification.

¹ The conditions under which these recommendations apply and more details on their implementation are discussed in the following chapters.

Other people at risk

8. People who are initiating anti-TNF treatment, or receiving dialysis, or preparing for an organ or haematological transplant, or who have silicosis should be systematically tested and treated for LTBI.

9. Systematic LTBI testing and treatment may be considered for prisoners, health workers, immigrants from countries with a high TB burden, homeless people and people who use drugs.

10. Systematic LTBI testing and treatment is not recommended for people with diabetes, people who engage in the harmful use of alcohol, tobacco smokers and underweight people unless they also belong to other risk groups included in the above recommendations.

1.2. Algorithms to rule out active TB disease

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

12. Adults and adolescents living with HIV who are screened for TB according to a clinical algorithm and who report any of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases and offered preventive treatment if active TB is excluded.

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

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

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

1.3. Testing for LTBI

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

1.4. TB preventive treatment options

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

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

Tuberculosis is the world's top infectious killer. TPT preserves health, reduces deaths and transmission, and saves families from catastrophic costs.

It's time for governments and donors to be more proactive to help all people at higher risk of TB to access TPT



Chapter 2. Identification of populations for TB preventive treatment

Decision point on target populations for systematic testing and TPT

Which of the at-risk populations are priority targets for the programmatic scale-up of TPT, based on your country context?

The WHO guidelines on TPT recommends target populations fulfilling one or more of the following criteria for PMTPT (12):

- High **prevalence** of TB infections
- High **risk of progression** to TB disease
- High **incidence** of TB disease compared to the general population, indicating high TB transmission setting
- **Benefits of TPT** outweighing potential risk of acquiring TB or drug toxicity.

WHO recommends two broad groups of at-risk populations that fulfil the above criteria for systematic assessment of eligibility and provision of TPT.

1. **People with elevated risk of progression from infection to TB disease**

- People living with HIV
- Patients suffering from silicosis, patients starting or preparing for anti-tumour necrosis factor (TNF) treatment, patients receiving dialysis, and patients preparing for organ or haematologic transplantation.

2. **People with increased likelihood of exposure to TB disease**

- Household contacts of people with bacteriologically confirmed TB, usually subdivided into:
 - a. Children below five years of age
 - b. Children five years and above, adolescents and adults
- Persons 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.

Although, systematic testing and treatment of people with diabetes, people who engage in harmful use of alcohol, tobacco smokers and underweight people are not specifically recommended for systematic testing and TPT, these populations may still be considered for TPT on a case-by-case basis to reduce the risk of TB, especially if they have heightened likelihood of unfavourable outcome should disease develop or if the person has multiple risk factors for TB.

The following paragraphs detail the rationale and implementation considerations that national programmes may use to inform policies on the choice of target populations for PMTPT.

People living with HIV

PLHIV are around 20 times more likely to develop TB disease than those without HIV infection and should be prioritized for systematic evaluation and TPT in all settings (10). Despite major progress in access to and effectiveness of antiretroviral treatment (ART), TB is the most frequent cause of acquired immunodeficiency syndrome (AIDS)-related deaths worldwide (16). In 2018, TB caused over 250 000 deaths among PLHIV i.e. about one third of all HIV deaths (10). Existing evidence shows that TPT increases the survival of PLHIV even when they are on ART (17). TPT also provides additional protection when given immediately after the successful completion of treatment for TB disease in PLHIV (17–19) (the box below presents relevant recommendations from the 2020 WHO guideline on TPT (12)).

WHO recommendations:

1. Adults and adolescents living with HIV who are unlikely to have active TB should receive TB preventive treatment as part of a comprehensive package of HIV care. Treatment should also be given to those on antiretroviral treatment, to pregnant women and to those who have previously been treated for TB, irrespective of the degree of immunosuppression and even if LTBI testing is unavailable.
2. Infants aged < 12 months living with HIV who are in contact with a person with TB and who are unlikely to have active TB on an appropriate clinical evaluation or according to national guidelines should receive TB preventive treatment.
3. Children aged ≥ 12 months living with HIV who are considered unlikely to have active TB on an appropriate clinical evaluation or according to national guidelines should be offered TB preventive treatment as part of a comprehensive package of HIV prevention and care if they live in a setting with high TB transmission, regardless of contact with TB.
4. All children living with HIV who have successfully completed treatment for TB disease may receive TB preventive treatment.

While TPT should be considered in infants aged < 12 months living with HIV who have a history of contact with a TB patient, children living with HIV (CLHIV) aged ≥ 12 months should be considered for TPT irrespective of contact with a TB patient. TPT is recommended for CLHIV, regardless of whether they are on ART or not. The evidence for additive benefit of TPT among CLHIV 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 CLHIV after successful completion of TB treatment is largely extrapolated from benefits observed in adults exposed to reinfection and recurrence of TB.

Similar to infants aged < 12 months who are living with HIV, infants born to HIV-infected mothers are vulnerable to early TB infection due to the mother's risk of contracting TB disease (20,21). Given the poor outcomes of TB disease in infancy, it is important to consider TPT for such infants who show no signs of TB disease. Prevention of mother-to-child transmission (PMTCT) of HIV offers an important platform to screen these infants for TB disease. A strong linkage should therefore be established between PMTCT services and national TB programmes (22).

WHO also recommends provision of TPT among CLHIV who successfully complete treatment for TB disease. PLHIV face higher risk of recurrence of TB disease compared to HIV-negative individuals. While a complete course of TB treatment with a four-drug regimen has a very high treatment success rate and very low incidence (2–3%) of recurrence, in HIV-infected patients, the risk is several times higher, possibly due to treatment failure, emergence of drug resistance during therapy or reinfection

with a new strain of *M. tuberculosis* (23–26). In a study among HIV-infected patients whose initial episode of TB was deemed cured, 14% experienced a recurrence of TB, of which close to 90% were due to reinfection with a different strain of *M. tuberculosis* (27). Key interventions to minimize recurrence of TB include: ensuring completion of the initial course of TB treatment, effective infection control measures in clinical and community settings frequented by PLHIV, and secondary TB preventive treatment (28,29).

Household contacts (regardless of HIV status)

Child household contacts below five years of age who are household contacts of TB patients, have significantly higher risk of acquiring TB infection and progressing rapidly to TB disease. Children below two years of age are also at greater risk for severe and disseminated forms of TB with very high risk of morbidity and mortality. Therefore, TPT is strongly recommended once TB disease is ruled out. Similarly, other household contacts of TB patients have high risk of acquiring TB infection compared to the general population and should be considered for inclusion in PMTPT.

WHO recommendations:

5. Children aged < 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have active TB on an appropriate clinical evaluation or according to national guidelines should be given TB preventive treatment even if LTBI testing is unavailable.
6. Children aged ≥ 5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have active TB by an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment.
7. In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualized risk assessment and a sound clinical justification.

WHO also recommends consideration of TPT for select household contacts of multidrug-resistant TB (MDR-TB) patients (such as children, people receiving immunosuppressive therapy and PLHIV), as the available evidence shows more benefits than harm (12). The decision to treat MDR-TB contacts should be taken on an individual basis both with respect to the selection of person to treat and the TPT regimen. There is limited evidence to support one single regimen for MDR-TB contacts: studies that informed this recommendation used levofloxacin with or without ethambutol/ethionamide daily for six months.

TPT should be considered only after TB disease is ruled out by an appropriate clinical evaluation or according to national guidelines and after a careful risk assessment, including intensity of exposure, certainty of the source of disease, reliable information on the drug resistance pattern of the source and potential adverse drug reactions. Confirmation of infection by tuberculin skin test (TST) or interferon-gamma release assay (IGRA) is desirable before the start of TPT to confirm TB infection. This maximizes the likelihood of TPT not being given unnecessarily. There is less evidence on the balance of benefit to harm of medicines used in the TPT of MDR-TB than for drug-susceptible TB, and therefore the decision to give TPT needs to consider any potential risk carefully. If levofloxacin is used for TPT of MDR-TB, it is important to ascertain careful exclusion of TB disease so as to limit the risk of emergence of resistance to levofloxacin (a key drug in second-line treatment regimens), should the person require treatment for MDR-TB disease in the future. Strict clinical observation for signs of TB disease for at least two years after exposure should be ensured, regardless whether TPT for MDR-TB is given or not.

Clinical and other at-risk population groups

WHO recommendations:

8. People who are initiating anti-TNF treatment, or receiving dialysis, or preparing for an organ or haematological transplant, or who have silicosis should be systematically tested and treated for LTBI.
9. Systematic LTBI testing and treatment may be considered for prisoners, health workers, immigrants from countries with a high TB burden, homeless people and people who use drugs.
10. Systematic LTBI testing and treatment is not recommended for people with diabetes, people who engage in the harmful use of alcohol, tobacco smokers and underweight people unless they also belong to other risk groups included in the above recommendations.

Benefits of TPT outweigh the potential harm among other HIV-negative clinical risk groups considering increased risk of exposure and/or progression to TB disease. However, despite evidence of increased prevalence of TB infection and TB disease among persons with diabetes, people who engage in the harmful use of alcohol, tobacco smokers and underweight people, there is a paucity of data from clinical trials on the relative benefits and harm of systematic testing and TPT. Testing and treatment among people with one or more of these risks may be considered on a case-by-case basis. Additional evidence on systematic TPT services among these populations is required to inform future WHO guidelines.

Integrating active TB case finding in PMTPT

Complementary to recommendations on target populations for systematic testing and TPT for TB infection above, WHO also recommends systematic screening for TB disease among various at-risk populations. National programmes may consider integration of TPT services with TB case finding among these populations (30,31). WHO is currently reviewing latest evidence to update the recommendations for at-risk populations for active TB case finding (ACF) and recommend optimal TB screening strategies. National programmes may integrate systematic evaluation for TPT eligibility among 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 is ruled out. National programmes may adapt the algorithm for **other risk groups (Fig. 4.1)** when integrating ACF and TPT in populations at risk.

Key point: National programmes implementing ACF among at-risk populations should consider integration of TPT services within the package of care to increase coverage with minimal additional investment, and vice versa programmes implementing TPT should link eligible individuals to services for TB disease diagnosis and treatment.

The scope of activities performed during contact investigations may also be expanded beyond TB services, based on country context. For example, when the index TB patient is HIV positive, household contacts should also be offered HIV counselling and testing systematically or when malnutrition is noted during contact investigation, nutrition screening and assessment should be done.

Implementation steps to identify TPT target populations

1. **Establish a national technical working group** or expand the mandate of an existing technical working group or equivalent mechanism to advise the ministry of health and national TB and HIV programmes. The technical working group may consist of national experts, stakeholders from national TB, HIV, maternal and child health and other relevant programmes, representatives from patient groups, civil society, frontline health providers/nurses, national research institutes, technical partners and WHO. The group may be mandated to lead the identification of target populations and strategies to reach these populations under PMTPT (**Annex 2**).
2. **Review national policies and guidelines.** The technical working group may review current national policies and guidelines for PMTPT and lead the process of updating them and aligning with the latest global guidelines.
3. **Undertake a situational assessment.** The technical working group and/or national programme may undertake the following reviews to guide decisions on identification of target populations for PMTPT:
 - Burden of TB disease (and TB infection) among various at-risk populations
 - Capacity of the existing health system (staff, skills and equipment) to assess intensity and risk of TB exposure and exclude TB disease
 - Availability of financial resources and identifying gaps to support nationwide scale-up of TPT services
 - Opportunities to mobilize additional resources.
4. At a minimum, all countries should aim to achieve **universal coverage of TPT** among PLHIV and household contacts of TB patients under five years of age.
5. **Identify other target populations.** This may be guided by small scale demonstration or phased implementation of PMTPT among the various target populations to identify operational issues. Experience from demonstration projects may inform identification of populations and strategies to reach them with TPT services. Extensive research to review efficacy of TPT regimen is not required, given that the WHO guideline process involves in-depth review of latest clinical trial evidence. Moreover, such country-specific or population-specific studies risk delaying the scale-up of TPT services thereby denying benefits of TPT to vulnerable populations.
6. **Prioritize individuals who are likely to have recently acquired TB infection** (e.g. children, recent and young immigrants from countries with a high TB burden to low TB burden countries, recent contact with a TB patient, or documented conversion of TB infection test from negative to positive).

It is important to consider, particularly for populations in congregate settings, that surveillance and treatment of TB disease and infection control measures are effectively implemented (32). These are essential prerequisites in deciding about the implementation of TPT services in such populations. Without implementation of good measures for airborne infection control, sustained benefits from TPT may be jeopardized due to high risk for reinfection. Therefore, once target populations for TPT are identified, ministries of health, donors and stakeholders should support capacity building of programmes to strengthen infection control measures and establish access to rapid TB diagnosis and treatment.

Key point: ACF with linkages to TB treatment and TB infection prevention and control are essential elements of programmatic scale-up of TPT among at-risk populations, particularly in congregate settings.

Implementation considerations to reach TPT target populations

Reaching PLHIV and other target populations

- All HIV testing and treatment facilities including community-based HIV care and support, should systematically implement intensified TB case finding, TPT and TB infection control. This requires close collaboration between national TB and HIV programmes (33).
- All PLHIV should be screened for TB symptoms at every opportunity or when in contact with a health worker. Those with TB symptoms should be referred for diagnostic testing, and those without symptoms should be evaluated for eligibility and started on TPT, as appropriate.
- National TB and HIV programmes should provide resources and undertake site monitoring to ensure implementation and quality improvement measures when gaps are noted (such as lack of screening, cursory screening, lack of linking to TPT).
- For other target populations, the national programme should tailor TB screening and TPT services to the needs and capacities of existing health infrastructures. The approach should aim to optimize and synergize delivery of TPT services along with other health and social welfare services. Target populations and screening approaches should be monitored regularly to improve delivery of services.

Reaching household contacts

Household contacts of TB patients are well recognized at-risk groups for TB infection and TB disease, including prevalent TB detected at the time of initial contact investigation, as well as incident TB that occurs within the subsequent two to five years. TPT among household contacts may have important potential benefits since prevalence of TB infection exceeds 50% in many low and middle income countries (LMICs) (34,35). In systematic reviews, the prevalence of TB disease among household contacts in LMICs ranged from 3% to 5% (34,35). Results of the PHOENIX Feasibility study (cross-sectional) from eight high TB burden countries, showed that of a total 1007 household contacts of 284 MDR-TB patients with no TB at diagnosis, systematic household contact investigation helped detect new TB disease in 12% contacts; TB infection prevalence (defined as either TST or IGRA positivity) in this group was 72% (36). Thus, screening of household contacts for TB disease is considered a high priority for virtually all TB control programmes because it is a very high yield and cost-effective ACF strategy (37). This further paves the way to effective treatment for TB disease and TPT and thus optimizes public health impact on transmission as well as improves TB-related outcomes for contacts. It is a key strategy for infection control as well in all settings.

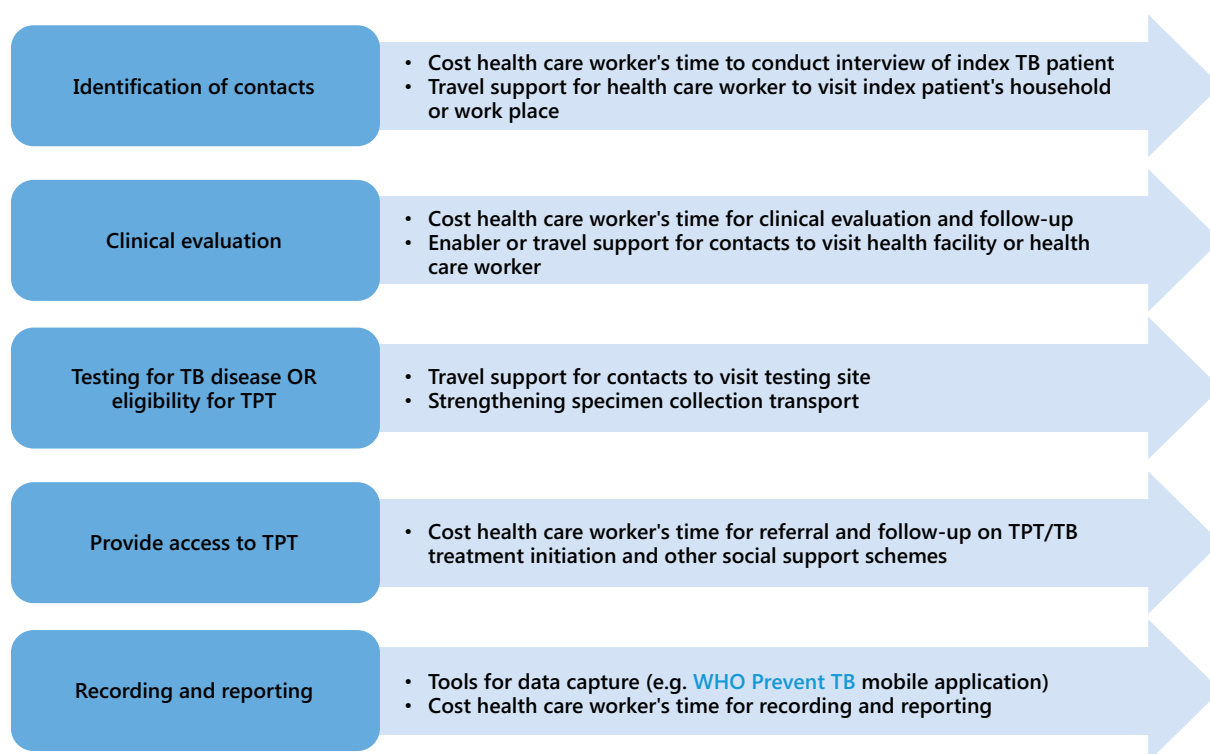
Investigation and treatment of all household contacts have important advantages and can provide important health and financial benefits to the entire family. Occurrence of TB in the family has serious social and economic effects including catastrophic costs due to loss of income or cost of health care. By investigating, detecting and treating both TB disease and TB infection, transmission in the household can be stopped and the catastrophic costs and dire health outcomes due to TB prevented. This is a holistic 'family health' approach, offering more efficient TB care to all members. Offering TPT to all family members at the same time and during the period when the index TB patient is still receiving treatment and care, can help maximize the understanding and impact of TPT, as well as enhance cost-effectiveness of interventions such as home visits. Further, a strong contact investigation programme will pave the way for achievement of commitments made by the Member States to provide TPT to 24 million household contacts by 2022.

Key point: Investments to strengthen national programme capacity to undertake contact investigation prevents future TB disease by improving access to TPT for children and adult contacts and identifying missed TB patients for treatment, thus reducing onward transmission.

Strengthening household contact investigation

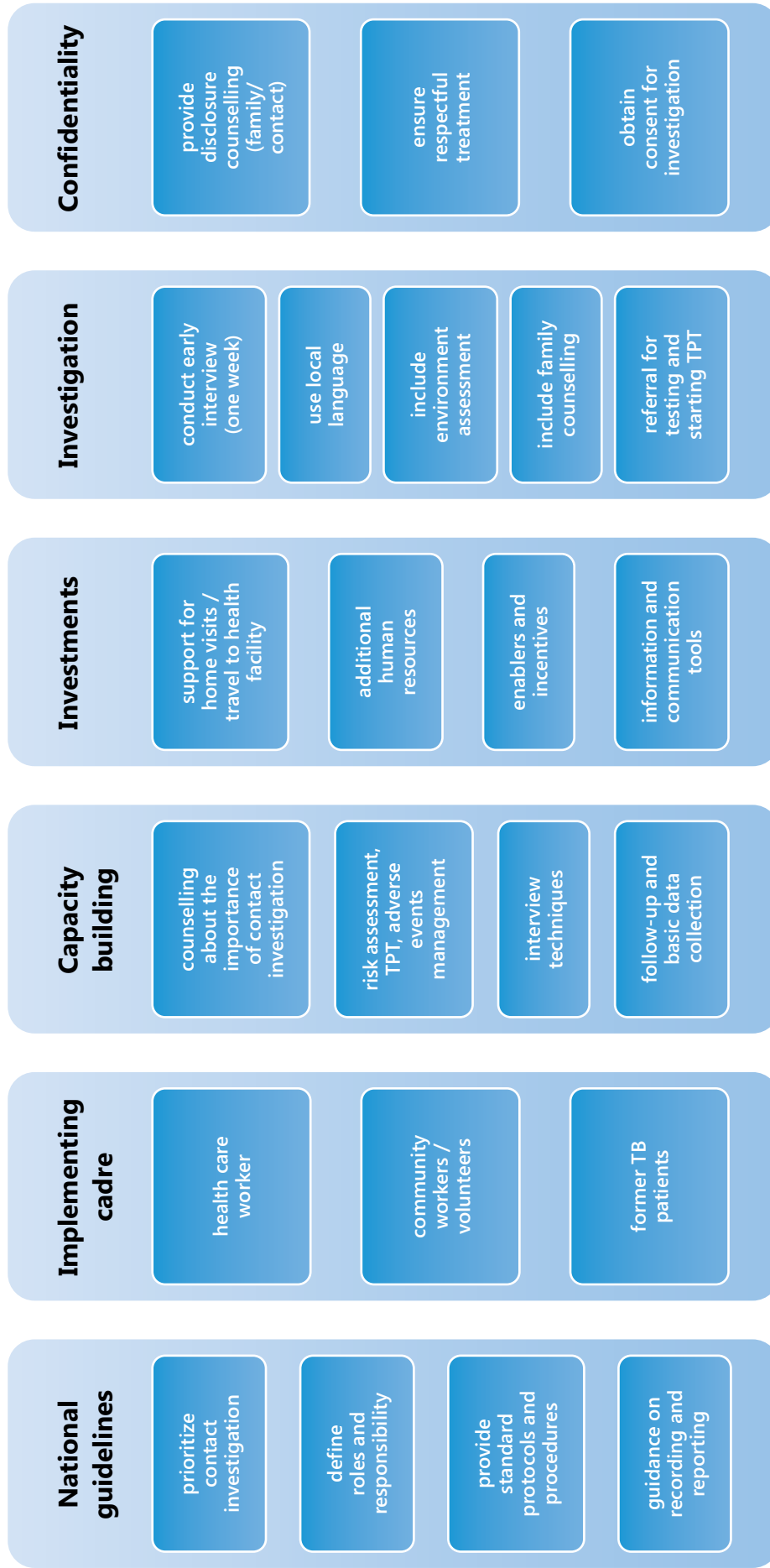
Contact investigation is an important first step both for ACF and TPT. It is a systematic process to identify people with TB disease and contacts of index TB patients who need TPT. It consists of identification, clinical evaluation and/or testing and provision of access to appropriate anti-TB therapy (for people with confirmed TB) or TPT (for those without TB disease). It should be a standard component of all national TB control efforts. Moreover, contact investigation is a good public health practice and essential for tracking several infectious diseases (such as COVID-19) and therefore the ministries of health should invest in strengthening health system capacity. If the mechanisms to undertake contact investigation are in place, national programmes need to strengthen the same to ensure that contacts above five years of age are also covered. If such mechanisms are lacking, the ministry of health should dedicate necessary human and financial resources to establish effective mechanisms for contact investigation. **Fig. 2.1** provides an indicative list of items to consider for determining appropriate unit costs for budgeting and planning to strengthen contact investigations.

Fig. 2.1: Indicative costing items to strengthen contact investigations



In addition to extra funding, national TB programmes should consider and strengthen activities highlighted in **Fig. 2.2** to ensure effective contact investigation.

Fig. 2.2: Building blocks for a strong contact investigation component



Key implementation steps in contact investigation

1. Provide standard guidance and approaches to reach contacts and undertake investigations to ensure uniformity in implementation.
2. Provide national guidance that:
 - defines priority populations for contact investigation (household and beyond);
 - defines model of care, i.e. facility- or community-based;
 - defines the role and responsibilities of programme personnel, health care worker and community health worker, in reaching the contacts, symptom screening, referral for testing and clinical evaluation (e.g. cadre of health care workers responsible for contact investigation and its inclusion in respective job descriptions, health care workers responsible for supervision of personnel conducting contact investigation if community-based model is implemented);
 - defines data elements to capture the index patient's record and/or digital tools (see also **Chapter 7**);
 - includes tools/referral slips to record TB screening and referral of identified contacts for further care if the community-based model is implemented;
 - defines level of service delivery points for systematic recording and reporting as well as frequency; and
 - provides locally tested messages for demand generation and patient education.
3. Leverage existing human resources and mechanisms across multiple disease programmes (such as public health response model promoted by U.S. President's Emergency Plan for AIDS Relief (PEPFAR) for PLHIV) to implement contact investigation and ensure sustainability and efficiency. TB and HIV screening could be integrated throughout the process.
4. Implement contact investigation
 - The index patient should be interviewed as soon as possible after diagnosis, preferably within one week, to elicit details about household and other close contacts. Health providers should clearly and sensitively explain the urgency of initiating contact investigations to the index patient, considering the increased risks of progression to TB disease with recent exposure. A second interview may be required to elicit additional contacts as well as complete any missing information.
 - Ideally, the interview should be conducted by a person who speaks the same language as the index patient and is familiar with his or her social and cultural context.
 - Education of the index patient and household members regarding the benefits of taking TPT and risks of NOT taking it, should be central to the contact investigation process. The overall aim should be to enable informed decision by the individuals to receive a complete course of TPT regimen.
 - Counselling to index TB patients should also help them to appreciate the importance of identifying all significant contacts. This will permit preventive action to reach more people at risk.
 - Where the community-based model is implemented, it is desirable to seek approval from the index patient for a home visit. In addition to counselling of the index patient, arrangements should be made to counsel contacts before starting TPT.
 - Preferably, the health provider conducting the contact investigation should visit the home or workplace of the index patient, conduct interviews and underscore the importance of identifying and evaluating contacts, perform symptom screening and document, gather more accurate information about the intensity and duration of exposure and ensure that all relevant contacts are referred for further evaluation and a treatment decision (**Box 2.1**) (38). Visits may need to be done outside of normal working hours since contacts may be at work or school during these hours.
 - Home visits also provide the opportunity to identify the needs for social support, nutrition and education on infection control measures. After the visit, the health provider may link the index patient and contacts to relevant social and nutritional support programmes.

- During the home visit the health provider should make an assessment of the residence and provide counselling and education to family members on TB symptoms. If required, prompt medical attention and referrals should be made especially for child contacts and PLHIV, in whom TB could progress rapidly. HIV testing and counselling should be offered as part of this process, including to biological children of any adults living with HIV.
- If the home or workplace cannot be visited, the index patient may be interviewed at a health facility and contacts listed. Complete address and modality for future communication should be mutually agreed with the index patient (such as phone numbers, email, contact of an intermediary or treatment provider). Responsible persons or health care workers should then systematically follow up with the index patient or treatment provider and mobilize all relevant contacts to the health facility for symptom screening, testing for TB and TB infection when indicated and evaluation for eligibility of TPT.
- While the focus of the contact investigation should be household members, contacts at the workplace, residential care facilities, residential schools, long-term care facilities, prisons, correctional facilities and acute medical care facilities, should be considered as per national guideline for evaluation, especially when exposure is likely to have been prolonged and the index patient is likely to be highly infectious (due to prolonged cough, strongly acid-fast bacilli (AFB) smear-positive sputum and/or extensive cavitary disease on chest radiograph).
- Maintaining confidentiality during contact investigation is a challenge because of the social connections between index patients and their contacts. All persons should be treated with respect, and confidentiality should be maintained. National programme guidelines on data protection, confidentiality and consent should be adhered to.
- When the index patient is reluctant to give information regarding both household and social contacts, counselling efforts should continue over time to gain the trust of the patient. The index patient should not be coerced, nor should her/his TB treatment or services provided be made conditional on cooperation with contact investigation.

Key point: Index TB patients should not be compelled to disclose contacts or help ensure completion of contact investigation. Due diligence is necessary in safeguarding the index patient's privacy and rights and avoiding stigma. Ongoing patient education is preferred over use of force and coercion.

- Information from the interview should be recorded (37).
 - Contact investigations should also be conducted for people who died of TB by gathering information from family members and service providers.
5. Provide guidance on monitoring and evaluation (see also **Chapter 8**):
- Use standard tools and a protocol for data collection during contact investigation, data entry and analysis.
 - Monitor yield of contact investigations and the proportion of TB disease and TB infection detected to inform programme adjustments.

Box 2.1: 10 key steps in contact investigation*

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

**These steps may not always be done in sequential order*

Key point: The biggest component of UNHLM targets is to provide TPT to at least 24 million household contacts of TB patients between 2018 and 2022. Global progress towards achieving this target has been negligible. Scaling-up TPT among this target population is likely to generate significant community dividends and return on investment. Hence ministries of health and stakeholders should commit adequate funding and resources to build capacity of programmes to undertake effective contact investigations.

Additional funding considerations to find target populations

- Integrating contact investigations into the roles and responsibilities of existing health and community workforce.
- Dedicating human resources as required to implement and to monitor implementation of contact investigations.
- Training and capacity building of health care workers, community workers and other implementers.
- Travel support or incentives for health care workers, community workers or other implementers of contact investigations.
- Travel support for index TB patients and contacts to reach facilities for screening, testing and continuation of TPT.
- Strengthening 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 (39)).
- Awareness generation among patients, contacts and communities.

Also refer to **Annex 3**.

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



Chapter 3. Ruling out TB disease before TB preventive treatment

Decision point on how to exclude TB disease before offering TPT

How can TB disease be reliably ruled out among target populations identified for TPT?

Offering TPT to someone who has TB disease can delay the resolution of disease and favour the emergence of drug resistance. Thus, excluding TB disease before initiating TPT is one of the critical steps in the preventive TB care pathway. This chapter covers WHO recommendations as well as key policy and implementation considerations in the development of national algorithms to rule out TB disease, mindful of the barriers that additional steps could create towards successful implementation of TPT. The process has much in common with screening for TB disease: similar risk groups, same tests, and same monitoring principles. The decision points centre around determining HIV status, eliciting history of the household or other close contacts, other risk factors, eliciting suggestive signs and symptoms depending on the person's age, results of TST or IGRA and abnormality on chest radiography. TB disease must be excluded using available tools within the context and policies of the country, before starting TPT. Once at-risk populations that are likely to benefit from TPT are identified, the ministry of health should choose appropriate screening and diagnostic approaches best suited for the respective target population. Systematic implementation of clinical symptom screening and testing among target populations requires assessments of health system capacity and availability of human and financial resources. The programme would need to mobilize funds from domestic and external sources to address these needs adequately.

Screening for TB disease using signs and symptoms

Using a standard set of signs and symptoms to screen for TB disease has multiple advantages. Firstly, in many settings it has a high sensitivity and a high negative predictive value, meaning that it can reliably rule out TB if none of the clinical manifestations are present (even if presence of only one of the features has a low specificity for TB disease and could be due to other conditions). Secondly, it is a straightforward intervention inherent to any clinical encounter and can be repeated as often as necessary without special equipment. Additional tests such as chest radiography can be combined with a symptom screen to improve its accuracy.

Evidence reviewed by WHO over the past decade, ahead of updates to its guidelines, showed that among:

- PLHIV aged 10 years and older, the absence of current cough, fever, weight loss or night sweats had a sensitivity of 79% and a negative predictive value of 97%.
- Infants and children living with HIV, the absence of poor weight gain, fever or current cough or a history of contact with a TB patient had a sensitivity of 90% and a negative predictive value of 99%.
- HIV-negative household contacts aged five years and older and other clinical risk groups, the absence of cough of any duration, haemoptysis, fever, night sweats, weight loss, chest pain, shortness of breath or fatigue had a sensitivity of 73% and a negative predictive value of 99%.

Therefore WHO recommends that screening for the absence of symptoms could be used to rule out TB disease (78,40). It is suggested that for PLHIV aged 10 years or above the standard four-symptom screening be applied; in younger children a broader set of clinical manifestations may be used to decide on who to refer for diagnostic work-up before offering TPT.

WHO recommendations:

11. Adults and adolescents living with HIV should be screened for TB according to a clinical algorithm. Those who do not report any of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered preventive treatment, regardless of their ART status.
12. Adults and adolescents living with HIV who are screened for TB according to a clinical algorithm and who report any of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases that cause such symptoms.
13. Chest radiography may be offered to people living with HIV and on ART and preventive treatment given to those with no abnormal radiographic findings.
14. Infants and children living with HIV who have poor weight gain, fever or current cough or who have a history of contact with a person with TB should be evaluated for TB and other diseases that cause such symptoms. If TB disease is excluded after an appropriate clinical evaluation or according to national guidelines, these children should be offered TB preventive treatment, regardless of their age.
15. The absence of any symptoms of TB and the absence of abnormal chest radiographic findings may be used to rule out active TB disease among HIV-negative household contacts aged ≥ 5 years and other risk groups before preventive treatment.

WHO recommends that chest radiography may be offered to PLHIV who are receiving ART. If there are no abnormal radiographic findings, TPT should be considered. However, chest radiography should not be considered a mandatory requirement and become a barrier in starting TPT for PLHIV as there is only a marginal gain in accuracy as compared with symptom screening alone.

Role of chest radiography

One of the key policy decisions with financial implications is whether to consider systematic use of chest radiography along with TB symptom screening to rule out TB disease.

Chest radiography is known to have high sensitivity but low specificity for TB (41). Use of chest radiography in an asymptomatic child, five to nine years of age (as for < 5 years) has poor specificity and thus a very low yield of true positive TB, with a risk of over-diagnosis for conditions caused by other conditions (such as pneumonia or perihilar adenopathy) and unnecessary treatment for TB. Moreover, addition of chest radiography to symptom screening may present logistical difficulties and increase cost to programmes and individuals, leading to missed opportunities to give TPT to people who could benefit from it. Among PLHIV, symptom screening alone before TPT is not only less costly but also prevents more TB deaths and cases (42). However, use of chest radiography together with TB symptom screening is likely to increase the confidence of health providers given the very high sensitivity of the combination (less chance of missing TB disease). This may conceivably reduce provider concerns around the development of drug resistant-TB resulting from inadvertent treatment of TB disease with a TPT regimen. This is particularly important among HIV-negative household contacts who are adolescents and adults, other close contacts and clinically at-risk populations. Similarly, use of chest radiography may increase provider confidence among PLHIV who are receiving ART.

Chest radiography may therefore be considered in TB screening algorithms where it is available and not burdensome to the individual. If there are no abnormal radiographic findings, TPT should be considered. However, chest radiography should not be considered a mandatory requirement and become a barrier for starting TPT. When chest radiography is not available, the absence of symptoms alone suffices to exclude TB disease before starting TPT.

When any abnormal chest radiographic findings are noted (not just those suggestive of TB), detailed investigation for TB disease and other diseases should be undertaken in accordance with national guidelines and sound clinical practice.

With the increase in availability of digital radiography, the use of computer aided detection (CAD) to interpret films, and the engagement of private health facilities to purchase radiography services is expected to increase access to radiography in TB screening and diagnostic algorithms. In mid-2020 WHO will review evidence to assess whether guidance can be issued on the use of CAD for chest radiograph reading as part of screening algorithms for TB and continue to monitor evidence emerging from this rapidly evolving technology.

Key point: Chest radiography can play a role in ruling-out TB before TPT and increase the confidence of the provider and person radiographed that TB disease is absent. Governments and donors should invest to scale up access to chest radiography, including from private sector providers. However, lack of access to chest radiography should not be a barrier to TPT introduction and scale-up.

Implementation considerations to rule out TB disease

Health ministries should coordinate implementation of activities articulated below to screen for and exclude TB disease ahead of TPT provision.

- Make ACF among at-risk populations for TB an integral part of the overall package of health care for these populations (such as a HIV care package for PLHIV). In principle, the overall responsibility for planning, resource allocation, service delivery (ACF and activities to rule out TB disease) and monitoring and evaluation, should be vested in the national authority responsible for services to the respective populations. The national TB programme, in collaboration with primary care and maternal and child health services, should assume responsibility for ACF among contacts of index TB patients; the national HIV programme should organize services for PLHIV in collaboration with the national TB control programme; the clinical services within the ministry of health should support ACF and linkages to treatment and care among other clinical at-risk populations, and likewise for state agencies responsible for prisons, occupational health and migrant care.
- Receive advice from a national coordinating body or technical expert group or similar body for respective national programmes in the development of a national scale-up plan for programmatic implementation of ACF and services to rule out TB disease across different target populations and geographies. The coordinating body or group may also advise on standard operating procedures (SOPs), plan for capacity building of various types of providers and coordinate procurement and supplies of commodities for interventions across different programmes.
- Develop a standard implementation guide including roles and responsibilities, operating procedures, implementation tools, job-aids and recording and reporting tools (integrated across HIV, TB and maternal and child health services) for ruling out TB disease among at-risk populations.
- Develop communication materials for display and use at all service delivery sites implementing intensified TB screening.

- Identify a cadre of health care workers at different levels of the health care system to perform clinical screening as well as referral for further testing for TB disease, infection and evaluation, as per national guidelines.
- Undertake training and on-the-job capacity building for health care workers, community health workers and other service providers in systematic TB symptom screening.
- Conduct regular supportive supervision at national, provincial and district levels for TB screening activities, especially those carried out by community health workers to ensure good quality screening and adherence to national algorithms.
- Develop job-aids highlighting steps in ruling out TB disease.
- Organize access to chest radiography through: public or private health facilities or mobile vans as required by the national policy; memoranda of understanding (MoU) with private hospitals and radiologists; as well as free vouchers for people to access private services.
- 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 key steps in the cascade and report indicators of programme performance to the national level (see also **Chapter 8**).

Table 3.1 provides an overview of the considerations for ruling out TB disease among various target populations before starting TPT. While effective TB symptom screening forms the backbone of TPT services, tests for TB infection, chest radiography and diagnostic testing may be used.

Table 3.1: Key steps in ruling out TB and considering TPT

	Adults and adolescents living with HIV ^b	Children living with HIV ^a	HIV-negative household / close contacts of TB patients	Clinical at-risk populations
Clinical symptom-based screening^a	Current cough, fever, weight loss or night sweats	Absence or poor weight gain, fever or current cough or history of contact with a case of TB, reduced playfulness, night sweats	Cough of any duration, haemoptysis, fever, night sweats, weight loss, chest pain, shortness of breath, fatigue	
Frequency of symptom screening	At every visit to a health facility or contact with a health worker			
Chest radiography	Not mandatory although desirable. May be considered among PLHIV on ART; among asymptomatic adolescent and adult contacts and clinical at-risk groups where facilities are available and human resources and health system capacity permits			
Diagnostic testing for TB if screen test is positive	WHO recommends rapid diagnostics (such as Xpert MTB/Rif, urine lipoarabinomannan assay among seriously ill PLHIV) or as per national guidelines			
Test for TB infection (TST or IGRA)	Not required among PLHIV and contacts below five years of age. In other populations these tests limit unnecessary treatment of uninfected individuals (such as settings with low prevalence of TB infection) Unavailability of tests should not be a barrier to provision of TPT to those in need			
Contraindication to TPT	<ul style="list-style-type: none"> • Active hepatitis (acute or chronic), regular and heavy alcohol consumption and symptoms of peripheral neuropathy • Concurrent use of other hepatotoxic medications (such as nevirapine) • History of hypersensitivity to TPT 			
Counselling	Information on TB infection, need for TPT, schedule of medication collection, medication adherence support and follow-up visits, benefits from completing the course, adverse events, actions on development of TB symptoms or adverse events			

a Screening for children and pregnant or breastfeeding women may be integrated into various entry points for care (such as maternal and child health, immunization, well baby clinics, nutrition clinics).

b Among PLHIV, all the above steps should be incorporated if differentiated HIV service delivery models are implemented. ACF and TPT should be an integral part of the care package for PLHIV.

Additional funding considerations to rule out TB disease

- Support regular convening of and consultation with the national technical working group or a similar existing mechanism to review strategies for ruling out TB disease before TPT among target populations.
- Develop and implement a plan for human resource development including hiring, training, mentoring, and ongoing sensitization in TB symptom screening, family counselling and evaluation of eligibility for TPT.
- If chest radiography is used for TB screening as per national guidelines, funding allocation will be required for
 - equipment (such as for digital radiography),
 - supply of logistics,
 - maintenance of equipment,
 - training of clinicians and health care workers in reading chest radiographs, and/or
 - hiring of radiography services from the private sector (such as free vouchers for individuals receiving care either in public or private facilities).
- Expand access to rapid TB diagnostics, such as Xpert MTB/Rif, lateral flow urine lipoarabinomannan assay (LF-LAM).
- Establish or strengthen specimen collection and transportation based on needs of different target populations (including children).
- Printing and dissemination of SOPs and job-aids for TB symptom screening.

Also refer to **Annex 3**.

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



Chapter 4. Testing for TB infection

Decision point on role of TST or IGRA

What is the role of testing for TB infection before starting TPT among target populations prioritized by the ministry of health?

Just as excluding TB disease is a critical step before starting TPT, confirming TB infection before starting TPT may increase the certainty that individuals targeted for TPT would benefit from it. However, there is no gold standard test to diagnose TB infection. Currently available tests are indirect and require the person to mount an immune response in order to work properly. A positive test result by either method is not by itself a reliable indicator that the person will progress to TB disease. Conversely, a negative test result does not rule out TB infection, given the possibility of a false-negative test result among at-risk groups, such as young children or among those recently infected. National health authorities need to decide how to implement tests for TB infection within their PMTPT components, considering these uncertainties, the balance of benefit to harm to the individual of waiting for a test result before starting TPT, and logistic difficulties to procure and implement testing wherever it is needed most.

WHO recommendation:

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

The currently recommended tests for TB infection are TST and IGRA. Both tests measure immune sensitization (type IV or delayed-type hypersensitivity) to mycobacterial protein antigens that occurs following infection by *M. tuberculosis*. While the TST measures delayed hypersensitivity reaction to exposure to purified protein derivative (PPD) of the mycobacterium, IGRAs measure the amount of interferon-gamma released in vitro by white blood cells when mixed with *M. tuberculosis* antigens (QuantiFERON-TB Gold In-Tube) or the number of T-lymphocytes producing interferon-gamma (T-SPOT.TB). A diagnosis of TB infection needs to be complemented by a negative test outcome for TB disease, through clinical evaluation, chest radiography and examination of sputum or another suitable specimen if symptomatic, as per national policy.

A meta-analysis conducted in 2015 found that the pooled prevalence of positive results to these tests among people eligible for testing to be 61% in LMICs versus 25% in high-income countries, implying that on an average every second person in target populations is likely to test positive (74). National programmes may consider such evidence to decide on the role of testing for TB infection.

Either a TST or IGRA can be used to test for TB infection. There is no strong evidence that one test should be preferred over the other in terms of predicting progression from TB infection to TB disease. Neither TSTs nor IGRAs should be used in persons having a low risk of TB infection and disease.

The choice of test for programmatic use depends on cost, availability, human resources and infrastructure to provide testing services in the country. **Table 4.1** summarizes characteristic features of currently available TSTs and IGRAs. More details are provided in **Annexes 5** and **6**.

Role of testing for TB infection

The decision on whether to test for TB infection before TPT, is influenced by the expected prevalence of TB infection in the at-risk population, risk of progression to TB disease and the risk of harms due to unnecessary TPT (**Fig. 4.1** summarizes the pathway to decision on choice of test). For individuals or populations with higher risk of harms due to TPT or (relatively) lower risk of progression to TB disease, confirmation of TB infection may be preferred. On the other hand, for individuals or populations that are more likely to be infected and at risk for progression to TB disease and adverse outcomes if TB disease develops, TPT without testing is justified.

PLHIV who are on ART benefit from TPT regardless of whether they test positive or negative for TB infection. However, PLHIV who are not on ART and who test positive for TB infection are shown to benefit more from TPT than those with a negative test (18). However, WHO recommends that testing for TB infection should not be a requirement for initiating TPT among PLHIV and child contacts below five years of age, particularly in countries with high TB incidence, given that benefits of treatment (even without testing) clearly outweigh the risks (40). 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. Immune response to TB antigens varies among people, and TST and IGRA could remain positive even after successful completion of TPT. Therefore, results of TST and IGRA should not be used to assess the efficacy of TPT. Overall, testing with TST or IGRA should not be considered a mandatory requirement for starting TPT (especially where access to testing services remains very limited) given that the benefits of treatment (without testing) still outweigh the risks.

Where national programmes recommend testing for TB infection before TPT, TST/IGRA should be employed only among at-risk groups (such as clinical risk groups, contacts above five years of age, prisoners, health care workers). Targeted testing helps identify, evaluate and treat persons who are at high risk for TB infection or at high risk for developing TB disease when infected with *M. tuberculosis*. Availability of 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 and to start TPT.

Key point: It is desirable that governments and donors invest and build health system capacity (human resources, logistics and supply chain and monitoring and evaluation (M&E)) for TST and/or IGRAs to avoid unnecessary TPT and related harms and to improve acceptance. This will also enable rapid adoption of any new TB infection test endorsed for programmatic use in the future. However, testing for TB infection is not a mandatory requirement for TPT introduction and scale-up.

Implementation considerations for testing services for TB infection

General requirements

- Define the target population for testing and choice of test in the national guidelines.
- Build capacity of health care workers responsible for different components of testing services for TB infection (such as administration of TST and test reading, collection and processing of blood specimen for IGRAs, specimen collection and transport).
- Develop SOPs for administration of TST, collection and processing of a blood specimen for IGRA and interpretation of test results.
- Develop SOPs for appropriate follow-up after testing including access to clinical evaluation, chest radiography and other TB investigations to decide the eligibility of individuals for TPT.
- Develop job-aids to assist providers in educating the test recipient and to respond to frequently asked questions regarding utility and procedure of TST or IGRA.
- Develop tools for systematic recording and reporting of test results and linkage to care and treatment (such as WHO *Prevent TB* mobile application (39)).
- Strengthen mechanisms for supportive supervision and monitoring of accurate implementation.

TST

- Ensure availability and supply of tuberculin in cold chain as well as syringes, needles and consumables.
- Train personnel in intradermal injections as well as reading and interpretation and provide ongoing capacity building and supportive supervision to maintain skill levels.
- Develop mechanisms to ensure standardized application of test procedures, mentoring and supervision and periodic standardized reliability testing for quality assurance.
- Develop and provide job-aids for health care workers showing the correct technique for TST administration and measurement of induration.
- Establish mechanisms to call people who have been tested to return for the test reading within 48–72 hours of tuberculin administration, or alternatively ensure test reading at the person's residence.
- Provide funding support for people to travel for testing or for health care workers to administer and read test results.
- Develop and supply TST request forms and update the HMIS to enable documentation and reporting of TST results.

IGRA²

- Develop capacity of the laboratory system to conduct IGRA (phlebotomy, processing of blood specimen, incubation and enzyme-linked immunosorbent assay (ELISA) reading). National programmes may leverage collaboration with other, non-TB-specific laboratories, having capacity for blood draws and ELISA testing or private institutions and laboratories through MoUs or free vouchers for individuals requiring testing.
- Ensure availability of trained laboratory technicians in laboratories performing IGRA tests.
- Establish mechanisms to ensure rapid transportation of blood specimens from peripheral centres to the IGRA testing laboratory (within 8–30 hours to allow incubation depending on type of IGRA).
- Ensure functioning of laboratory equipment and establish a mechanism for regular equipment maintenance for optimal functioning of the laboratory.

² One of the IGRAs assessed and endorsed by WHO was QuantiFERON-TB Gold In-tube (QFT-GIT) test. Manufacturers of this test plan to phase it out and substitute it with the QuantiFERON-TB Gold Plus, 4-Tube test.

- Ensure supply of appropriate reagents and testing tubes for IGRA, suitable for use at different altitudes (e.g. Johannesburg, South Africa which is close to 1700 m from sea level needs different reagents or tubes than a place closer to sea level).³
- Ensure supply of updated laboratory request forms, registers and update laboratory information systems to document and report IGRA test results.

Additional funding considerations for implementation of testing programmes

- Cost per test and estimated number of target populations for testing.
- Travel support to individuals considered for TPT and health care workers to access TST and IGRA testing and TST reading.
- Incentive for health care workers or laboratory technicians.
- Maintenance of 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 uninterrupted supply of tuberculin or IGRA blood collection tubes and reagents.
- Tools for routine data capture, preferably electronic.

Also refer to **Annex 3**.

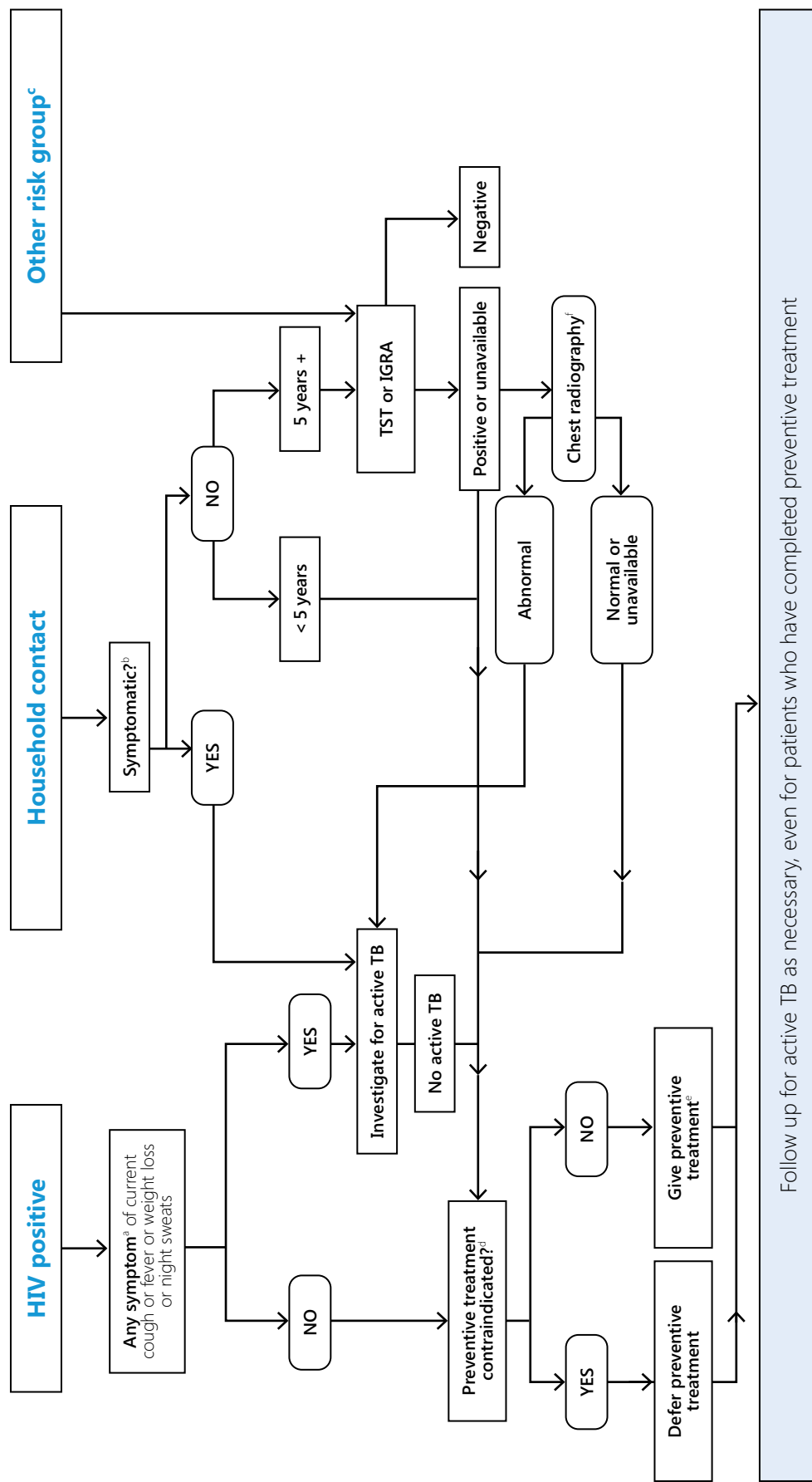
Table 4.1: Characteristic features of TST and IGRA (43)

	TST	IGRA
Test requirements	<ul style="list-style-type: none"> • A valid TST requires proper intradermal administration of 0.1 ml of tuberculin-PPD into the volar surface of the forearm • PPD requires cold chain • Trained staff are required to administer and read skin induration • Needs to be read within 48–72 hours 	<ul style="list-style-type: none"> • IGRAs are in vitro blood tests that detect interferon gamma in blood using ELISA • Requires fresh blood specimens to mix with antigens and controls, to be processed within 8–30 hours after collection while white blood cells are viable • Need an efficient sample transport mechanism • Need different blood collection tubes for different altitudes
Potential inaccuracy	<ul style="list-style-type: none"> • False-positive TSTs can result from contact with nontuberculous mycobacteria or vaccination with bacille Calmette-Guérin (BCG) • Potential for inaccuracies and bias in reading skin induration • False negatives in immunodeficiency conditions 	<ul style="list-style-type: none"> • Delay in transportation of blood specimen • Errors in processing of blood specimen • Wrong interpretation of assay • False-negative results likely in immunodeficiency conditions, faded immune memory, technical-operational variability, and in children below two years of age

³ http://www.quantiferon.com/wp-content/uploads/2017/04/English_QFT_ELISA_R04_082016.pdf, accessed 12 March 2020.

	TST	IGRA
Advantages	<ul style="list-style-type: none"> • Can be performed in the field • Significantly fewer resource needs compared to IGRA • No laboratory setup required • More familiar to practitioners in resource-constrained settings 	<ul style="list-style-type: none"> • Single visit required to conduct test; however, test result may be shared with the person on the second visit, when like the TST, clinical management decisions are made • Results possible within 24 hours • No booster effect • No false-positive results due to BCG
Challenges	<ul style="list-style-type: none"> • Need for training in intradermal injection, reading and interpretation • Second visit (by individual or health care worker) required for test reading • Recurrent global shortages and stock-outs of quality assured PPD • Requirement for cold chain • Repeat test (two-step testing) for individuals whose immunity may have waned 	<ul style="list-style-type: none"> • Higher test cost • Need for phlebotomy • Need sophisticated laboratory equipment, highly skilled laboratory personnel to perform and interpret test results • Potential for delays in sample transportation due to long distances to laboratories that offer IGRA testing • Processing and results take at least one day (often longer), hence the person may need to return to collect results • If the laboratory SOP requires batching of tests to reduce costs there may be delays in reporting results beyond a week
Preferred test	<ul style="list-style-type: none"> • Children less than two years of age • Settings with poor laboratory infrastructure 	<ul style="list-style-type: none"> • Persons who have received BCG (either as a vaccine or for cancer therapy), although this is less applicable in 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 persons and people who use drugs or due to reasons like long distance, job security, or other pressing commitments

Fig. 4.1: Algorithm for TB screening and TPT



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

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

c. Including silicosis, dialysis, anti-TNF agent treatment, preparation for transplantation or other risks in national guidelines. People in this category should also have TB disease ruled out if they have suggestive clinical manifestations.

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.

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

f. Chest radiography may have been carried out earlier or as part of intensified case finding.

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



Chapter 5. TB preventive treatment

Decision point on choice of TB preventive treatment

Which of the WHO recommended TPT regimens should be used for different individuals in the country?

TPT regimen recommendation and availability

TPT broadly falls into two categories: (i) isoniazid monotherapy for six or nine months, or (ii) rifamycin-based shorter preventive treatment, on the assumption that the infecting strain is susceptible to these medicines. Isoniazid preventive treatment (IPT) for six months has been the most widely used regimen under programmatic conditions and has emerged as a standard for TPT 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 those infected with *M. tuberculosis*. A systematic review of randomized control trials (RCTs) involving PLHIV in 2009 showed that IPT reduces 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) (44). This review also demonstrated that the efficacy of the six-month regimen was not significantly different from that of a 12-month daily isoniazid monotherapy (RR 0.58; 95% CI 0.3;1.12). A recent systematic review of RCTs also showed a significantly greater reduction in TB incidence among participants given the six-month regimen than in those given a placebo (odds ratio 0.65; 95% CI 0.50;0.83) (45).

Clinical trial evidence generated over the past two decades shows similar preventive efficacy with shorter rifamycin-based TPT regimen, both in HIV-positive and HIV-negative individuals, as monotherapy or in combination with isoniazid (45–48). The clear advantages of these regimens are better adherence due to the shorter duration and fewer adverse events. The use of shorter rifamycin-based regimens is associated with at least 20% greater treatment completion rate (82% vs 61%) (14). WHO recently assessed and recommended several shorter rifamycin-based regimens as alternatives to six months of isoniazid.

WHO recommendation:

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

The external experts convened by the WHO as Guideline Development Groups (GDGs) to advise on treatment policies assessed available evidence for the various TPT options, taking stock also of values and preferences of the beneficiaries and key considerations such as regimen acceptability, feasibility, resource implications and likely impact on health equity. Based on these elements the GDGs recommended various regimens where the benefits are likely to outweigh potential harms of acquiring TB disease or drug toxicity (see Recommendation 17 in Box above). When choosing a regimen, the

health caregiver and the person taking the treatment should consider the circumstances under which TPT would be given to increase the likelihood of it being completed. The choice may also depend on 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 acceptability to recipients in the country context.

The 2020 guidelines broaden the applicability of a number of previous recommendations on testing for TB infection and on TPT treatment regimen options to any TB burden setting, on 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. In this context, the importance of appropriate resource mobilization and health system strengthening is stressed.

Recommendations for IPT and other regimen alternatives have already featured in past WHO guidance (40,49,50). In the 2020 update of the WHO guidance two new regimens have been added for use regardless of the setting (but subject to certain conditions): (i) daily rifapentine plus isoniazid for one month (1HP), and (ii) daily rifampicin monotherapy for four months (4R). In addition, instead of a previous range of three to four months, WHO now recommends a duration of three months for daily isoniazid plus rifampicin (3HR) and four months for daily rifampicin alone (4R) to reflect the usual length of time for which these regimens are currently employed. Moreover, three previous recommendations on the use of 6H, 3HR among people below 15 years of age and 3HP in high TB prevalence settings that featured separately in previous guidance are now proposed as an equivalent alternative for TPT. The revised recommendations thus makes all TPT options applicable across all settings.

Key point: The 2020 update of WHO guidelines on TPT makes 9H, 6H, 4R, 3HP, 3HR, 1HP as alternative options for use across all disease burden settings and target populations including the PLHIV. The choice will depend on availability of appropriate formulations and considerations for age, safety, drug–drug interactions and adherence.

Table 5.1 below summarizes all currently available TPT options for introduction and programmatic scale-up. National programmes need to weigh various factors including country context, resources and capacity of the health system. Moreover, given the current availability of safer and shorter options, efforts to introduce and scale up shorter TPT regimen are likely to enhance coverage, improve adherence and ensure TPT completion.

Six or nine months daily isoniazid: has historically been most often used worldwide. However, it is anticipated that isoniazid will be increasingly replaced with rifamycin regimens that are becoming increasingly affordable and feasible, with more studies about their efficacy and safety in different populations expected to bear results in the coming years. It is likely that 6H or 9H will continue to be an important choice for TPT, particularly in situations where rifamycin-based regimens cannot be used. In such situations national programmes may consider the use of a triple pill combination of isoniazid, cotrimoxazole and B6 for PLHIV, available at a discounted price through the Stop TB Partnership's Global Drug Facility (STBP/GDF) instead of isoniazid only regimen (57). Isoniazid is the preferred regimen among HIV infected children on protease inhibitor-based regimen (lopinavir–ritonavir), nevirapine, or integrase inhibitors (dolutegravir) due to potential drug–drug interactions. Isoniazid monotherapy should also be protective in contacts of TB patients with laboratory confirmed isoniazid-susceptible, rifampicin-resistant disease (mono rifampicin resistant TB).

Three-month weekly isoniazid plus rifapentine or one-month daily isoniazid plus rifapentine: National programmes may consider either of these two rifapentine-containing regimen options. Both regimens have been shown to have similar efficacy as that of isoniazid for TB prevention, but there is currently no direct evidence of efficacy from a head-to-head comparison between 1HP and 3HP (52–54). Due to lack of data on appropriate dosing of 1HP among children 12 years and

younger, WHO currently recommends the use of 1HP among people aged 13 years and above (this was the age limit used for the study population in the single RCT of the regimen whose results have been published to date (54)). Also, rifapentine 150 mg tablets are now available at a discounted price from the STBP/GDF as well as the Global Fund Pooled Procurement Mechanism (55). A FDC tablet of rifapentine 300 mg/isoniazid 300 mg is expected to become available later in 2020, which will reduce the pill burden substantially for people prescribed 3HP. The 1HP regimen may be used where the shorter duration is preferred even if the total number of doses increases from 12 in 3HP to 28 (such as among prisoners incarcerated for a short term, patients awaiting start of anti-TNF treatment or preparing for transplantation). For younger children who cannot swallow pills, there is no child-friendly (i.e. dispersible) formulation of rifapentine currently available.

Four-month daily rifampicin: Rifampicin has a long history of use in TB treatment with national procurement systems experienced in acquiring it, but mostly with other TB medicines as part of FDC tablets. Rifampicin has an excellent safety profile compared to isoniazid and the cost is lower than rifapentine. This regimen is useful to give to contacts of people with confirmed isoniazid-resistant, rifampicin-susceptible TB disease (Hr-TB). One of the main challenges with 4R however may be to deal with the perception that rifampicin needs to be protected for use as a first-line TB medicine and concerns that its use in TPT may increase levels of rifampicin resistance in the community or promote misuse of the agent as monotherapy for TB disease. There is however no evidence till date demonstrating the significant increase in rifampicin resistance levels due to scale-up of TPT services. Other challenges to consider are: drug–drug interactions with ARVs (refer to the section on drug–drug interactions in **Chapter 6**), child-friendly formulations are not available currently, and the supply of single dose formulations may be limited due to widespread availability of FDCs of first-line TB treatment.

Three-month daily isoniazid plus rifampicin: Infants and young children (< 5 years of age) are particularly vulnerable due to increased risk of progressing 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 the paucibacillary nature of the disease (3,56). Therefore, averting paediatric TB by delivering preventive treatment is strategically important. For TPT among children, the 3HR regimen provides a better tolerated and child-friendly option compared to isoniazid, since dispersible FDC formulations are now available for young children. As data on rifapentine dosage for younger children are lacking, in the short term national programmes could consider (57) scale-up of 3HR for TB prevention among children of all age groups. Those weighing under 25 kg may receive (including children < 2 years of age) the same RH formulation used for the continuation phase of TB treatment (R/H, 75/50 mg), while children weighing more than 25 kg may either receive 3HP if it is rolled out for adults or 3HR using adult FDCs of RH. Child-friendly FDCs of RH have the added benefit of already being in the national supply chain for treatment of children < 25 kg.

Children on protease and integrase inhibitors (such as lopinavir/ritonavir, dolutegravir or nevirapine-based ART), could be given six-month isoniazid regimen. However, because of likely drug–drug interactions, due vigilance for signs of isoniazid-induced hepatitis (see section on drug–drug interactions in **Chapter 6**) is necessary. However, with the use of 3HR in adults the risk of hepatotoxicity is expected to be similarly high as with 6H/9H; hence 3HP may be a preferred option.

Over medium-to-long term, 3HP (or 1HP) may become the preferred regimen across all ages provided evidence on appropriate dose for children < 2 years of age as well as safety and tolerability are established, and dispersible FDC formulations of HP become available. The shorter duration of treatment with 3HP and the higher rates of treatment completion will likely make it more cost-effective in the long term. In the meantime, 3HR can be used for young children.

Key point: 3HR should be a preferred TPT option among children since child-friendly dispersible FDCs are available and already used for TB treatment. 3HP or 1HP may become the preferred option when data on dosage are available across all age groups, and adult and child-friendly FDC formulations become available, given its advantage of once-a-week or just one-month medication.

Table 5.1: Available preventive treatment options (58)⁴

	6H	3HP	3HR	4R	1HP	H + B6 + CPT (Q-TB)
Medicines	Isoniazid	Isoniazid + rifapentine	Isoniazid + rifampicin	Rifampicin	Isoniazid + rifapentine	Isoniazid + pyridoxine + cotrimoxazole (only for those living with HIV)
Duration (months)	6	3	3	4	1	6
Interval	Daily	Weekly	Daily	Daily	Daily	Daily
Doses	182	12	84	120	28	182
Pill burden per dose (total number of pills for average adult)^a	1 (182)	9 singles (108) 3 with FDC (36)	3 (252)	2 (240)	5 (140)	1 (182)
Cost for a full treatment (unless otherwise specified)⁵ (51)	US\$ 3.50	Rifapentine US\$ 17 for singles US\$ 15 for FDC Isoniazid US\$ 1–2 3HP FDC US\$ 15 (expected to become available in mid-2020)	US\$ 10:60 (for 12–15 kg child)	US\$ 24	Rifapentine and isoniazid US\$ 27 for singles US\$ 26 for FDC + rifapentine single	US\$ 12
Children	All ages; child-friendly (dispersible) formulation available; preferred in HIV + children on LPV-RTV, NVP, or DTG	≥ 2 years; no child-friendly formulation available	All ages; child-friendly (dispersible) formulation available and recommended up to 25 kg weight	All ages; no child-friendly formulation available; no formulation available for infants < 8 kg weight	> 12 years; no rifapentine dosing available until 13 years of age	All ages; need to split scored adult tablet, lower dose pills suitable for children not available)

⁴ See text and Table 5.2 for TPT options in multidrug-resistant tuberculosis (MDR-TB).

⁵ Pricing from StopTB/GDF Reference Price and Global Fund Catalogues – Stichting Iplusolutions, Global Fund Quality Assurance Suppliers, IDA Foundation, and the Partnership for Supply Chain Management <http://www.stoptb.org/assets/documents/gdf/20191015%20GDF%20TB%20Medicines%20Budgeting%20Prices.pdf>.

	6H	3HP	3HR	4R	1HP	H + B6 + CPT (Q-TTB)
Pregnant women	Safe for use ^c	Not known ⁶	Safe for use ^{c,d}	May be safe, although no safety or efficacy data available specifically in this population ^d	Not known	Safe for use; preferred option – in PLHIV ^c
Interactions with ART^b	No restriction	Contraindicated: All PIs, NVP/ NNRTIs, TAF Use: TDF, EFV (600 mg), DTG, ^e RAL ^e	Contraindicated: All PIs, NVP/most NNRTIs Use with caution: TAF Adjust dose: DTG, RAL Use: TDF, EFV (600 mg)	Contraindicated: All PIs, NVP/most NNRTIs, TAF Adjust dose: DTG, RAL Use: TDF, EFV (600 mg)	Contraindicated: All PIs, NVP/most NNRTIs, TAF Use: TDF, EFV (600 mg), DTG, ^e RAL ^e	No restriction
Toxicity	Hepatotoxicity (more), peripheral neuropathy, rash, gastrointestinal (GI) upset	Flu-like syndrome, hypersensitivity reactions, GI upset, orange discolouration of body fluids, rash, hepatotoxicity (less)	Hypersensitivity reactions, hepatotoxicity (less), rash, GI upset, hypoprothrombinaemia, orange discolouration of body fluids	Rash, GI upset, hepatotoxicity (less), hypoprothrombinaemia, orange discolouration of body fluids	Hepatotoxicity (more), hypersensitivity reaction, rash, GI upset, orange discolouration of body fluids	Hepatotoxicity, rash, GI upset
Absorption	Best absorbed on an empty stomach; up to 50% reduction in peak concentration with a fatty meal	Oral rifapentine bioavailability is 70% (not HP); 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 3HP	Same as 6H

Note: B6 = pyridoxine, CPT = cotrimoxazole, DTG = dolutegravir, EFV = efavirenz, H = Isoniazid, LPV-RTV = lopinavir-ritonavir, NNRTI = non-nucleoside reverse transcriptase inhibitors, NVP = nevirapine, P = rifapentine, PIs = protease inhibitors, R = rifampicin, RAL = raltegravir, TAF = tenofovir alafenamide, TDF = tenofovir disoproxil fumarate

a Average available adult formulations: H-300 mg, R-300 mg/150 mg, P-150 mg.

b For women living with HIV (as well as HIV-negative) receiving rifamycin-based TPT and oral contraceptives, consider additional barrier contraception methods to prevent pregnancy.

c One randomized trial has shown increased risk of poor birth outcomes for mothers taking isoniazid during pregnancy; however, several other studies have shown benefits of IPT; hence caution is required.

d Bleeding attributed to hypoprothrombinaemia has been reported in infants and mothers following the use of rifampicin in late pregnancy. Vitamin K is recommended for both the mother and the infant postpartum if rifampicin is used in the last few weeks of pregnancy (FDA).

e Indicates that drug interaction has been studied in adults and not children; applies to adults taking DTG or RAL only.

⁶ Data from clinical trial NCT02651259. Evaluating the pharmacokinetics, tolerability, and safety of once-weekly rifapentine and isoniazid in HIV-1-infected and HIV-1-uninfected pregnant and postpartum women with latent tuberculosis infection to be presented at Conference on Retroviruses and Opportunistic Infections 2020.

Key point: Multiple TPT options are now recommended. National programmes should progressively transition to shorter rifamycin-based regimen given the better safety profile and better prospects of TPT completion.

Recommended dosages of TPT medication

The WHO task force on pharmacokinetics and pharmacodynamics analysed available evidence from clinical trials of rifapentine and suggested a simplified dose for various weight bands for 3HP and 1HP as summarized in Table 5.2 (2020 guideline update). Table 5.2 presents standard dosing for the recommended TPT regimens by age and body weight.

Table 5.2: Recommended dosages of medicines for TB preventive treatment

Regimen	Dose by age and weight band					
6 or 9 months of daily isoniazid monotherapy (6H, 9H) ^a	Age 10 years & older: 5 mg/kg/day Age < 10 years: 10 mg/kg/day (range, 7–15 mg)					
Four months of daily rifampicin (4R)	Age 10 years & older: 10 mg/kg/day Age < 10 years: 15 mg/kg/day (range, 10–20 mg)					
Three months of daily rifampicin plus isoniazid (3HR)	Isoniazid:					
	Age 10 years & older: 5 mg/kg/day Age < 10 years: 10 mg/kg/day (range, 7–15 mg)					
	Rifampicin:					
	Age 10 years & older: 10 mg/kg/day Age < 10 years: 15 mg/kg/day (range, 10–20 mg)					
	Weight band	4–7 kg	8–11 kg	12–15 kg	16–24 kg	> 25 kg
	RH 75/50 mg (FDC)	1	2	3	4	Use adult formulations

Regimen	Dose by age and weight band					
Three months of rifapentine plus high dose isoniazid weekly (12 doses) (3HP)	Age 2–14 years^d					
	<i>Medicine, formulation</i>	10–15 kg	16–23 kg	24–30 kg	31–34 kg	> 34 kg
	Isoniazid 100 mg ^b	3	5	6	7	7
	Rifapentine 150 mg	2	3	4	5	5
	Isoniazid + rifapentine FDC (150 mg/150 mg) ^c	2	3	4	5	5
	Age > 14 years^d					
	<i>Medicine, formulation</i>	30–35 kg	36–45 kg	46–55 kg	56–70 kg	> 70 kg
	Isoniazid 300 mg	3	3	3	3	3
	Rifapentine 150 mg	6	6	6	6	6
	Isoniazid + rifapentine FDC (300 mg/300 mg) ^c	3	3	3	3	3
One month of rifapentine plus isoniazid daily (28 doses) (1HP)	Age ≥ 13 years (regardless of weight band) Isoniazid 300 mg/day Rifapentine 600 mg/day					
Six months of levofloxacin daily (preventive treatment of MDR-TB)	Age > 14 years, by body weight: < 46 kg, 750 mg/day; > 45 kg, 1g/day Age < 15 years ^e (range approx. 15–20 mg/kg/day), by body weight: 5–9 kg: 150 mg/day; 10–15 kg: 200–300mg/day; 16–23 kg: 300–400mg/day; 24–34 kg: 500–750mg/day					

a A triple pill combination containing isoniazid 300 mg + pyridoxine 25 mg + sulfamethoxazole 800 mg + trimethoprim 160 mg (scored) is the preferred alternative regimen for PLHIV being considered for isoniazid monotherapy (1 pill daily for adults, half pill for children 5 years and older of age and quarter for children < 5 years of age).

b 300 mg formulation can be used to reduce the pill burden.

c Expected to become available in a near future.

d Dosage may differ among adults and children in overlapping weight-bands.

e Levofloxacin 100 mg dispersible tablets available for children.

Regimens containing isoniazid and rifampicin can be used in individuals of all ages, however there are limited pharmacokinetic data to inform appropriate dosage and safety of rifapentine among children < 2 years of age and hence the 3HP regimen is recommended only for use in children two years and older. Furthermore, data from the 1HP trial relates only to individuals 13 years of age and above. Appropriate dose of *daily* rifapentine in children < 13 years is therefore not yet established and hence suitability of 1HP for those under 13 years of age needs to be reviewed after data from pharmacokinetic and safety studies from children become available.

Availability of appropriate formulations

Rifampicin: Given the widespread use of rifampicin-containing FDCs to treat drug-susceptible TB, single-dose rifampicin is less commonly used, hence less procured, and therefore likely to be available only in limited quantities to national programmes. Additionally, child-friendly dispersible formulations of single-dose rifampicin are not available currently. If 4R is the regimen of choice, the demand for loose tablets of rifampicin will increase and programmes would need to identify quality-assured suppliers for rifampicin single doses. Use of rifampicin should also be regulated and limited for use as part of the TPT regimen and not diverted for use as a broad-spectrum antibiotic. The supplies of 4R to peripheral centres (primary care facilities, HIV programmes) should be accompanied by stepwise guidance on specific use of rifampicin.

Isoniazid plus rifampicin FDC: Child-friendly dispersible FDCs of 3HR are available and already used in many countries for treatment of TB disease among children. The same formulations can be used for TPT. Child-friendly FDCs should be preferred over single pills to reduce the pill burden. Similarly, FDCs used for treatment of adult TB disease may be used for TPT among adults.

Isoniazid plus rifapentine (weekly/daily): The only formulation for rifapentine currently available is the 150 mg single tablet. The pill burden for both 3HP and 1HP among adults with the single formulation is very high. Development of 3HP FDCs (with a one-to-one ratio of rifapentine and isoniazid) has begun with an adult 3HP FDC likely to be available in 2020. This will reduce the pill burden for 3HP in adults from nine to three pills. There is also a single rifapentine 300 mg tablet being developed, which may also be available in 2020, to reduce the pill burden for 1HP to just three pills as well. Similarly, child-friendly 3HP FDC formulations (150 mg/150 mg) when available will reduce the pill burden for children. Further research to define the appropriate dose of rifapentine and identify drug–drug interactions (such as dolutegravir) among children under two years of age for both 3HP and 1HP will facilitate the use of 3HP/1HP in this age group.

Isoniazid + cotrimoxazole + pyridoxine combination: is available at discounted price through STBP/GDF and the Global Fund Pooled Procurement Mechanism. These combination pills may be considered as an alternative for PLHIV when: shorter rifamycin-containing regimens are not available, drug–drug interactions occur, or during gradual scale-up. These are single scored tablets. Therefore, if the required dose is one third of the adult formulation, this FDC cannot be used for children below five years of age living with HIV.

Role of pyridoxine and its availability

Pyridoxine (B6): One of the undesirable side-effects of long term treatment with high-dose isoniazid is peripheral neuropathy that develops secondary to a deficiency of vitamin B6 (pyridoxine) during therapy. Individuals at risk for peripheral neuropathy, such as those with malnutrition, chronic alcohol dependence, HIV infection, renal failure or diabetes, or who are pregnant or breastfeeding, should receive vitamin B6 supplements when taking isoniazid-containing regimen. Additionally, pregnant and postpartum women and exclusively breastfed infants should receive vitamin B6 while taking isoniazid. The standard dose of pyridoxine when used prophylactically for prevention of neuropathy among patients taking isoniazid is 10–25 mg/day. Peripheral neuropathy occurs infrequently among other patients taking standard doses of isoniazid, which is easily recognized (as symmetrical numbness and tingling of the extremities) and usually easily reversible upon withdrawal of isoniazid and institution of high-dose pyridoxine therapy (100–200 mg/day). Therefore, routine pyridoxine supplementation with isoniazid is probably not necessary and its absence should not become a barrier to TPT initiation.

In vivo, pyridoxine is converted into coenzymes which 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 (59). The incidence of peripheral neuropathy correlates closely with the dose of isoniazid used. Studies from

the 1950s (60–62) reported that while a large proportion (> 40%) of people receiving high-dose isoniazid (16–24 mg/kg/day) developed signs and symptoms of peripheral neuropathy, only 2% of those receiving 4–6 mg/kg/day developed neuropathy. While high-dose isoniazid may be relevant to the treatment of certain forms of TB disease, in TPT the standard dose of isoniazid is used. Signs of toxicity appear much later among those taking lower doses of isoniazid. The earliest symptom is usually paraesthesia, followed by pricking pain and 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 reversible upon withdrawal of isoniazid and institution of pyridoxine therapy.

Routine pyridoxine supplementation in otherwise healthy individuals receiving standard dose isoniazid is probably not justified and not required (62). However, even low doses of isoniazid can produce neuropathy among malnourished patients (up to 20%) (63), and among slow acetylators of isoniazid⁷ (reaching 20% with 4–6 mg/kg isoniazid). Other individuals known to have higher risk for peripheral neuropathy include those with chronic alcohol dependence, HIV infection, renal failure or diabetes, or women who are pregnant or breastfeeding. Concurrent administration of pyridoxine with isoniazid protects against the development of peripheral neuropathy in these individuals.

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. Otherwise, a small daily dose of 10–25 mg pyridoxine may be given alongside TPT in high risk individuals. Pyridoxine may be given as a part of vitamin B-complex supplements, especially in those who may also be deficient in other vitamins. For established isoniazid-induced peripheral neuropathy, pyridoxine should be given at a larger therapeutic dose of 50–75 mg daily and even up to 100 mg to 200 mg per day (64). It is important to maintain pyridoxine supplementation at the right dose because higher levels may interfere with the antibacterial activity of isoniazid. Moreover, excessively high doses of pyridoxine–2000 mg daily or more have been reported to cause toxicity, including peripheral neuropathy (65–67).

Currently, the pyridoxine formulation available on the Global Fund’s Pool Procurement Mechanism, and the Global Drug Facility products list are 50 mg uncoated tablets and 100 mg film coated tablets (51). Both formulations are primarily suited for therapeutic use and are difficult to fraction to the dosage recommended for prophylactic supplementation. National programmes may consider local procurement of a quality assured product of lower dose pyridoxine (10–25 mg) for use among high risk individuals, or alternatively procure vitamin B-complex. Among PLHIV, use of isoniazid-B6-cotrimoxazole combination tablet may be considered. Programmes are nonetheless also advised to stock higher dose pyridoxine (which is available through the GDF products list) for the treatment of peripheral neuropathy.

Key message: During the scale-up of TPT services, lack of pyridoxine should not become a barrier to starting TPT. Clinical evaluation of the risk for neuropathy should be undertaken before prescribing of pyridoxine supplementation.

⁷ Isoniazid is metabolized by N-acetyltransferase 2 (NAT2), and a mutation in the NAT2 genotype leads to a persistence of isoniazid in the body and predisposing it to toxicity. The prevalence of NAT2 mutations differs geographically, with slow acetylators (known to be at risk of most drug-induced toxicity) being very common in some settings (83% in Egypt and 67% in the USA) but rare elsewhere (12% in China).

Introduce and scale-up TPT

Considerations for programmatic implementation of TPT

- Define roles and responsibilities for cadre of health care workers to prescribe TPT. Trained doctors, nurses and peripheral health care workers can evaluate and start TPT once TB disease is reliably ruled out following national protocol. Nurses and frontline health care workers in the periphery can also be trained to monitor TPT and make decisions about whether TPT should be suspended or changed (e.g. in the case of adverse events) or restarted (e.g. after an interruption by the person on treatment). In most instances there is no need to seek opinion of a medical doctor or a specialist for such decisions however, there should be a provision to solicit such support in case it becomes necessary.
- Define levels of health care system where TPT can be started and medicines refilled for continuation.
- Develop SOPs for TPT initiation and follow up to:
 - maintain flow of persons considered for TPT in various health facilities and across different service points within those facilities;
 - ascertain the role and responsibilities of health providers, community health workers and key stakeholders (such as malnutrition care services, prisons, correctional facilities, refugee camps, mining communities) in evaluation of eligibility and start of TPT;
 - provide adherence support for TPT;
 - manage TPT interruptions; and
 - identify, document and manage adverse drug events.
- Establish TPT services in all relevant service delivery sites (such as TB treatment site, ART centres, maternal and child health services centre, community health centre).
- Decentralize to TB facilities providing ART or TB treatment (initiation and continuation) closest to person's residence to minimize travel time to receive TPT.
- Leverage on existing TB, HIV and general health services to provide specialized care as needed for people receiving TPT (such as management of adverse events, drug–drug interactions, special situations (pregnancy)).
- Evaluate capacity and availability of health care workers and assess additional needs for nationwide scale-up of TPT services.
- Evaluate availability and capacity of community health workers and other networks (such as former TB patients) that can contribute to TPT service delivery and support to individuals.
- Build capacity:
 - through initial training, sensitization and capacity building of staff;
 - of primary care doctors, nurses and other health care workers in history taking, symptom screening and referral for investigations, assessment of eligibility for TPT and starting TPT; and
 - of 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 transitions to shorter TPT regimens. This is important during the introduction of the new regimen.
- Review and strengthen the mechanism for quantification, ordering and un-interrupted supply of commodities (such as TPT medications, pyridoxine).
- Address specific issues regarding TPT for children to:
 - coordinate TPT with multiple family member households (parents/grandparents) as children may receive care at multiple service delivery sites (such as maternal and child health services, TB or HIV centres);
 - build capacity on counselling and actions on post-dose emesis and indications for redosing; and
 - provide information on food to mask the taste of medication.

- Strengthen systematic recording and reporting, including information from the case form or alternatively capture data on electronic platforms. Key data variables should be integrated into the HMIS for monitoring and evaluation of performance.

TPT initiation and pre-TPT baseline assessment

Once TB disease is ruled out, and decision to consider TPT is made, baseline assessment to determine the eligibility of an individual for TPT should be undertaken. The baseline assessment includes personal and medication history and investigations as per 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:** assess presence of comorbidities (such as malnutrition, diabetes, viral hepatitis) and record medications being taken
 - **contacts of drug resistant TB** patients (isoniazid, rifampicin only or MDR-TB)
 - **potential contraindications to TPT:** such as active hepatitis (acute or chronic) or known elevation in transaminases (> 3x Upper Limit of Normal), regular and heavy alcohol consumption and symptoms of peripheral neuropathy. These conditions should prompt detailed investigations and application of clinical judgement to weigh harms versus the benefits of TPT, and timing to start TPT if benefits outweigh harms. History of past TB treatment or current pregnancy should not be considered as contraindications for starting TPT.
- **History of medication:** elicit medication history to guide the choice of TPT regimen or determine the need for modification of treatment of comorbid conditions. Certain drug classes – ARVs, opioids, antimalarials – often affect TPT.
- **Liver function test (LFT):** There is insufficient evidence to support mandatory or routine LFT at baseline (68), and perhaps the benefit of TPT without LFT would likely outweigh harms, particularly with less hepatotoxic regimen. However, where feasible, baseline testing is strongly encouraged for individuals having risk factors – such as history of liver disease, regular use of alcohol, chronic liver disease, HIV infection, age more than 35 years and pregnancy or immediate postpartum period (within 3 months of delivery). In individuals having abnormal baseline LFT results, sound clinical judgement is required to determine if the benefit of TPT outweighs the risk of adverse events. These individuals should be tested routinely at subsequent visits.

Key point: Routine LFT is not necessary prior to starting TPT. Available evidence suggests that close clinical monitoring of signs and symptoms of liver disease is sufficient for early detection and management of adverse events, more so with shorter rifamycin-containing TPT regimen. However, LFT is encouraged for individuals having additional risk factors.

- **Social and financial situation:** of the person and the family should be assessed and support required to overcome the barriers for TPT completion identified.
- **Counselling:**
 - Explain to the individual that (s)he is eligible for TPT and provide key messages to the individual and her/his family/treatment supporter on:
 - rationale for TPT and benefits to the individual, the household and the wider community;
 - TPT being available free of charge through national programmes;
 - TPT regimen prescribed, including the duration, directions for intake of medicines and follow-up schedule;
 - potential side-effects and adverse events involved and what to do in the event of various side-effects;

- the importance of completing the full course of TPT;
 - reasons and schedule of regular clinical and laboratory follow-up for treatment monitoring; and
 - signs and symptoms of TB and advise on steps if they develop them.
- Agree on the best approach to support treatment adherence, including the most suitable location for drug intake and treatment support based on each individual's preference. Options may include:
- Location: Home, community or health facility (with counselling support).
 - Treatment supporter: Assess if a treatment supporter is needed or self-administration is possible. If a treatment supporter is needed, options may include an oriented family member/ community volunteer/workplace treatment partner or health care worker. For a weekly regimen, it is preferable that intake of each dose is directly observed by the oriented family member, community member, workplace treatment partner, or health care worker (either in person or through a digital tool).
 - Digital tools: include video observed treatment (VOT)/phone missed call/SMS reminders.

Adherence

Adherence to the TPT course and treatment completion are important determinants of clinical benefit, both at individual and population levels (**Chapter 7**). Irregular or inadequate treatment reduces the protective efficacy of TPT regimen. Further, poor adherence or early cessation of TPT can potentially increase the risk of the individual developing TB including drug-resistant TB (although not supported by existing evidence from research settings). It is known that the efficacy of TPT is greatest if at least 80% of the doses are taken within the duration of the regimen. The total number of doses taken is also a key determinant of the extent of TB prevention (69,70).

Trials have used varied definitions for completion of course of preventive treatment – 80% of recommended dose consumed within 120% of planned TPT duration (71), or 90% of recommended dose consumed within 133% of planned TPT duration (72). Table 5.3 below summarizes all recommended regimens and suggested criteria to assess the completion of different regimen. It is expected that shorter regimens are better adhered to and have higher rate of treatment completion..

Table 5.3: Preventive TB treatment completion

	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	11 ^a	120
4R (daily)	4	120	96	160
1HP (daily)	1	28	23	40

^a 90% of recommended number of doses

National programmes should tailor mechanisms to improve adherence to the specific needs of risk groups and local country context. In general, all TPT options can be effectively self-administered. TPT is unlikely to increase the risk of selection of drug-resistant mycobacteria, contrary to treatment of TB disease. The modality for treatment provision and adherence support should be determined primarily by the individual's preference. WHO 2015 TPT guidelines reveal heterogeneous results with inconclusive evidence regarding interventions to improve treatment adherence and completion (73). However, pill counting by providers at every contact with the person on TPT is inexpensive and feasible, and has been shown in a clinical trial to have excellent predictive value for TB risk reduction (69); this should be incorporated into all TPT services. Also, procurement of blister packaged products may facilitate better adherence monitoring compared to pill bottles.

WHO guidelines for treatment of drug-susceptible TB proposes several interventions to support adherence, which could also be applied to TPT (74). These include peer support networks, coaching and educational interventions including quality counselling and VOT. National programmes should dedicate necessary financial and human resources to strengthen adherence mechanisms for TPT and not allow concerns about adherence or the lack of adherence tools to become a barrier in scale-up of TPT services.

Management of treatment interruptions: No recommendations informed by evidence exist on how to manage interruption of TPT, i.e. how many missed doses can be made up for by prolonging treatment without compromising efficacy. **Chapter 7** summarizes suggested actions to manage preventive treatment interruptions based on the above indicative definition of preventive treatment completion. National programmes may choose between more or a stringent definition for treatment completion (90% of recommended doses within 120% of treatment duration or 80% of recommended doses within 133% duration or a combination of both).

In addition to monitoring treatment completion (see also **Chapter 8**), a number of unfavourable endpoints are proposed that could be used to trigger a review of case management and, in some instances, changes to treatment (see list below).

- **Failed** – development of TB disease any time while on TPT
- **Died** – death for any reason while on TPT
- **Lost to follow-up** – TPT interrupted by person for eight consecutive weeks or more for 6H, four consecutive weeks or more for 3HP, 3HR and 4R, and 10 consecutive days for 1HP
- **TPT discontinuation due to toxicity** – by clinician due to adverse events or drug–drug interactions, with or without restart or switching of regimen
- **Not evaluated** – such as records lost, transfer to another health facility with record of TPT completion.

Monitoring and support during TPT

Individuals receiving TPT should be monitored at every contact with health care providers. This may be done at least monthly or more frequently as required for care of persons on TPT or as per national policy mandate. Nurses and other frontline health care workers in the periphery can be trained to monitor and decide whether TPT should be changed due to adverse events or restarted (e.g. after an interruption by the person on treatment). Medical doctors or specialists are not required routinely for such decisions, but their services should be made available when required.

Alternatively, monitoring may be aligned with mechanisms under differentiated service delivery (DSD) model for PLHIV where implemented, or schedule for collection of other medication (such as ARV). As a principle, the schedule for follow-up visit or drug collection should consider the individual's convenience as paramount. It is important that an informed decision to not take treatment by a person offered TPT, or to stop it after having started it, be respected; people should not feel coerced to take treatment (see also ethical principles in **Chapter 9**). During every 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.
- check for presence of signs or symptoms of TB disease; and if diagnosed with TB disease, TPT should be stopped and curative TB treatment started.
- measure weight, if possible, and adjust dosage accordingly. This is especially important for young children as rapid weight gain can normally occur in growing infants and young children over the period of TPT, thus requiring dosage adjustment. On the other hand, documented weight loss or failure to thrive is an early clinical indicator of TB disease.
- check for adverse drug reactions, and manage any toxicity identified or refer for specialist care if needed.
- remind the person on TPT of the need to contact a health care worker/provider if they notice adverse events, such as anorexia, nausea, vomiting, abdominal discomfort, persistent fatigue or weakness, dark-coloured urine, pale stools or jaundice. These are suggestive of liver injury and require urgent evaluation. If a health care provider cannot be consulted at the onset of such symptoms, the person on TPT should be advised to stop treatment immediately.
- elicit reasons for any missed dose and extend necessary support to enable future adherence to TPT.
- continue the management of comorbid conditions and consult with the treating doctor when necessary.
- ask about pregnancy, breastfeeding and contraceptive use.
- make a record of the visit, drug intake and findings using information from individual case files or forms prescribed by the national programme.

Key point: At every opportunity TPT providers should remind the recipients about potential adverse events and re-emphasize signs and symptoms that should alert them to contact the health care worker and/or stop TPT.

Differentiated HIV service delivery and implications for TPT scale-up

High HIV burden countries, particularly in sub-Saharan Africa, are increasingly scaling up HIV DSD. DSD models for recipients of HIV care who are stable use a person-centred approach and aim to shift people who are doing well on treatment, to less-intensive models requiring fewer visits to health facilities. DSD models for delivery of TB services can be modified to accommodate the different needs of PLHIV of different ages. They can also be expanded to non-PLHIV populations at increased risk of developing TB disease, including household contacts of TB patients.

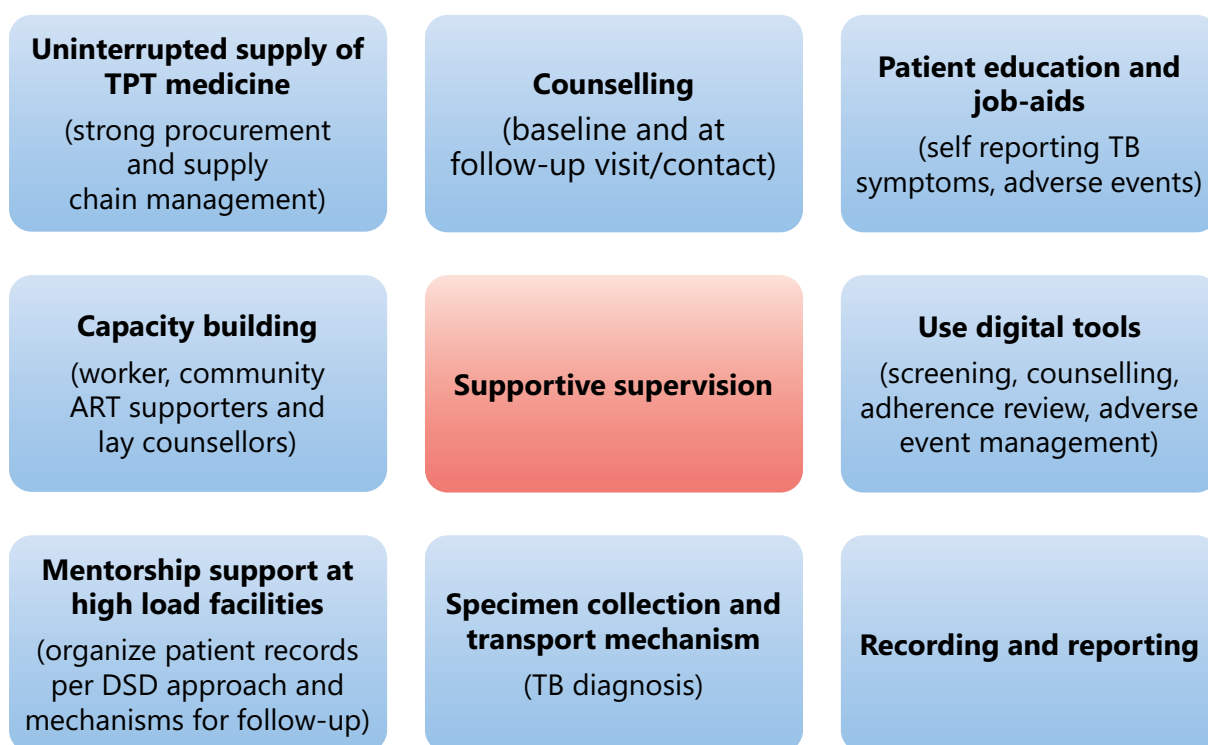
Various models of differentiated ART delivery have been tested recently including health care worker-managed group models; models driven by people taking TPT; facility-based individual models; and community-based individual models. A few examples of implemented DSD models (75,76) are listed below.

- Appointment spacing (facility-based, individual model): multimonth prescriptions and rapid circuit established at high-volume facilities to enable stable patients to have a quick check-up and proceed directly to the pharmacy to collect medication.
- Community-based points of ART distribution (community-based individual models): screening and drug distribution are provided by lay health workers.
- Adherence clubs (facility- and community-based): treatment distribution during support group meetings (every three to six months).
- Specialized child-friendly clinics providing two to eight weeks of supply of TPT and ART, depending on travel schedules of the individual recipient.

- Remote pick-ups from commercial pharmacies or pillboxes (“medication ATMs”) without any community health care worker involvement.
- DSD approaches for PLHIV who are stabilized are expected to reduce overcrowding at ART clinics, enhance the quality of care, improve adherence and viral suppression rates, and increase convenience for people. DSD is expected to enable appropriate support and education on potential adverse events, tolerability and importance of treatment completion. In principle, all recommended TB services should be incorporated within these models of service delivery and existing mechanisms to review the quality of ART services should be harnessed for monitoring the implementation of intensified TB case finding (ICF) and TPT services. The following interventions should be considered for TB care under all DSD programmes.
- All recommended TB/HIV services offered to PLHIV – including regular TB screening, referral for diagnosis when TB symptoms are noted, and TPT if TB disease is ruled out – should be done at regular intervals (at least once a quarter).
- TPT may be started during pre-ART evaluation or before starting spaced appointments under DSD, particularly for the shorter regimens (1HP) or at the time of follow-up visit to the health centre if longer regimens (6H, 4R, 3HR, 3HP) are implemented as per national guidelines.

While TPT regimens of any length can be provided under DSD, it is critical to establish a mechanism to identify and manage any adverse event considering the duration of TPT regimens and document TPT indicators systematically (see **Chapter 8**). Fig. 5.1 depicts the key elements to integrate TPT into DSD initiatives.

Fig. 5.1: Key elements for integrating TPT services into DSD models for ART



As more countries implement DSD, one key opportunity to scale up TPT services is presented by a country’s decision to transition to dolutegravir (or other new regimens) based ART. Several countries in eastern and southern Africa have decided to align transition to TLD (tenofovir, lamivudine, dolutegravir) regimen with the scale-up of shorter TPT regimens (3HP). As transition to new ART entails more

frequent clinical follow-up, national programmes are also leveraging this opportunity to start TPT and generate implementation experience to guide national scale-up.

Key point: Differentiated HIV service delivery is being scaled up for ARV services. Intensified TB case finding and TPT should be integrated within these models. Establishing DSD should not become a reason for delaying or denying benefits of TPT to PLHIV. In fact, patient visits should be scheduled such that they can pick up ARV and TPT drugs at the same time.

Provision of TPT for special populations

TPT among pregnant and postpartum women

Pregnant women living with HIV are at higher risk for TB during pregnancy and postpartum, which can have severe consequences for both the mother and the infant (77,78). Pregnancy should not disqualify women living with HIV or HIV-negative pregnant women who are eligible for receiving TPT since isoniazid and rifampicin, the medicines commonly used in preventive treatment, are considered safe for use in pregnancy (classified as Pregnancy Category C by U.S. Food and Drug Administration) (79,80). WHO conducted a systematic review for the 2019 update of LTBI guidelines, to assess evidence in support or against a recent report from one RCT showing increased risk of adverse pregnancy outcomes with IPT (81). However, review of all other existing evidence did not reproduce an association of IPT with adverse pregnancy outcomes, such as foetal/neonatal death, prematurity, low birth weight, congenital anomaly. Similarly, no statistically significant risks for maternal hepatotoxicity, grade 3 or 4 events or death were reported. Therefore, deferral of TPT to the postpartum period may not be required, and preventive treatment should be started during the antenatal and postnatal periods along with due care. Routine LFT is not indicated when TPT is given during pregnancy unless there are other hazards. Vitamin B6 supplementation should be given routinely to all pregnant and breastfeeding women on TPT. Rifampicin is generally considered safe for use during pregnancy, and no dose adjustment is needed although no safety or efficacy data are available specifically for pregnant and postpartum women (82). There are limited data on the efficacy and safety of rifapentine in pregnancy and therefore 1HP and 3HP should not be used in pregnancy until more safety data are available.⁸ Until such data become available, the triple pill combination of isoniazid + cotrimoxazole + B6 may be used for TPT among pregnant and postpartum women with HIV with due supportive care and monitoring.

Preventive treatment using isoniazid and or rifampicin can be safely given to breastfeeding women (83). Supplemental pyridoxine (vitamin B6) should be given to the infant who is taking isoniazid or whose breastfeeding mother is taking isoniazid. Similar to pregnant women living with HIV, the triple pill combination of isoniazid + cotrimoxazole + B6 may be used among breastfeeding women with HIV.

Key point: The triple pill combination of isoniazid + cotrimoxazole + B6 may be the preferred option for TPT among pregnant and postpartum women with HIV until more safety data on the use of rifapentine-based shorter regimens are available.

⁸ The IMPAACT 2001 study due to be presented at Conference on Retroviruses and Opportunistic Infections 2020, showing pharmacokinetic and relative safety of 3HP in pregnant women but highlighting the need for more studies.

Women receiving oral or hormonal contraceptives

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

- change the oral contraceptive pill and use an alternative (such as depot medroxyprogesterone acetate (DMPA) every eighth week (84) or higher dose oestrogen (50µ)) in consultation with a clinician; or
- use another form of contraception, a barrier contraceptive or intrauterine device.

In women having hormonal contraceptive implants, the interval for replacing the implants may need to be shortened from 12 weeks to eight weeks (ACTG study A5338).

Liver disease or history of liver disease

Isoniazid and rifampicin/rifapentine are associated with hepatic damage. TPT should be initiated with caution among individuals whose baseline liver transaminase values are available and found to be more than three times the upper limit of normal. Preventive treatment should not be given to individuals with end-stage liver disease. However, it is known that IPT is well-tolerated among individuals with chronic hepatitis B or hepatitis C infections (85,86).

Acute hepatitis (and acute viral hepatitis)

Defer preventive treatment until the acute hepatitis has resolved.

Renal failure

Isoniazid and rifampicin/rifapentine are eliminated by biliary excretion. These drugs, therefore, can be given in standard dosages to patients with renal failure. Patients with severe renal failure should receive isoniazid with pyridoxine (vitamin B6) to prevent peripheral neuropathy.

People living with HIV

A key challenge in TPT with rifamycin-based regimen among PLHIV is drug–drug interaction. While, rifampicin and rifapentine can be coadministered with efavirenz or dolutegravir without dose adjustment, in PLHIV receiving raltegravir and rifamycins, a higher dosage of raltegravir (800 mg twice daily) should be used. Rifampicin or rifapentine TPT regimens should not be coadministered with protease inhibitors or nevirapine (for details see section on drug–drug interactions).

Management of babies born to mothers with TB disease

- Assess the newborn. If the newborn is not well, refer to a specialist/paediatrician. It is important to ensure that the mother receives effective TB treatment so that she is no longer infectious. Also, ensure that infection control measures are in place in the nursery, especially if the baby is in an inpatient facility for care when preterm or small at birth.
- If the newborn is well (absence of any signs or symptoms presumptive of TB), provide TPT and delay bacille Calmette-Guérin (BCG) vaccination until TPT is complete. Administer pyridoxine at 5–10 mg/day.
- If the infant is HIV-exposed (mother is HIV infected) and on nevirapine, IPT should be started. TPT with RH and HP cannot be given along with nevirapine prophylaxis since rifamycins decrease nevirapine levels and may result in increased mother-to-child transmission of HIV (87).
- At the end of TPT, perform TST or IGRA. If test for TB infection is negative or not available, give BCG (unless the baby is HIV-positive).
- If the mother is taking anti-TB drugs, she can safely continue to breastfeed. Mother and baby should stay together, and the baby may be breastfed while on TPT.

- Infant breastfeeding from a mother on either TB treatment or TPT should receive pyridoxine for the duration of the mother's treatment.

Contacts of MDR-TB patients

Household contacts of patients with MDR-TB or isoniazid mono-resistance are at higher risk of TB infection than contacts exposed to drug-sensitive TB, however the risk of progression to TB disease does not differ among contacts in both groups (88). Studies have reported approximately 90% reduction in MDR-TB incidence with TPT (89). WHO recommends TPT among contacts exposed to MDR-TB patients following consideration of intensity of exposure; confirming the source patient and her/his drug resistance pattern (i.e. MDR-TB confirmed bacteriologically and susceptibility to a fluoroquinolone established); and ascertaining TB infection using IGRA or TST. This is to avoid potential adverse events with fluoroquinolone use for six months and preserve the option of using fluoroquinolone in the eventuality of MDR-TB disease among the contacts.

WHO suggests the use of levofloxacin for six months (paediatric formulation for child contacts) (see dosage in Table 5.2) along with other TB agents such as ethambutol or ethionamide if tolerated. Regardless of whether treatment is given or not, clinical follow-up should be done for two years and any emergent signs and symptoms suggestive of TB should be actively investigated and curative regimens started as needed. Contacts of individuals with rifampicin-resistant TB may be treated similarly to those for MDR-TB, but if isoniazid susceptibility is confirmed in index patients, contacts may be given 6H/9H. Among contacts exposed to individuals with known isoniazid-resistant TB, little evidence on choice of TPT regimens exists. However, data from Peru suggests that IPT is still effective (88). Also, 4R may be a TPT option in these situations.

Randomized controlled trials on MDR-TB preventive treatment are urgently needed to improve the evidence base. Results from following three RCTs of TPT among household contacts of MDR-TB patients are expected to become available in the next few years:

- **TB CHAMP:** testing six months of levofloxacin (Lfx) vs placebo in infants and young children less than five years of age exposed to MDR-TB (South Africa; ongoing recruitment and intending to publish by end 2021; <http://www.isrctn.com/ISRCTN92634082>).
- **V-QUIN:** testing 24 weeks of Lfx vs placebo in all ages with evidence of infection (Viet Nam; recruitment completed; date of ending data collection March 2022; <https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=369817>).
- **PHOENIX:** testing 26 weeks of delamanid vs isoniazid in all ages (11 countries; estimated completion in mid-2025; <https://clinicaltrials.gov/ct2/show/NCT03568383>).

TPT and treatment for hepatitis C virus (HCV)

Rifamycins including rifapentine, are not recommended for use together with many of the direct-acting ARV drugs used to treat HCV, since rifamycins can decrease the concentration of HCV drugs to subtherapeutic levels (90,91). People with HCV should consult with their health care providers and start rifamycin-based TPT either before or after completing treatment for HCV.

TPT among people who use drugs

People who use drugs have a higher prevalence of TB infection and incidence of TB disease (92). Rifapentine has not been systematically studied among people who use drugs (PWUD). However, rifampicin is known to reduce exposures to opioid substitution therapies (OST) such as methadone and buprenorphine (93). In some people, this results in opiate withdrawal. For this reason, people taking 3HP, 3HR or 4R with OST should be closely monitored for signs of opiate withdrawal and other adverse events. Increasing the dose of methadone or buprenorphine when taking rifamycins can lessen the risk of withdrawal. IPT is safe to use among PWUD, although careful monitoring for liver toxicity is important (94). Drug use should never be taken as a blanket rationale for denying someone TPT. It is the responsibility of health care providers to proactively manage drug–drug interactions for PWUD safely (95).

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



Chapter 6. Safety, management of adverse reactions and other drug-related issues in TB preventive treatment

WHO has for long recommended the use of TPT for populations at risk of TB, particularly PLHIV and child household contacts of TB patients. However programmatic scale-up of TPT has remained limited in most high TB and HIV burden countries due to other competing priorities. Concerns about the efficacy and safety of TPT and interactions with other medicines, particularly ARVs, may also be barriers to programmatic scale-up. Other frequently raised questions are about the potential for TPT to increase TB drug-resistance in the community and the durability of TPT to protect against disease or mortality. This chapter discusses available evidence around some of these important issues to facilitate TPT uptake and programmatic scale-up.

Drug safety and adverse drug reactions

Overall, the occurrence of serious adverse events leading to death or requiring withdrawal of TPT is rare. However, it is critical to identify any sign of drug toxicity early on and manage it vigorously, particularly among people who are usually healthy. Apart from harming the individual such eventualities can also damage the reputation of the programme and result in suspension of further TPT on a large scale due to loss of public confidence. As with any preventive action, the health care provider must weigh the risks and benefits of TPT for every individual. Obtaining a detailed and accurate medical history (inclusive of medicines being taken and known past adverse drug reactions) and keeping up-to-date information at every contact with the person on TPT, can help identify persons who require close monitoring and the most appropriate course of action if an adverse event emerges. Individuals receiving TPT should also be monitored regularly through scheduled visits (monthly if feasible, or as required for individual care or national programmes).

Table 6.1 summarizes known adverse events associated with currently used TPT drugs. As a part of initial counselling, the health worker should explain the rationale for TPT, importance of completing the course and re-emphasize the risk associated with TB disease. The person on TPT should also be educated about the likely adverse events and urged to contact the health care provider if they develop events suggestive of drug toxicity in between visits (such as loss of appetite, persistent fatigue or weakness, abdominal discomfort, nausea, vomiting, dark-coloured urine, pale stools, rash or itching, yellowing skin or eyes, tingling or numbness in 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 in advance about the pink discolouration of secretions due to this medicine.

Table 6.1: Likely adverse events with drugs used for TPT

	Known adverse events	Rare adverse events
Isoniazid	Asymptomatic elevation of serum liver enzyme concentrations Hepatitis Peripheral neuropathy (paraesthesia, numbness and 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 Pseudoadrenal crisis Acute renal failure Shock Haemolytic anaemia Flu-like syndrome
Rifapentine	Gastrointestinal reactions (abdominal pain, nausea, vomiting) Hypersensitivity reactions (flu-like symptoms) Hepatitis Discolouration of body fluids	Hypotension/syncope Decrease in white blood cell and red blood cell count Decreased appetite Hyperbilirubinemia

The following paragraphs discuss some of the adverse events associated with drugs used in preventive treatment and their management.

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. However, it is generally recommended that isoniazid be withheld if transaminase levels exceed three times the upper limit of normal and symptoms develop, or five times the upper limit of normal even in the absence of symptoms.
- **Clinical hepatitis** occurs in about 0.1% of people taking isoniazid and is more common when it 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 which are metabolized in the liver. Symptomatic hepatitis is rare among people younger than 20 years of age, although severe and fatal cases have been reported. Younger people with underlying risk factors for liver disease should be monitored clinically with the same precautions as older people.
- **Peripheral neuropathy** (paraesthesia, numbness and limb pain) occurs in less than 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 alcoholism. Routine pyridoxine (vitamin B6) supplementation is recommended only in such conditions or when there is other risk of isoniazid toxicity.
- Isoniazid is recognized as a secondary cause of **pellagra**. It interrupts cellular niacin (vitamin B3) production in persons 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

persons who consume excess alcohol and those with an undiversified reliance on unfortified maize staples.

- Other known side-effects due to isoniazid are skin rash, sleepiness and lethargy.

Rifampicin

- **Gastrointestinal symptoms**, such as nausea, anorexia and abdominal pain, are rarely severe enough to discontinue treatment.
- **Hepatotoxicity**, evidenced by transient asymptomatic hyperbilirubinemia, may occur in 0.6% of persons taking rifampicin. Hepatitis is more likely when rifampicin is combined with isoniazid.
- **Cutaneous reactions**, such as pruritis (with or without a rash), may occur in about 6% of persons taking rifampicin. These are generally self-limiting and may not be true hypersensitivity. Continued treatment may be possible.
- **Rifamycin hypersensitivity syndrome** has been reported in the past with use of intermittent, high-dose rifampicin characterized by flu-like symptoms. This usually develops after three to six months of treatment and in most instances, TB treatment can be tolerated subsequently (96,97). Rarely, rifamycins can be associated with **hypersensitivity reactions**, including hypotension, nephritis or thrombocytopenia manifested by symptoms such as fever, headache, dizziness/light-headedness, musculoskeletal pain, petechiae and pruritis.
- **Orange discolouration of body fluids** is expected and harmless, but persons prescribed rifamycins should be advised beforehand.

Rifapentine

- Overall rifapentine is associated with fewer number of adverse events on TPT and is well-tolerated, even among individuals with varying degrees of hepatic dysfunction (98).
- Clinically significant systemic drug reactions, mostly flu-like, are reported in up to 3.5% individuals receiving 3HP, most being mild and resolved within 24 hours (99). However, clinical monitoring and continued vigilance for systemic drug reactions are warranted. While there are reports of people experiencing hypotension or syncope after taking 3HP, hypersensitivity episodes overall are uncommon and usually resolve quickly after medication is stopped without any long-term effect.
- Other common side-effects include change in the colour of body fluids to orange-red (benign), gastrointestinal side-effects (such as nausea, vomiting, loss of appetite), decrease in white and red blood cell counts, skin rash or itching, joint pain and red eyes (100).

A network meta-analysis conducted in 2014 (updated in 2017) compared adverse events associated with the use of standard isoniazid regimen versus 3-4R and 3-4HR (45,101). The rifampicin only and rifampicin plus isoniazid regimen were reported to have a lower risk of hepatotoxicity compared to isoniazid monotherapy. Another systematic review that included data from 23 randomized and 55 nonrandomized studies in 2017 (102) reported high hepatotoxicity rates with 6H/9H (2-6%) and lowest rates with 3HP (1%) and 3-4R (0.01-2%) (Table 6.2). However, this review clearly stated overall weak documentation of adverse events, heterogeneity in data (different definitions of hepatotoxicity) and high risk of bias in the studies. The data however provided pointers to the frequency of any adverse events and events that eventually lead to stopping preventive treatment. The highest median rates for withdrawals from adverse events were associated with 6H, followed by 9H and lowest rates with 3HP. Possible hypersensitivity reactions were reported in up to 4% of individuals on 3HP and 2% on 3HR. Data on deaths due to any cause during TPT is reported less often, but in the studies included in the analysis no deaths were reported among participants on 9H, 3HP and 3-4R, while few deaths occurred in those on 6H and 3-4HR largely from studies in PLHIV not on ART or other comorbid conditions. Reassuringly, anaphylaxis was rarely reported for any regimen.

Table 6.2: Summary of adverse events and treatment withdrawals because of adverse events

Regimen	Participants in studies included in the systematic review	Median percentage of study participants experiencing adverse events (minimum–maximum)
Any adverse events		
6H ^a	1098	36.1% (6%–63.4%)
9H	4482	17.6% (0.18%–71.8%)
3HP	4991	11.5% (1.9%–41.5%)
3–4R	838	20.0% (0.2%–57.4%)
3–4HR	745	29.7% (12.2%–41.3%)
Grade 3–4 adverse events^b		
6H	880	8.2% (0.0%–12.0%)
9H	4714	3.3% (0.0%–6.5%)
3HP	5787	6.0% (1.3%–8.9%)
3–4R	788	1.7% (1.7%–2.1%)
3–4HR	1023	2.3% (NA)
Withdrawn from study because of adverse events		
6H	1738	3.8% (0.0%–12.0%)
9H	5304	6.4% (0.0%–16.8%)
3HP	5993	1.7% (0.5%–4.9%)
3–4R	846	2.8% (1.7%–10.1%)
3–4HR	1797	2.2% (0.0%–7.3%)

a H-isoniazid, R-rifampicin, P-rifapentine

b Grade-3 adverse event: medically significant but not an imminently life-threatening event. Grade-4 adverse event: life-threatening event.

A study that compared tolerability of 3HP versus 9H among HIV-positive and HIV-negative individuals found higher rates of grade 3 and 4 toxicity, hepatotoxicity and serious adverse events among HIV-positive persons receiving 9H. However, PLHIV experienced lower rates of flu-like or systemic drug reactions (1.0% vs 4.6%; $P = 0.01$) compared to HIV-negative individuals (53).

Management of adverse events

Individuals receiving TPT are otherwise healthy, and therefore adverse events during preventive treatment must be minimized. If a severe adverse reaction is encountered, TPT must be immediately discontinued, and supportive medical care provided. Conservative management and continuation under observation can be considered in the presence of mild-to-moderate adverse events as determined by the health care provider.

Where available, clinician discretion should be exercised and a complete history, including concomitant medication and supplements, must be taken. The following steps may help in the assessment and actions for management of adverse events.

1. How severe is the adverse event (mild, moderate, severe)?
2. How serious is the event (i.e. likely to lead to death or a life-threatening experience; hospitalization or prolongation of hospitalization; persistent significant disability; congenital anomaly)?
3. What is the immediate management (reassurance, symptomatic relief, hold/discontinue TPT, or requires an intervention to avert severe outcomes)?
4. What is the underlying cause (drug related, other factors)?
5. How will the adverse event affect future adherence (tolerability, consideration of substitution with an alternative regimen)?
6. What is the next step (continue or restart, substitute, follow up and reassess)?

Key point: National programmes are encouraged to use communication technology, including SMS and video-calls, for early reporting of adverse events and prompt action by health care workers. A mechanism to record data on the occurrence and management of adverse events is advised.

A. Isoniazid and rifampicin (64)

• Drug-induced hepatitis

- *Features that indicate the need to stop medication:* Transient, asymptomatic increases in serum liver transaminases occur during the early weeks of treatment. There is no need to interrupt or change treatment 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 suggestive of 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 two weeks after the jaundice has disappeared before starting TPT. Other causes of hepatitis must be explored.
- *Reintroduction:* Once hepatitis has resolved, the same drug regimen can be reintroduced, either gradually or all at once (“rechallenge”). However, if hepatitis has been life-threatening and was unlikely to have been caused by something else (such as alcohol, viral infection), it is probably safer to switch to an alternative regimen.

• Skin reactions

- *Itching with no rash or with a mild rash:* Symptomatic treatment with antihistamines may be tried and TPT continued.
- *Itching with moderate/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 in 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 ramped up 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.
- Persons with isoniazid-associated **pellagra** who discontinue isoniazid and receive high-dose nicotinamide (a form of vitamin B3) treatment can fully recover, however pellagra may result in

severe illness or death if untreated (103). The recommended treatment for pellagra is 300 mg of nicotinamide daily for three to four weeks. Good dietary sources of vitamin B3 are similar to those for vitamin B6.

- **Peripheral neuropathy**
 - To prevent peripheral neuropathy, administer 10–25 mg daily dose of vitamin B6 (pyridoxine), or vitamin B complex.
 - For established peripheral neuropathy, pyridoxine should be given at a larger dose of 100–200 mg daily. Also see **Chapter 5** for details on pyridoxine.
- **Gastrointestinal reactions with rifampicin (abdominal pain, nausea, vomiting):** If symptoms are mild, the episode is usually self-limiting, and reassurance may suffice. If gastrointestinal intolerance 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 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 rifampicin.
- **Lethargy:** Reassurance.
- Discolouration of body secretions (urine, tears, semen and sweat) red or orange: reassurance.

B. Isoniazid and rifapentine

Table 6.3: Management of potential adverse reactions following treatment with 3HP⁹

Adverse event	Stop and consider reintroduction with caution	Stop and do not reintroduce
Flu-like syndrome (attacks of fever, chills and malaise, sometimes with headache, dizziness or bone pain)	If mild and not increasing, continue treatment and observe closely	If moderate to severe symptoms, consider alternative TPT options without a rifamycin (such as 6H)
Drug-associated fever only	Consider reintroduction if fever settles below 39°C, but stop permanently if fever recurs	If fever > 39°C after previous episode of drug-associated fever
Persistent nausea, frequent vomiting and/or persistent episodes of unformed watery stools	<ul style="list-style-type: none"> • Administer antiemetic or antidiarrhoeal medication • Consider reintroducing 3HP with caution once the symptoms have resolved 	If there is nausea, vomiting or diarrhoea which requires aggressive rehydration
Cutaneous reactions	<ul style="list-style-type: none"> • Diffuse rash (no vesicles) • Diffuse rash with limited vesicles 	If there are extensive bullous lesions/ulceration of mucous membranes/Stevens Johnson or toxic epidermal necrolysis, contact a specialist and use steroids
Other hypersensitivity reactions (hypotension, acute bronchospasm, conjunctivitis, thrombocytopenia)	Assess the clinical severity of the symptoms and if severe consider alternative TPT options without a rifamycin (6H)	

⁹ Most adverse drug reactions associated with HP regimens are mild, self-resolving and without sequelae.

Adverse event	Stop and consider reintroduction with caution	Stop and do not reintroduce
Hepatitis (early symptoms weakness, fatigue, loss of appetite, persistent nausea)	Alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) < 5 times the upper limits of normal and absence of symptoms	<ul style="list-style-type: none"> • ALT/AST is ≥ 5 times the upper limit of normal in the absence of symptoms • ALT/AST is ≥ 3 times the upper limit of normal in the presence of symptoms
Psychosis	Psychiatric evaluation, antipsychotic therapy, pyridoxine	Attributable to isoniazid
Seizures	Withhold isoniazid pending resolution of seizures, evaluate possible causes of seizures (104)	Attributable to isoniazid

Please note: Rifamycins are potent enzyme inducers and any side-effects should be assessed and managed together with potential drug–drug interactions (see elsewhere in this chapter).

C. Routine monitoring: should include tolerability and adherence. Look for following components at every contact with the person on TPT,

- Signs or symptoms of TB disease (“breakthrough” or missed diagnosis at start of TPT)
- Pregnancy: discontinue 3HP, consider alternative TPT regimen (e.g. FDC of isoniazid, vit. B6 and CPT)
- Adverse event: type, onset and duration, severity
- Assess adherence and provide necessary support: any interruptions in treatment should be discussed with the person on treatment and her/his treatment supporter, and interventions to address problems in adherence should be instituted
- Other diseases, such as malaria
- Relevant physical examination
- Check for any medication (including traditional cures) that may interact with TPT
- LFTs among individuals: who had raised levels at baseline or previous visit; with history of regular use of alcohol. Routine LFTs are not indicated when IPT is given in pregnancy unless there are other risk factors for liver toxicity.

Key point: LFTs prior to initiating TPT are not routinely indicated. Baseline and follow-up LFTs are only needed when there is a defined risk, such as pre-existing liver dysfunction, liver cirrhosis or other indications.

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

Drug–drug interactions

Rifamycins and ARVs

When rifamycins and ARVs are given together, there can be a change in effect of either drug on the body. 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 (P-gp), and uridine diphosphate glucuronosyltransferase (UGT) 1A enzymes. Similarly, rifapentine induces P450 enzymes, specifically the CYP3A4, CYP2C8, and CYP2C9 isoenzymes (105). Rifampicin and rifapentine have similar potency as inducers, while rifabutin is a less powerful inducer. Consequently, rifamycins accelerate the metabolism of many companion drugs, including some ARV drugs. Coadministration of these ARVs with rifamycins therefore may cause reduction in ARV drug bioavailability and increase the risk of HIV treatment failure or resistance. ARVs most affected by CYP 450 induction due to rifamycin include all protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs) (such as dolutegravir) and CCR5 antagonist (such as maraviroc). Rifamycins also interact with many other medicines summarized in **Table 6.4**. Sound clinical judgement is therefore required when these medicines are to be coadministered with rifamycin-based TPT, either by avoiding these regimens or adjusting the dose of other coadministered drugs (106).

In general, care should be taken when prescribing regimens containing rifampicin and rifapentine to PLHIV who are on ART. These regimens should not be administered to PLHIV on a PIs or nevirapine-based regimen. While dose adjustment is not required when rifampicin is coadministered with efavirenz, the dose of dolutegravir needs to be increased to 50 mg twice daily for adults when given together with rifampicin (107). This dose is well tolerated and gives equivalent efficacy in viral suppression and recovery of CD4 cell count compared with efavirenz (108). 3HP can be administered to persons receiving efavirenz-based ARV regimens without the need for dose adjustment (109). Administration of rifapentine with raltegravir is also safe and well tolerated (110).

Coadministration of rifapentine and dolutegravir

While once-weekly rifapentine is known to reduce dolutegravir exposure, blood levels of dolutegravir remain above target concentrations associated with viral suppression in adults taking both medicines. One study showed that a reduction in dolutegravir concentration – even as high as 75–80% – is unlikely to be clinically significant as even a dose of 10 mg dolutegravir once daily (along with nucleotide reverse transcriptase inhibitor (NRTI) backbone) produces high rates of virologic suppression over 96 weeks, similar to efavirenz-containing regimen (111). Dolutegravir can therefore be given with weekly rifapentine without any dose modification.

Coadministration of these drugs is also shown to be safe overall. Phase I/II trials of 3HP and dolutegravir among adults with HIV with suppressed viral load reported good tolerance and maintenance of viral load suppression. No grade 3 adverse events were reported, and findings indicated that there was no need to adjust the dose of dolutegravir among adults living with HIV on dolutegravir-based ART (112).

However, there is a need for more studies on the pharmacokinetics of 3HP concomitantly administered with other medicines, particularly boosted PIs and tenofovir alafenamide, and including both pregnant women and children. Studies assessing dolutegravir levels with daily rifapentine and the need for dolutegravir dose adjustment with 1HP for adults and children are ongoing (ACTG 5372).

ARV options for concomitant administration with rifamycin-based TPT

A change of ART to accommodate a certain TPT regimen should be done with utmost caution. The clinician should seriously weigh the risks versus benefit of such a change since frequent change in

ART is associated with loss of virologic control and hence should be avoided to the extent possible, particularly when the person is virologically suppressed with current ART. In addition, changing to efavirenz-based ART in many areas with high rates of NNRTI resistance (including many areas in sub-Saharan Africa) is not ideal. Overall, successful ART should have primacy in decision over choice of TPT regimen. The following options exist if changing of ART regimen is being considered for compatible use with rifamycin-containing TPT.

- Most NRTIs and fusion inhibitors do not have significant drug interactions with rifamycins.
- Pharmacokinetic data do not show significant drug–drug interactions of rifapentine with the NNRTI efavirenz (113–115) and INSTI raltegravir (110).
- No significant drug–drug interactions are reported with use of rifapentine and ART regimen containing abacavir (ABC), emtricitabine (FTC), tenofovir-disoproxil fumarate (TDF), lamivudine (3TC), or zidovudine (AZT). Efavirenz or raltegravir based regimens used in combination with either ABC/3TC or TDF/FTC can be used with 3HP.

Tenofovir alafenamide is a notable exception, where being a P-gp substrate may result in unacceptably low drug exposure as a result of 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 (116). Of note, tenofovir alafenamide given with rifampicin produces similar intracellular levels of the active drug tenofovir diphosphate (TDF-DP) as TDF given alone, suggesting that this combination could be used together, but clinical data are limited (117).

Isoniazid

Isoniazid is known to inhibit certain cytochrome P-450 enzymes. Coadministration of isoniazid with drugs that undergo biotransformation through these metabolic pathways may decrease elimination thereby increasing drug levels/exposure. Consequently, dosages of drugs metabolized by these enzymes may require adjustment when starting or stopping concomitantly to maintain optimum therapeutic blood levels. Isoniazid has been reported to inhibit the metabolism of the following drugs: 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. Similar drug–drug interactions of rifamycins are summarized in Table 6.4.

Table 6.4: 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 ¹⁰
Antiarrhythmics	Disopyramide/ mexiletine/ quinidine/tocainide		↓
Antibiotics	Chloramphenicol/ clarithromycin/ dapsone/ doxycycline/ fluoroquinolones		↓
Anticoagulants	Warfarin	↑	↓

¹⁰ For many agents the magnitude may depend upon daily dosing of rifamycins versus once weekly dose (rifapentine).

Medication class	Examples	Isoniazid inhibits metabolism and increases blood levels	Rifamycins accelerate metabolism and decrease blood levels ¹⁰
Anticonvulsants	Phenytoin	↑ (Phenytoin, carbamazepine, primidone, valproic acid)	↓
Antidepressants	Amitriptyline/nortriptyline	↑ Some SSRI (selective serotonin reuptake inhibitors)	↓
Antimalarials		↑ Halofantrine	↓ Quinine
Antipsychotics	Haloperidol	↑	↓
Antivirals		↑ Ritonavir (ARV) ↑ Efavirenz	↓ PI, INSTI ↓ 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		↓
Corticosteroids	Prednisone		↓
Fibrates	Clofibrate		↓
Oral hypoglycaemic agents	Sulfonylureas		↓
Hormonal contraceptives/progestins	Ethinyl oestradiol/levonorgestrel		↓ (Rifapentine)
Immunosuppressants	Cyclosporine/tacrolimus		↓
Methylxanthines	Theophylline	↑	↓
Narcotic analgesics	Methadone	↑ Levomethyldate acetate	↓

Medication class	Examples	Isoniazid inhibits metabolism and increases blood levels	Rifamycins accelerate metabolism and decrease blood levels ¹⁰
Phosphodiesterase-5 (PDE-5) Inhibitors	Sildenafil		↓ (Rifapentine)
Thyroid preparations	Levothyroxine		↓

Key points

- Coadministration of commonly used ARVs with TPT is safe, and alternatives are available when low ARV exposure is suspected due to drug–drug interaction.
- Caution is required when an individual receiving TPT is also on treatment for a comorbidity.
- Women on hormonal contraceptives should use an additional barrier contraceptive to avoid pregnancy when using rifamycin-based TPT.

Rifamycin-based TPT and antimalaria treatment

Being potent CYP3A4 inducers, rifampicin and other rifamycins, decrease exposure to quinine in adults on malaria treatment, leading to a fivefold recrudescence rate (64). Similarly, concomitant administration with mefloquine causes threefold decrease in exposure to mefloquine. Similar decrease in levels of exposure was reported with coadministration of rifampicin and artemether, dihydroartemisinin and lumefantrine (9-, 6- and 3-fold decrease respectively). There is insufficient evidence to change the current mg/kg body weight dosing recommendations for these antimalarial agents, hence close monitoring should consider the higher risk of recrudescence. The following guidance may be applied until clear evidence becomes available on ways to enhance exposure to antimalarial drugs:

- If a person is diagnosed with malaria but is not yet on rifamycin-containing TPT, the episode of malaria should be prioritized and treated first.
- If a person is diagnosed with malaria while on rifamycin-based TPT, malaria treatment should be started concomitantly and clinically monitored according to national guidelines to ensure that the malaria is cured. There is insufficient evidence to indicate that doses of either TPT or ACT (artemisinin-based combination therapies) need to be adjusted.
- If a person has malaria recurrence while on TPT, he should be retreated for malaria according to national guidelines. Preventive treatment should be withheld only if the new malaria treatment also includes drugs with known interactions with rifamycins. TPT may be resumed once the episode of malaria is resolved.
- If a person meets 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 urgently treated according to national guidelines. TPT should be recommenced only when the episode of malaria is fully resolved.

How long does a course of TPT protect a person?

Durability of protection from TB is a function of both the potency of the TPT regimen to sterilize TB infection and the risk of reinfection post treatment. TB infection that is not adequately treated due to a less potent regimen or poor adherence to treatment may result in reactivation of TB infection leading to TB disease.

PLHIV have a high risk of reactivation of TB infection as well as progressing to TB disease when infected. In the pre-ART era, several studies found an escalating risk of TB after a course of TPT in high TB burden countries; and on the contrary a more lasting protection in low/medium TB burden countries in terms of reduced mortality and incident TB. Recent trials conducted in an era of wide-scale access to ART however, suggests that the protection offered by TPT even in high TB burden settings can last as long as in low/medium TB burden settings.

- In Côte d'Ivoire, where TB incidence was last reported as 159 per 100 000 people, six months of IPT had a strong protective effect in reducing mortality among HIV-infected people, who had started ART even when CD4 cell counts were high, and the protective effect lasted for up to six years (118).
- In Brazil (medium TB prevalence), IPT significantly reduced TB risk among HIV-infected patients with a positive TST. A six months course of isoniazid reduced TB risk for over seven years, in contrast to results from studies in high-burden settings in Africa where TB incidence increased immediately following IPT (119,120).
- Recent studies from Myanmar and Indonesia (high TB burden) reaffirm the durability of protection with six months IPT among PLHIV. In Myanmar, completing a course of IPT significantly reduced the risk of TB disease and death for as long as eight years. In Indonesia the protective benefit lasted more than five years (121,122).
- In the BRIEF-TB trial (97% of participants from high TB burden countries), TB incidence following a complete course of TPT using either one-month isoniazid and rifapentine or nine-month isoniazid regimen remained stable throughout the three-year follow-up period of the trial. Almost all PLHIV in this trial received ART (54). Among household contacts of TB patients receiving TPT in the pre-HIV era, IPT was demonstrated to have a long-lasting benefit even in settings with very high rates of TB disease.
- The United States Public Health Services sponsored several studies to assess the efficacy of IPT in the 1960s. A large group of individuals at risk of TB due to recent or remote contact with a pulmonary TB patient in Alaska were studied (123). 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 more than among the highest transmission settings, such as mines in South Africa, which had an estimated occurrence of 4.2% in 2005 (124). Participants received isoniazid 300 mg daily or 5 mg/kg for children or a matching placebo for one year. Active follow-up was done for two years and passive reporting for the next 10 years. Follow-up data from a study of 28 villages and two boarding schools in Alaska that started in 1958, showed that the protective effect of isoniazid persisted for up to 19 years (125). The calculation that six to nine months of preventive therapy was optimal was derived from follow-up data in this study and a study by the International Union Against Tuberculosis and Lung Disease that found that isoniazid given for more than nine months does not improve effectiveness (69,126).
- A systematic review published in 1999 (127) 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 prescribed isoniazid for six months, one case of TB disease was prevented over the next five years.

When is it necessary to repeat or restart TPT?

There is no evidence to date on the utility of repeated courses of TPT. Therefore, WHO 2020 TPT guidelines do not specifically recommend a repeat course of TPT. However, in settings with high TB transmission (as defined by local authorities), isoniazid for 36 months (as a proxy for life long therapy) is recommended for PLHIV (see Recommendation below). One of the priority areas for research in such settings is to assess whether repeated courses of short course regimens are needed and if so, how frequently.

WHO recommendation:

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

A randomized pragmatic trial (WHIP3TB), among PLHIV 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). Treatment completion was better with 3HP than 6H. Follow-up for 24 months after randomization showed similar rates of TB incidence, incidence of rifampicin resistant TB and mortality between participants receiving 3HP once or twice, suggesting that 3HP for PLHIV on ART in high TB transmission settings provides protection and that repeating it annually did not improve benefits (128). Longer term follow-up of this trial will be important to understand the durability of this effect.

A repeat course of TPT should however be considered among HIV-positive or HIV-negative persons who previously completed a course of TPT but have been thereafter a household or close contact of a TB patient. Since currently available tests (TST and IGRA) do not convert to negative after a complete course of TPT, they cannot be used to determine eligibility for a repeat course if a new exposure or reinfection occurs. Therefore, careful assessment of intensity of exposure and balance between benefits and harms should guide the decision to administer a repeat course of TPT.

Restarting TPT may be necessary if there has been a significant interruption in the treatment given. **Chapter 5 (Table 5.3)** and **Chapter 7 (Table 7.1)** propose some thresholds to determine loss to follow-up for different regimens informed by criteria applied in trials. This is another area where reliable evidence about the “forgiveness” of regimen interruption is lacking.

Does TPT cause drug resistance?

One of the concerns commonly expressed about the large-scale use of TPT is its potential risk of propagating drug resistance. These concerns have not been supported by high quality evidence to date (58). Multiple trials have failed to find scientific evidence of a significant association between TB drug-resistance and the use of isoniazid or rifamycin for TPT (129,130). Concerns such as these have effectively deprived countless populations from the benefit of a potentially life-saving intervention. Most drug resistance arises from suboptimal treatment of TB disease. An increase in drug resistance is unlikely if good TPT practices are observed by programmes, namely that TPT is used in people without TB disease. Individuals with TB infection have a small number of slowly replicating bacteria in their body, and hence there is a low risk for TPT to select drug-resistant strains (129). On the contrary, TPT may actually lower the overall burden of TB disease and thus reduce the number of people who could receive suboptimal TB treatment that favours the development and spread of MDR-TB.

TB disease should be excluded using 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. Surveillance

may also be strengthened for drug resistance among individuals who develop microbiologically confirmed TB during or following TPT.

Key point: Common beliefs that large-scale use of TPT will fuel drug resistance are not supported by reliable evidence and represent the type of barriers that withhold vulnerable populations from access to interventions that can protect them and their communities from avoidable TB disease and death.

Isoniazid resistance after IPT

In a systematic review of 13 published studies since 1951, which included 18 095 people on IPT and 17 985 controls, there was no suggestion of increased risk of isoniazid-resistant TB after IPT; these results were similar when stratified for HIV (129). In addition, in the Thibela study cohort from South Africa, proportions of TB episodes with drug resistance among patients who had received IPT did not significantly differ from those in comparison groups (131).

Rifamycin resistance after TPT

In an analysis of six RCTs of rifamycin-containing regimens for TPT versus active control or placebo showed that the occurrence of rifampicin resistant cases was 0.09% in 6808 individuals receiving rifamycin-based TPT vs 0.01% in 7415 individuals receiving alternate regimens (RR = 3.45, 95%CI 0.72–16.56; P = 0.12) (130). In three of these studies where intermittent rifamycin-based TPT was used, there were two cases of rifampicin resistance among 4673 individuals on intermittent rifamycin-containing regimen compared to one case with rifampicin resistance among 4427 individuals from control regimens (RR = 3.89; 95%CI 0.44–34.56; P = 0.22). In placebo-controlled trials, there were no cases of rifampicin resistance among participants receiving rifamycin-containing regimens whereas several cases of rifampicin resistance occurred in those on placebo (RR 0.20, 95%CI 0.02–1.66) (130).

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



Chapter 7. Adherence to TB preventive treatment

Decision point on strategies to promote adherence to TPT

What strategies should national programmes adopt to ensure adherence to the prescribed regimen by all individuals started on TPT?

Adherence to treatment is a complex behaviour that is influenced by many factors such as personal motivation, beliefs about health, risks and benefits from treatment, comorbidities, competing demands that conflict with the taking of medicine, family environment, complexity of the drug regimen, drug toxicity, trust and relationship with the health provider (58). Effective person-centred strategies to promote adherence to TPT may incorporate the following components:

- Ensure **confidentiality** when seeking a person's commitment to complete the course before initiating TPT.
- Ensure that the **person understands** the role of TPT regimen options and the duration required to complete for maximizing protection. Provide information materials in the primary language and at the appropriate literacy level of the person concerned.
- Involve **family members and caregivers** in health education when possible. Children often move between households and health facilities; it may be helpful to include additional facility members and caregivers in adherence support.
- **Reinforce supportive educational messages** at each contact during treatment.
- Give clear information regarding **adverse drug reactions ("side-effects") and triggers on when to stop treatment** and contact the health care worker.
- Invite clarification **questions** and provide clear and simple answers. Provide a telephone number to call for other queries or a need to contact health services for advice.
- Develop a personal **adherence plan** with the support of family member, caregiver or health worker as per treatment regimen being provided (**Box 7.1**).

Interventions to ensure adherence and treatment completion should be tailored to the specific needs of risk groups and the local context. It should be recognized that protection from a course of TPT depends upon the level of adherence. However, concerns about perfect adherence should not become a barrier in providing TPT. The 2017 WHO guidelines for treatment of drug-susceptible TB proposes several interventions to support adherence that could be applied to TPT, including digital technologies (74). Similarly, the best practice for the care of TB patients produced by The Union indicates support considerations to enhance adherence to TPT (732). A systematic review conducted for earlier WHO guidance on TPT provided inconclusive results about whether direct observation could improve treatment adherence and completion when compared with self-administered treatment (49).

Supportive messages to improve adherence and treatment completion

Acceptance by a person at risk to take TPT is often influenced by information given by counsellors, nurses, doctors, pharmacists and other health care staff. To help people appreciate fully the rationale behind TPT explain about the following benefits:

- TPT can hold back 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 such as contacts of people with TB disease, especially children under five years of age
 - People with HIV and other medical conditions that lower immunity
 - People taking medication that may lower their immunity such as anti-TNF, steroids.
- TPT with new medicines that shorten the treatment span to three months or less is now recommended by WHO, whereas TB disease requires at least six months of treatment, starting with four medicines.

Providers should also alert people about the risks associated with TPT and the likelihood of their occurring (**Chapter 6**). A person on TPT should remember that:

- Red discolouration of urine and other body fluids while taking 3HR/3HP/1HP/4R is a normal accompaniment of rifamycin therapy and is harmless.
- Some frequent adverse drug reactions are gastrointestinal disturbances, flu-like symptoms, liver injury (hepatotoxicity) or a rash.
- Persons on TPT should be alerted to:
 - Early signs of hepatotoxicity that include weakness, fatigue, loss of appetite, persistent nausea. When identified early, hepatotoxicity is reversible and without permanent sequelae. Late signs of hepatotoxicity include liver tenderness, liver enlargement (hepatomegaly) and jaundice
 - Flu-like and other acute symptoms appearing shortly after taking a dose of rifapentine-containing TPT (most commonly with the third dose), rash, pain or numbness in hands and feet.

If a person on TPT experiences any of the above symptoms or a change in their health situation, they should contact a health care provider for advice and only continue taking preventive treatment if advised to do so.

Furthermore, people on TPT should understand that:

- **TB disease can develop during TPT**
 - While an effort is usually made to exclude TB disease through a symptom screen prior to starting TPT, persons on TPT should be vigilant as they can still develop TB disease while on treatment.
 - If they start having a cough, unexplained weight loss, fever and night sweats, they should immediately let the provider know and undergo tests for TB disease. Among 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 pointers to TB disease.
- **Pregnancy can occur during TPT**
 - Women of child-bearing age should be counselled to use barrier methods of contraception while using TPT.
 - Safety data for use of regimens containing rifapentine during pregnancy remain sparse. If pregnancy occurs during 3HP or 1HP, it would best be to switch TPT to six months of daily isoniazid.
 - The triple combination FDC of isoniazid + cotrimoxazole + B6 may be used for TPT among pregnant and breastfeeding women with HIV along with supportive care and monitoring.

Potential barriers to adherence

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

- Clinic opening hours conflict with person's schedule
- Competing priorities, such as work, school, caring for children or elderly
- Long waiting times at clinics
- Cost of clinic visits (transport, time, loss of work)
- Incorrect or insufficient information about:
 - TB infection
 - treatment regimen
 - TB disease
- Real or perceived stigma related to TB infection, disease and treatment
- Health beliefs and practices
- Conviction that TPT is more of a nuisance than useful
- Treatment-related issues:
 - coexisting medical conditions
 - concomitant use of other medicines, conventional or otherwise, or food supplements that could interfere with adherence or with effectiveness of the medicines
 - adverse drug reactions associated with the medicines and a person's past history of reactions to medicines
 - alcohol intake during medication
 - difficulty remembering daily or weekly dose
 - religious practices such as fasting.

Strategies to improve adherence and treatment completion

To improve the chances of adherence and regimen completion, the following needs to be considered when providing guidance to individuals receiving TPT.

- Explore and unpack an individual's understanding about TB, TPT and elicit support from family members or a companion in a similar situation ("treatment buddy").
- Explain the importance of taking treatment at a fixed scheduled time of the day or time/day every week (3HP). The exact timing does not matter but it is easier to remember if the same time is retained.
- Explain the importance of completing the full course of treatment for optimum protection from TB.
- In case of adverse drug reactions, even mild ones, stress the importance of informing and seeking care from the provider. In most cases symptomatic treatment will suffice without the need to stop or defer TPT.
- Taking all medications together at once and not dividing the dose over a few hours or a few days. Pills can be separated if the whole dose can be taken within 30 minutes.
- Use reminders to help take medication regularly such as daily/weekly events
 - Electronic reminders on cell phones: bidirectional SMS and voice calls can improve communication with the caregiver, such as on suspected toxicities
 - Take medication with one of the meals or before sleeping every night (daily) or around Sunday/Saturday/Friday prayers (weekly)
 - Be cautious about overreliance on a TV or radio show to remember when to take a dose given that a programme may be rescheduled, moved to a different time slot or there may be electricity outages.

Options that can be used for supporting adherence

- Align TPT delivery and follow-up with TB/HIV/other services that the person may be receiving simultaneously, including use of DSD models, and motivational counselling through trained providers.
- Identify an appropriate treatment supporter such as a family member, neighbour, colleague.
- Record additional information about the person on TPT – such as contact numbers at home, work and cellphone numbers, and email address, as well as names and contact details of close friends, or relatives living in the same city, or same country – with a clear commitment of confidentiality from the providers. The treatment supporter should be counselled in detail with regards to care and provided supportive supervision.
- Schedule in-person encounters for individuals whose treatment has been interrupted or who often miss 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.
- Provide incentives to encourage or motivate individuals depending on acceptability within the country context and availability of funds (such as airtime/grocery store coupons/food parcels or supplements). While these are commonly used, their link to improved adherence has not been clearly demonstrated (133).
- Provide enablers such as reimbursement of transport cost and phone calls, to make it easier to keep appointments depending on acceptability within the country context and availability of staff resources and funds.
- Develop an **adherence plan** with the person on TPT and discuss it at each visit. Such a plan may include information on:
 - motivators for the person to want to be TB free
 - using the person's individual and family routines and their variations to identify best time to take the medicines
 - taking medicines with food to reduce nausea and vomiting or at night three/four hours after dinner.

Special considerations for adherence among children

Infants and children are dependent on caregivers for medication administration, and therefore the barriers faced by their adult caregivers can contribute to missing doses for children. The considerations laid out above would apply to caregivers of children and infants on preventive treatment.

Potential barriers for children

- The absence of child-friendly formulations makes medication more difficult to administer and increases the chances that the child refuses treatment with crushed pills.
- Lack of conviction among the caregiver about importance of TPT. Only if both the caregiver and health care worker are invested in the successful completion of TPT, will the adherence of child be ensured.
- Family factors
 - Not having one or more appropriate caregivers among relatives. Given that young children may move around different homes within the family, the involvement of multiple caregivers (grandparents, father's family) may be necessary
 - Caregivers lack of knowledge
 - Age and developmental stage at which children can take more responsibility for taking their own medications while still being supervised by an adult
 - Changes in routine for the family or child (such as school vacations) that disrupts administration schedule.

Strategies for managing and enhancing adherence among children

- Explain and emphasize to the caregiver and child why they must take the full course of treatment.
- For dispersible FDCs, child-friendly formulations, ensure that the health care workers can explain and provide clear instructions to caregivers regarding how to dissolve the FDCs in water.
- Provide a person-friendly schedule for appointments for drug refills.
- Take note of risk factors for poor adherence and attempt to address them: such as long distance/transport; orphans (especially if the mother has died); past adverse reactions to medicines or primary caregiver being unwell.
- Provide adolescents with education and adherence support directly, especially if they are living with HIV.
- For young children refusing to take medicine:
 - change the food type so as 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
 - provide a treat as reward for taking medication completely
 - if a child vomits within 30 minutes of a dose, ensure that a new dose is given to the child. This means families are given a few extra doses every month (the programme should estimate the extent of such losses and reflect the same 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 there is a new caregiver present.
- Review knowledge and barriers at each visit. Examples of questions to be asked are listed below.
 - Who is the primary caregiver (parent, grandparent, aunt/uncle, other child)?
 - Does the child sometimes sleep in another family member's home?
 - Is the caregiver aware that the treatment is daily (isoniazid, 3HR) or once weekly (3HP) for three months?
 - Is the caregiver aware of dose/pill number at each time?
 - Is the caregiver being counselled regarding the need for adherence, adverse drug reactions, when to seek health care worker's advice, and what to do when the child vomits after medication (repeating dose)?

Box 7.1: Example of an adherence plan

- Review the understanding of persons on TPT or caregivers about TB
 - Ask the persons what they know about TB infection, TB disease and TPT.
 - Give information to correct a false belief or wrong information about TB, as necessary.
- Understand individual's motivation to start TPT
 - What motivates them to stay healthy?
 - Find out if the person is ready to start TPT, and if not advise appropriately.
 - What are their views on disclosure to others?
 - Are they willing to disclose their treatment status with anyone? If yes, to whom?
- Discuss medication issues
 - Explain the role of TPT and how treatment is supposed to be taken (daily/weekly, within 30 minutes).
 - Ensure the person understands possible adverse drug reactions and what to do if they occur.
 - Concurrent intake of conventional and traditional medications that may interact with TPT.
 - For children in their care
 - Explain actions following vomiting after medication and when to repeat the dose of TPT; provide families with extra doses or request that they report early if such vomiting occurs.
 - Types of foods that can be used to mask the taste of crushed medication.
 - Discuss how early signs of hepatotoxicity may present in children.
- Discuss person's lifestyle and advice on
 - Choice of a time of day or a day in the week (3HP) for medication.
 - Routine for medication – before sleep, with a meal, or every Sunday (weekly regimens).
 - Reminder strategies for medication, e.g. cellphone alarm, daily/weekly routine or a ritual.
 - Choosing more than one strategy or reminder system.
 - Keeping alcohol consumption low.
- TPT planning for family
 - For household contacts, regimen planning should be done for the family collectively along with plan to support adherence.
 - For each household if a medication box is used discuss how to organize the medicines for each member.
- Agree on a TPT support option
 - Ask which mode of support is preferred to stay in touch with the health care worker: telephone call, home visit, clinic visit, digital adherence technology.
 - Preferred mode of contact when TPT doses are missed – cellphone call, home visit, contact family member or TPT buddy.
 - Assess need for travel support for routine medicine collection.
 - Share details of persons to contact if adverse events are noted during TPT.
 - Assess and link to other needs such as nutrition support or other social support schemes in the country.
- Ongoing support
 - Reassure people that you have an open-door policy for them to return at any time if they miss a TPT dose or face any other challenges to continued medication.

Processes to support retention on TPT

People on TPT should be seen by health care workers at scheduled intervals appropriate to the country context (fortnightly, monthly, quarterly). These encounters may happen in clinics, 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 as well as strategies being used to assist with adherence; show that you are also interested in helping them to adhere to treatment; discuss how many daily/weekly doses were missed and how this can be avoided in the future.
- for adherence counselling as appropriate by
 - discussing any identified barriers and proposing joint solutions, as well as
 - using motivational interviewing techniques to improve adherence (134) (How do you feel when you have missed a dose? How do you want to change that?).
- for checking used blister packs and examining all remaining pills to assess if the pill count corresponds with the expected consumption in the interval.
- to ask specifically about adverse events and TB symptoms.
- to check contact information against clinic records, including one verified cellphone number and the number of a close contact person.
- to update the monitoring system and flag any person who misses a visit for a follow-up call within one week of missing the scheduled clinic visit to enquire:
 - about adverse events, TB symptoms, pregnancy
 - whether the person still has medicines available
 - and fix the next clinic appointment as soon as possible.

Management of missed doses

Table 7.1: Management of interruptions in TB preventive treatment¹¹

TPT regimen	Duration of treatment interruption	Next step	Suggested actions
3HR, 4R, 6H	Less than 2 weeks	<p>Resume preventive treatment immediately upon return 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 the last follow-up visit will be postponed by the number of extra days to compensate for missed doses (e.g. If a child on 3HR missed 3 days of treatment, continue preventive treatment for a total duration of 3 months + 3 days from the date of start).</p>	<p>Address the reason for interruption</p> <p>Counsel the person on TPT and the caregiver on the importance of adherence to preventive treatment</p> <p>Review and agree with the person on TPT and the caregiver about the best ways to improve adherence</p>
	More than 2 weeks	<p>If treatment interruption occurred after more than 80% of doses expected in the regimen were taken, no action is required. Continue and complete the remaining treatment as per original plan.</p> <p>If less than 80% of doses expected in the regimen were taken, and the treatment course can still be completed within the expected time for completion, i.e. treatment duration + 33% additional time, no action is required. Continue and complete the remaining treatment as per original plan.</p> <p>If less than 80% of doses expected in the regimen were taken, and the treatment course cannot be completed within the expected time for completion, consider restarting the full TPT course.</p>	

¹¹ See also Table 5.3 for the thresholds of regimen prolongations due to consecutive or erratic interruptions.

TPT regimen	Duration of treatment interruption	Next step	Suggested actions
3HP	Weekly schedule of one dose missed	<p>If the missed dose is remembered within the next 2 days, the person can take the dose immediately. Continue the schedule as originally planned (i.e. continue to take remaining doses following the same schedule).</p> <p>If the missed dose is remembered more than 2 days later, the person can 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 less than 4 days apart.</p>	
1HP	More than 1 weekly doses of 3HP missed	<p>If between 1–3 weekly doses are missed, treatment is continued until all 12 doses are taken, thus prolonging the treatment duration to a maximum of 16 weeks.</p> <p>If, however, 4 or more weekly doses are missed, consider restarting the full TPT course.</p> <p>If adherence to a weekly routine is not possible, consider discontinuing 3HP and offering an alternative (daily) regimen.</p>	
1HP	Less than 1 week	<p>If more than 80% (23) of doses expected in the regimen were taken no action is required, just complete the remaining doses.</p> <p>If less than 80% (23) of doses expected in the regimen were taken, resume treatment immediately upon return and add the missed doses to the total treatment duration to complete the course within a maximum of 6 weeks.</p>	
1HP	More than 1 week	<p>If more than 7 consecutive doses were missed, consider restarting the complete course of 1HP regimen.</p> <p>If more than 7 doses were missed intermittently, resume preventive treatment immediately upon return and add the missed doses to the total treatment duration to complete the course within a maximum of 8 weeks.</p> <p>If adherence to 1HP is not possible, consider discontinuing it and offering an alternative daily regimen or 3HP.</p>	

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



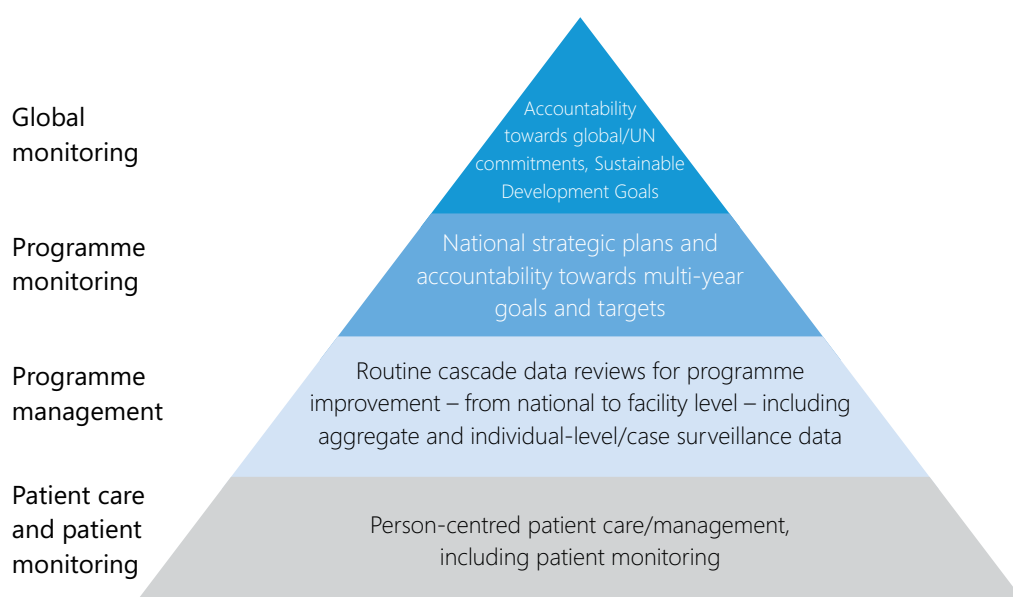
Chapter 8. Monitoring and evaluation

Decision point on minimum data for routine recording and reporting

- What data should be routinely captured and reported to the national level for programme management?
- What is the minimum dataset needed to monitor individual case management and monitor progress across the TPT pathway?
- What tools and methods should be used to facilitate data collection and reporting?

Monitoring and evaluation (M&E) play an important role in patient care and in assessing national programmes and global response (**Fig. 8.1**). Accurate recording and reporting of programmatic data informs managers about immediate outputs and outcomes of programme services, as well as the larger impact of resources invested into a programme. If services are adequately accessed, if key activities are occurring in a timely manner, and if expected results are achieved, then it is very likely that the overall goals will also be met. When running well, M&E should be able to provide health care providers and programme managers with information on how many contacts were in a TB patient's household and how many of them were effectively evaluated. Or, how many people offered TPT in an ART clinic decided to take it, and how many of those starting TPT continued it until the end.

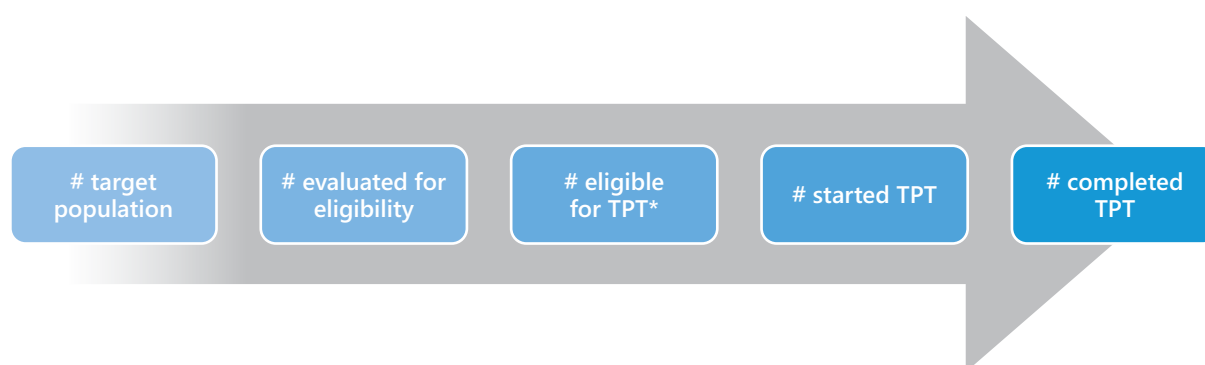
Fig. 8.1. Use of health data at different levels of the health system



Monitoring programmatic implementation of TPT

As several activities under PMTPT – such as contact investigation and TB preventive care of PLHIV, overlap with screening for TB disease, and involve similar at-risk populations, M&E activities should be aligned to promote synergies and limit duplication. It is important to ensure that all individuals who are most at risk of developing TB are systematically identified, and once TB disease is excluded, offered TPT to improve both their individual health as well as community disease burden (some principles on how to estimate the numbers eligible for TPT are given in Box 8.1). Programmatic implementation and scale-up of TPT requires strengthening of each element in the cascade of care starting from identification of the target population to provision and continuation of TPT (**Fig. 8.2**).

Fig. 8.2: Critical numbers to monitor at different steps of the TPT pathway



total number

* if chest radiography and IGRA or TST are not used, this would be the number without clinical evidence of TB disease; if chest radiography and IGRA or TST are available this would be the number without clinical or radiological evidence of disease +/- with positive test for TB infection

Indicators for monitoring of PMTPT

The generation of indicators is a critical endpoint for the process of recording and reporting. It is traditionally done every quarter at regional and national levels, depending on the number of people being monitored. Data on TPT services are aggregated at regular intervals and reported to higher levels for monitoring progress. If an electronic case-based data system is available with nationwide coverage, then aggregation may be done at lower levels at any required frequency to inform about programme performance.

Box 8.1: How to calculate the number of people eligible for TPT?

This is a common question facing the programme manager and is important strategic information that helps assign human resources judiciously, order enough medicines and assess other elements of logistics management.

The majority of people eligible for TPT are from two groups – PLHIV and contacts of TB patients – and their numbers can be calculated as follows:

(i) for PLHIV: the number is derived either from in-country research on the number of PLHIV on ARV who are eligible or else based on programme data of the subpopulations below.

- a. Total number of PLHIV on ART at the end of the reporting period.
- b. [minus] Total number of PLHIV currently on treatment for TB disease or being evaluated for TB disease.
- c. [minus, where possible] Total number – or estimate – of PLHIV who previously completed TPT within the timeframe as per national policy (or who are currently on TPT).
- d. [minus, where possible] Total number – or estimate – of PLHIV not eligible for TPT due to comorbidities 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 on b, c or d are not available, an estimate may be derived by discussions with clinical staff.

(ii) for contacts of TB patients: the number will be based upon the estimated number of household contacts of pulmonary TB patients in the country. In addition to the latest available number of pulmonary TB patients notified in the country, the following demographic data would be needed:

The average size of the household and the proportion of the population in the age group 0–4 years (demographic indicators for countries are updated each year by the World Bank¹²). For example, if the country had 20 000 pulmonary TB patients in the previous year, the average size of the household is 5 and 16% of the country population is < 5 years then an expected 100 000 contacts would be exposed, of whom 16 000 would be 0–4 years of age. This total may need to be adjusted downward because: some of the notified pulmonary TB patients would be from the same household; some of the contacts would need treatment for TB disease; some of the contacts would be PLHIV newly on ARV care and therefore already included in estimate (i) above; or some would opt out or have a contraindication for TPT.

[add] to the above number, individuals in other risk groups, such as clinical risk groups and people in prisons, immigrants (this information should be collected from respective hospitals, prisons, testing centres or other sources) who would need treatment.

Finally, before placing an order for medicines, it is essential to factor in what is feasible. For example, if there is no system for contact investigation in place yet, then a realistic target is needed for the coverage that can be achieved in the short term as capacity is gradually ramped up. It is important to know what proportion of PLHIV receiving ARV can be reached by the national HIV and TB programmes (especially where there is an active private sector). If more than one TPT regimen option is available, the programme needs to apportion the number of people who would be assigned to the different treatments.

¹² World Bank Open Data. World Bank (<https://data.worldbank.org/>, accessed 21 March 2020).

While Table 8.1 represents a minimum set of PMTPT indicators, the programme may decide to monitor other activities, such as the coverage of testing for TB infection (TST/IGRA) among people targeted for testing as part of investigation of eligibility for TST.

Key point: Ministries of health and national programmes should integrate M&E for TPT into the existing national HMIS. Establishment of a parallel and stand-alone data collection and reporting system for PMTPT is not required or desirable.

Minimum individual level dataset for monitoring TPT

A minimum set of variables is proposed to be collected at the individual (case-based) level at three important instances for PMTPT

1. Assessment of contacts of TB patients
2. Assessment of PLHIV and other at-risk groups
3. Initiation and completion of TPT.

1. Assessment of contacts of TB patients

Identifier of contact (or name)

Identifier of index TB patient (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* (opted out, medical contraindication)?)

2. Assessment of PLHIV 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* (opted out, medical contraindication)?)

3. Initiation (start) and completion of TPT

Identifier of person on TPT (link to dataset for contacts (1 above) or other risk groups (2))

TPT regimen prescribed (3HP, 3HR, 6H, etc.)

TPT initiation (start) date

TPT completion date

** this detail would only be registered if a standard coding is available and an electronic tool is being used.*

Table 8.1: Description of monitoring indicators for PMTPT

Indicator	Definition	Numerator	Denominator	Remarks
Contact investigation coverage	Number of contacts of bacteriologically confirmed TB patients evaluated for TB disease and TB infection out of those eligible, expressed as a percentage	Total number of contacts of bacteriologically-confirmed TB patients who completed evaluation for TB disease and TB infection during the reporting period	Total number of contacts of bacteriologically-confirmed TB patients 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 needs urgent improvement to achieve the UNHLM targets. It is also one of the top 10 indicators of the WHO End TB strategy.
TPT coverage	Number of individuals initiated on TPT out 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	This indicator (also referred to as <i>TPT initiation</i> indicator) should include all people deemed to be at risk and eligible for TPT by the national policy. A time trend analysis of the numerator provides information on the trajectory of TPT scale-up and help assess progress towards UNHLM targets. Disaggregation by PLHIV (newly or currently enrolled on ARV), contacts < 5 years of age and 5 years and older allows reporting to WHO for monitoring of UNHLM targets. Disaggregation by TPT regimen (e.g. 3HP, 3HR, 6H) helps assess the uptake of shorter rifamycin-containing regimen and inform the procurement and supply chain management.
TPT completion	Number of individuals completing TPT out of those initiating treatment, expressed as a percentage	Total number of individuals who completed a course of TPT* during the reporting period	Total number of individuals who initiated a course of TPT during the reporting period	This indicator helps assess the quality of implementation of PMTPT given that the effectiveness of TPT depends upon its completion. When reported alongside the other two indicators above, the reporting period should be earlier (e.g. 6 months or 12 months preceding) to allow time for completion of the TPT. Disaggregation by regimens lasting 6 months or more and others lasting less to handle TPT completion in “cohorts” within a practical time window.

* Please see text and Table 5.3 for proposed thresholds of completion by regimen type.

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

In places where the capacity to undertake routine M&E for the minimum indicators is still being built, the ministries of health and national programmes may consider a periodic analysis of medical records that can be done using a simple sampling methodology. Likewise, investigations on medication adherence and drug safety may be done as part of such a survey. **Box 8.2** outlines an example on how to conduct annual patient record reviews which can be run rapidly by the programme staff with minimum financial and training resources focusing on household contacts. In many settings, service data for PLHIV on ART are captured within electronic data systems enabling varied analyses using unique personal identification (UID) across different data systems (such as cohort analysis of PLHIV newly enrolled in HIV care who were screened for TB, evaluated for TPT eligibility, started on TPT and completed TPT). Availability of UID enables de-duplication of entries and increases the reliability of data for programme management.

Monitoring TPT completion

It is important to monitor TPT completion both for individual care and programme management. The electronic data capture tool should record details of treatment outcomes for each individual starting TPT. TPT may be considered completed when an individual takes 80% or more of the prescribed number of doses of treatment within 133% of the scheduled duration of the respective TPT regimen and remains well or asymptomatic during the entire period (see also Table 5.3 on minimum number of doses to determine completion for different regimens. Other outcomes for TPT adherence are proposed in **Chapter 5** to help in decisions for care of a person on TPT).

Data recording tools

National TB and HIV programmes use patient cards, medical histories, case files or electronic medical records as sources for information on TPT services. One of the key challenges in the scale-up of TPT services is the need to capture a diverse set of data, often relying on paper-based records and the involvement of multiple health care service providers. Programmes that monitor PMTPT usually capture data on paper tools, such as lists of contacts investigated in a household, or additional columns on an ARV register to record TPT initiated among PLHIV. These tools are reviewed periodically to derive indicators, usually requiring manual computation. Printing and updating of paper records adds to the burden on health care workers.

Data from TB programmes are increasingly being recorded electronically for people with TB disease who need treatment including ART. These databases are used to generate M&E indicators as well as to follow up patient treatment response. For PMTPT activities, in contrast, many programmes are yet to develop systematic electronic data collection mechanisms to generate programmatic indicators. WHO promotes the development of existing or new electronic systems to capture data elements that are needed for PMTPT care and monitoring to generate indicators automatically. Hand-held devices such as smartphones are particularly suitable because they can capture data from different sites critical to PMTPT activities, be it in the index patient's home, an ARV clinic, hospital or an occupational/immigration health centre (see Box 8.3).

Box 8.2: Example of a review of medical records to assess coverage and completion of TPT among household contacts of TB patients

If the capacity to undertake routine programmatic monitoring of TPT is still being built, a review of medical records can be conducted every year to evaluate the following key indicators:

- Proportion of household contacts of bacteriologically confirmed TB patients that were investigated for TB
- Proportion of household contacts eligible for TPT, who were prescribed treatment
- Proportion of household contacts eligible for TPT who initiated TPT
- Proportion of household contacts who initiated TPT and, completed TPT (see text for definition of completion).

The number of household contacts investigated (any contact who showed up at a designated health centre or visited a household), the number who started TPT and the number who completed TPT should be written on the card of the respective index patient (patient with bacteriologically confirmed TB), by writing the names of the contact individuals who showed up at the health facility for investigation and ticking the relevant boxes next to the name. Only household contacts living in the same apartment or house as the index patient should be recorded. The medical record review requires the following steps:

1. Sample at least 12 health facilities treating TB patients randomly. If a list of national health facilities is available, number them consecutively and select facilities using a random number generator (such as in Excel) until 12 different facilities have been selected.
2. Staff in a chosen health facility should retrieve (with bacteriologically confirmed TB) cards or medical files of all index patients corresponding to the same quarter of the previous year.
3. Staff should then count the number of contacts, the number investigated for TB, the number who were eligible for TPT, the number initiated on TPT and the number who completed TPT from each retrieved patient card and calculate the totals for each of those categories and communicate them to the national team.
4. The national team then compiles the totals from each of the chosen health facilities and calculates the proportions described at the beginning of the box.

Such a sample would be self-weighted (equal probability of sampling at the first stage of facility selection, variable number of records in the second stage (record selection) proportional to the number of records in one year) and nationally representative (as ensured by the randomness of the selection process of the listed health facilities), requiring no sophisticated statistical analysis. The measured indicator values may be extrapolated to the national level for the year. A sample of approximately 100 index patient cards should suffice for programme M&E purposes, unless a high precision of national estimates is required. Missing data should be recorded and reported as such. If the proportion of missing data is high (greater than 30%), corrective action should be initiated to ensure a lower proportion of missing data in subsequent medical record reviews.

Box 8.3: Prevent TB: a prototype mobile application to support PMTPT and screening

The Global TB Programme of WHO has developed a mobile application (app) to facilitate monitoring and evaluation of PMTPT (39). This app was built using the District Health Information Software 2 (DHIS2; <https://www.dhis2.org/>) and is compatible with a number of electronic data systems in use. It is designed to help health care workers collect person-specific data and visualize them on an online dashboard for real-time monitoring. The app can be adapted to meet country programme needs. WHO conducted field-testing of this application in two high-burden countries and has now developed a second generation of the original tool released in 2017, with more user-friendly features and utilities to link up more easily to other information systems available to the programmes. To fully implement this platform, software development work will be required in the country for local adaptation, including a decision on the site of data hosting and supporting capacity building of staff.

With an increasing number of people being evaluated for TPT, more diverse options for TPT regimens (of differing compositions and durations), and a desire to disaggregate by various subpopulations at risk, it is more important to invest in electronic recording systems to enable accurate quantification, procurement and supplies of consumables. This information is also useful for planning of 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 capacity at national and subnational levels in the use of data for decision-making. Countries should allocate a dedicated budget to digitize data capture and reporting and request funding from donors if there is a shortfall in funding.

Data confidentiality

Providing optimal TPT and care involves 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 persons who need to know, usually those providing direct care. All documents containing confidential information must be securely stored. Duplicate and unnecessary paper-based work should be discouraged and destroyed when it is no longer needed. Computerized databases that contain sensitive information should be protected by coded passwords and encryption, with users granted access rights depending on their role. It is desirable to assign UIDs to individuals being evaluated for or administered TPT. The UID can help in matching and de-duplication of individual entries. Entries may be immediately de-identified after data aggregation. Personal details should be removed as soon as possible in data collection or reporting if they are no longer required for reporting purposes. Care should be taken when referrals are made to other services and when information on an individual is transferred from one care facility to another (either manually or electronically). Each programme should develop a policy to ensure confidentiality of personal data and if a national policy exists it should be enforced in all parts of the health sector. Information on how these data are handled should be part of the counselling provided to people who are offered TPT. Just as they are empowered to opt out of TPT, their decision about the use of their personal information should also be respected.

Supportive supervision

Good supportive supervision is an essential element for routine M&E of health facilities from central or district levels. It includes quality checks for data recording and reporting, including inspection and validation of a person's case files and data collection tools for validity and completeness of recording. National programmes may provide a standard checklist to assess data quality and implementation across the cascade of care starting from identification of the target population for TPT initiation and completion. The frequency of supportive supervision depends on resources and needs, but closer monitoring may be needed for data quality assurance given that PMTPT is a relative novelty in many countries. Supervisory visits may also gather data for HMIS reporting. At least once a year, a data quality audit of routine monitoring systems may be carried out by the supervision team. This should involve members of both TB and HIV programmes and possibly others (such as prison health services and occupational health).

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

It's time to stand against stigma and discrimination



Chapter 9. Ethics and TB preventive treatment

Decision on ethical issues in TPT implementation

What are ethical considerations and related actions for programme management of TPT?

Implementation considerations

In general, only about 5–10% of people infected with *M. tuberculosis* will develop TB disease at some point in their lifetime. The risk of TB infection progressing to TB disease is much higher for some groups, such as PLHIV, very young children and people who have just recently acquired infection. Treatment always carries some risk of adverse drug reactions, so understanding the individual risk versus benefit of taking TPT, helps to make an informed decision. TPT should be administered following an evaluation of benefits against potential harms to the individual. Routine testing and treatment should be limited to those groups with 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 the affected individual and the community (135). Whether or not 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 persons (95). The absence of an immediate risk of transmission makes it unethical to restrict the movement of someone with TB infection who refuses treatment.

The WHO TB ethics guidance clearly states that taking TPT should never be compulsory. National programmes should strengthen counselling services for eligible persons to ensure effective and adequate communication around protective benefits, uncertainties and likely adverse events. The risks and uncertainties should be communicated in culturally appropriate messaging. Feedback should be invited regularly with the aim to adjust programme implementation. It is desirable to document and monitor counselling efforts and informed consent of TPT recipients systematically to ensure effective implementation. Proactive measures including routine clinical and laboratory (when indicated) monitoring should be made an integral part of PMTPT to ensure that those treated remain safe throughout TPT.

Informed consent

Explicit consent is generally required for TPT since the subject does not pose an immediate risk to others and the potential benefits are highly context specific and may be outweighed by risk of harm for some individuals. The provider usually has a professional obligation to do this. Whether this is documented in writing or not depends on local practice. Informed consent requires effective and adequate communication of the possible uncertainties, as well as prospects of risk reduction (often

uncertain due to risk of reinfection). Nurses and other frontline health care workers can be trained to counsel people about TPT, the options of treatment and to interpret the results of testing for TB infection or for active TB disease. In addition to the benefits and risks for individuals, information should also be given on the implications of TPT on a person's family and the community. National programmes should consider formulating appropriate TPT communication strategies, with special attention to communicating benefits, risks and uncertainties in a culturally and linguistically appropriate manner, by involving the community, people who have taken TPT and ex-TB patients.

Key point: Counselling before TPT is of paramount importance to safeguard human rights. National programmes should prominently factor in resources to strengthen the counselling component both in planning and fund allocation, to ensure that all individuals identified as eligible for TPT can make an informed choice between accepting or opting out of TPT, based on a clear understanding of the potential benefits and harms of taking treatment.

Ethical issues around TPT services

- In the absence of specific risk factors, most individuals having 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 lowers the certainty of effectiveness of TPT at the individual level.
- There are currently no tests to establish that TPT has been successful for the individual.
- There is a risk of emergence, although very low, of drug resistance if TPT is given in the presence of TB disease.
- TPT carries a risk of adverse events, some of which are serious (such as hepatotoxicity). Considering that these reactions are provoked by a treatment given to someone who is usually healthy makes its occurrence more unfortunate.
- Apart from toxicity, TPT presents the added inconvenience of psychological burden and anxiety costs.
- TPT carries the risk of stigma and discrimination that is attached to TB.
- TPT carries a financial implication for the household for testing, adhering to treatment and care.
- While TPT protects from disease there is always the risk of reinfection. Risk of TB disease is higher among groups who are already marginalized and furthermore likely to reside in crowded places with poor infection control. Access to TB screening and TPT for these groups should be prioritized to enhance equity, human rights and solidarity. Efforts must be made to address existing inequities in access to services and to uphold human rights, so that the vulnerability of target groups does not impede their access to screening and treatment or violate their rights. Any interventions for vulnerable groups, including those who are criminalized, those in prisons, and children, should include measures to minimize the risk of stigmatization, such as protecting confidentiality of personal data and informed consent. This may require providing support to cover social and economic costs associated with screening, treatment and interventions that minimize the burden on a person on TPT (such as requiring only one visit, access to shorter and safer TPT regimen).

Mandatory TB screening at borders and in at-risk groups:

- **Migrants** who are screened for TB disease, may also be automatically screened for TB infection. Screening for either condition should always be done with the intention to provide appropriate medical care, and never to deport or deny entry into the country. Since TB infection indicates a potential future risk to a small minority of people, excluding or deferring immigration on the basis of infection alone is unjustified and unethical. The individual's status – testing positive for TB infection or receiving TPT – should not affect the immigration procedure. This should be reflected

in existing laws or other policy regulations. People should be tested for TB infection and receive TPT in strict adherence to human rights and ethical considerations.

- **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 but with the professional obligation to act in a way that minimizes risk of harm to persons under their care. Any consideration of mandatory screenings should take into account both the burden imposed on health care workers and potential risks for others. Policies should evaluate the likelihood of transmission (i.e. if health care workers are in a clinical or ambulatory setting with heightened exposure to them or their patients), and how likely are patients to suffer harm by developing TB disease (such as immunosuppressed patients). If health care workers are occupationally exposed to TB or even undergo screening and treatment, then there is a reciprocal obligation on the health system to alleviate the burdens imposed on them by infection as much as possible, through free screening and TPT, and importantly investing in improving infection control measures to reduce the risk to 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 always be based on high quality evidence of the risk of transmission, and the benefit to both health care workers and others potentially affected.

Community engagement: Affected communities often do not appreciate the value of preventive action, the need to protect community members from TB and what is TB infection versus TB disease. Community engagement and health education play an important role in ascertaining that individuals and communities can make informed choices regarding TPT.

In conclusion, policies should be evaluated by end-users from an ethical perspective and the views and experiences of affected populations gathered after implementation, both to consider possible unexpected effects and to ensure that the evidence on which they are based remains current and relevant. Person-centred TPT care entails, among others, that it is provided in an equitable fashion without placing marginalized and vulnerable populations at an added disadvantage. It focuses on human rights aspects of TPT interventions so that there are appropriate safeguards in law, policy and practice to minimize additional stigma, discrimination, violation of bodily integrity or restrictions on freedom of movement. People offered testing and treatment should understand the associated uncertainties well enough to be able to participate in decisions on care options. These guiding principles would best draw upon a set of established human rights principles, such as consent, noncoercion, confidentiality.

Key point: Ministries of health should consider formulating appropriate TPT communication strategies by involving people who have taken TPT from different target populations. A review of the adequacy of communication resources at their disposal and dissemination can enable individuals and communities to be more autonomous when making informed choices regarding TPT.

Annex 1. List of key messages

Messages for the ministry of health

- National governments have made a commitment at the first ever UN High Level Meeting on TB on 26th September 2018 towards *“preventing tuberculosis for those most at risk of falling ill through the rapid scaling up of access to testing for tuberculosis infection, according to the domestic situation, and the provision of preventive treatment, with a focus on high-burden countries, so that at least 30 million people, including 4 million children under 5 years of age, 20 million other household contacts of people affected by tuberculosis, and 6 million people living with HIV, receive preventive treatment by 2022, and with the vision of reaching millions more, and further commit to the development of new vaccines and the provision of other tuberculosis prevention strategies, including infection prevention and control and tailored approaches, and to enacting measures to prevent tuberculosis transmission in workplaces, schools, transportation systems, incarceration systems and other congregate settings.”*(11).
- 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, with targets to reduce TB deaths by 95% and to cut new cases by 90% between 2015 and 2035. The strategy also lays down targets to provide TPT to 90% of those eligible by 2025 (8).
- TPT is a proven and effective intervention to avert the development of TB disease, reducing this risk by about 60–90% when compared to people who do not get TPT (136).
- TPT, given to people at the highest risk of progressing from TB infection to disease, remains a critical intervention worldwide to end TB. TPT is part of a larger set of actions – ranging 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, to eradicate poverty.
- Large numbers of TB deaths could have been avoided if TPT had been rolled out worldwide following WHO recommendations for its programmatic use in 2008 (137). Urgent steps for nationwide implementation are therefore necessary to prevent massive suffering, catastrophic costs and deaths. If programmes start now, countries can accelerate the achievement of End TB targets.
- PMTPT is a key element of the framework for TB elimination in all settings and needs to be pursued aggressively particularly in low TB incidence settings.
- Shorter rifamycin-based TPT (4R,3HR,3HP,1HP) provides alternative options to IPT, which has historically been the main approach until of late. A shorter TPT regimen is more likely to be completed, as it is more tolerable and easier to manage programmatically, and hence may 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, chest radiography, urine LAM, TST/IGRA) should be enhanced through investments in infrastructure, human resources and logistics in support of a nationwide scale-up of TPT.
- There is a need to establish mechanisms and invest in capacity building of nurses and health care workers in counselling PLHIV and TB patients and their family and contacts, to educate them on TPT, initiate TPT, follow-up treatment, identify and manage adverse events, as well as signals of potential toxicity and decide when it is necessary to stop TPT.
- Investing in strengthening of systematic recording and reporting using digital tools for PMTPT would enable monitoring of progress for programme management and resource allocation.
- Priority groups for TPT include household and close contacts of TB patients, PLHIV, persons with other immune-deficiency or predisposing clinical conditions (such as silicosis, dialysis, organ or blood transplant). National programmes may consider integrating TPT into an active TB case-finding component of their programme for at-risk populations.

Messages for health care workers

- TPT saves lives, cuts transmission of infection, prevents illness, and averts suffering due to TB. Some of the strongest proof comes from the TEMPRANO trial, which studied IPT among PLHIV in Cote d'Ivoire. Participants receiving IPT had a 37% reduction in mortality, independent of whether they were also on ART, with those on both IPT and ART having the greatest protection against severe disease and death (17).
- Currently recommended TPT regimens offer a durable protection following one course of TPT among PLHIV, HIV-negative contacts and other at-risk populations. The protection is shown to range between 6 to 19 years with IPT.
- There are various TPT regimens, with some of them combining two TB drugs – isoniazid and rifapentine or rifampicin – and lasting only 3 to 4 months. Evidence shows that they are as effective as older treatments in preventing progression to TB disease and are easier to complete than older treatments. While they may cost more in the short-term, they could provide a more cost-effective protection given that more people complete their treatment as prescribed. People taking shorter drug regimens are much more likely – up to three times – to complete their course of TPT than those on longer regimens, leading to better outcomes and more lives saved.
- Before starting TPT, counselling of people at risk and their families are key to: enabling an informed decision on accepting TPT, adhering to the schedule of TPT and encouraging the reporting of adverse events promptly. It is critical to educate people on TPT about signs and symptoms of serious adverse events, such as drug-induced hepatitis.
- It can be challenging and time-consuming to 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 complete the full course of TPT.
- There is no clear evidence to date showing increased TB drug resistance due to PMTPT. However, all efforts should be made to rule out TB disease using recommended procedures. If screening is negative, the likelihood of TB disease is very minimal. Withholding TPT is a missed opportunity to protect individuals and communities from avoidable disease and death and could hence be viewed as unethical.
- Concerns of harming otherwise healthy individuals need to be addressed. However, a very small proportion of people on TPT develop adverse events, and most adverse events are self-limiting and reversible. The shorter rifamycin-based regimens have a better safety profile. Having options for different populations can help in minimizing the risk.
- All people prescribed TPT should be informed clearly of the schedule of treatment, possible adverse events (“side-effects”), and health alerts to look out for, to contact their health care provider or to stop TPT.
- Systematic recording and reporting are important both to inform about individual care as well as to monitor the indicators of programme performance.
- With appropriate training in knowledge and skills, nurses and other frontline health care workers in the periphery can undertake most of the clinical duties required of PMTPT. This includes decisions on testing for TB infection and active disease, interpretation of results, eligibility for TPT, starting TPT and monitoring adherence to it, making decisions about whether TPT should be suspended or changed (e.g. in the case of adverse events) or restarted (e.g. after an interruption by the person on treatment). In most instances there is no need to solicit the opinion of a medical doctor or a specialist for these decisions on TPT although provision for this should be available in case it becomes necessary.

Messages for PLHIV and individuals offered TPT

- You (your family members) do NOT have TB disease. You (your family members) may have an infection that could become active TB. TB is a serious disease and could threaten your life and it could spread to your family/neighbours/coworkers.
- Your doctor/provider has determined that you would benefit from TPT (for you or your family members) despite you (your family members) being healthy at present. 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 develop, your caregiver will follow up with you regularly and provide care to overcome them. Your health care provider will inform you of the common adverse events of TPT you are offered. Even so you are free to take TPT or opt out or stop it after starting.
- 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 giver.
- If you (your family members) notice any adverse event, consult your health care worker at the earliest. 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 (your family members) are on rifamycin-based TPT and wish to avoid pregnancy it is important to note that rifapentine (and other rifamycins) decreases the effectiveness of hormonal contraceptives (138). You (your family members) should consider using a different, or barrier form of contraception when taking rifapentine or a rifampicin-based TPT.
- Parents or legal guardians: giving your children TPT will protect them from getting TB which can be difficult to diagnose and could have long lasting negative effects. Child-friendly medicines that dissolve in water and have a nice taste are now available and make it easier for your child to take treatment regularly.

Messages for the community

- TB is a contagious disease that is transmitted through air when a person with infectious TB coughs. Having TB is associated with considerable morbidity and mortality even when treated. Even if people with TB successfully complete treatment, some are left with considerable damage to the lung or to other organs which can seriously affect quality of life.
- However, TB is preventable, and prevention is much better than cure. There are a number of options available to prevent TB and reduce the burden of TB in the community. These include early detection and treatment of people with TB disease, BCG vaccination to infants and providing TPT to individuals who are currently well but have been exposed to TB or are at a higher risk of developing TB disease.
- In an effort to reduce the number of individuals who develop TB each year, countries have committed to provide TPT to people who have been exposed or those who already have TB infection in their bodies even if this has not yet progressed to TB disease, such as among PLHIV, children and family members of TB patients. Providing treatment to these individuals will prevent TB disease in them and result in a healthier community.
- TB infection is extremely common. People in the community who require TPT are not sick, are not coughing and are at no risk of transmitting TB to anyone else. TPT is prescribed to minimize future risk of developing TB disease in an individual. This also protects the community because TB is a contagious disease.
- The drugs used for TPT are generally very safe. Shorter TPT regimens that combine two TB drugs – isoniazid with rifapentine or rifampicin – are now available. Evidence shows that these are effective treatments to prevent progression to TB disease. These TPT regimens have fewer side-effects and are easier for people to take. It can still be challenging for people with TB infection who do not show symptoms to understand that they need to take a medication to treat the infection.

- Unlike the treatment of TB disease, which lasts 6 months or more, shorter TPT regimens that can be completed in 4 to 12 weeks are now available. All TPT needs to be completed as prescribed in order to be effective.
- It may be challenging for an individual to complete a full course of TPT. There are ways to support people who are taking TPT to finish it by working with community health workers, affected communities, TB survivors, civil society organizations and nongovernmental organizations.
- By keeping adults free from TB, children will be able to avoid being exposed to TB and live healthier lives growing up. At the same time, keeping PLHIV free from TB reduces their suffering and help them live healthier and longer TB-free lives.
- PLHIV who are responding well to ART may still get TB. Their TB infection may go unnoticed and untreated for long, until it is too late. Taking TPT will ensure that PLHIV 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 a higher risk of developing TB in the following years and would benefit from TPT. It is important that when someone within the family has been identified to have a TB disease, family members, including children, should be evaluated and encouraged to take TPT.
- There is a need to create demand by sharing information to communities to access TPT and promote TPT among people who need to be protected from TB infection and disease.
- The PLHIV community, people affected by TB, TB survivors, civil society organizations working with children, and civil society organizations and NGOs working on TB are in a unique position to advocate strongly for TPT. Their role is important for symptom screening of household and community contacts, encouraging and referring people to access TPT, lobbying and advocating with the local and national health ministries for allocation of resources and increasing demand to access TPT in their countries and localities.

How to Protect Ourselves from TB

About TB Preventive Treatment



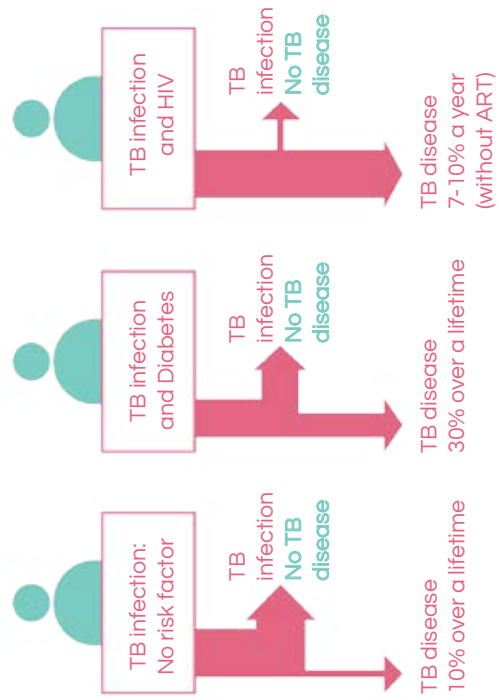
Tuberculosis (TB) is one of the top 10 causes of death globally. It is caused by TB bacteria, passing through air when someone with TB disease talks, coughs or sneezes.

One of two things will happen if the TB bacteria enters a body.

- The bacteria will get killed by the body's immunity before they can cause harm.

OR

- The TB bacteria will be contained by your immune system. A TB infection can become active later in the life of an infected person. This is more likely if your immune system becomes weak.



TB Preventive Treatment (TPT) is one of the most powerful ways to prevent TB disease after exposure to the TB bacteria. Chances of contracting the TB bacteria rise significantly when someone you are in close contact with has TB and your immunity is low. Conditions like HIV infection, diabetes, and silicosis lower immunity. Some drugs prescribed for other diseases can also lower immunity. Treating TB infection even when one is not ill is important and will provide protection, much like fire proofing a house even when there is no fire.

Who needs TB Preventive Treatment?

People living with HIV (PLHIV)	Other at-risk groups
Close contact with TB patients	Patients on dialysis, anti-TNF (tumour necrosis factor) treatment, and patients preparing for an organ or haematological transplant.
Adults, adolescents and children of all ages.	Patients with silicosis should also be systematically tested and treated for latent TB infection.
Children under the age of 5 are specifically vulnerable.	

Target groups for TPT as identified in WHO TPT Guidelines 2020

Diagnosing TB Infection

- Tuberculin skin test (TST) or interferon-gamma release assay (IGRA) can be used to test for TB infection. The availability and affordability of the tests may vary in countries as per national policy. Neither TST nor IGRA can be used to diagnose active TB disease.
- Testing by TST or IGRA is not an essential requirement for initiating TPT in PLHIV or child household contacts under 5 years of age. However, countries are expected to build infrastructure around the provision of these tests.



TB Preventive Treatment (TPT)

There are multiple options and your doctor will be able to choose the best one for you.

3HP

1 Once-weekly isoniazid (INH or H) plus rifapentine (P) for 12 weeks, total 12 doses for adults, adolescents and children above 2 years of age.

1HP

2 A daily dose of isoniazid plus rifapentine for one month for adolescents and children above 12 years of age.

Both these regimens (3HP and 1 HP) can also be given to PLHIV.

3HR

3 Daily rifampicin (R) plus isoniazid for 3 months for adults and children. The regimen can also be given to PLHIV who are on rifampicin-friendly ART regimen. Child-friendly formulations are available in several countries.

6H/9H/36H

4 Either daily isoniazid for 6 months for adults and children, or daily INH for 9 months for adults and children, or daily INH for 36 months for PLHIV in high TB transmission settings.

4R

5 Daily rifampicin for 4 months for adults and children.



While on INH containing regimens, supplementary vitamin B6 may be taken to prevent peripheral neuropathy. Vitamin B6 is required among individuals who have high risk e.g. PLHIV, malnourished individuals and pregnant women.

If B6 is unavailable, vitamin B complex can be an alternative. Unavailability of B6 should not become a barrier in starting TPT, which is at present the case in some countries.

Need for community demand generation

Despite the recognized benefits of TPT, there is a lack of knowledge among community members. Community members need to get the right information and take up a TPT demand generation campaign as a strategy to improve the uptake of TPT. This is important because those infected with TB bacteria and at-risk of developing the disease may feel well and hence may not consider it necessary to take the medicine.

Frequently asked questions from People Living with HIV



I have never been in contact with a person who I know has TB. Do I still need to take preventive treatment?

Yes. PLHIV are at higher risk of progressing rapidly to active TB due to their weak immune status.

I am already on ART, what is my risk of getting TB?

Although regular ART reduces the overall risk of developing TB, the risk of acquiring TB infection remains high even with ART compared with HIV-negative people. Combined use of TPT and ART significantly reduces the risk of TB.

Can I take both ART and TPT together?

Yes. Both ART and TPT can be taken together.



I have already been treated for TB three years back. Do I still need to take preventive treatment?

Yes, because prior treatment of TB disease does not protect you against re-infection with TB.

How long am I protected from TB if I take TPT?

Several studies have shown that TPT reduces the incidence of TB over 7–15 years. TPT saves lives, prevents illness, and averts suffering.

Do I need to take TPT if I am living with HIV and receiving ART, and have a high CD4 cell count?

Yes, all adults and adolescents living with HIV should take TPT as part of a comprehensive package of care for HIV, regardless of their CD4 cell count.

I am a HIV positive injecting drug user on opioid substitution therapy (OST). I haven't started ART. Do I need to take TB preventive treatment?

Yes. People who use drugs (PWUD) have a higher prevalence of TB infection and incidence of TB disease. People taking 3HP with OST should be closely monitored for signs of opiate withdrawal and any other adverse events. Rifampicin is best avoided.

I am a PLHIV who is also infected with hepatitis C. Can I take TPT?

Yes, but this may need some modifications. People with HCV should consult with their health care provider/treating physician.

How can we rule-out active TB in PLHIV prior to TB preventive therapy?

Active TB can be ruled out in adults and adolescents living with HIV by symptom screening for TB. Those who report current cough, fever, weight loss and night sweats should be further

tested for TB. Those with no symptoms should be offered TPT along with their ART.



Should pregnant women living with HIV take TPT?

Yes. Pregnant women living with HIV are at risk for TB, which can have severe consequences for both the woman and the unborn child. Pregnancy should not disqualify pregnant women from receiving TPT, although close monitoring must be done for any side effects.

General Questions

Why should I take pills to treat TB infection when I do not feel ill?
If you have been advised to take TPT it is because your health-care worker or clinician believes you have an increased chance of developing active TB disease. Taking a complete course of TPT can prevent the infection from becoming active disease.

What should I do if I develop adverse drug reactions?
If you are receiving TPT, and develop any symptoms you should immediately contact your health-care provider. The usual symptoms include anorexia (loss of appetite), nausea, vomiting, abdominal discomfort, persistent fatigue or weakness, dark-coloured urine, pale stools or jaundice.

Who should receive testing and treatment for TB infection?
Adults, adolescents, children and infants living with HIV, infants and children < 5 years who are contacts of TB patients, and HIV-negative clinical risk groups, such as person initiating anti-TNF treatment, receiving dialysis, preparing for organ transplantation have the highest likelihood of developing active TB disease and should be prioritized for systematic testing and treatment of TB infection, regardless of the setting.

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Overcoming key barriers to scale up tuberculosis preventive treatment (TPT)

A Call to Action

In 2018, governments at the UN High Level Meeting on Tuberculosis (UNHLM) made bold commitments to end TB.

Foremost among these actions was to scale up tuberculosis (TB) preventive treatment (TPT) rapidly to at least 30 million people by 2022, including 24 million household contacts of TB patients and 6 million people living with HIV (PLHIV). In 2018, countries reported achieving TPT coverage in 1.8 million PLHIV, in about 350,000 contacts < 5 years and in 79,000 older contacts.

Less than three years are now left until the end of 2022. At the current rate of recruitment, the target for TPT in PLHIV should be reached, but the targets for household contacts will not. The current COVID-19 emergency presents an additional challenge for TB programmes worldwide. Nonetheless, this should not stop TB programmes from planning and launching a systematic and invigorated drive to boost contact investigation, TPT and treatment for TB.

Reaching the UNHLM targets requires collective efforts and more investment. A comprehensive strategy that includes TPT is an excellent investment.

To overcome the main barriers standing in the way of global scale-up in TPT, countries, partners, donors and communities should work together to:

- ensure that all TB programmes aiming to end or eliminate TB include TPT as an integral part of a comprehensive strategy
- advocate strongly and communicate widely for TPT scaleup
- strengthen contact investigation in the community and in households of people with active TB especially in the current context of the COVID-19 pandemic
- initiate contacts of all ages on TPT after TB disease is ruled out
- expand TPT in HIV services and in facilities caring for other people eligible for TPT
- develop capacity to test for TB infection and to exclude TB disease
- provide better tolerated and shorter TPT options on a large scale
- ensure adherence and completion of the full course of TPT
- collect data on contact investigation, and the initiation and completion of TPT to monitor programme performance

Overcoming key barriers to scale up tuberculosis preventive treatment (TPT)

A Call to Action

Tuberculosis (TB) preventive treatment (TPT) is an essential intervention towards achieving the goals of the End TB Strategy. Its effectiveness in reducing progression from TB infection to disease ranges from 60% to 90% and protection can last many years. Despite this, global action to expand TPT has been very slow and urgent steps should now be taken to accelerate the programmatic uptake of TPT.

The current COVID-19 emergency will challenge TB prevention and care worldwide, including the roll-out of TPT. Nonetheless, TB programmes should continue to scale up TB services and seek synergies when measures to combat COVID-19 are implemented. People who are confined at home due to COVID-19 may be more exposed to TB in their household, making it more important for contact investigation to target both conditions and to expand massively the TPT coverage among contacts.

This call to action highlights the main considerations that countries need to take when integrating TPT into their TB preventive measures, aligned to other recent guidance on the subject¹. It addresses primarily programme managers and technical agencies helping them to revise their strategies and prepare funding proposals. This call stresses the specific need to strengthen contact investigation, a key activity that is underdeveloped in many countries and where a huge unmet need exists for TB preventive action. This does not diminish the importance of ensuring good coverage among people living with HIV (PLHIV) and others who could benefit from TPT¹.

TPT must be framed as an indispensable component of a comprehensive TB strategy. This is more critical without the prospect of an immunizing vaccine in a near future. National TB strategic plans and funding proposals should include TPT activities, with ambitious targets and proper budgets.

Programmatic considerations for contact investigation and TB preventive treatment

- People who are exposed to active TB are at increased risk for TB infection and disease. TB disease may be as high as 5% or more among household contacts, particularly children. PLHIV exposed to active TB have a higher risk for rapid progression to TB disease. Contact investigation aims to identify these people and evaluate if they need treatment for TB disease or TPT. These activities can arrest the progression of infection and treat disease early on in its course, reducing its severity, lethality and transmission.
- Contact investigation can also identify people exposed to drug-resistant TB. This requires different approaches to TPT and follow up, but they can still benefit from TPT. This is particularly common in eastern European and central Asian countries as well as other settings elsewhere with a high prevalence of resistance to the rifamycins and isoniazid, the mainstay components of TPT regimens in use today.
- TPT for contacts who are also in HIV care may be integrated in differentiated HIV service delivery (DSD) as these are scaled up for ARV services and for intensified TB case finding, particularly in high HIV burden settings. Provision of TPT for PLHIV should not however be delayed until DSD is firmly in place.
- In addition to households, contact investigation and active TB case finding are also important in congregate settings and healthcare facilities.

¹ These include people initiating anti-TNF treatment, or receiving dialysis, or preparing for an organ or haematological transplant, or who have silicosis, as well as prisoners, health care workers, migrants, homeless people and people who use drugs.

- Governments and donors should commit adequate funding and human resources to undertake effective household contact investigation and management by enrolling enough staff, mobilizing communities, providing transport support, providing access to appropriate diagnostics, supplying medication and treatment adherence support and modernizing record keeping and funding operational research into the best models of care to scale up TPT activities.

Testing for TB infection

- Testing for TB infection using tuberculin skin testing (TST) or interferon-gamma release assays (IGRAs) helps direct TPT to people who may benefit most from it and avert unnecessary TPT and related harms. A positive test could also motivate better people to take TPT. However, national programmes currently have limited capacity for testing. Quality-assured TST is in limited supply and IGRAs are more expensive and require blood samples to be taken and transported to well-equipped laboratories.
- Overcoming the infrastructural and supply barriers to the provision of TST/IGRA is desirable and the longer-term goal should be to build the health system capacity needed for this, in terms of human resources, logistics and supply chain and monitoring and evaluation. This will also lay the foundation for the swift roll-out in future of new improved point-of-care tests for TB infection.
- However, in the short term, any unavailability of TST/IGRA should not be a barrier to giving TPT to those groups most at risk of developing TB disease. In children under five years who are in contact with active TB and in PLHIV, TB infection testing is **not** required given the urgency to treat exposure in these sub-populations.
- In addition to testing for TB infection, exclusion of TB disease is important before starting TPT. Chest radiography can play an important role in ruling out TB disease and increase confidence in TPT. Counselling is another important component of people-centred care, to help individuals make an informed choice when offered TPT, based on a clear understanding of the potential benefits and harms of treatment.
- Governments and donors should factor in the human and infrastructural resources necessary to bring testing of TB infection and chest radiography within reach of more people

TB preventive treatment options and support

- The 2020 update of the WHO TPT guidelines recommends multiple treatment options that may be better suited to certain target populations, including children and PLHIV in high or low TB burden settingsⁱⁱ.
- Transition to shorter, better tolerated rifamycin-based TPT regimens, with better prospects for adherence should be one of the goals of programmes.
 - Rifapentine-containing regimens lasting 4 or 12 weeks (3HP and 1HP) are now recommended for many people in need of TPT;
 - These regimens may also be used in children but 3 months of isoniazid-rifampicin (3HR) is currently preferred due to availability of child-friendly dispersible fixed-dose combinations;
 - The triple combination of isoniazid-cotrimoxazole-B6 may be a preferred option for TPT among PLHIV, including pregnant and postpartum women;
 - TPT to protect people exposed to MDR-TB under programmatic settings should also be considered
- While shorter rifamycin-based regimens and other TPT are generally safe, ancillary medicines (e.g. pyridoxine) and tests (e.g. liver function tests) should be available if needed. They are not routinely required and should therefore not be a barrier to the scale-up of TPT.
- Until supplies to optimize TPT with newer regimens are secured countries should not withhold older approaches – like 6 months isoniazid – from adults and children who need it.

- People on TPT should be actively supported to complete their treatment and maximize the benefit of treatment. For this purpose, programmes may organise in-person encounters and use communication technologies for medication adherence support, no different from what is employed to treat active TB.
- Governments and donors should provide for the uninterrupted supply of TPT medicines and promote transition to optimal TPT approaches for both drug-susceptible and drug resistant TB. They should strive for person centred approaches, upholding privacy and protection from stigma.

Monitoring and evaluation of TB preventive treatment

- Monitoring and evaluation (M&E) of programmatic performance should focus on three indicators
 1. Coverage of contact investigation
 2. TPT coverage (initiation)
 3. TPT completion
- M&E activities should be integrated into the existing national Health Management Information Systems. Governments and donors should promote the use of electronic data capture to generate the top indicators for strategic information and to help collect other data useful for individual care, such as patient-level reporting on adverse events while on treatment and any corrective actions put in place.

Key references

- ⁱ <https://www.who.int/activities/preventing-tb/>
- ⁱⁱ https://www.theglobalfund.org/media/6949/core-tbhumanrightsgenderequality_technicalbrief_en.pdf ; https://www.theglobalfund.org/media/4765/core_hiv_infonote_en.pdf
- ⁱⁱⁱ These treatments are available from the Global Drug Facility of the Stop TB Partnership <http://www.stoptb.org/assets/documents/gdf/drugsupply/GDFMedicinesCatalog.pdf>

Annex 2. Coordination mechanisms to support PMTPT

The ministry of health should create and strengthen a joint national coordinating body and/or national technical expert working group to support national scale-up of PMTPT through implementation of the latest global guidelines. Alternatively, the mandate of an existing body that can serve both a management and technical function may be expanded to advise the ministry of health and national TB, HIV and other programmes. This will guide and support the efforts of governments towards fulfilling their national commitments on PMTPT made at the first UN High Level Meeting on TB in 2018. While technical expert inputs may be established at the national level, advice is required for all levels. The administrative bodies should be chaired by the highest administrative heads in the federal and local governments and have equal or reasonable representation of all relevant stakeholders.

Terms of reference

The **joint national coordinating body for implementation of TPT** services should be responsible for the governance, planning, coordination and implementation of PMTPT as well as mobilization of financial resources from the government as well as donors. The coordinating body should put together or identify an existing technical working group to provide advice on technical matters in the scale-up of PMTPT.

The National **technical working group** may be mandated to:

- review emerging national and global evidence, review current national policies and guidelines for PMTPT and lead the process of updating and aligning local guidelines with latest evidence.
- undertake situational assessments to guide policy decisions for PMTPT such as,
 - estimates of burden of TB disease (and TB infection) among different at-risk populations;
 - capacity of the existing health system (staff, skills and equipment) to assess intensity and risk of TB exposure and exclude TB disease;
 - available financial resources and gaps to support nationwide scale-up of TPT services and implications of different approaches for impact and cost (using various regimens, using tests of TB infection);
 - potential to mobilize additional resources as needed; and
 - programme performance and implementation bottlenecks.
- provide scientific underpinnings for PMTPT components of national strategic plans and policy advice to the joint national coordinating body and/or national programmes.
- lead the identification and prioritization of target populations for PMTPT and strategies to reach these populations.
- develop national implementation guidance, standard operating procedures and job-aids (including content for training modules) suitable to the country context.
- develop tools to address the concerns of TPT providers and dispel myths around TPT to promote implementation and national scale-up.

Membership

Joint national coordinating body for implementation of TPT may consist of:

- Programme head in the ministry of health
- Programme heads from other relevant ministries as per country context (such as working on harm reduction, prison or mining health services)
- Members from the federal ministry responsible for public funding

- National TB, HIV and other relevant programme managers (such as from Reproductive, Maternal, Newborn, Child and Adolescent Health services, prison health services)
- Programme heads from key implementing partners in TPT
- Representatives from civil society
- People at risk of or affected by TB
- Country leads from key technical partners and funding agencies.

National technical working group for TPT scale-up may consist of:

- national TB and HIV experts
- stakeholders from national TB, HIV, Reproductive, Maternal, Newborn, Child and Adolescent Health and other relevant programmes
- representatives of clinicians, frontline health providers/nurses and community service providers
- representatives from agencies dealing with drug procurement and regulatory/safety affairs
- representatives from TB and HIV patient groups, civil society, people at risk of or affected by TB
- representatives from national research institutes
- local and/or international technical partners
- WHO country officer.

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

Secretariat: The national TB and HIV programmes may function as the secretariat for both the coordinating body and the technical expert working group and alternate to convene meetings of the groups based on priority issues for discussion. Both programmes should allocate funding for regular convening of these groups.

Annex 3. Costing considerations for programmatic management of TB preventive treatment

When preparing a budget for PMTPT, the following considerations need to be made given that these are major cost determinants:

- **Estimated burden**
 - Populations of each target group (PLHIV, 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
- **Investigation of target populations**
 - Test for TB infection (TST/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)
- **Human resources**
 - Hiring additional personnel/incentives for community workers or volunteers
 - Contact investigation
 - Transport of health care workers to
 - 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
 - Capacity building and support
 - Training for health care workers at different levels
 - Job-aids
- **TB preventive treatment**
 - Costs of medications for the regimens for different at-risk populations
 - Procurement (such as freight, procurement fees, warehousing, repacking)
 - Additional drug costs (such as buffer stock, procurement of supportive medicines like vitamin B6)
 - Adherence support (such as phone calls, SMS, video communication, additional home visits)
- **Demand creation**
 - Advocacy with policy makers and key stakeholders
 - Sensitization of specialists and health care workers
 - Community sensitization of TB survivors, PLHIV networks, and others
 - Counselling of index patient/family counselling
 - Health education material for at-risk populations and their family

- **Monitoring and evaluation**

- Data system(s) to aim for electronic tools for recording and reporting
- Update existing tools or create new ones for TB and/or HIV recording to capture key data elements for programmatic indicators and clinical management (such as adverse events)

Annex 4. Planning checklist for PMTPT

Activity	Current status	Next Steps
National TB Strategic Plan (NSP)		
Planning meeting of key stakeholders as a PMTPT coordinating mechanism		
Funding estimates to implement new guidelines		
National PMTPT indicators agreed		
NSP revision		
Guidelines update		
National technical expert group meeting		
Identification of (priority) risk groups		
Diagnostic algorithm (role of test for TB infection and chest radiography)		
Treatment options (regimens, criteria for choice)		
Dissemination to key stakeholders		
Expansion plan		
Multistakeholder group meeting to support TPT scale-up (TB and HIV programme managers, representatives from other relevant ministries responsible for prisons, migrants, drug users, private or hospital providers)		
Coverage of PLHIV		
Coverage of child household contacts < 5 years of age		
Coverage of household contacts 5 years of age and older		
Coverage of clinical risk groups and other contacts		
Training		
Needs assessment		
Training modules and public education materials (consider eLearning tools)		
Advocacy with key policy makers		
Orientation of physicians, doctors, nurses, health staff and community workers on regimens, treatment, management of adverse events		

Activity	Current status	Next Steps
Community outreach		
Mapping of community-based health facilities/community health workers/volunteers		
Mapping of community-based organizations		
Plan for engagement of community stakeholders in awareness generation and implementation of TB screening, TPT and follow-up		
Monitoring and evaluation		
Update of recording and reporting tools aligned to national TPT indicators		
Electronic tools for data capture 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 PLHIV, child household contacts and other contacts		
Data collected on other clinical risk groups (silicosis, dialysis, anti-TNF treatment, transplant)		
Procurement and Supply Management (PSM)		
Inclusion of rifapentine into the national essential medicines list (EML)		
Registration of rifapentine or importation waiver mechanisms to facilitate supply		
Forecasting needs for medicines and diagnostics		
Placement of orders for medicines and diagnostics		
Packaging and supply		
Stock management		

Annex 5. Answers to frequently asked questions on TST

What is tuberculin skin testing (139)?

Tuberculin skin test (TST), first introduced in 1908, remains the most commonly used test for TB infection in the world due to its low cost and feasibility to implement in low resource settings. There is no need for complex laboratory equipment or procedures or trained technicians, although training is required for proper intradermal administration of the tuberculin purified protein derivative (PPD). Intradermal injection of tuberculin causes delayed hypersensitivity reaction if a person has TB infection. The T-cells in such individuals are sensitized due to prior *M. tuberculosis* infection and the tuberculin causes recruitment of these immune cells to the skin test site, causing a local inflammatory reaction. The reaction reaches its peak after 24–48 hours of injection of the antigen. Nurses and other health care workers with the right training and skills can administer and read a TST. They should also be able to explain to the persons tested what the result of the test implies in their specific case.

How is TST administered?

TST administration should be standardized for each country using either 5 tuberculin units (TU) of purified protein derivative (PPD-S) or 2 TU of tuberculin PPD RT23, which give similar reactions in individuals infected with *M. tuberculosis*. For standardization of readings and interpretation of results, 5 TU of tuberculin PPD RT23 is used more widely.

Tuberculin should be injected strictly intradermally on the inner surface of the forearm. A discrete wheal (6–10 mm) should be produced when the injection is given correctly. If improperly administered, another test dose can be given immediately at a site at least 5 cm (2 inch), away from the original injection. A note in the record should indicate the site chosen for the second test. After the test, it is extremely important to make sure that the individual returns for the test reaction read within 48–72 hours. The person is instructed to keep the test site clean, uncovered and not to scratch or rub the area.

What are the steps in tuberculin skin testing?

1. Preparations and test administration
 - Counsel the person about the test and explain the need to come back within 48–72 hours to read the test result.
 - Ideal injection site is the palmar side of the left forearm, 5–10 cm from the elbow joint, free from muscle margins, hair, veins, tattoos, sores or scars. The area should be cleaned with soap and water, if visibly dirty. Other sites can also be used (such as the right forearm, both sides of chest and back) if there is injury, wound, big scars, bandage, surgical casts and complete tattoo of left forearm or amputation.
 - Tuberculin vials are multidose vials (10 doses or 50 doses). The vials should be stored at 2–8°C and not exposed to direct sunlight. The vial can be used up to one month after opening and should be discarded if the fluid colour changes or after 30 days.
 - Use 1 ml graduated syringe/tuberculin syringe which can dispense 0.1 ml solution accurately using a one quarter to one half inch, 27-gauge needle. Draw 0.1 ml (5 Units) of tuberculin or as per manufacturer instructions, expel air and excess drops.
 - Tuberculin should be injected within 20 minutes of loading into the syringe.
 - After gentle cleaning of the site with an alcohol swab, stretch the selected area of the skin using the thumb and forefinger, insert the needle slowly with the bevel pointing upwards at an angle of 5 to 15 degrees, advance the needle through the epidermis approximately 3 mm so that

the entire bevel is covered and visible just under the skin. Release the stretched skin and slowly inject tuberculin and check for leakage. If there is no leakage, continue to inject slowly until the complete 0.1 ml solution has been administered and remove the needle quickly. Gently blot the injection site if a drop of blood appears with alcohol-based disinfectant without squeezing out tuberculin.

- Proper injection will result in a pale wheal 6–10 mm in diameter. If the wheal is less than 6 mm in diameter the test needs to be repeated.

2. Reading TST reaction

- The test should be read between 48–72 hours (NOT before 48 hours or after 72 hours).
- Reading should be performed in a good light, with the forearm slightly flexed at the elbow. Gauge presence of induration (palpable, raised, hardened area or swelling), starting with inspection and then palpation with light, gentle motions. Sweep fingertips over the surface of forearm in all four directions to locate margins or edges of induration. Using the fingertip as a guide, mark the widest edges of the induration across the forearm lightly with a fine line or dot. If the margins of induration are irregular, mark and measure the longest diameter.
- The diameter of induration is measured across the forearm, from the thumb side of the arm to the little finger side. Using a plastic scale, place the zero-ruler line inside the edge of marked fine line or dot and measure the ruler line inside the right dot or edge of fine line. If the measurement falls between two divisions on the millimetre scale, record the lower division.
- Do not measure the redness or bruise.
- Alternatively, use the ballpoint pen method for reading (140). A ball point pen line may be drawn on the transverse axis of the forearm, starting 1–2 cm away from the visible skin test reaction and moving slowly towards its centre, exerting moderate pressure against the skin. The point where resistance to pen displacement occurs determines the outer limit of the induration. Mark lightly with a fine line or dot at the widest edges of the induration across the forearm and use a ruler to measure the diameter as above.

3. Recording variables

- Note exact location of TST administration.
- If there is no induration, record as “Zero”. Otherwise, record the exact size of the induration in millimetres. Do not record as positive or negative.
- Record adverse events at the test site if any, such as formation of vesicles, bullae, lymphangitis, ulceration or necrosis.

How are TST reactions interpreted?

TST does not measure immunity to TB but the degree of hypersensitivity to tuberculin. A skin test result is interpreted considering the person’s risk of being infected with TB and progression to disease when infected as well as size of the induration in millimetres. However, there is no correlation between the size of induration and likelihood of current TB disease (poor positive predictive value) or future risk of developing TB disease (141). There is no correlation between the size of TST reactions post-BCG vaccination and protection against TB disease. Overall, results of TST must be interpreted carefully considering individual clinical risk factors before determining the size of the induration that is positive (5 mm, 10 mm or 15 mm). Formation of vesicles, bullae, lymphangitis, ulceration and necrosis at the test site should also be noted as they may indicate a high degree of tuberculin sensitivity and hence the presence of TB infection (142).

A negative test may indicate lack of infection with *M. tuberculosis* or that the person has acquired infection recently and not enough time has elapsed for the body to react to the skin test. From the time of infection to the development of cell-mediated immunity there is a window period of up to 12 weeks, when TST would be negative. Most children with a negative result may not be infected with *M. tuberculosis*. Immunologically compromised individuals, especially those with HIV and low CD4 T-cell counts or severe malnutrition, frequently show negative results from the PPD test. The

absence of cell-mediated immunity to tuberculin may be due to lack of previous sensitization or due to anergy because of immune suppression. The following table classifies conditions where different induration sizes are considered to indicate TB infection.

Induration of 5 mm or more is considered positive among	Induration of 10 mm or more is considered positive among	An induration of 15 mm or more is considered positive among
<ul style="list-style-type: none"> • HIV-infected persons • severely malnourished children • a recent contact of a person with TB disease • people with fibrotic changes on chest radiograph consistent with prior TB • organ transplant recipients and other immunosuppressed individuals who are on cytotoxic immune-suppressive agents such as cyclophosphamide or methotrexate • people who are immunosuppressed for other reasons (such as taking the equivalent of > 15 mg/day of prednisone for one month or longer, taking TNF-α antagonists) 	<ul style="list-style-type: none"> • recent immigrants (within five years) from high-prevalence countries • injection drug users • residents and employees of high-risk congregate settings (such as prisons, nursing homes, hospitals and health facilities, homeless shelters) • mycobacteriology laboratory personnel • persons with clinical conditions that place them at high risk (such as diabetes, prolonged corticosteroid therapy, leukemia, end-stage renal disease, chronic malabsorption syndromes, low body weight) • children below 5 years of age, or children and adolescents exposed to adults in high-risk categories 	<ul style="list-style-type: none"> • Persons with no known risk factors for TB. Reactions larger than 15 mm are unlikely to be due to previous BCG vaccination or exposure to environmental mycobacteria

What are false-positive reactions?

Some persons may react to TST even though they are not infected with *M. tuberculosis*. The causes may include

- Infection with non-tuberculosis mycobacteria
- Previous BCG vaccination (prior vaccination may cause false-positive result for many years) (143)
- Low risk of TB exposure (due to low specificity of TST, most positive reactions in low-risk individuals should be considered false-positives) (144)
- Errors in TST administration or interpretation of reaction.

What are false-negative reactions?

A negative TST result usually signifies that the individual has never been exposed to *M. tuberculosis*. However, the following factors may cause a false-negative result or diminished ability to respond to tuberculin.

- Cutaneous anergy (i.e. inability to react due to weakened immune system or immune suppressive medication)
- Recent TB infection (within 12 weeks of exposure) or very old TB infection (many years)
- All children below five years of age; the younger the child, the higher the probability
- Recent live-virus vaccination (measles and smallpox) or viral illnesses (measles and chicken pox)
- Overwhelming TB disease (miliary TB, TB meningitis)
- Error in TST administration (subcutaneous injection, insufficient dose) or interpretation of reaction.

What are the adverse reactions of TST?

- **Within 12 hours:** fever, injection site pain, pruritus, discomfort, erythema, rash.
- **Up to 3 days** of TST: injection site haemorrhage or haematoma, vesicles, ulcers and necrosis (highly sensitive individuals). Injection site scar may also occur due to strongly positive reactions.

Who can receive a TST?

Most persons can receive a TST. It is contraindicated only for persons who have had a severe reaction (such as necrosis, blistering, anaphylactic shock or ulcerations) to previous TST. It is not contraindicated even among infants, children, pregnant women, persons who are HIV-infected, or persons who have been vaccinated with BCG.

How often can TSTs be repeated?

In general, there is no risk associated with repeated TST placements. If a person does not return within 48–72 hours for a TST reading, a second test can be placed as soon as possible.

When is TST contraindicated?

- Known hypersensitivity to any of the contents of TST
- Severe reactions to previous tuberculin tests
- Situations where repeat test will not provide any new information (such as past TST reactions ≥ 15 mm, diagnosed TB disease or known previous TB disease)
- Infants under 12 weeks old.

What is a boosted reaction?

When sensitization to mycobacteria has occurred many years earlier, an initial TST may produce negative or weakly positive response, there being too few sensitized lymphocytes in the circulation to produce a significant local response. If the test however is repeated, a larger reading may be obtained due to the immune response being 'recalled' or 'boosted' by the first test. Administering such a second TST after an initial negative reaction is called two-step testing. The second boosted reading is considered for decision-making or future comparison. Boosting is maximum within one to five weeks of the initial test and may continue for up to two years (145).

Why is two-step testing conducted?

Two-step testing is useful for initial skin testing among adults who are going to be retested periodically, such as health care workers. This two-step approach can reduce the likelihood that a boosted reaction to a subsequent TST will be misinterpreted as a recent infection (considered in low TB burden settings).

What is TST conversion?

While boosting is recall of hypersensitivity response in the absence of new infection, conversion is the development of new or enhanced hypersensitivity due to infection with tuberculous or non-tuberculous mycobacteria, including BCG vaccination. A change in TST reactivity within two years of a negative test (146) is called conversion, negative to a positive reaction and increased induration ≥ 10 mm compared to the previous reading.

Conversion has been associated with an annual TB incidence of 4% among adolescents (147) and up to 6% among contacts of smear-positive TB patients (148). If it is decided to retest a contact for conversion, the second tuberculin test should be done after eight weeks of last contact with the source patient.

What is TST reversion?

TST reversion is defined as change of TST result from positive to negative. This is uncommon among healthy individuals however it is noted among the elderly during two-step testing.

Can TST be given to persons receiving vaccinations?

Vaccination with live viruses may interfere with TST reactions. For persons scheduled to receive a TST, testing should be done:

- either on the same day as the vaccination with live-virus vaccine, or
- 4–6 weeks after the administration of the live-virus vaccine (such as for pertussis, measles, rubella, polio, yellow fever).

How does BCG vaccination affect TST results?

BCG vaccination may give false-positive result among children. When BCG is given at birth, as done in most parts of the world, it has a variable, limited impact on TST. History of BCG vaccination however has limited effect on interpretation of TST results later in life.

Annex 6. Answers to frequently asked questions on IGRAs

What are IGRAs?

Interferon gamma release assays (IGRAs) are whole-blood tests that can aid in diagnosing *M. tuberculosis* infection (43). Like TST, IGRAs cannot differentiate between TB infection and TB disease. WHO reviewed available evidence around the two most widely used IGRAs in 2017, QuantiFERON®-TB Gold In-Tube test (QFT-GIT) and T-SPOT.TB test (T-Spot), to facilitate recommendation on their use to identify individuals having TB infection.

How do IGRAs work?

White blood cells from individuals infected with *M. tuberculosis* release interferon-gamma (IFN-g) when mixed with antigens derived from *M. tuberculosis*. Recognition that interferon gamma plays a critical role in regulating cell-mediated immune responses to *M. tuberculosis* infection led to development of IGRAs (149–151). IGRAs detect sensitization to *M. tuberculosis* by measuring IFN-g release in response to antigens representing *M. tuberculosis*. IGRAs assess response to synthetic overlapping peptides that represent specific *M. tuberculosis* proteins, such as early secretory antigenic target-6 (ESAT-6) and culture filtrate protein 10 (CFP-10). These proteins are present in all *M. tuberculosis* complex species and stimulate measurable release of IFN-g in most infected persons but are absent from BCG vaccine strains and from most nontuberculous mycobacteria. For IGRAs to measure IFN-g response accurately, a fresh blood specimen that contains viable white blood cells is needed.

QFT-GIT¹³: In QFT-GIT the control materials and antigens are contained in special tubes used to collect blood for the test, thus allowing more direct testing of fresh blood. One of the tubes contain heparin and the test antigens (single mixture of 14 peptides representing the entire amino acid sequences of ESAT-6 and CFP-10 and part of the sequence of TB7.7), while two accompanying tubes serve as negative and positive controls. The negative/control tube contains heparin alone, and the positive-control tube contains heparin, dextrose and phytohaemagglutinin. Blood (1 ml) is collected into each of the three tubes, mixed with the reagents already in the tubes and incubated for 16 to 24 hours. Plasma is separated, and the IFN-g concentration in the plasma is determined using a sensitive ELISA. To interpret QFT-GIT, the response is calculated as *difference in IFN-g concentration in plasma from blood stimulated with antigen* (i.e. the single cocktail of peptides representing ESAT-6, CFP-10 and TB7.7) *minus the IFN-g concentration in plasma from blood incubated without antigen* (i.e. nil).

T-SPOT: Peripheral blood mononuclear cells (PBMCs) are incubated with control materials and two mixtures of peptides, one representing overlapping sequences of the entire amino acid sequence of ESAT-6 and the other representing the entire amino acid sequence of CFP-10. It identifies *M. tuberculosis* sensitized effector TB cells, activated by the presence of CFP 10 and ESAT-6 antigens. Effector T cells have a short life cycle; however, their continuing presence indicates that the individual's immune response is currently encountering and fighting a pathogen somewhere in the body. Measuring the presence of effector T cells in a blood specimen therefore indicates ongoing TB infection. The blood specimen is centrifuged, and the sample is diluted to ensure that a standard number of PBMCs get added to each of the four test wells (nil control, panel with CFP 10 antigen, panel with ESAT-6 antigen and positive control), which are precoated with antibodies to IFN-g and incubated for 16–20 hours. In the presence of activated effector T cells (infected individuals), the TB specific antigens, ESAT-6 and CFP 10, stimulate the release of IFN-g which binds the antibodies to IFN-g on the base of the well. Wells are washed and a secondary antibody to IFN-g is added. Following another incubation

and washing step, the substrate is added. This produces spots on the well floor, where the IFN-g was secreted by T Cells. The spots are enumerated in each of the test wells to provide the test results and the difference between antigen panels and nil is compared. Reading is performed manually or by an Elispot reader.

Currently available IGRAs

	QFT-GIT	T-Spot
Initial processing	Process whole blood within 16 hours	Process PBMCs within 8 hours, or if T-Cell Xtend® is used, within 30 hours
<i>Mycobacterium tuberculosis</i> antigens	Single mixture of synthetic peptides representing ESAT-6 and CFP-10	Separate mixtures of synthetic peptides representing ESAT-6 and CFP-10
Measurement	IFN-g concentration	Number of IFN-g producing cells (spots)
Interpretation criteria	TB responses 25–50% of nil are interpreted as positive, < 25% of nil is negative	Results are interpreted by subtracting the spot count in the negative (nil) control from the spot count in panels A and B: positive > 8 spots, negative < 4 spots, borderline 5, 6 or 7 spots and invalid
Possible results	Positive, negative, indeterminate	Positive, negative, borderline, invalid

What are the advantages of IGRAs?

- Requires a single visit to conduct the test. But results can be available only within 24 hours which requires a second visit.
- Prior BCG vaccination does not cause a false-positive IGRA test result.
- 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 compared with TSTs. Two-step testing is not required for IGRAs, because IGRA testing does not boost subsequent test results.
- American Academy of Paediatrics revised its guideline to include use of IGRA down to children two years of age, suggesting use of IGRA in children two years and older (152).

What are the disadvantages and limitations of IGRAs?

- Blood samples must be processed within 8–30 hours after collection while white blood cells are still viable.
- Errors in collection or transportation of blood specimens or running the test can decrease accuracy.
- Tests are expensive.
- A greater risk of test conversion due to **false-positive** IGRA results with follow-up testing of **low-risk health care workers** who have tested negative at prior screening. An IGRA conversion is defined as a change from negative to positive within two years. Association between IGRA conversion and subsequent disease risk has not been demonstrated.
- Limited data on the use of IGRAs to predict who will progress to TB disease in the future.
- Limited data on the use of IGRAs for children younger than two years of age (higher risk of indeterminate results), persons recently exposed to *M. tuberculosis*, immunocompromised persons, and serial testing.

What are the steps in conducting an IGRA test?

- IGRAs should be performed and interpreted according to established protocols.

- Arrangement for IGRA testing should be made prior to blood collection to ensure that the blood specimen is collected in the proper tubes.
- Draw a blood sample from the person according to the test manufacturer's instructions.
- IGRAs should be performed and interpreted according to established national protocol.
- Arrange for delivery of the blood sample to the laboratory in the time the laboratory specifies to ensure testing of samples while the blood cells are still viable.
- Schedule a follow-up appointment for the person to receive test results.
- Based on test results, provide follow-up evaluation and treatment as needed.

Nurses and other health care workers who have been trained in phlebotomy can request an IGRA and deliver the result to the person tested, explaining its significance.

How to interpret IGRA test results?

IGRA interpretations are based on the amount of IFN-g released or on the number of cells that release IFN-g. Both the standard qualitative test interpretation (positive, negative, or indeterminate) and the quantitative assay measurements (nil, TB and mitogen concentrations or spot counts) should be reported. This will permit a more refined assessment of results and promote better understanding of the test result. Like TSTs, IGRAs should be used as an aid in diagnosing *M. tuberculosis* infection. A positive test result suggests that *M. tuberculosis* infection is likely, and a negative result means that infection is unlikely. An indeterminate result indicates uncertain likelihood of *M. tuberculosis* infection. A borderline test result (T-Spot only) also indicates an uncertain likelihood of *M. tuberculosis* infection.

For healthy persons with a low likelihood both of TB infection and progression to TB disease, a single positive IGRA or TST result should not be taken as reliable evidence of *M. tuberculosis* infection. Because of the low probability of infection, a false-positive result is more likely. In such situations, the likelihood of *M. tuberculosis* infection and of disease progression should be reassessed, and the initial test results should be confirmed. Repeat testing, with either the initial test or a different test, may be considered on a case-by-case basis or alternatively assume that the initial result is a false-positive, without additional testing.

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Preventive treatment for tuberculosis



TB preventive treatment 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 active TB 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 TB infection, most of whom are well.

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



The chance of getting active TB disease is higher if you:

- live in the same household or are in close contact with a TB patient
- are living with HIV

Other high-risk groups include 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 active TB disease before assessing if you need TB preventive treatment.



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

What are the treatment options?

Today, there are many preventive treatment 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!

