National Guideline on Latent Tuberculosis Infection (LTBI) Management

NATIONAL PROGRAMME FOR TUBERCULOSIS CONTROL AND CHEST DISEASES

&

SRI LANKA COLLEGE OF PULMONOLOGISTS

EDITORIAL BOARD

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MESSAGE FROM DIRECTOR GENERAL OF HEALTH SERVICES

At the integral transition from the 2015 Millennium Development Goal (MDGs) to the Sustainable Development Goal (SDGs) for 2030 the WHO launched a novel and all-inclusive strategy accelerating the fight against TB, the *End TB Strategy* with a vision of " a world free of TB" signifying zero deaths, disease and suffering due to the disease.

Sri Lanka having adopted the above strategy is committed to achieving its targets in bringing about a drastic reduction in TB incidence, TB related deaths and catastrophic expenditures incurred by affected families.

TB places its heaviest burden on the world's most poor and vulnerable, further widening existing inequalities. Given the enormous social and economic burden imposed by TB not only to the individual, his/her family but also to the community and country at large, hastening concerted efforts towards ending the TB epidemic cannot be overemphasized.

The End TB Strategy emphasizes the need for early identification and treatment of latent tuberculosis infection (LTBI) which would invariably contribute to the reduction in TB incidence with subsequent decline in suffering and death.

Apprehending the importance of accelerating the End TB Strategy in substantial reduction of economic and social cost due to TB, I firmly believe the LTBI guideline would serve as a valuable and effective guide to all relevant stakeholders for programmatic management of LTBI that would contribute to end TB in Sri Lanka by 2035.

My earnest appreciation to all authors and stakeholders for their invaluable contribution.

Dr. Asela Gunawardana

Director General of Health Services

Ministry of Health

MESSAGE FROM THE DIRECTOR - NPTCCD

Tuberculosis is a communicable disease which has been with us for many millennia, and yet we have failed to eliminate. It is one of the top 10 causes of death worldwide. Therefore, it remains a major public health problem globally, despite of being preventive and curative.

The Latent Tuberculosis Infection (LTBI) is called when the *Mycobacterium Tuberculosis*, the causative agent of TB, remains persistent to the host immune response, without any clinical manifestations. It has been estimated that one fourth of the global population is having LTBI, with a 5-10% of them with risk of developing the TB disease over their lifetime. According to the WHO estimates, Sri Lanka has 4000- 5000 TB cases undetected per year. Thus, stringent strategies should be adopted to ensure successful control of TB in the country, including detection & treatment of LTBI.

The National Programme for Tuberculosis Control and Chest Diseases (NPTCCD) has pledged to achieve END TB targets, by 2035. It is well evident that it would not be possible to achieve this target by only focusing on treating TB patients alone. Therefore, considering the current country scenario, more focus should be given to preventive TB treatment as well. The new National Strategic Plan 2021-2025 has included it as the first objective indicating its grave importance. Thus, this LTBI guideline was developed as a collaborative effort of NPTCCD and the Sri Lanka College of Pulmonologists to strenghthen the Active Case Finding among high risk groups.

I hope this guideline would be a milestone in the pathway of elimination of TB in Sri Lanka. I would like to acknowledge the support provided the writing panel and other stakeholders who contributed in numerous ways, making this tedious task a success.

Dr. H D B Herath

Director – NPTCCD

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ABBREVIATIONS

ACSM	Advocacy Communication and Social Mobilization
ADRS	Adverse Drug Reaction Surveillance
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine aminotransferase
ART	Antiretroviral treatment
AST	Aspartate aminotransferase
ATT	Anti-TB treatment
BCG	Bacilli Calmette-Guérin
CBO	Community-based organization
CKD	Chronic Kidney Diseases
CKDU	Chronic Kidney Disease of Unknown Origin
CT	Computed Tomography
CXR	Chest Radiography
DCC	District Chest Clinics
DOT	Directly Observed Treatment
DTCO	District Tuberculosis Control Officer
FDA	Food and Drug Administration
GDG	Guideline Development Group
HCW	Health Care Workers
HIV	Human Immunodeficiency Virus
HP	Isoniazid and Rifapentine
HR	Isoniazid and Rifampicin
HSCT	Haematopoietic Stem Cell Transplantation
IFN-g	Interferon gamma
IGRA	interferon gamma-release assay
INH	Isoniazid
LTBI	Latent TB Infection
MDR-TB	Multi drug-resistant TB
MoH	Ministry of Health
MTB	Mycobacterium tuberculosis
NCD	Non-Communicable Diseases
NGO	Non-Governmental Organizations
NPTCCD	National Programme for Tuberculosis Control and Chest Diseases
PBMC	Peripheral Blood Mononuclear Cells
PLHIV	People Living with HIV
PPD	Purified Protein Derivative

PTB	Pulmonary tuberculosis
QFT-GIT	QuantiFERON®-TB gold in-tube test
RCT	Randomized Control Trial
RIF	Rifampicin
RPT	Rifapentine
SEA Region	South-East Asia Region
SOT	Solid Organ Transplantation
TB	Tuberculosis
TNF	Tumour Necrosis Factor
TOT	Training of Trainers
TPT	TB Preventive Treatment
T-spot	T-SPOT®.TB test
TST	Tuberculin Skin Test
WHO	World Health Organization
ACSM	Advocacy Communication and Social Mobilization
ADRS	Adverse Drug Reaction Surveillance
AIDS	Acquired Immunodeficiency Syndrome
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TPT	TB Preventive Treatment
T-spot	T-SPOT®.TB test
TST	Tuberculin Skin Test

KEY DEFINITIONS

Adolescent	A person 10–19 years of age.
Adult	A person older than 19 years of age unless national law defines a person as being an adult at an earlier age.
Bacteriologically confirmed TB	TB is diagnosed in a biological specimen by smear microscopy, culture or a WHO-approved molecular test such as Xpert MTB/RIF.
Child	A person under 10 years of age.
Clinically diagnosed TB	A patient who does not fulfill the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician and after consultation with a Consultant Respiratory Physician and decided to treat the patient with a full course of TB treatment.
Close contact	Any person who repeatedly and regularly shares the living space with a person having infectious TB. (it has further subclasses; household contacts or non-household contacts as mentioned below).
Contact investigation	A systematic process for identifying previously undiagnosed cases of TB among the contacts of an index case. In some settings, the goal includes testing for latent TB infection (LTBI) to identify candidates for preventive treatment. Contact investigation consists of identification, prioritization and clinical evaluation.
Household contact	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 3 months prior to commencement of treatment.
Index case (index patient) with TB	The initially identified case of new or recurrent TB in a person of any age, in a specific household or other comparable setting in which others may have been exposed. An index case is the patient on whom a contact investigation is centered, but who is not necessarily the source case.
Infant	A child under 1 year of age.
Latent tuberculosis infection	A state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens with no clinical manifestations of active TB. There is no gold standard test for direct identification of M. tuberculosis infection in

	humans. The majority of infected people have no signs or symptoms of TB but are at risk for developing active TB disease.
Low TB-incidence country	A country with a WHO-estimated TB incidence rate of <100/100 000 population.
Non household close contact	A person who is not in the household but shared an enclosed space, such as a social gathering place, workplace or facility, for an extended period during the day with the index case during the 3 months before commencement of the current treatment episode.
Preventive treatment	Treatment offered to individuals who are infected with TB bacillus and considered to be at risk for TB disease, in order to reduce that risk. Also referred to as LTBI treatment or preventive therapy.
Source Case	A person with TB disease who is responsible for transmitting M. tuberculosis to another person or persons.
Tuberculosis	The disease state due to M. tuberculosis. In this document, it is commonly referred to as “active” TB or TB “disease” to distinguish it from LTBI.
Xpert-MTB/RIF	WHO-recommended, rapid, automated, nucleic acid amplification assay that is used widely for simultaneous detection of Mycobacterium tuberculosis complex and rifampicin resistance in specimens.

EXECUTIVE SUMMARY

Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of clinically manifested active tuberculosis (TB). Sri Lanka, being a country with low TB incidence (<100/100,000 population), has pledged to achieve the End TB targets by the year 2035. The World Health Organization's (WHO) End TB Strategy requires diagnosis and treatment of LTBI at a wider scale along with concerted efforts of management of all forms of active TB diseases to accelerate the decline in TB incidence. Such a combined package of curative and preventive treatment of TB is cost-effective in decreasing the rate of TB incidence, in averting disability-adjusted life years (DALYs) and saving lives.

World Health Organization updated the guidelines for programmatic management of LTBI in 2018 to assist Member States in strengthening their capacities and systems to streamline LTBI screening and treatment. This updated version provides a comprehensive set of recommendations for programmatic management of LTBI and is the basis and rationale for national guidelines. Based on these recommendations, the Guideline Development Group (GDG) of Sri Lanka has developed guidelines on programmatic management of LTBI for Sri Lanka considering the local epidemiology of at-risk groups, human and financial resources to ensure sustainable implementation, feasibility of monitoring and evaluation and many other factors.

The recommendations are presented logically according to the cascade of care for managing LTBI: identification of populations at-risk (adults and children living with HIV, HIV-negative adult and child close contacts and other HIV negative at-risk groups), algorithms including ruling out of active TB disease, testing for LTBI, clinical management and programmatic management.

IDENTIFICATION OF POPULATIONS AT-RISK FOR TESTING AND TREATMENT OF LATENT TUBERCULOSIS INFECTION

People living with HIV (PLHIV)such as adults and adolescents, including those who have previously been treated for TB will be considered for TB preventive therapy. Infants aged < 12 months only if they are in contact with a case of PTB, children aged ≥12months but under 5 years of age irrespective of their contact history of TB will be given TPT. Children> 5 years, adolescents and adults with HIV will tested for LTBI and if positive (or determined by a consultative team if it is negative) will be given TPT after excluding active TB disease.

HIV-negative close contacts of a person with pulmonary TB (both bacteriologically confirmed and clinically diagnosed): Infants and children under 5 years of age who are household contacts of a patient with PTB subjected to treatment after excluding active TB disease. Children who are non-household close contacts of patients with PTB a risk assessment will done by a consultative team to determine whether a child should receive TPT and based on the risk assessment TPT will be given to the child whenever indicated. Children

above 5 years of age, adolescents and adults who are household contacts of a patient with pulmonary TB will be tested for LTBI and if positive will be treated for LTBI after excluding the active TB disease while non-household close contacts will be tested and treated after risk assessment. For contacts of patients with multidrug-resistant tuberculosis (MDR), preventive treatment may be considered based on individualized risk assessment and sound clinical justification.

HIV-negative at-risk groups will be subjected for testing and treatment for LTBI after excluding active TB disease. The **clinical risk group** consists of patients initiating anti-TNF alpha treatment, receiving dialysis, preparing for Solid Organ Transplant (SOT) or Hematopoietic Stem Cell Transplantation (HSCT) and patients with silicosis. An additional group will be selected based on **social vulnerability** such as prisoners and drug addicts and based on **occupational vulnerability** such as Health Care Workers (HCW**).** However, the scaling up of LTBI testing for these groups will be carried out based on programmatic factors and the assurance of treatment completion (e.g., prisoners).

SCREENING FOR LATENT TB INFECTION AND RULING OUT ACTIVE TB DISEASE IN THE IDENTIFIED AT-RISK POPULATIONS

Prior to LTBI testing, at risk individuals should be subjected to active TB screening according to the algorithm specified for the respective risk group. The algorithm commenced by evaluating symptom criteria together with radiological evidence and will proceed in to more advance diagnostic testing to rule out active TB disease for suspected individuals. The GDG decided to use symptom checklist and Chest Xray (CXR) as the initial screening too. Except children <5years, all other individuals who are close contacts of pulmonary TB patients will be tested for LTBI.

TESTING FOR LATENT TB INFECTION

In majority of risk groups, TST will be used alone to diagnose LTBI but in specific clinical risk groups, both TST and IGRAs will be used. This decision was based on the facts that the LTBI diagnosis does not have a gold standard test, both TST and IGRAs require competent immune response to react and the advantages and disadvantages of the two tests are mostly similar but are different in certain clinical risk groups.

CLINICAL MANAGEMENT OF LATENT TB INFECTION

Under the clinical management of LTBI, the GDG focussed mainly on treatment options, adverse events & monitoring of adverse events and strategies to ensure adherence and completion of treatment. Considering all treatment options, the WHO recommends, the group decided to prioritize 3 options as TB Preventive Treatment (TPT) for Sri Lanka to maintain the uniformity and to minimise complications. The treatment options thus prioritized were 6H (isoniazid daily monotherapy for 6 months), 3HR (isoniazid and rifampicin daily for 3 months), and 3HP (once a week treatment with isoniazid and rifapentine for 3 months).

However, each risk group will be offered the best possible treatment regime considering the clinical and epidemiological background, and acceptability and continuity of treatment.

PROGRAMMATIC MANAGEMENT, MONITORING AND EVALUATION

Effective rolling out of LTBI plan considerably depends on the programmatic management. Therefore, for the smooth implementation of LTBI scale up programme, the GDG emphasized on advocacy and communication, provision of dedicated resources for programme implementation, capacity building, uninterrupted supply of quality drugs, and programme monitoring and evaluation.

1. BACKGROUND AND RATIONALE

1.1. Background

Worldwide, tuberculosis (TB) is one of the top 10 causes of death and the leading cause of death due to a single infectious agent ranking above HIV/AIDS. It was estimated that around 10.0 million people developed TB disease and 1.5 million died of TB in 2018. This included an estimate of 1.1 million childhood tuberculosis and 230 000 child deaths. Further, The South-East Asia Region (SEAR) which is the home to one fourth of the world's population; accounts for nearly half of the global burden in terms of new TB cases appearing each year (1).

Although many public health strategies were implemented to combat TB disease, it still remains a major public health problem in many parts of the world, especially among low- and middle-income countries. Sri Lanka, being a country with low TB incidence (WHO estimated TB incidence <100/100,000 population) has been facing the same challenges despite many initiatives. In Sri Lanka, TB case finding has become stagnant between 8000 to 9000 cases per year over a decade. This has led to a gap of nearly 4000 cases compared to WHO estimates for Sri Lanka with a noticeable widening since the year 2011 (2).

TB develops in only 10% of humans who are infected with *M. tuberculosis*. However, active TB disease generally develops within 1–2 years of *M. tuberculosis* infection in 5% of those infected, and at any other time in the remaining 5% (3). Latent TB infection (LTBI) is the state in which humans are infected with *M. tuberculosis* without any clinical symptoms, radiological abnormality, or microbiological evidence (4). One-third of the world's population is infected with TB, and the prevalence rate of LTBI in low- or middle-income countries is estimated to be as high as 51.5%of the population (5-7).

Sri Lanka has committed to achieve the End TB targets with a goal to reduce the incidence of TB<10/100,000 by the year of 2035 (8). The main focus of the End TB plan of the National TB programme is to achieve this case gap through intermediate targets for each year by focusing on increasing case finding. Hence, the programme has to follow an accelerated pathway to increase the case detection which in turn will reduce the active transmission of the disease leading to low TB incidence. Global- and regional-level scientific evidence clearly indicate that the required rate of decline in TB incidence can be achieved only if the treatment of active TB disease is combined with the treatment of TB infection (preventive treatment) and therefore, treatment of LTBI has been emphasized in the WHO End TB strategy as a critical component (9).

When considering the dual challenges that Sri Lanka faces to reach the End TB targets within the-time frame, the country has to apply multipronged approaches towards accelerated case finding and prevention of emergence of new cases. Therefore, if we fail to address LTBI as a country it would impose a considerable challenge to achieve End TB targets.

1.2. Rationale

Proper treatment of latent TB can reduce the risk of developing active TB by 60-90%. Preventive treatment is not only a standard of care, but a cost-effective intervention that will also reduce TB-related mortality and avert disability adjusted life years (DALYs), thus contributing to socioeconomic development of the individual as well as the country (9).

Although there is no research evidence on the prevalence of TB infection, Sri Lanka annually reports an average of 8000 to 9000 active TB cases. An infected individual has a potential to get the active TB disease in their lifetime, which is especially higher in the first 5 years of acquiring the infection (10). Based on the pattern of transmissions of the disease, screening of close contacts is the mainstay of detecting TB early, especially pediatric TB. Currently, the contacts screening at the time of diagnosis of the index case is being implemented island wide. However, subsequent screening at six-month interval up to two years, is not being implemented in a uniform manner in all the districts, despite many patients who had a contact history of TB are subsequently being diagnosed with active TB disease (11). Therefore, prevention of active disease among contacts by treating them for TB infection outweigh the socio-economic cost of diagnosing and treating the contacts once they develop active disease.

Comorbid conditions such as malnutrition, HIV, diabetes, silicosis and lifestyle factors such as problematic alcohol use and smoking contribute to increase risk of conversion of TB infection to active TB disease. TB is the most frequent cause of AIDS-related deaths worldwide, despite improvements in access to ART. TB caused about 250 000 deaths among people living with HIV in the world in 2018, representing one third of all HIV deaths (1). Global data in 2016 indicated that people living with HIV were 19 times (95% confidence interval [95% CI] 16; 27) more likely to develop active TB than those without HIV infection (12). Hence, treatment of latent TB infection in PLHIV would alleviate significant consequences of TB-HIV co-infection. In Sri Lanka, TB prevalence among PLHIV is 12% (13)

Current demographic transition as well as epidemiological transition of diseases has led to a rise in elderly population who are more vulnerable to develop age-related chronic diseases. Also, a rise in the population with immunosuppression due to diseases or treatment leads to higher rates of TB among older age groups. The share of elderly population over 60 years old in 2012 was 12.4% and is expected to further rise in the future (14). About 45% of people aged 60 years or over population have non-communicable diseases which increases the risk of developing active TB disease. This is further evidenced by the national TB data which shows the highest incidence of TB among the age groups 55- 64 (156/100,00) and 65 and above (59.4/100,00) in 2018 (2).

With the epidemic of Chronic Kidney Disease (CKD) and Chronic Kidney Disease of unknown origin (CKDu) in Sri Lanka, the proportion of patients undergoing dialysis and organ transplantation has become considerable and this again impose a high chance of developing active TB disease (14). Similarly, clinical risk groups such as patients receiving

anti TNF alpha treatment are on the rise as patients with inflammatory diseases are increasingly being treated with biological agents. Occupational exposure to crystalline silica dust causes multiple diseases, but silicosis and silica dust-associated TB, in particular, are the two diseases that remain high on the list (16). The high risk of mycobacterial infection among silica-exposed individuals is well known and therefore screening and treatment of latent TB among this group is recommended.

Though its rare TB remains a clinically significant complication of Solid Organ Transplant recipients (90) while the overall frequency of TB in transplant populations has been estimated to be roughly between 20 and 74 times that of the general population (90,91). It is estimated that areas with low endemicity of TB, the prevalence among SOT recipients is 0.5–6.4%, (91, 92).Although TB may affect any transplanted patient, recipients of lung transplants have the highest rate of TB relative to other transplanted organs (relative risk 5.6) .Factors such as use of T-cell depleting antibodies, enhanced immunosuppression in the setting of rejection, chronic renal insufficiency or haemodialysis for kidney transplant recipients, diabetes mellitus, hepatitis C virus infection for kidney transplant recipients, chronic liver disease, or increased recipient age affect the incidence of TB among SOT recipients (91, 93, 95). When compared to non-immunocompromised patients SOT recipients have an increase adverse outcome with mortality rates of 19%-40% representing a 10-fold increase compared to the overall mortality of TB (93, 94, 95).

Health Care Workers (HCW) are considered as ahigh-risk group due to repeated exposure as an occupational hazard, especially those who are exposed to TB patients regularly in their occupational settings. The situation is further aggravated due to the poor adherence to infection control measures. There are significant number of HCW diagnosed with TB disease yearly. Among HCW, number of reported new TB cases was 0.9% (78/8511) and 0.8% (76/8856) of total TB cases in 2017 and 2018 respectively (2, 17). WHO has recommended to include HCW for the screening of LTBI (18).

TB generally affects the most vulnerable people – those who live in poverty, marginalized or economically and socially deprived. Prison community in particular has a greater risk of getting TB. Available data around the globe show that prevalence of TB among prisoners are 10 to -100-fold higher than that in the general population (19). The latest study to assess TB prevalence among prison inmates in Sri Lanka was done in 2013 and the prevalence was found to be 1.7% (95% CI=1.6% - 1.7%) (20). Further, the National Programme for Tuberculosis Control and Chest Diseases (NPTCCD)has detected 58 prisoners with TB in Sri Lanka in 2018, with the highest proportion from Colombo (38; 0.74% of the screened) in 2018 (2).

Based on available evidence, LTBI management is particularly important in countries with moderate to lower TB incidence such as Sri Lanka. A significant population infected with Mycobacterium tuberculosis remain undetected due to absence of symptoms. With the emergence of increasing number of risk factors as stated above if latent TB progresses to

become active disease, it will create an additional burden on the health system. Therefore, screening and treating for LTBI in Sri Lanka could be considered a timely initiative.

2. DEFINITION OF LATENT TB INFECTION

LTBI is a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without the evidence of clinically manifested active TB (9).

A surveillance case definition is a set of uniform criteria used to define a disease for public health surveillance. Surveillance case definitions enable public health officials to classify and count cases consistently across reporting jurisdictions. Surveillance case definitions are not intended to be used by healthcare providers for making a clinical diagnosis or determining how to meet an individual patient's health needs (22).

Persons with Latent TB infection (LTBI)

- Are infected with the TB bacteria but do not have signs of active TB disease.
- Do not feel ill.
- Cannot spread TB to others.
- Without treatment, approximately 10% of these people (5% in the first two years after infection and 0.1% per year thereafter) will go on to develop active TB during their lifetime.
- Without treatment, can advance to TB disease, especially in people with weakened immune systems such as those with HIV infection, on anti-cancer therapy, on dialysis etc. The risk of developing active TB disease in this group is considerably higher than that for persons with normal immune system.

Surveillance case definitions used in LTBI management

A new case of latent TB is an incident TB Infection case that meets the suspected or confirmed case criteria and has not previously been diagnosed or treated for TB Infection OR previously treated for TB Disease.

Case Classification of LTBI

- **Suspected:**
  A case that meets one or more of the laboratory criteria **AND***M. tuberculosis* complex was not isolated from a clinical specimen, if a specimen was collected.
- **Confirmed:**
  A case that meets one or more of the laboratory criteria for TB infection **AND***M. tuberculosis* complex was not isolated from a clinical specimen, if a specimen was collected **And** does not meet the clinical criteria for active TB disease.

Active TB should be excluded BEFORE treating for latent TB infection at ALL times

Absence of clinical criteria alone is not sufficient to classify a case of LTBI. To confirm a suspected case of Infection, clinical, microbiological and radiological evidence to rule out active TB disease should be considered. **These criteria include**,

1). No clinical evidence compatible with TB disease including no signs or symptoms consistent with TB disease **AND** chest imaging without abnormalities consistent with TB (chest radiograph or CT scan).

OR

2)**.** No clinical evidence compatible with TB disease including no signs or symptoms consistent with TB disease, having abnormal chest imaging that could be consistent with TB disease, but microbiological testing is negative for *mycobacterium tuberculosis* (MTB) complex.

Chest radiographic features suggestive of active PTB

- Ghon's Focus/ Hilar Lymphadenopathy/ Primary Complex
- Cavitation, thick walled, mainly older children and adults
- Patchy, poorly defined consolidation in the apical and posterior segments of the upper lobes, and in the superior segment of the lower lobe
- Pleural effusion
- Milliary mottling
- Infiltration of lower lobe
- Pneumothorax
- Collapse/ atelectasis

Laboratory criteria to confirm LTBI

Laboratory criteria to confirm a suspected case of TB Infection include, "A positive tuberculin skin test (TST), otherwise known as Mantoux test, OR a positive interferon gamma release assay (IGRA)".

Investigations that could be used to detect latent TB infection

- Either a TST or IGRA can be used to test for LTBI.
- These investigations measure immune sensitization (type IV or delayed-type hypersensitivity) to mycobacterial protein antigens that might occur following exposure to (and infection by) mycobacteria.
- There is no strong evidence that one test should be preferred over the other to predict progression to active TB disease.
- Neither the TST nor IGRA can be used to diagnose active TB disease.
- The choice of investigation depends on the availability, cost and the health care infrastructure.

3. IDENTIFICATION OF POPULATIONS FOR TESTING AND TREATMENT OF LATENT TUBERCULOSIS INFECTION

As specified earlier, not all individuals infected with *M. tuberculosis* develop active TB. It is estimated that the lifetime risk of an individual with LTBI progressing to active TB is 5–10%. The risk is particularly high among children under the age of 5 years and among people with compromised immunity (9).

As preventive treatment entails risks, benefits and the costs to the health system, preventive treatment of LTBI should be selectively targeted to the population groups at highest risk for progression to active TB disease and would benefit most from treatment of LTBI. Hence, local epidemiology and pattern of transmission of TB have been key factors in selecting population groups at-risk, to ensure treatment offers long lasting protection. Therefore, importance should be given for a comprehensive individual clinical assessment that takes into account the balance between the risks and benefits for the individual receiving the treatment.

Following categories should be considered for latent TB screening and treatment

Box 1: People Living with HIV (PLHIV)

1. All adults and adolescents including those who have previously been treated for TB and pregnant women living with HIV
2. Infants aged < 12 months, and are in contact with a case of PTB
3. Children aged ≥12 months, even when there is no contact with a case of TB
   All children living with HIV who have successfully completed treatment for TB disease will be evaluated for reactivation on a monthly basis or at each encounter with a health worker

Box 2: HIV-negative close contacts of a person with pulmonary TB who is either bacteriologically confirmed or clinically diagnosed (based on strong clinical suspicion by a Respiratory Specialist after excluding other pathologies)

1. Infants and children under 5 years of age who are close contacts of patients with pulmonary TB
2. Children above 5 years of age, adolescents and adults who are close contacts of patients with pulmonary TB
3. In selected high-risk household contacts of patients with multidrug-resistant tuberculosis (MDR), preventive treatment may be considered based on individualized risk assessment and a sound clinical judgement

Box 3: HIV-negative other at-risk groups

1. Patients initiating anti-TNF treatment, receiving dialysis, preparing for solid organ transplant or hematopoietic stem cell transplant and patients with silicosis
2. Prisoners, health-workers, immigrants from high TB burden countries, and people who are using illicit drugs may be considered based on local research evidence, individualized risk assessment and sound clinical judgement by experts.
   Scaling up of LTBI testing for this risk group will be carried out based on programmatic factors and assurance of treatment completion.

TESTING FOR LATENT TB INFECTION USING TST OR IGRAs ARE NOT AN ESSENTIAL REQUIREMENT FOR INITIATING PREVENTIVE TREATMENT IN PEOPLE LIVING WITH HIV OR CHILDREN AGED < 5YEARS WHO ARE CLOSE CONTACTS OF A PULMONARY TB PATIENT.

HOWEVER, BASED ON THE CLINICAL SCENARIO OF THE CHILD, GRADING OF SPUTUM RESULTS OF INDEX CASE, PERIOD AND INTENSITY OF EXPOSURE, TST MAY BE PERFORMED AS A SUPPORTIVE EVIDENCE OF TUBERCULOSIS INFECTION.

4. ALGORHITHMS FOR SCREENING FOR LATENT TB INFECTION AND RULING OUT OF ACTIVE TB DISEASE

4.1. People living with HIV (PLHIV)

4.1.1. Adults and adolescents

PLHIV were 19 times (95%CI: 15 – 22) more likely to develop TB than those without HIV (1). The risk for developing active TB among HIV positive individuals increases in many folds even during anti-HIV treatment (9, 21). Further, HIV infection is among the most important risk factors for the progression of LTBI to active TB (9, 23). Worldwide, an estimated 862 000 PLHIV developed TB in 2018 (1).

Many systematic reviews conducted before the use of Anti-Retroviral Treatment (ART) showed preventive treatment for TB reduced the overall risk for TB by 33% (RR; 0.67, 95% CI 0.51; 0.87) among PLHIV (9, 23). For those who were TST positive, the reduction increased to 64% (RR 0.36, 95% CI 0.22; 0.61) and the reduction was 14% among TST-negative persons (RR 0.86, 95% CI 0.59; 1.26) (9, 24). However, recent studies showed increasing evidence of the efficacy of TPT in people receiving ART and some indicated that PLHIV and receiving ART with negative TST or IGRA benefited more from TPT than those who were TST or IGRA positive (24,25). Recent randomized controlled trials (RCT)highlighted the additive benefits of preventive treatment plus ART in reducing both TB incidence and overall mortality. The protective effect lasted for more than 5 years (25, 26).

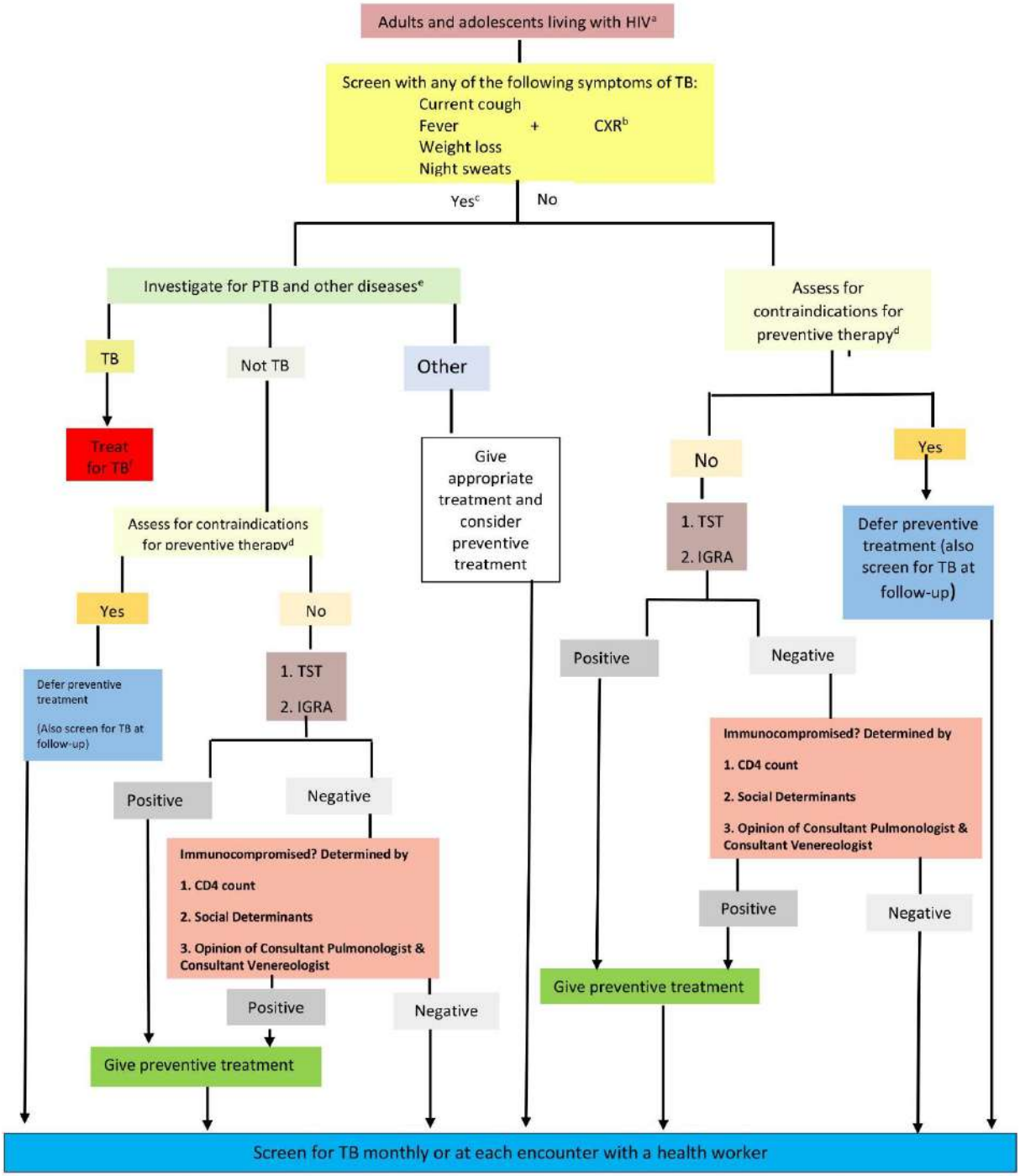
Adults and adolescents living with HIV should be screened for active TB according to a clinical algorithm. Based on research evidence, WHO recommends a symptom-screening rule of a combination of **current cough, weight loss, night sweats and fever** in order to exclude active TB (23). The pooled sensitivity of the four-symptom screening rule for people living with HIV on ART was 51.0% (95% CI 28.4; 73.2), and the specificity was 70.7% (95% CI 47.7; 86.4); the pooled sensitivity of the rule for people living with HIV but not receiving ART was 89.3% (95% CI 82.6; 93.6), and the specificity was 27.2% (95% CI 17.3; 40.0) (9).

The spectrum of radiographic manifestation of pulmonary TB is dependent on the relative level of HIV-related immunodeficiency (27). During the early phase of HIV when individuals are not immunosuppressed, the radiographic pattern is similar to HIV uninfected individuals with more typical lesions, such as upper lobe infiltrates with or without cavities. With advancing immunosuppression, extra pulmonary involvement, intra-thoracic/mediastinal lymphadenopathy, lower lobe infiltrate and miliary TB are featured on chest X-rays (27). Study evidence on addition of abnormal chest radiographic findings to the symptom-screening rule for people living with HIV who are on ART showed higher sensitivity but lower specificity than those of the symptom screen alone (9). Further, the negative predictive value of the symptom screening rule (99.3%) increased only by 0.2% by adding an abnormal chest radiographic finding. Therefore, chest radiography should be added as an additional investigation only if it does not pose a barrier to the provision of preventive treatment for people living with HIV (9).

However, considering the local context of ray availability, GDG has decided to add Chest Xray to rule out active TB disease among all high-risk groups identified by the current guideline including PLHIV (Box 4 and Figure 3).

Box 4: Guide to rule out active TB and to screen and initiate treatment for LTBI among adults and adolescent living with HIV

1. Follow **four symptoms rule and Chest Xray** to exclude active TB disease
2. TST and IGRA will be done on patients after excluding active TB disease
3. If TST/IGRA testing are positive TPT can be initiated after confirming that the liver enzyme tests after initiation of ART is not significantly elevated within **3 months of testing for LTBI.**
4. If TST/IGRA tests are negative a team of Consultant Pulmonologist and Consultant Venereologists will assess the patient for severe immunocompromised status based on CD4 count and clinical determinants. If the consultative team determines that the patient is severely immunocompromised and/or has poor social determinants TPT is initiated despite negative TST/IGRA testing.
5. Pregnancy is not a contraindication for TPT. All pregnant women with HIV should be evaluated for latent tuberculosis and appropriate TPT should be initiated without delay.



a. Every adult and adolescent should be evaluated for eligibility to receive ART. Infection control measures should be prioritized to reduce M. tuberculosis transmission in all settings in which care is provided.
b. Chest radiography is included in to the initial screening tool / can be done if available, particularly for people living with HIV on ART, but is not required to classify patients into TB and non-TB groups.
c. Either symptoms or Xray or both are suggestive of TB or other diseases
d. Contraindications include: active hepatitis (acute or chronic), regular and heavy alcohol consumption and symptoms of peripheral neuropathy. History of TB and current pregnancy should not be contraindications for starting preventive treatment.
e. Xpert MTB/RIF should be used as the initial diagnostic test for TB.
f. Resume regular screening for TB reactivation after completion of treatment for active TB disease.

Figure 1: Algorithm for screening adults and adolescents living with HIV for LTBI

4.1.2. Children living with HIV

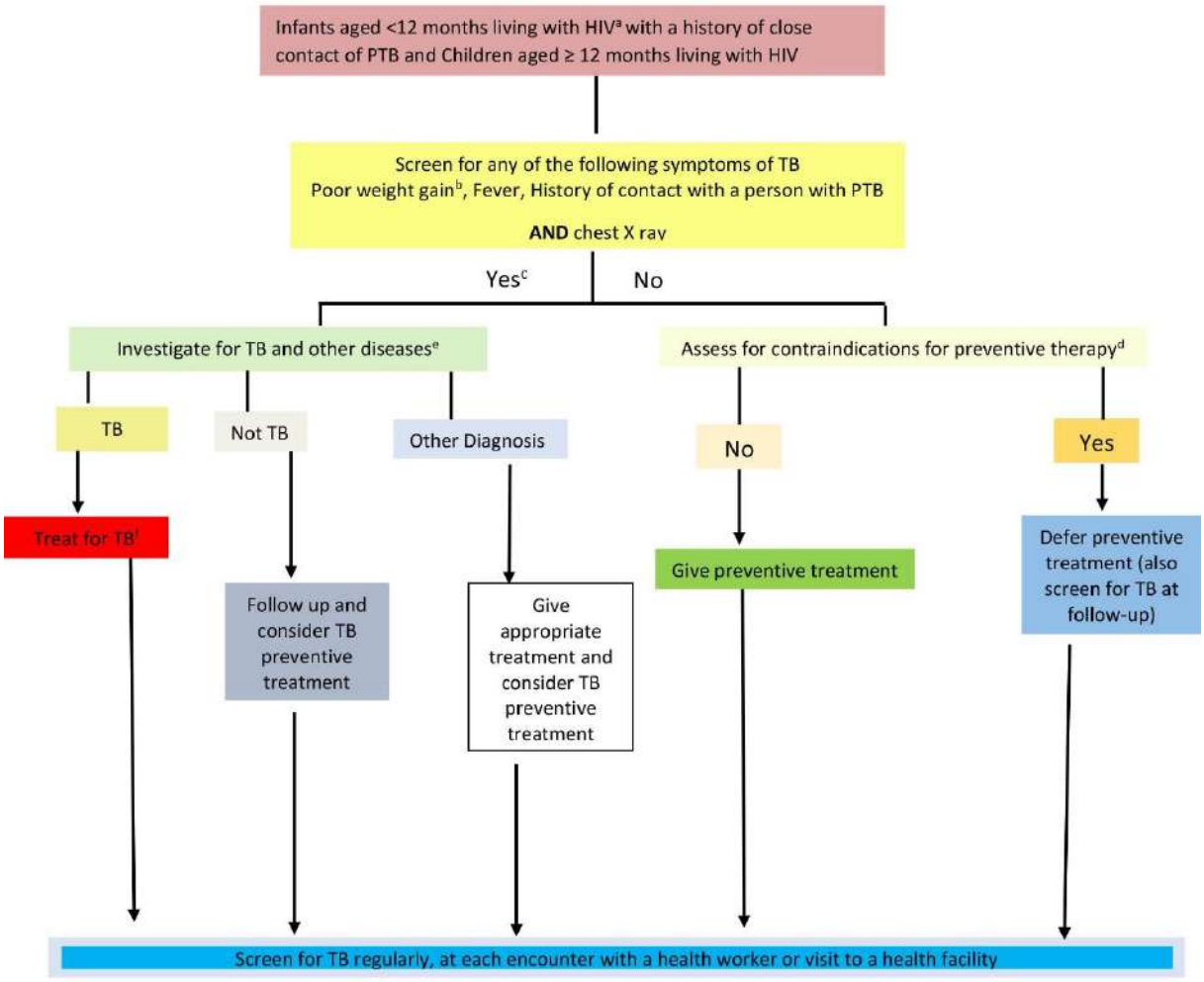
According to WHO estimates the HIV prevalence among children with TB in countries with moderate to high TB prevalence, ranges from 10 to 60%. HIV has made the diagnosis of TB in children more difficult due to overlapping clinical and radiographic manifestations with other lung diseases resulting in missed or delayed diagnosis (28). The manifestations of TB are more severe and progression to death is more rapid in HIV-positive than in HIV-negative children. Conversely, TB accelerates the progression of HIV disease by increasing viral replication and reducing the CD4 count (29, 30). TB is a common cause of death in HIV-infected children (30, 31).

Infants and children living with HIV should be screened for active TB routinely, as part of standard clinical care regardless of whether they are receiving TB prophylaxis or ART. However, there are limited evidence on best approaches of symptom screening among children with HIV (32). A screening rule which consists of **poor weight gain, fever, current cough and a history of contact with a TB case** was recommended by the WHO (9).

Among few available research evidence, one study showed the evidence of considerable reduction in mortality and protection against TB among HIV-infected children who received isoniazid for 6 months (33). A RCT conducted among children on ART showed the incidence of TB was lower in those given preventive treatment than in those who were not, though the difference was not statistically significant (34). A cohort study suggested an additive protective effect of preventive treatment in children receiving ART (35). Some other studies pointed out that there was no benefit of TPT for HIV-infected infants with no known exposure to a TB case, who were identified in the first 3–4 months of life and given rapid access to ART (9).

Box 5: Guide to rule out active TB and to screen and initiate treatment for LTBI among children living with HIV

1. Provide TPT for infants aged <12 months living with HIV only if particular infant has a history of household contact with a person with TB and do not have TB disease according to investigations conducted.
2. Provide TPT for children aged ≥ 12 months living with HIV, irrespective of their contact history, after ruling out active TB disease.
3. Recommend preventive treatment for children, regardless of whether they are on ART or not.
4. Provide TPT for all children living with HIV who have been successfully **treated for TB** only if they are living in a residential area with high TB incidence and transmission. This decision should be taken with expert opinion considering the local epidemiology of the disease, socio economic background and other relevant factors (Preventive treatment can be started immediately after the last dose of TB therapy or later, according to clinical judgement).



a. All infants < 1 year of age should be given preventive treatment if they have a history of household contact with a TB case.

b. Poor weight gain is defined as reported weight loss, very low weight-for-age (< –3 z-score), underweight (weight-for-age < –2 z-score), confirmed weight loss (> 5%) since the last visit or growth curve flattening.
c. Either symptoms or CXR abnormality or both are suggestive of TB or other diseases
d. Contraindications include active hepatitis (acute or chronic) and symptoms of peripheral neuropathy. A past history of TB should not be a contraindication for starting preventive treatment
e. Xpert MTB/RIF should be used as the initial diagnostic test for TB
f. Resume regular screening for TB reactivation after completion of treatment for active TB disease..

Figure 2: HIV- negative close contacts of a person with pulmonary TB

4.2. HIV- negative close contacts of a person with pulmonary TB

A person who shared the same enclosed living space for one or more nights or for frequent or extended periods during the day in the last 3 months before commencement of the current treatment in the index case is defined as a close contact (36). Close contacts could be either household or non-household. A person who is not in the household but shared an enclosed space, such as a social gathering place, workplace or facility, for extended periods during the day with the index case during the 3 months before commencement of the current treatment episode is defined as a non-household contact (36).

TB infection is almost exclusively transmitted through air from patients with pulmonary disease. The risk of transmission to household contacts is greatest when the index case is sputum smear positive, closeness of the index case with the contacts is increased, living

conditions are overcrowded, bacillary density in respiratory secretions are high, and lung fields involvement is high (37-40). Therefore, those living within the same household are at higher risk than casual contacts (41, 42). Further, among the household contacts, younger age and absolute or relative immunodeficiency status increases the risk of acquiring TB from the index case (43, 44).

Current policy on contact screening in Sri Lanka is to screen all close contacts of all TB patients with symptom check list and Chest Xray for active TB irrespective of the type of TB of the index case. Further, the NPTCCD conducts follow-up screening of contacts for up to 2 years at 6-month intervals to identify incident cases. However, currently the TPT is offered only for children less than 5years who are contacts of bacteriologically confirmed TB cases.

4.2.1 Infants and children under 5 years of age who are close contacts of PTB patients

It is noted that the risk of developing active TB among infants and children < 5 years is significantly higher when they get exposed. Furthermore, the disease can develop rapidly in young children, and they are at greatest risk for severe and disseminated disease associated with high morbidity and mortality. Children <5years who were positive for LTBI will have 24 and 22 times more risk of developing active TB diseases compared to general population when followed up for <12 months and <24months respectively. When the study was conducted regardless of baseline LTBI status, the risk of developing the disease was 25 times and 14 times greater compared to general population in the respective follow up periods. This highlights the importance of TPT for children <5years who are close contacts of PTB patients irrespective of their LTBI status (9).

Algorithm to rule out active TB and initiation of latent TB treatment among children <5years who are close contacts of PTB is given in Figure 3.

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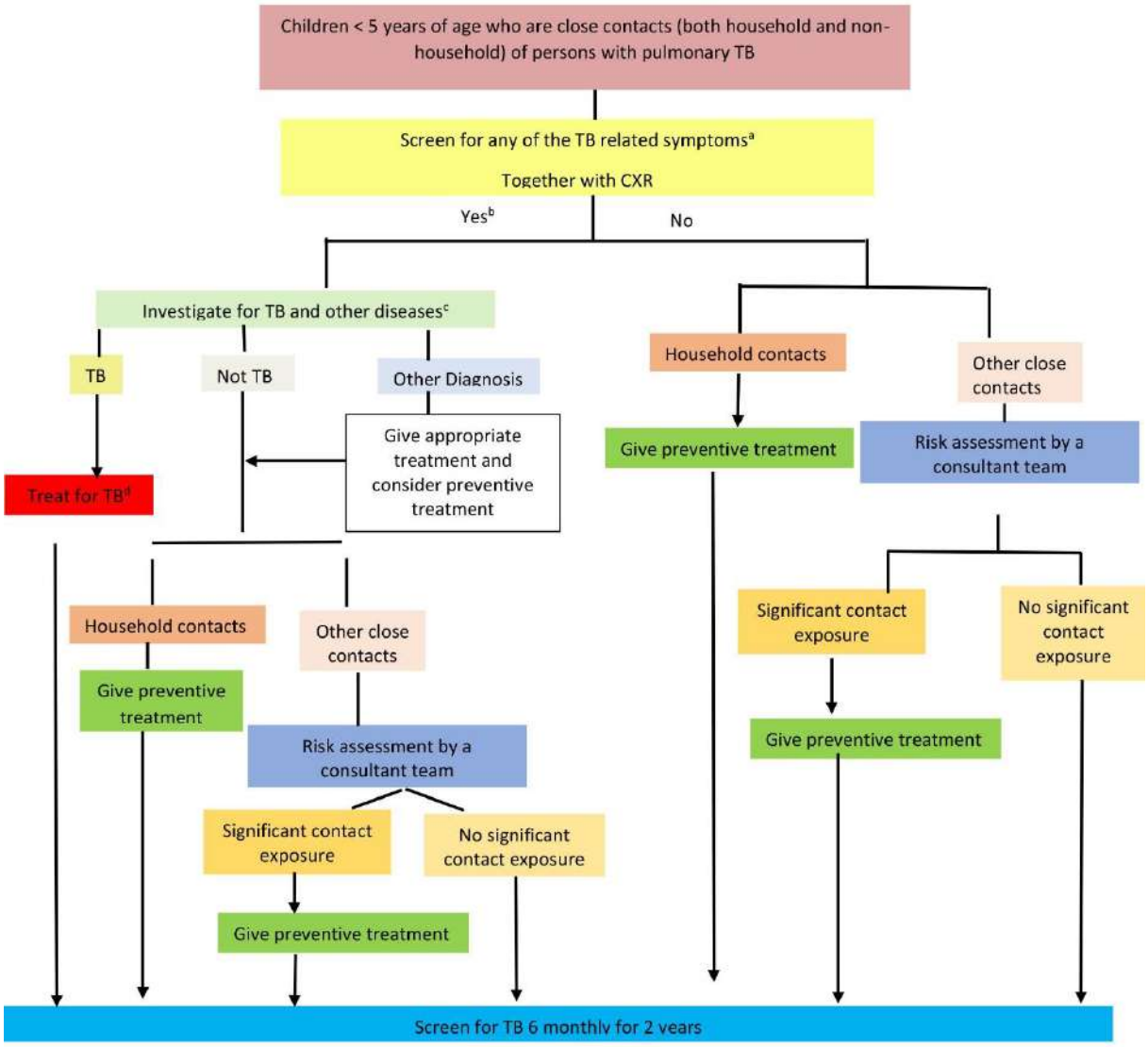


a. The commonest TB-related symptoms are persistence of: cough, fever, not eating well/anorexia, weight loss/poor weight gain, reduced playfulness and decreased activity. Poor weight gain is defined as reported weight loss, very low weight-for-age (< –3 z-score), underweight (weight-for-age < –2 z-score), confirmed weight loss (> 5%) since the last visit or growth curve flattening.
b. Either symptoms or Xray or both are suggestive of TB or other diseases
c. Xpert MTB/RIF should be used as the initial diagnostic test for TB.
d. Resume regular screening for TB reactivation after completion of treatment for active TB disease..

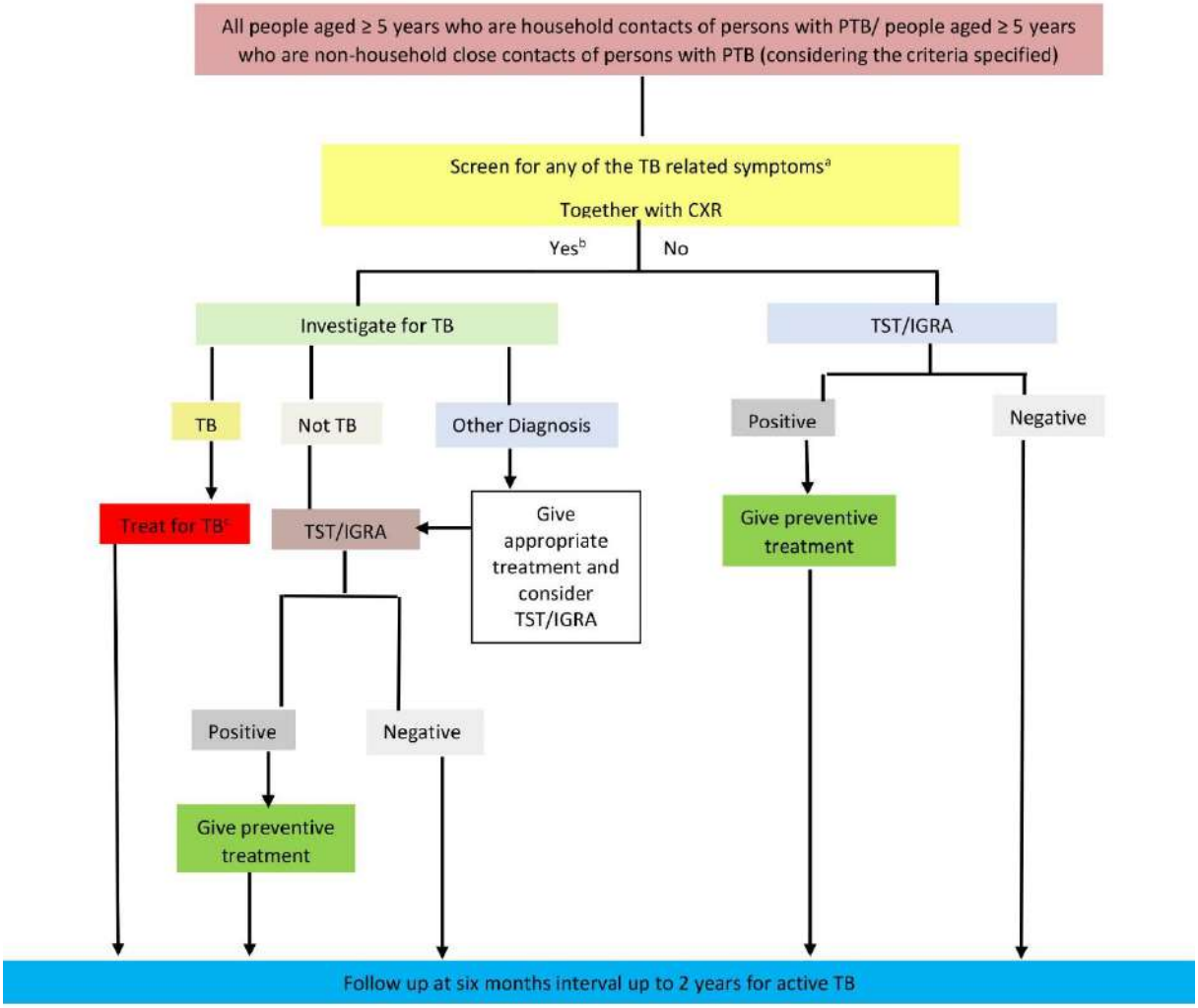
Figure 3: Algorithm for screening HIV-negative infants and children < 5 years of age who are close contacts of PTB cases for LTBI

4.2.2 Children above 5 years of age, adolescents and adults who are close contacts of patients with pulmonary TB

In comparison with child household contacts < 5 years, the pooled risk ratios for progression to active TB were lower in children aged 5–15 years (0.28, 95% CI 0.12;0.65, four studies) and for those > 15 years (0.22, 95% CI 0.08;0.60, three studies). All household contacts, regardless of their age or LTBI status, were nevertheless at substantially higher risk for progression to active TB than the general population. Household contacts aged 5-14years and ≥15years showed 27 and 30 times more risk of developing active TB disease respectively compared to general population during initial 12 month follow up period. The WHO conditionally recommends TPT for household contacts in the above age groups considering

clinical judgement, the balance between harm and benefit for individuals, the national and local epidemiology of TB, and on-going transmission of TB (9).

Algorithm to rule out active TB and to screen for and initiate treatment for LTBI among close contacts aged ≥5years is given in Figure 4.



a. Any symptom of TB: cough, hemoptysis, fever, night sweats, weight loss, chest pain, shortness of breath, fatigue.
b. Either symptoms or CXR or both are suggestive of TB or other diseases.
c. Resume regular screening for TB reactivation after completion of treatment for active TB disease..

Figure 4: Algorithm for screening and treatment of LTBI among HIV-negative aged ≥ 5 years who are household contacts of PTB cases for LTBI

4.2.3. Close contacts of patients with multidrug-resistant tuberculosis (MDR-TB)

Preventive treatment for contacts of patients with MDR TB should be more individualized than that of other contacts. Decision to treat should be based on individual risk assessment of the contacts. Risk of contacts to progress into active disease, e.g., Children, PLHIV, people under immunosuppressive treatment should be considered when prioritizing treatment. Similarly, intensity of exposure, certainty of the source case, information on pattern of drug resistance of the index case and potential adverse events should be taken into account when

deciding to treat the contacts. Treatment regime that should be used for contacts of MDR TB patients should be decided by an expert on MDR TB treatment.

Box 6: Procedures to rule out active TB and to screen for LTBI among close contacts of PTB (bacteriologically confirmed or clinically diagnosed) patients

1. Screen close contacts of PTB (bact. confirmed or clinically diagnosed) patients for LTBI.
2. Utilize symptom screening and CXR together as the initial screening tool to rule out active TB.
3. Provide TPT to all household close contacts aged <5yearswithout testing for LTBI after excluding active TB.
4. Non-household contacts who are < 5 years, the degree of exposure should be evaluated by the respective group of clinicians and the decision to commence TPT will be taken on an individual basis.
5. Provide TPT to all household contacts aged ≥5years who are positive for LTBI after excluding active TB.
6. Screen all non-household close contacts aged ≥5years for LTBI depending on the circumstance, intensity of exposure, grading of sputum status of the index case, and other factors which the experts consider is important and provide TPT. However, routine screening of all close contacts for active TB will continue as planned.
7. Treat household contacts of MDR TB patients after a risk assessment and obtaining expert opinion as stated above.
8. Follow up all suspected LTBI cases at regular interval.

4.3. HIV-Negative clinical risk groups

4.3.1. Patients on Anti-TNF alpha therapy

Anti tumour necrosis factor (TNF) agents are increasingly being used for patients with immune mediated inflammatory diseases (45, 46). Patients treated with TNF inhibitors are at increased risk of developing TB, mostly through reactivation of LTBI (47). Hence, diagnosis and treatment of LTBI is strongly recommended before initiation of anti TNF agents in these patients.

Different group of TNF alpha agents such as Infliximab, etanercept, adalimumab, golimumab and certolimumab are being used to treat different groups of immune-mediated inflammatory diseases such as rheumatoid arthritis and Chron's disease. It is well known that TNF alpha plays an important role in interactions, modulations and regulation of immune system. Hence, TNF alpha along with other cytokines plays an important part in the reactions that cause inflammation and killing of TB bacilli. Thus, use of anti-TNF alpha agents interferes with this process and increases the risk of reactivation of LTBI.

RCTs on infliximab first reported four-fold increase in the risk of TB infection. Furthermore, in recent years, studies have shown that the TB risk caused by monoclonal antibody

(infliximab) is generally higher than the receptor antibody (etanercept). According to meta-analyses of randomized control groups, the use of TNF alpha inhibitors in inflammatory bowel disease patients increased the relative risk of TB incidence by 2.5 folds. **Therefore, diagnosis and treatment of LTBI is strongly recommended before initiation of Anti TNF agents in patients.**

Traditionally, latent TB has been diagnosed on the basis of clinical factors and tuberculin skin test. There is an added value of IGRA for the patients diagnosed with immune mediated inflammatory diseases who are already on immunosuppressive agents.

Asymptomatic persons with evidence of previous pulmonary TB on chest X-rays and without a history of adequate treatment of TB are regarded as LTBI irrespective of their TST or IGRA test results after excluding active TB disease. **(Treatment for LTBI is not recommended for patients who had been adequately treated for previous active TB disease.)** However, these patients should also be evaluated for active TB disease.

After confirmation of LTBI, treatment should be initiated. Ideally, TNF antagonist treatment can be started 4 weeks after initiation of LTBI treatment. All patients who are on TNF antagonist treatment should be observed carefully for development of active TB disease during their treatment period. The patients receiving LTBI treatment should be closely monitored for adverse outcomes since they may be receiving other medications which may cause similar side effects.

If contacted with a PTB patient during TNF antagonist treatment, they should be promptly offered investigations to diagnose active TB and treatment for LTBI should be immediately commenced after excluding active TB disease. Therefore, it is very important to inquire regarding this exposure history at each encounter with the healthcare provider. TNF antagonist therapy could be continued with close monitoring for the development of active TB disease if LTBI is excluded.

If a patient develops active TB disease during Anti TNF therapy, TNF antagonists should be stopped immediately and treatment for active TB should be started. Re-initiation of a TNF antagonist is considered after 2 months of intensive phase with a good response to TB treatment. In the absence of a good response to anti TB treatment, the decision to re-start TNF antagonist must be a decision from an expert panel including a respiratory physician and the clinician treating for the disease involving TNF antagonist.

4.3.2. Non-Anti-TNF alpha targeted biologics

Several non anti TNF alpha targeted biologics such as Anti - CD 20 Rituximab (RTX), Anti - CD28 Abatacept (ABA) ,IL-6 inhibitor Tocilizumab (TCZ), IL-17 inhibitor (Secukinumab)and Anti IL-1 Anankinra are licensed for treatment of Rheumatoid Arthritis, ankylosing spondylitis and psoriatic arthritis. Even though the Studies done in the West have shown the risk of TB reactivation is negligible from these agents, the GDC decided that all patients who are started on other biologics should also be screened for latent TB after

excluding active TB diseases. However, those who are positive for Latent TB will not be commenced on LTBI treatment and will be followed up three monthly at the DCC for development of active TB. In case of positive results for Latent TB non-anti-TNF alpha biologics represents the safest option.

Box 7: Procedure to rule out active TB and to screen and initiate treatment for LTBI among patients on anti-TNF therapy and other biologics

1. Diagnose and treat latent TB infection (LTBI) before initiation of Anti-tumor necrosis factor agents.
2. Carry out clinical assessment, chest x –ray, if necessary, CT chest and further evaluation to exclude active TB disease before starting treatment for latent TB.
3. Consider two step TST (please refer page 38) to minimize false negativity due to cutaneous anergy.
4. Employ both modalities, TST and IGRA test results since one test result cannot successfully indicate the immune response and as the sensitivities of TST and IGRA do not overlap fully
5. **Start TPT on all positive TST (induration ≥ 5 mm for those who are on immune modulatory therapy) and/or positive IGRA patients after excluding active tuberculosis**
6. Start TNF antagonist treatment 4 weeks after initiation of LTBI treatment once the diagnosis of LTBI is made
7. If contacted with a PTB patient during TNF antagonist treatment, to investigate for active TB and to initiate LTBI treatment after excluding active TB. TNF therapy could be continued with close monitoring for the development of active TB if LTBI testing is negative.
8. Discontinue Anti TNF therapy immediately if a patient develops active TB during TNF antagonist treatment and re-start TNF antagonist after 2 months of intensive phase of TB treatment once good response to TB treatment is assured

4.3.3. Patients with silicosis

Silicosis is a fibrosing lung disease caused by inhalation of crystalline silica particles in various occupations including mining, stone cutting, sand blasting, employment in abrasive industries such as stone, clay, glass and cement manufacturing and foundry. In spite of technical advances such as personal protective measures, exposure to free silica or crystalline quartz is still a major occupational hazard which leads to lung fibrosis in a dose response manner after many years of exposure (48-50).

The diagnosis of silicosis is made based on a history of exposure to silica accompanied by the clinical and radiological features consistent with the disease. Simple nodular silicosis is the most common form and usually asymptomatic. Progressive massive fibrosis (PMF) is the more advanced form and presents with progressive dyspnea, restrictive lung functions and radiographic changes.

Radiographic changes of silicosis:

- Chest radiographs shows changes only after many years of exposure.
- Usually multiple, small (<1cm) lung opacities which are round and well circumscribed, found in the upper and posterior regions of the lungs and vary very little in size.
- In simple silicosis, Computer Tomography (CT) shows upper lobe predominant multiple small nodules accompanied by calcification. Furthermore, hilar and mediastinal lymphadenopathy may precede the appearance of parenchymal nodular lesions. Calcification of lymph nodes commonly and typically occurs at the periphery of the lymph nodes (Egg shell calcification).
- In complicated silicosis CT features consist of focal soft tissue dense masses with irregular or ill-defined margins and calcifications. These lesions are usually surrounded by emphysematous areas.

Silicosis has been identified as an independent risk factor for TB. Various studies show that the risk of developing pulmonary TB is reported to be 2.8 to 39 times higher for patients with silicosis than healthy controls. In addition, the risk of developing extra pulmonary TB is 3.7 times higher than in healthy controls (51). Most of the studies have shown that silicosis and HIV increase the risk of TB multiplicatively (51). A study found that silica exposure was prevalent among TB patients and the risk of TB to be associated with higher intensity of silica exposure, older age and cigarette smoking (52). Another study revealed that the prevalence of TB in silica-exposed workers without silicosis was 5.2-fold and prevalence in silicosis workers was 27.8-fold higher than the general population and the incidence of TB in silica-exposed workers without silicosis was 3.3-fold and incidence in silicosis cases was 21.8-fold higher than general population (53).

Accordingly, it is extremely important to exclude the coexistence of active TB in patients with silicosis. However, the diagnosis of active TB superimposed on silicosis can be very difficult, because the clinical manifestations can be subtle, and the radiological alterations can be indistinguishable from those resulting from the preexisting silicosis (54). Therefore, in cases with clinical suspicion of concomitant active TB, an appropriate additional investigation such as Xpert MTB/RIF sputum TB culture, and High-Resolution CT (HRCT) should be performed even if sputum smears are negative. If in further doubt, bronchoscopy with Broncho-Alveolar Lavage (BAL) can be used in conjunction with trans-bronchial biopsy when possible (55).

It is strongly recommended to screen all patients with silicosis for LTBI. TPT needs to be started on all TST positive (induration > 10 mm) patients after excluding active TB.

Procedures to rule out active TB and to screen for LTBI among patients with silicosis

1. Carry out clinical assessment, chest x –ray, sputum AFB, Xpert MTB/RIF, and if necessary further evaluation by sputum culture, HRCT and bronchoscopy with BAL in

case of clinical suspicion of concomitant active tuberculosis before starting treatment for latent TB.
2. Consider either doing TST (please refer page no.38) or IGRA.
3. Start TPT on all patients with positive TST (induration > 10 mm) or positive IGRA after excluding active tuberculosis
4. Consider TST positive (induration ≥ 5 mm) for persons with fibrotic changes on chest radiograph consistent with prior TB

4.3.4. Patients receiving dialysis

TB remains an important factor in the morbidity and mortality of hemodialysis patients. Patients in the End Stage Renal Disease (ESRD) on hemodialysis with LTBI have 10 to 25 times the risk of reactivation into active TB disease compared with healthy adults (56, 57, 58, and 59). However, because extra pulmonary manifestations of TB are common, diagnosis of TB is usually delayed in patients on dialysis. It is well known that ESRD is accompanied by disturbances of the immune system (mainly the T lymphocyte and the antigen-presenting cell), thereby increasing susceptibility to infections (60, 61). The interaction between the T lymphocyte and the macrophage plays an important role in the response to *Mycobacterium tuberculosis* (61). In addition, diabetes is a major cause of ESRD (causing over 40% of incident ESRD (62) and results in an increased risk (2 to 4 times) of active TB (63). Therefore, ESRD patients with diabetes are at dual risk of developing active TB.

A study comparing the prevalence of LTBI among non-dialysis patients with severe CKD and patients receiving dialysis, indicated patients receiving dialysis have a higher prevalence of LTBI than those with severe CKD (25% and 11% respectively). Therefore, severe CKD patients not receiving dialysis may not be the priority group for LTBI screening if resources are limited (64). Old age, prior TB lesion in the chest radiography, reduced serum albumin level, and long-term dialysis are predictors of LTBI among patients receiving dialysis (64). Hemodialysis itself may contribute to immune deficiency in ESRD patients through a proapoptotic effect due to direct blood contact with dialysis membranes that may affect the cell-mediated immune reactions (56). This was further evidenced in a study indicating a longer dialysis vintage (≥4 years) associated with a negative QuantiFERON®-TB Gold In-Tube test (QFT-GIT) response (56).

Patients who have chronic renal failure and receive hemodialysis are an example of a population that typically manifests cutaneous anergy to skin test antigens yet are at high risk for developing active TB. In immunocompromised populations, sensitivity declines in parallel with decreasing cellular immune system function. Different strategies to improve the sensitivity of the TST in this population have been advocated including two-step TST. However, performing two-step TST is likely to increase test sensitivity at the expense of specificity.

IGRA has many advantages over the TST as a diagnostic tool for LTBI among this population. Like the TST, IGRA assesses the immune response to TB antigens, but with

increased specificity (65). Although IGRA is also subjected to anergy (66), they may be less susceptible to uremic immunosuppression. Furthermore, the "boosting" effect that can be seen in patients subjected to repeated TST testing is absent in these patients (65, 66). IGRA eliminates diagnostic variability and is less cumbersome for the patient since a follow-up assessment is not needed. While the immediate cost of IGRA is higher than TST, it may be more cost-effective in this population when considering long-term outcomes. Some studies have shown that the sensitivity of IGRA may be reduced post hemodialysis, but even under these conditions, IGRA has a higher sensitivity than the TST (67). **Considering this situation, screening for LTBI by TST and/or IGRA recommended before commencing renal replacement therapy.**

There are two forms of IGRA test, T-SPOT.TB and QuantiFERON Gold test. In theory, the T-SPOT.TB may be less prone to produce indeterminate results than the QuantiFERON Gold test. This is because as an enzyme-linked immunosorbent spot test, T-SPOT.TB test requires the enumeration of T cells before measurement of IFN release (65). In a study that involved a head-to-head comparison of the T SPOT.TB test and the QuantiFERON Gold test, 11.2% of QuantiFERON test results were indeterminate compared with 3.1% with the T SPOT.TB test (68). However, immunosuppression was strongly associated with indeterminate results for each of the two commercially available assays (69). Therefore, when IGRA is indicated in this clinical context, T-SPOT.TB is preferable over QuantiFERON Gold test, where available.

Follow up Patients on dialysis who have received TPT for LTBI

The patients on dialysis who received TPT should be followed up 6 monthly or more frequently if clinically indicated while awaiting kidney transplant to exclude development of active TB.

Box 8: Guide to rule out active TB and to screen for LTBI among patients receiving dialysis

1. Carry out clinical assessment, chest x –ray, if necessary, CT chest and further evaluation to exclude active TB disease before starting treatment for LTBI
2. Consider two step TST to minimize false negativity due to cutaneous anergy.
3. Employ both modalities, TST and IGRA test results since the sensitivities of TST and IGRA do not overlap fully
4. Prioritize T-Spot. TB over QuantiFERON Gold test when IGRAs are indicated in this clinical context

4.3.5. Patients preparing for Solid Organ Transplantation (SOT)

The risk of latent TB, progressing into active TB disease is related to the extent to which the host immune system has failed to provide a successful immune response and therefore, is seen in situations that compromise immunity. Similarly, recipients of Solid Organ Transplantation (SOT) and Hematopoietic Stem Cell Transplantation (HSCT) who require

prolonged immunosuppression, are more prone to develop TB than the immunocompetent persons.

The risk for active TB disease in SOT recipients is estimated to be 20-74 times higher and twice as frequent as in HSCT (70) than in the general population and more often fatal, up to 31% in SOT (71) and up to 50% in HSCT recipients (72). This frequency of active TB among SOT patients differs according to the organ transplanted and the region they live. A higher rate of TB is found in patients undergoing renal transplantation than those who are undergoing other SOT. However, the recipients of lung transplants have the highest rate of TB relative to other transplanted organs (71).

Most fatalities (57-83%) are directly attributable to TB (72) and some are related to immunosuppression, comorbidities. In addition, complex interactions between agents used to treat TB and the agents typically used to prevent rejection may result in allograft loss in up to one third of cases.

A previous history of treated TB in SOT recipients is a risk factor for development of post-transplant active TB disease. The risk is highest in the first post-transplant year, the time of maximal immunosuppression, with a median onset at 9 months. However, in renal transplant patients, the onset is typically later. An early-onset TB is associated with;

- A history of a positive TST or IGRA results
- Radiographic evidence of past-TB
- Patients who receive lymphocyte-depleting antibodies as the induction therapy (73).

Clinical presentation of active TB among recipients of SOT (74)

- Among transplant recipients presenting with TB, majority present with pulmonary TB (51%). Another 16% have extrapulmonary disease of specific organs and 33% have disseminated TB.
- Extrapulmonary disease with unsuspected or elusive sites of involvement, and disseminated TB are commoner among SOT recipients than the general population.
- The hallmark symptoms of TB i.e. fever and constitutional symptoms, such as night sweats and weight loss, occur frequently but not universally. Atypical presentations may also frequently occur, particularly in patients with disseminated TB and in some, allograft dysfunction may be a feature.
- Atypical presentation would result in delays in early diagnosis and subsequent delays in initiation of therapy, and an increased incidence of disseminated TB by the time of diagnosis. Therefore, up to a third of patients may not have TB suspected initially and 3-5% may only be diagnosed after the death of the recipient.
- In patients with pulmonary disease, a wide range of radiographic manifestations, including focal infiltrates (40%), miliary pattern (22%), pleural effusions (13%), and nodules (5%) have been described. However, cavitation is rare.

Risk factors for TB in SOT recipients

The rates and risks of TB in transplant recipients are highly dependent upon key features, such as,

1. A past history of treated TB
2. Prevalence of TB in the recipient and donor population
3. The organ transplanted (highest in lung transplant recipients)
4. The type and intensity of recipient screening for TB, and the use of prior or current anti-TB drug intake, preventively or curatively
5. The use of T-cell depleting antibodies
6. High intensity immunosuppression in post-transplant period
7. Enhanced immunosuppression in the setting of rejection
8. Diabetes mellitus
9. Haemodialysis for kidney transplant recipients
10. Hepatitis C virus infection in kidney transplant recipients
11. Chronic liver disease
12. Increased recipient age

Treatment of LTBI adds effectiveness to the outcome of organ transplants, even in the face of difficulties associated with treatment related adverse drug events and drug–drug interactions. It is therefore, of great importance to identify transplant candidates with LTBI and, whenever possible, treat before transplantation. It is also necessary to monitor and identify newly acquired TB after transplantation.

As shown in figure 5, infection with *M. tuberculosis* in the transplant setting can occur in four different clinical scenarios (74).

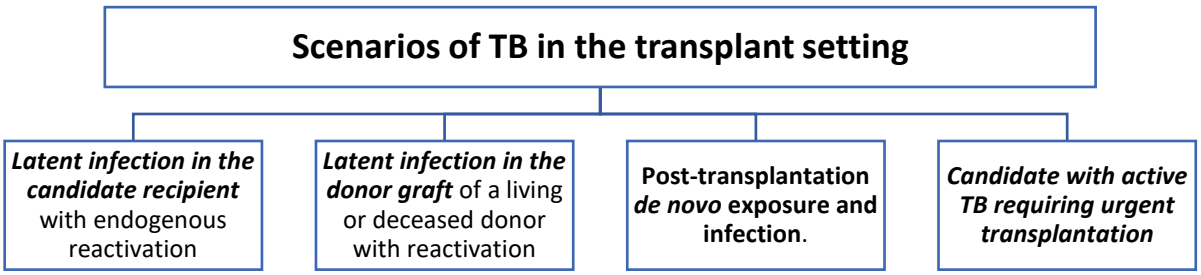


Figure 5: Scenarios of tuberculosis in the transplant setting

a) ***Latent infection in the candidate recipient*** with endogenous reactivation.

The risk of TB decreases with increasing time after infection and therefore, the risk of post-transplantation reactivation is probably inversely related to the interval between infection and transplantation.

b) ***Latent infection in the donor graft*** of a living or deceased donor with reactivation.

In this scenario, the risk of reactivation is probably highest early post-transplant period given the enhanced immunosuppression. A later onset may also occur with intensification of immunosuppression, in the event of a graft rejection. Transmission via lung transplantation is most likely as the pathogen load may be higher. Treatment of living donors previously identified as LTBI or risk factors for LTBI may reduce the risk of reactivation.

c) **Post-transplantation *de novo* exposure and infection**.

The infection has got a very high chance for immediate progression to disease but, it is not always readily recognized. Even if suspected, available immunodiagnostic tests for screening are less reliable in these immunosuppressed patients.

d) ***Candidate with active TB requiring urgent transplantation***

i.e., urgent liver transplantation.

Evaluation of transplantation donors and recipients

It is recommended that all SOT recipients and possibly all donors be routinely evaluated for LTBI, and this is best carried out prior to transplantation when feasible. It is also recommended that the SOT recipients should be evaluated in the post-transplant period where relevant (74).

Identification of LTBI in transplant recipients can be challenging. The optimal screening and testing strategies are not largely based on controlled trials. A generally consistent recommendation is that the epidemiologic risk factor assessment and chest radiography be performed as important components of the evaluation.

Recommendations for specific methods of testing for latent TB vary slightly among different settings, but all include a TST and/or IGRA tests. Positive screening results in individuals from high-risk groups for development of TB should receive preventive chemotherapy.

Testing with both TST and IGRAs simultaneously may minimize false-negative results. As with the 'boosting' seen with TST when repeated, a negative IGRA result may also become positive when performed at least 3 days after a TST, evoking a "false positive" boosted IGRA result. Boosting is evident by day 7, but not by day 3 post-TST administration. Day-3 cutoff appears to be a safe window within which to perform a standardized IGRA after a TST. Hence, it is recommended to perform TST and IGRAs simultaneously. Here, any positive

result may be considered as having latent TB, especially when there is a high pretest probability for latent TB or a concern over false-negative test results.

Box 9: Specific evaluation of transplantation donors and recipients for LTBI

1. A careful history of previous exposure to individuals with active TB should be taken from all transplant candidates including exposures and travel to/from areas highly endemic for TB
2. Previous history of active TB, the length and types of treatment and previous treatment for latent TB should be documented.
3. Chest radiographs should be examined for evidence of active or old healed TB
4. Conventional TST can be used in all situations, (refer page 38 for interpretation)
5. Patients with negative reactions should have a second skin test performed after one week, but before four weeks as the TST can convert from being falsely negative to positive due to "boosting" in some individuals with remote MTB exposure
6. QFT in liver transplant candidates indicate their utility in patients with advanced liver disease. However, indeterminate results are more common in candidates with higher MELD scores (75).
7. In transplant candidates with epidemiological evidence of high risk for latent or asymptomatic active TB, thorough evaluation should be done by an expert to exclude active TB.
8. Since the sensitivities of TST and IGRAs may not overlap, both tests should ideally be done on the first day. If facilities are not available to perform both tests on the first day, TST should be performed on the first day and if the TST is negative, IGRAs should be performed on day three after performing the TST (on the day of TST reading). The importance of reading the TST on the 3rd day should be emphasized to the patient on the day of the test performance.
9. Patients with a prior history of positive TST or IGRAs should be screened for active TB and then treated as appropriately without retesting for LTBI.
10. Individuals having a reliable prior history of being treated for latent TB infection or treated for TB disease need not undergo TST or IGRAs. However, these individuals should have a symptom review and chest X-ray, as well as additional testing if indicated, to screen for active TB.

Evaluation of LTBI among transplantation living donors

1. Donor-transmitted TB is typically due to either transplantation of organs from a donor with unrecognized active TB or due to reactivation of latent infection in the graft.
2. Living donors should undergo an evaluation starting with a symptom review and chest x-ray
3. TST should be interpreted as positive or negative according to the national guidelines for the general population which is ≥ 10 mm.

4. For living donors with LTBI, treatment should be considered prior to organ donation, especially for recent TST or IGRA converters. It is advisable to complete LTBI treatment prior to transplantation and therefore, a shorter regime is preferable.
5. Organs from potential living donors with active TB disease should not be used. In such occasion, the donor with active TB should be properly evaluated for disseminated TB and TB in the donor organ. Active TB should be treated with the appropriate standard treatment regimen and the donor should be re-evaluated for active disease after a time period as decided by the treating clinician on an individual basis.

Evaluation and use of deceased donor organs

1. Adequate screening for TB on deceased donors is challenging
2. A detailed history must be obtained from the donor's family or relatives on active or past TB
3. If the deceased is with higher risk of TB or the past imaging studies were suggestive of TB, respiratory samples should be collected for AFB smears and nucleic acid amplification tests. But even this approach may miss deceased donors with active TB disease who have subtle radiographic findings, or who have smear-negative TB.
4. In such a situation, consideration be given for chest CTs to evaluate for the evidence of prior healed TB or active disease, especially when a lung transplant is being considered.
5. The cell-mediated immunity may be depressed following brain death and therefore, the TST is not feasible.
6. *In vitro* assays with IGRAs to measure IFN-γ response accurately, a fresh blood specimen that contains viable white blood cells is needed. Though IGRAs would seem to be an attractive option for assessing LTBI, their performance in deceased donors has not been studied well. Nevertheless, it is advisable to draw blood to perform IGRAs for LTBI among all cadaveric donors as soon as a decision of organ donation is made by the transplant teams.
7. If the deceased donor is positive for IGRA it is, preferable to initiate TPT in the transplant recipient.
8. When deceased donors had TB risk factors but could not be tested for LTBI, active surveillance in the recipients (clinical monitoring at least during the first 6 months) for development of active TB disease and, on a case-by-case basis, provision of TPT, particularly to lung recipients is considered (74).

Evaluation of recipients

1. When evaluating recipients, the decrease in test sensitivity with increasing immunosuppression has important practical consequences. Therefore, screening should ideally be carried out before starting haemodialysis, transplant and administration of immunosuppressive drugs. At present, the advantage of either TST or IGRA for post-

transplant risk assessment is not known, as the positive predictive value of a positive test for the development of TB has not been sufficiently studied. The limited number of studies so far indicates that the value of IGRA may be higher in low-prevalence countries like Sri Lanka, as compared to highly endemic regions but, more studies are needed to comparatively assess different immunodiagnostic tests (74).

Box 10: Procedures to rule out active TB and to screen for LTBI among patients preparing for Solid Organ Transplantation (SOT)

1. Transplantation procedures should involve evaluation of living or deceased donors and recipients for LTBI.
2. Clinical and radiological assessment, to exclude active TB disease is mandatory before making a decision on management of LTBI.
3. A deceased donor whenever possible should be evaluated with radiological and microbiological investigations including respiratory samples for direct microscopy for AFB, culture, and Xpert as well as a fresh blood sample for IGRA.
4. Both TST and IGRAs should be performed within a proper time frame when evaluating transplant recipients. (As described in page 39)
5. Two step TST should be considered when evaluating transplant candidate/recipients to minimize false negativity due to cutaneous anergy.
6. The interpretation of TST is described in page 38.
7. Patients with a history of previous TB, but without evidence of treatment completion should be evaluated and managed by the pulmonologist on an individual basis.
8. Patients with radiological evidence of undiagnosed previous TB should be evaluated and managed by the pulmonologist on full course of anti-TB treatment or LTBI treatment on an individual basis, irrespective of TST and IGRA results.
9. Patients who had been adequately treated for previous active TB disease or latent TB infection will not need re-treatment for latent TB infection. However, these individuals should be evaluated for active TB.
10. Patients with a prior documented history of positive TST or IGRA should be treated for LTBI after excluding active TB. Retesting for LTBI among these patients is not indicated.

4.3.6. Patients preparing for Hematopoietic Stem Cell Transplantation

Haematopoietic Stem Cell Transplantation (HSCT) is a life-sustaining method of treatment. HSCT can be defined as the transfer of Haematopoietic Stem Cells (HSCs) from one individual to another (allogeneic) or the return of previously harvested HSCs to the same

individual (autologous) after manipulation of these cells and/or the recipient. The source of cells could be bone marrow, peripheral blood, or placental/umbilical cord blood (75,76).

T-cells play an important role in the protective immunity against TB. As a result of pre-transplant conditioning treatment regimens, post-transplant immunosuppressive therapies and Graft-versus Host Disease (GVHD) and its treatment causes severe impairment specially in the cell-mediated immunity and it is easy for them to get variety of infections including TB (77).

Tuberculosis is 10-40 times commoner in recipients of HSCT than in the general population but, the risk is 10 times less than compared to SOT recipients. This maybe because these patients do not receive lifelong immunosuppression as in the case of SOT. The incidence of *M. tuberculosis* infections in recipients of allogeneic stem cell transplantation ranges between 1-16% and varies considerably according to the type of transplant and the geographical location. Approximately 80% of *M. tuberculosis* infections in HSCT recipients have been reported in patients receiving allografts than in recipients of autografts. Usually, *M. tuberculosis* infections develop 45-365 days post-HSCT and most of the reported cases have occurred after 90 days of the HSCT (78).

The lungs are the most involved site of post-HSCT TB. At least one third of *M. tuberculosis* infections in recipients of HSCT are disseminated at presentation with predominant extra-pulmonary involvement. TB in HSCT may present in an atypical manner such as pyrexia of unknown origin, pancytopenia due to bone marrow involvement with a myeloid maturation arrest and other non-specific features particularly in patients with extra-pulmonary involvement. The lung involvement by TB may resemble that of invasive fungal pulmonary infections and patients may even present with mycobacteraemia causing a rapidly progressive illness (79,80).

In recipients of HSCT having *M. tuberculosis* infections, high mortality rates are encountered in patients with miliary TB and disseminated TB infections. Mortality rates are higher in allogeneic HSCT than in autologous HSCT recipients. Mortality rates due to *M. tuberculosis* infections in recipients of HSCT range from 0 - 75% and mortality is related to the type of HSCT, the degree of immunosuppression, and how early the diagnosis of TB infection is made (80).

In the pre-transplant diagnostic workup of patients who have clinical symptoms, chest imaging is important. At this stage, the typical pulmonary TB changes of fibrotic, infiltrating, and cavitary lesions may still be present. However, if patients are infected after HSCT, these may show different image findings. It can display miliary shadows and inhomogeneous fusion patch shadows. Proliferative lesions and cavitation may be uncommon. High resolution CT (HRCT) examination has a high value for the diagnosis at this stage, especially when patients are suspected of having other infections.

When the sputum microbiological evaluation gives negative results in repeated AFB direct smears, *M. tuberculosis* cultures and MTB/RIF tests, appropriate evaluation of other clinical specimens such as broncho-alveolar lavage fluid, urine, cerebrospinal fluid, pleural and ascitic fluid, and tissue biopsies are important (80,81).

TB screening using TST or Quanti-FERON-TB Gold in Tube (QFT-GIT) in HSCT is controversial. IGRAs tests rely on the fact that T-lymphocytes will release IFN-γ when exposed to specific antigens of *M. tuberculosis*. As a result of severe immune dysfunction, TB can easily get missed by false negative results, influencing the clinical application value.

Regarding TSTs, the value maybe limited due to depressed cell-mediated immune response yielding false-negative results. Another important fact to remember is whether TST-specific memory T-cells are transferred from the marrow donor to the recipient and persist in the long-term affecting its diagnostic value as a positive test may have been related to donor-derived T-cell memory (83, 84). IGRAs may be superior to TST in sensitivity and specificity, especially in those who have a significant hypo immunity (82).

Because of the high risk of reactivation or the development of a new infection, TB prophylaxis should be administered to HSCT recipients or candidates who, have been exposed to a person with active, infectious pulmonary (especially sputum-smear positive) or laryngeal TB, regardless of the recipient's or candidate's TST or IGRA status. Similarly, patients with a positive TST result should be started on TPT regardless of prior BCG vaccination if they did not receive a full course of treatment for active TB or LTBI. Patient with a positive IGRA result, without previous history of treatment for active TB or LTBI should also be started on preventive treatment after excluding active TB. However, exposure of a candidate or a recipient of HSCT to an active, but non-infectious patient with extra-pulmonary TB does not require preventive therapy.

Box 11: Procedures to rule out active TB and to screen for LTBI among patients preparing for Hematopoietic Stem Cell Transplantation (HSCT)

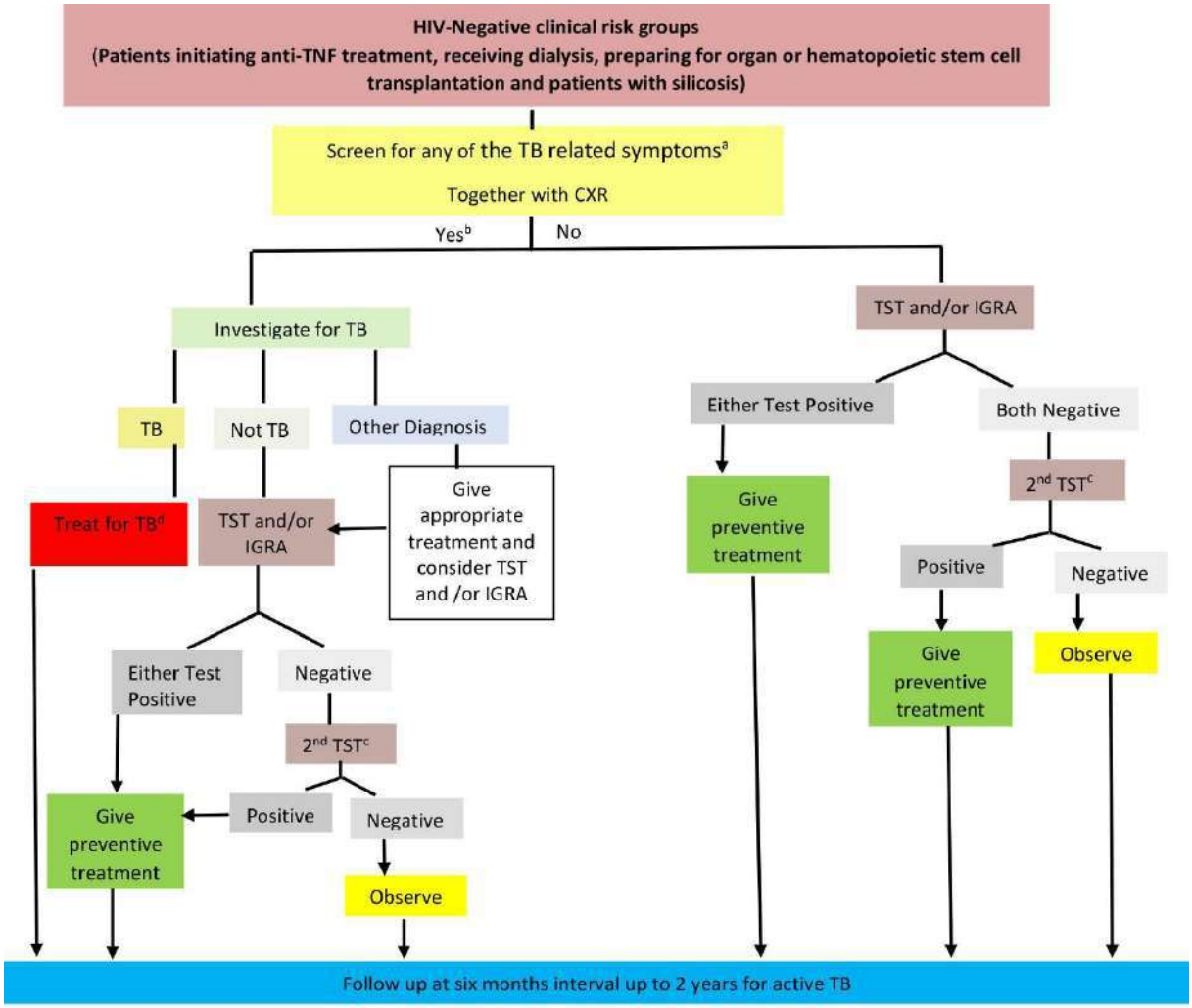
1. Clinical and radiological assessment to exclude active TB disease is mandatory before making a decision on management of LTBI.
2. Appropriate evaluation of other clinical specimens such as bronchoalveolar lavage fluid, urine, cerebrospinal fluid, pleural and ascitic fluid, and tissue biopsies for *M. tuberculosis* infection is also important depending on the circumstance.
3. In the pre transplant evaluation of the recipient both TST and IGRAs should be performed according to the proper time. (As described in pages 37-43)
4. Two step TST should be considered when evaluating transplant candidate/recipients to minimize false negativity due to cutaneous anergy.
5. TST should be considered as positive when there is ≥5 mm induration in the recipient and ≥10mm in the donor at 48–72 hrs. (Recommend a discussion between the transplant team and the respiratory physician when there are concerns about the value of the mantoux test in a child who has been Vaccinated with BCG.)
6. Recipients or candidates who, have been exposed to a person with active, infectious pulmonary or laryngeal TB, should be started on TPT regardless of their TST or IGRA status. (Risk will be assessed according to duration and the intensity of the exposure on a case basis. For Household contacts the duration is usually 3 months.
7. Patients with a history of previous TB, but without evidence of treatment completion should be evaluated and managed by the pulmonologist on full course of anti-TB treatment or LTBI treatment on an individual basis.
8. Patients with radiological evidence of undiagnosed previous TB should be evaluated and managed by the pulmonologist on full course of anti-TB treatment or LTBI treatment on an individual basis, irrespective of TST and IGRA results.
9. Patients who had been adequately treated for previous active TB disease or latent TB infection will not need re-treatment for latent TB infection. However, these individuals should be evaluated for active TB.
10. Patients with a prior documented history of positive TST or IGRA should be treated for LTBI after excluding active TB with the concurrence of the transplant team and respiratory physician. Retesting for LTBI among these patients is not indicated.

Timing of treatment for LTBI in SOT and HSCT recipients.

The timing of TPT in SOT recipients has not been well studied. The LTBI treatment may be administered pre- or post-transplant with the timing determined by treatment risks and benefits. Ideally, completion of the entire course of LTBI should be aimed before listing for SOT/HSCT as it reduces the risk of reactivation of TB and furthermore, it lowers the risk of drug interactions.

Organ transplantation may be performed in patients who are receiving treatment for LTBI, especially if the potential benefit of early transplantation outweighs the risk of reactivation TB. For these patients who are unable to complete the entire course of the LTBI treatment prior to transplant, all attempts should be made to complete the remainder of the course post-transplantation. After transplantation, the LTBI treatment should be resumed as soon as medically possible and continued until completion of the originally planned course.

If commencement of treatment of LTBI has been delayed until after transplantation, then the selected regimen should be initiated as soon as medically possible after the recipient is stabilized. In cases of deceased donors with untreated LTBI, chemoprophylaxis is recommended for the organ recipients, especially in the case of lung transplants.



a. Any symptom of TB: cough, hemoptysis, fever, night sweats, weight loss, chest pain, shortness of breath, fatigue
b. Either symptoms or chest Xray or both are suggestive of TB or other diseases.
c. If unable to perform IGRA or both initial TST and IGRA are negative perform 2nd TST. (As part of two step TST Refer page 44)
d. Resume regular screening for TB reactivation after completion of treatment for active TB disease..

Figure 6: Algorithm for diagnosis and treatment of LTBI among HIV-Negative clinical risk groups

4.4. HIV-Negative other vulnerable groups

WHO guideline states that the evidence for the benefits of systematic testing and treatment of LTBI might not outweigh the harm in the population risk groups such as HCW, immigrants from countries with high TB burden, prisoners, homeless people and people who use illicit drugs. The decision to test for and treat LTBI systematically in these population groups should be made in accordance with the local TB epidemiology and context, health system structure, availability of resources and overall health priorities.

4.4.1. Health Care Workers

By definition HCW are those who work to improve the health of the people. Medical officers, nurses, attendants and laboratory workers who are involved in the TB patient management are considered as high-risk groups for TB due to the exposure status as an occupational hazard. The situation is aggravated more due to the poor adherence to infection control

measures. There are significant number of HCW diagnosed with TB disease yearly as a result. According to the NPTCCD, the number of HCW diagnosed with TB was 78 in 2017 and 76 in 2018 (2, 17). A systematic review done in 2016 revealed that LTBI pooled prevalence among HCW was 47% in 7 high TB burden countries and the incidence ranged from 2.8% - 38%. Another study done in low- and middle-income high TB burden countries found that the prevalence of LTBI was 55% among HCW (85).

However, screening of HCW for LTBI will be carried out in a phased-out manner by prioritizing more risk categories.

Box 12: Procedures to rule out active TB and to screen for LTBI among Health Care Workers

1. Conduct screening in a stepwise manner considering human resources and logistics
2. Offer LTBI screening for any HCW who request LTBI screening
3. Prioritize LTBI screening among HCW who work in Outpatient Departments, Intensive Care Units, Medical wards, Chest wards, bronchoscopy rooms, laboratory workers etc.
4. Prioritize LTBI screening among HCW who have co-morbid immune suppressive conditions and/or a recent exposure to a known bacteriologically confirmed pulmonary TB case.
5. Utilize symptom screening and chest X-ray together as the initial screening tool to rule out active TB.
6. Utilize TST or IGRA as the screening test for TB.
7. If only TST is used, the "two-step method" should be implemented to prevent booster reactions leading to false positive results in serial testing in the future.
8. TST is considered as positive if there is ≥10mm induration at 48–72 h if there are no immunosuppressive conditions (refer table 2).

4.4.2. Prisoners

TB generally affects the most vulnerable people, those who live in poverty, are marginalized or economically and socially deprived. Prison community in particular has a greater risk of getting Tuberculosis. Available data around the globe shows that prevalence of TB among prisons are 10 -100-fold higher than that in the general population.

Poor living conditions in prisons, overcrowding and prolonged imprisonment periods are considered as the major contributory factors for such higher prevalence. In addition, adverse environment in prisons aggravates this situation, creating obstacles in accessing health care and promoting unhealthy behaviors.

Studies conducted worldwide have found high prevalence rates of TB among prisoners. A multi-center cross sectional study conducted among 1247 prisoners in Italy revealed that 17.9% were positive for TST (9). A study in Karachi among juvenile prisoners found a higher prevalence of TB (3.9%) among inmates (86). Prison survey conducted in 2013 in Sri Lanka revealed that the proportion of active TB among prisoners was 1.7% (87).

Although WHO guideline identifies prisoners as a vulnerable group, LTBI screening among prisoners in the local setting will be carried out considering factors such as the local epidemiology, assurance of treatment adherence, human resources and logistics to conduct screening programs in prisons.

Box 13: Procedures to rule out of active TB and screen for LTBI among prisoners

1. Conduct screening in a stepwise manner considering human resources and logistics
2. Carry out LTBI screening among those who were convicted for 6months or more
3. Utilize symptom screening and chest X-ray together as the initial screening tool to rule out active TB
4. Utilize TST or IGRA as the screening test for LTBI
5. TST is considered as positive if there is ≥10mm of induration at 48–72 provided there are no immunosuppressive conditions (refer table 2)
6. Treatment should be provided as Directly Observed Treatment (DOT)

5. DIAGNOSING LATENT TB INFECTION

There is no gold standard method for diagnosing LTBI. TST and IGRAs require a competent immune response in order to identify people infected with TB and hence are not perfect tests for measuring progression to active disease in all persons. Either a TST or IGRAs can be used to test for LTBI. The WHO strongly recommends the two tests as equivalent options, with relatively similar advantages and disadvantages. The availability, affordability and the relevance to the given clinical context will determine which test will be chosen by the clinicians together with the programme managers.

Both TST and IGRA tests can lead to false-negative results, particularly for very young children and immunocompromised individuals such as PLHIV. Therefore, LTBI testing by TST or IGRA are not an essential requirement for child household contacts under 5 years. However, it is recommended for the testing of LTBI among following groups.

- Adults, adolescents and children ≥5years who are close contacts of patients with pulmonary TB
- Patients initiating anti-TNF alpha treatment, patients receiving dialysis, patients preparing for organ or haematological transplant and patients with silicosis
- Prisoners and HCW (with considerations of programmatic capacity and treatment adherence)

The incremental cost-effectiveness of IGRAs and TST appear to be influenced mainly by their accuracy. BCG vaccination plays a decisive role in reducing the specificity of TST, leading the choice towards IGRA-only strategies. However, the impact of BCG vaccination on the specificity of TST depends on the strain of vaccine used, the age at which the vaccine was given, and the number of doses administered. When BCG is given at birth, as it is the case in most parts of the world including Sri Lanka, it has a variable, limited impact on TST specificity.

5.1. Tuberculin Skin Testing

The **Mantoux or** TST is the standard method of determining whether a person is infected with *Mycobacterium tuberculosis*. Reliable administration and reading of the TST requires standardization of procedures, training, supervision, and practice (88).

How is the TST Administered?

The TST is an intradermal injection. Itis performed by injecting 0.1 ml of tuberculin purified protein derivative (PPD) into the inner surface of the forearm (preferably the left). The injection should be made with a tuberculin syringe, with the needle bevel facing upward. When placed correctly, the injection should produce a pale elevation of the skin (a wheal) 6 to 10 mm in diameter.

How is the TST read?

The skin test reaction should be read between 48 and 72 hours after administration. A patient who does not return within 72 hours will need to be rescheduled for another skin test as soon as possible. Hence the importance of coming on 48-72 hours to read the test should be emphasized to the patient at the time of test performance.

The induration (palpable, raised, hardened area or swelling) should be measured **and recorded in millimeters.** The reading should not be recorded as negative or positive. Absence of an induration should be recorded as 0 millimeter. The reader should not measure erythema (redness). The diameter of the indurated area should be measured across the forearm (perpendicular to the long axis).

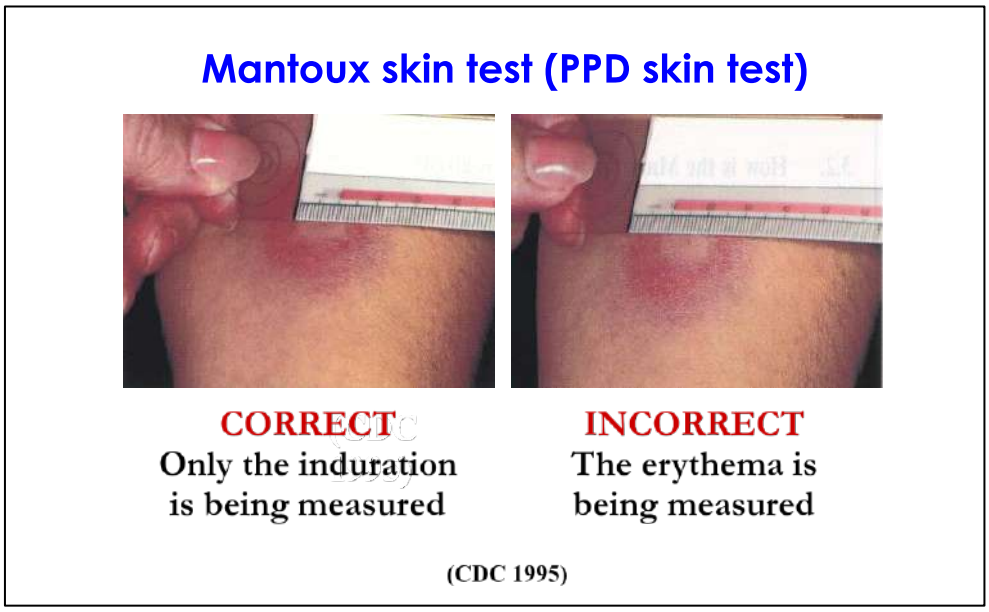


Figure 7: Interpretation of Mantoux skin test (CDC 1995)

How are TST Reactions Interpreted?

Importance of the skin test interpretation depends on two factors:

- Measurement in millimeters of the induration
- Person's risk of being infected with TB and of progression to disease if infected

1. **Cutoff values for TST in selected risk categories**

An induration of 5 or more millimeters is considered positive in patients who are immunosuppressed.

2. **Cut off value for others**
   - **An induration of 10 or more millimeters is considered positive for persons who are (Immunocompetent)**

****Seek advice from a respiratory physician for any concerns about the value of the mantoux test in a child who has been vaccinated with BCG.**

TST could give rise to false positive as well as false negative results due to numerous reasons. The most common reasons are indicated in Box 15 and 16 below.

Box 15

Reasons for False-Positive Reactions

- Infection with non-tuberculosis mycobacteria
- Previous BCG vaccination
- Incorrect method of TST administration
- Incorrect interpretation of reaction

Box 16

Reasons for False-Negative Reactions

- Cutaneous anergy (anergy is the inability to react to skin tests because of a weakened immune system)
- Recent TB infection (within 8-10 weeks of exposure)
- TB infection among elderly
- Very young age (less than 6 months old)
- Some viral illnesses (e.g. measles, chickenpox) and recent live-virus vaccination (e.g. measles)
- Incorrect method of TST administration
- Incorrect interpretation of reaction

Who can receive a TST?

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

How often can TST 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.

What is a boosted reaction?

Some people infected with *M. tuberculosis* may have a negative reaction to the TST if many years have passed since they became infected. They may have a positive reaction to a subsequent TST because the initial test stimulates their ability to react to the test. This is commonly referred to as the "booster phenomenon" and may incorrectly be interpreted as a

skin test conversion (going from negative to positive). For this reason, the "two-step method" is recommended at the time of initial testing for individuals in whom we anticipate periodic testing (e.g., health care workers).

What is two-Step-TST?

Giving a second TST after an initial negative TST reaction is called two-step testing. A two-step TST should be performed if subsequent TST is anticipated to be conducted in future (e.g., among HCW) or performed among immunosuppressive individuals to overcome anergy. The two-step protocol needs to be properly performed and documented. A two step is defined as two TST's done within 1-3 weeks of each other (Figure 8).

If the TST is administered to TB-infected individuals with faded immune memory, the reaction (induration) may be small or absent; i.e., falsely negative. However, this TST may restore (or boost) immune memory and there may be a recall response on repeat testing resulting in a positive reaction. This reaction, now positive on the second test, reflects the prior TB infection but not due to first TST.

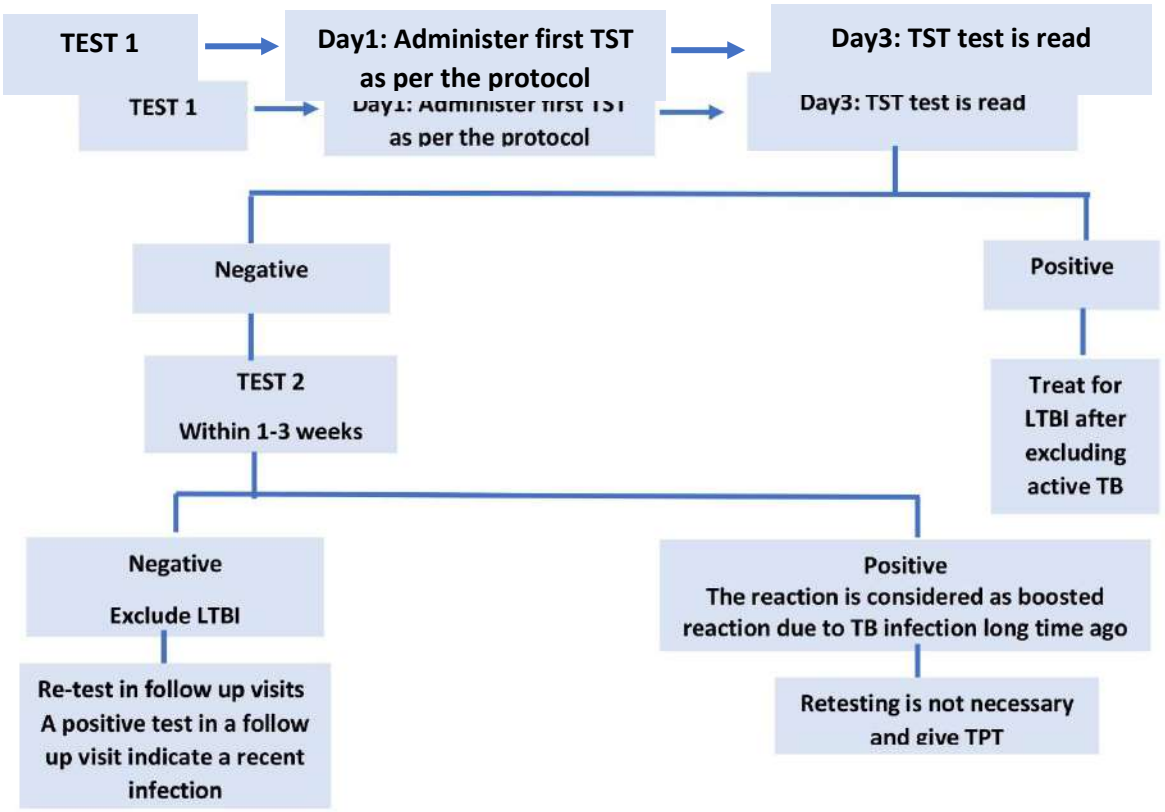


Figure 8: Schematic representation of two step TST

Can TST be given to persons receiving vaccinations?

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

- Either on the same day as vaccination with live-virus vaccine or 4-6 weeks after the administration of the live-virus vaccine

5.2. Interferon-Gamma Release Assays (IGRAs) – Blood Tests for TB Infection

IGRAs area whole-blood test that can aid in diagnosing *Mycobacterium tuberculosis* infection. They do not help to differentiate LTBI from active TB disease. Two IGRAs that have been approved by the U.S. Food and Drug Administration (FDA) are commercially available (89):

- QuantiFERON®-TB Gold In-Tube test (QFT-GIT)
- T-SPOT®.*TB* test (T-Spot)

IGRAs measure a person's immune reactivity to *M. tuberculosis*. White blood cells from most persons that have been infected with *M. tuberculosis* will release interferon-gamma (IFN-g) when mixed with antigens (substances that can produce an immune response) derived from M. tuberculosis. To conduct the tests, **fresh blood samples** are mixed with antigens and controls.

Table 1: Comparison between currently available IGRAs

	QFT-GIT	T-Spot
Initial Process	Process whole blood within 16 hours of collection	Process peripheral blood mononuclear cells (PBMCs) within 8 hours of collection, or if T-Cell Xtend® is used, within 30 hours of collection
***M. tuberculosis* Antigen**	Single mixture of synthetic peptides representing ESAT-6, CFP-10 & TB7.7.	Separate mixtures of synthetic peptides representing ESAT-6 & CFP-10
Measurement	IFN-γ concentration	Number of IFN- γ producing cells (spots)
Possible Results	Positive, negative, indeterminate	Positive, negative, borderline, invalid

Steps in administering an IGRA test

Prior to performing the test, contact the relevant laboratory for availability of test, method of collection, and transportation. Make sure that the samples are dispatched within the specified time to ensure testing with viable blood cells. Draw a blood sample from the patient according to the test laboratory instructions.

- ❖ Schedule a follow-up appointment for the patient to receive test results.
- ❖ Based on test results, provide follow-up evaluation and treatment as needed.

Interpretation of IGRA test results

IGRA interpretations are based on the amount of IFN-γ that is released or on the number of cells that release IFN-γ. 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.

As with the TST, the IGRA test should be used as an aid in diagnosing infection with M. tuberculosis.

- A positive test result suggests that *M. tuberculosis* infection is likely
- A negative result suggests that infection is unlikely
- An indeterminate result indicates an uncertain likelihood of *M. tuberculosis* infection. A borderline test result (T-Spot only) also indicates an uncertain likelihood of *M. tuberculosis* infection.

Recommendations to use IGRA test:

IGRAs can be used in place of TST in all situations that recommends TST as an aid in diagnosing *M. tuberculosis* infection, with preferences and special considerations noted below.

- Screening of HCW and others undergoing serial evaluation for *M. tuberculosis* infection.
- Persons from groups that historically have poor rates of return for TST reading.

TST is preferred over IGRA for testing children less than 5 years of age.

Advantages of IGRA

- Requires a single patient visit to conduct the test.
- Results are available within 24 hours.
- Prior BCG (Bacilli Calmette-Guerin) vaccination does not cause a false-positive IGRA test result.

Disadvantages of IGRA

- Blood samples must be processed within 8-30 hours after collection while white blood cells are still viable.
- Errors in collecting or transporting blood specimens or in running and interpreting the assay can decrease the accuracy of IGRAs.
- Limited evidence on the use of IGRAs for: Children younger than 5 years of age, persons recently exposed to M. tuberculosis, immunocompromised persons, and for serial testing.
- Tests are expensive.

6. CLINICAL MANGEMENT OF LATENT TB INFECTION

6.1. Treatment options for LTBI

The selection of treatment options by the treating clinicians should consider the characteristics of the persons who are to receive treatment to ensure that it is not only initiated but also completed. The decision can be taken on shorter to longer regimens after considering the acceptability and the suitability of the individuals receiving treatment, preference of the clinicians providing treatment and availability of the said regimen in the programme.

Following recommendations in the WHO guideline (9) was considered during the decision-making process on offering treatment options for different risk groups.

- 6 months isoniazid is an equivalent option to 9 months of isoniazid in countries with a low TB incidence and a strong health infrastructure.
- 6 months isoniazid is preferable to 9 months from the point of view of feasibility, resource requirements and acceptability to patients.
- Benefits of 3 months daily rifampicin plus isoniazid for infants and children < 15 years of age outweigh the harm, given its safety profile, the higher rate of completion as compared with isoniazid monotherapy and the availability of child-friendly, fixed-dose combinations of rifampicin and isoniazid.
- Regimens containing rifampicin should be prescribed with caution to PLHIV who are on ART because of potential drug interactions.

Recommended regimens for treatment of LTBI is stated in Table 2.

Table 2: Recommended regimens for treatment of LTBI

Regimen	Description
3HP/1HP	• 3HP - Once-weekly isoniazid–rifapentine for 12 weeks, total 12 doses for adults, adolescents and children above 2 years who are contacts of Pulmonary Tuberculosis patients: or • 1HP – a daily dose of HP for one month for adolescents and children above 2 years who are contacts of Pulmonary Tuberculosis patients • Both these regimens can also be given to PLHIV.
3HR	• Daily rifampicin plus isoniazid for 3 months for all contacts – total 90 doses • Can also be given to PLHIV who are on rifampicin-friendly ART regimen
6H/9H/36H	• Daily INH for 6 months for adult and child contacts and PLHIV – total 180 doses • Daily INH for 9 months for adult and child contacts and PLHIV – total 270 doses • Daily INH for 36 months for PLHIV, especially those PLHIV with positive TST – total 1080 doses
3-4HR	• low-transmission settings

Table 3: Recommendations of treatment options for identified LTBI patients in Sri Lanka, by risk category

Risk Category	Treatment Options			Remarks
	6H	3HR	3HP	Despite lack of strong evidence to recommend a single regimen, shorter regimen is preferred whenever possible
Adults and adolescents living with HIV	**X**	X	X	To be decided by an expert on the use of rifampicin containing regimen depending on the ART regimen
Children living with HIV	**X**	X	X	To be decided by an expert on the use of rifampicin containing regimen depending on the ART regimen
Adults and adolescents with LTBI who are contacts of PTB	**X**	X	X	
Children <5 who are contacts of PTB	X	X	**X**	
Non- Household close contacts			**X**	
Contacts of patients with Multidrug-resistant tuberculosis (MDR)				To be decided by an expert on individual basis
Patients **initiating anti-TNF treatment** diagnosed with LTBI	X	X	**X**	To be decided by an expert
Patients **receiving dialysis** diagnosed with LTBI	X	X	**X**	To be decided by an expert
Patients **undergoing organ or hematological transplantation** diagnosed with LTBI	X	X	**X**	To be decided by an expert
Patients with silicosis diagnosed with LTBI	X	X	**X**	To be decided by an expert
Prisoners, health-workers	X		**X**	To be decided by an expert

"X"-Preferred regime

Table 4: Recommendations of drug dosage for adults and children under respective

Drug regimen	Dose per kg body weight	Maximum dose
Isoniazid alone, daily for 6 or 9 months	Adults, 5mg; Children, 10mg (range 7–15 mg)	300 mg
Isoniazid plus rifampicin, daily for 3–4 months	Isoniazid: adults,5mg Children,10mg (range 7–15 mg) Rifampicin: Adults, 10 mg Children, 15 mg (range 10–20 mg)	Isoniazid,300mg Rifampicin,600mg
Rifapentine plus isoniazid, weekly for 3 months (12 doses)	Individuals aged ≥12 years: Isoniazid-15mg Individuals aged 2–11 years: Isoniazid: 25 mg Rifapentine: 10.0–14.0 kg = 300mg 14.1–25.0 kg = 450mg 25.1–32.0 kg = 600mg 32.1–50.0 kg = 750mg >50 kg = 900mg	Isoniazid,900mg Rifapentine,900mg

6.2. Adverse events and monitoring of adverse events

Individuals who need treatment for LTBI should be explained on the rationale of treatment and importance of completing it. As these individuals do not have active disease, their risk for adverse events during treatment must be minimized by adhering to the most appropriate regimen.

Table 5: Adverse effects, drug interactions and precautions - Isoniazid (INH)

Drug	Isoniazid (INH)
Possible adverse effects and recommended actions	Generally, well tolerated. Less common side effects. • Systemic or cutaneous hypersensitivity reactions • Asymptomatic elevation of liver enzyme level, more often at the onset of treatment. • Peripheral neuropathy (Weakness, numbness and tingling of hands and feet) is less common and more likely in malnourished, chronic alcoholics, pregnant women, breast feeding mothers, patients infected with HIV and diabetes. **This can be prevented or minimized by supplementary pyridoxine 10mg daily**. • Symptomatic hepatitis is an uncommon but potentially serious reaction that can usually be averted by promptly withdrawing the treatment.
Drug interaction	• Can cause increased serum levels of phenytoin, carbamazepine, theophylline, warfarin, selected benzodiazepines and vitamin D. • Inhibition of monoamine oxidase and histaminase by INH can cause significant drug-food interactions. • Food greatly decreases isoniazid bioavailability. Hence, it is advisable to take on empty stomach usually 1hour before a meal.
Precautions	• Patients on isoniazid should be cautioned on eating red fish (balaya, kelawalla) which contain high concentrations of histamine as Isoniazid is an inhibitor of histaminase.

It is recommended to withhold INH if a patient's transaminase level exceeds 3 times the upper limit of normal and/or associated with symptoms.

Table 6: Adverse effects, drug interactions and precautions- Rifamycins

Drug	Rifamycin -Rifampicin (RIF) and rifapentine (RPT)
Possible adverse effects and recommended actions	• Cutaneous reactions, such as pruritus are generally self-limiting. **Treatment could be continued.** • Hepatotoxicity, evidenced by transient asymptomatic hyperbilirubinemia. • Hypersensitivity reactions, including hypotension, nephritis or thrombocytopenia, and manifested by symptoms such as fever, headache, dizziness/lightheadedness, musculoskeletal pain, petechiae, and pruritis. • Gastrointestinal symptoms such as nausea, anorexia, and abdominal pain. If severe, should discontinue treatment • Orange discoloration of body fluids, such as breast milk, is expected and harmless. Patients should be advised beforehand. Soft contact lenses and dentures may be permanently stained
Drug interaction	• Reduced serum levels of methadone, warfarin, hormonal contraceptives, and phenytoin. • Women using hormonal contraceptives should be advised to consider an alternative method of contraception (e.g., a barrier method).
Precautions	• Should be prescribed with caution to people living with HIV who are on ART because of potential drug interactions. • 3-month regimen of weekly rifapentine plus isoniazid can be administered to patients receiving efavirenz-based antiretroviral regimens without dose adjustment. • Administration of rifapentine with raltegravir was found to be safe and well tolerated. • Rifampicin can be given with efavirenz-based regimens. However, it should be avoided with boosted protease inhibitors
Contraindications	• Known hypersensitivity to Rifamycins. • Active, unstable hepatic disease (with jaundice)

6.2.1. Potential drug interactions between Rifamycins and ARTs

ART regimes offered in Sri Lanka consists of a backbone of 2 drugs from antiretroviral belonging to Nucleoside/Nucleotide Reverse Transcriptase inhibitors (NRTIs) and a third agent from any of the following classes

1. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)
2. Protease Inhibitor (PI)
3. Integrase Strand Transfer Inhibitors (INSTI)

Significant drug-drug Interactions (DDIs) are found with this third agent and rifamycins.

Table 7: Use of ARTs and Rifamycins and possible drug-drug interactions (DDIs)

ART class	Combination with Rifampicin	Combination with Rifapentine
Non-Nucleoside Reverse Transciptase Inhibitors (NNRTIs)		
• Efavirenz	Efavirenz + Rifampicin – can be co administered without any dose adjustments.	Efavirenz +Rifapentine – Can be co administered.
• Nevirapine	Nevirapine + Rifampicin – co administration is contraindicated due to reduced Nevirapine concentration.	Nevirapine + Rifapentine – Co administration has not been studied.
Protease Inhibitors (PIs)		
• Lopinavir	Lopinavir/r +Rifampicin – Co administration is generally not recommended due to significant decrease in Lopinavir levels. When there is no other option, LPV/r in 400/400mg twice daily dose with rifampicin can be considered, however this can lead to a higher incidence of gastrointestinal and liver toxicity.	PIs + Rifapentine – Co administration has not been studied and is not recommended.
• Atazanavir	Atazanavir + Rifampicin – Co administration is contraindicated due to significant decrease in atazanavir levels which could lead to resistance development.	
• Darunavir	Darunavir + Rifampicin – Co administration is contraindicated. Higher doses of Darunavir may be considered if co administration is absolutely necessary.	
Integrase Strand Transfer Inhibitors (INSTIs)		
• Raltegravir		Raltegravir + Rifapentine – Can be used without any dose adjustment
• Dolutegravir		Dolutegravir + Rifapentine – Co administration can lead to reduction in dolutegravir levels.

Once diagnosed, treatment for LTBI should be commenced as soon as possible in all risk categories except PLHIV. TPT for the PLHIV can be initiated after confirming that the liver enzymes test after initiation of ART is not significantly elevated.

When presented with side effects manifesting clinical or biochemical abnormalities expert advice should be taken and appropriate management should be implemented.

6.3. Patient Monitoring and Education during Treatment

1. Explain the disease process and rationale for medication in the absence of symptoms or radiographic abnormalities. Review the importance of completing treatment for LTBI.
2. Discuss possible side effects of LTBI medications.
3. Patients receiving LTBI treatment should be advised to stop treatment and contact the health care provider immediately with the onset of above symptoms.
4. All patients receiving LTBI treatment should be evaluated at least **monthly** for the following:
    a. Adherence to the prescribed regimen
    b. Signs and symptoms of TB disease
    c. Adverse reactions
5. Laboratory testing at the start of LTBI therapy is mandatory for patients with any of the following factors:
    a. History of liver disease (e.g., hepatitis B or C, alcoholic hepatitis, or cirrhosis)
    b. Regular use of alcohol
    c. Risks for chronic liver disease
    d. HIV infection
    e. Pregnancy or the immediate postpartum period (i.e., within 3 months of delivery)
6. Baseline testing can be considered on an individual basis, especially for patients taking other medications for chronic medical conditions. For individuals with abnormal baseline test results. The decision to commence treatment should be reviewed by an expert.
7. After baseline testing, routine periodic retesting is recommended for persons who had abnormal initial results and other persons at risk for hepatic disease. Individuals with abnormal test results, should be reviewed by an expert.

6.4. Adherence and completion of preventive treatment

Adherence and completion are important to achieve the required outcome of LTBI treatment. Many factors affect adherence to LTBI treatment. Fixed Drug Combinations (FDCs) over individual drugs and shorter regimen improves the adherence and completion of treatment.

6.5. Management of LTBI treatment interruption

Table 8: Management of LTBI treatment interruption

Treatment regimen	Time and duration of interruption	Actions to be taken
Isoniazid alone, daily for 6 months Isoniazid plus rifampicin, daily for 3 months	Less than 2 weeks	Resume preventive treatment immediately upon return and add the number of days of missed doses to the total treatment duration. 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).
	More than 2 weeks	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. If less than 80% of doses expected in the regimen were taken, but the treatment course can still be completed without detailed reevaluation if **the total regimen can be completed with an addition of 33% to the total treatment duration.** EX: *For 6H, should be completed within 8 months of initiation of TPT. *For 3HP, should be completed within4 months of initiation of TPT. 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.

Rifapentine plus isoniazid, weekly for 3 months (12 doses)	Weekly schedule of one dose missed	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). 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.
	More than 1 weekly doses of 3HP missed	If between1–3 weekly doses are missed, treatment is continued until all 12 doses are taken, thus prolonging the treatment duration to a maximum of 16 weeks. If, however, 4 or more weekly doses are missed, consider restarting the full TPT course. If adherence to a weekly routine is not possible, consider discontinuing 3HP and offering an alternative (daily) regimen.

In addition to monitoring treatment completion, a number of unfavorable 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, and 3HR

• 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

7. PROGRAMMATIC MANAGEMENT, MONITORING AND EVALUATION

Implementation of LTBI screening and treatment involves a comprehensive part in relation to programmatic management. A conducive national policy, with a plan for programmatic LTBI screening and management including standard operating procedures to facilitate implementation of the recommendations in this guideline with the involvement of all stakeholders will be prepared by the NPTCCD.

7.1. Advocacy and raising public awareness

As LTBI screening programme is a novel intervention, it is very important to advocate all stakeholders to get their support during implementation. Use of proper communication channels to raise public awareness is also a mandatory requirement. This should be incorporated at the inception of the implementation of LTBI screening programme. All individuals should be made aware about the importance of screening, techniques of screening, whom should be screened and what the advantages are for the individual and the community. Publicity campaigns and capacity development of non-governmental organizations and community-based organizations would also be important to increase community awareness in a bigger scale.

7.2. Provision of dedicated resources for programme implementation

As LTBI screening and management add up an additional piece of work to the routine clinic work, provision of necessary human resources, and logistics will be prioritized by the NPTCCD as well as the provincial and regional health authorities. However, implementation of the programme at district level should be focused in a scaled-up manner prioritizing more vulnerable group first and gradually adding the other groups which are less vulnerable.

7.3. Capacity building of health staff

Capacity building of the District Chest Clinic (DCC) staff and if required the staff of relevant stakeholder institutions who engage in screening should be identified as key components. Central level Training of Trainer (ToT) programmes are important to educate and to build the skills of district teams in order to roll out the activities and to increase the awareness of all the stakeholders at district level.

During these training programs especial emphasis will be given on following

- Maintaining confidentiality
- Non-discriminating behavior
- Counselling on adherence
- Managing difficult situations

7.4. Uninterrupted supply of quality drugs

The National Programme will take the responsibility of continuous provision of WHO prequalified drugs. Similar priority will be provided to register newer drugs which has been identified by the GDGas treatment options.

7.5. Establishment of Adverse Drug Reaction surveillance system (ADRS)

An Adverse Drug Reaction surveillance (ADRS) system should be established to monitor the side effects of the drugs that has been used in the management of people with LTBI. Each and every adverse reaction should be notified to the NPTCCD in order to take actions based on the evidence collected through the ADRS.

7.6. Recording and reporting

Proper record keeping of the persons who are screened for LTBI and who are found to have LTBI and started treatment should be maintained at all DCCs. Status of LTBI screening and outcomes should be reported to the NPTCCD on a quarterly basis. An electronic system to keep records on LTBI patients will be developed and linked with the existing ePIMS. A monitoring system will be established to monitor the outcomes of the persons who have already completed LTBI treatment. Following are the records and reports that should be maintained and compiled at DCCs.

1. LTBI 01 - LTBI Screening Record (Annex I)
2. LTBI 02 - LTBI Treatment Card (Annex II)
3. LTBI 03 - LTBI DOTS Card (Annex III)
4. LTBI 04 - LTBI Treatment File (Annex IV)
5. LTBI 05 - District LTBI Screening Register (Annex V)
6. LTBI 06 - District LTBI Treatment Register (Annex VI)
7. LTBI 07 - Quarterly return on LTBI screening and case finding (Annex VII)
8. LTBI 08 - Quarterly return on treatment outcome of LTBI treatment of patients registered 12-15 months earlier (Annex VIII)

7.7. Programme monitoring and evaluation

LTBI screening programme at district level will be monitored during routine supervision of DCCs and through DTCO reviews at provincial and district Reviews. The identified key indicators to monitor the progress of the main activity is listed in the Annex IX.

7.8. Integration with other institutions

As LTBI screening programme involves other institutions under health sector such as National STD and AIDS Control Programme (NSACP), CKD unit and other curative care institutions, maintaining proper communication and getting them involved in planning LTBI activities are mandatory for a successful program. Issuing of circulars and standard of procedures to the curative care sectors and creating awareness among health care staff including clinicians have been identified as essential features for effective program implementation.

7.9. Scaling up of LTBI screening programs

Ultimate objective of implementation of the LTBI screening and treatment as an intervention is to reach the end TB targets by reducing the emergence of new TB cases. Currently

preventive treatment is offered to children less than 5years who are household contacts of bacteriologically confirmed pulmonary TB and PLHIV after excluding active TB. The new intervention will include more risk categories to exclude active TB and to screen and treat for latent infection which needs more resources. The implementation of the programme should be carried out in a scaled-up manner considering the need for human resources and logistics at district level, capacity building of the staff, assurance of coverage of particular risk group, assurance of treatment completion of each risk group once treatment is initiated, and capacity of treatment monitoring. Therefore, at the initial stage the national LTBI programme will address the risk groups which could be covered with available resources, and this will be expanded gradually covering more risk groups once the required resources are achieved fully (Figure 9).

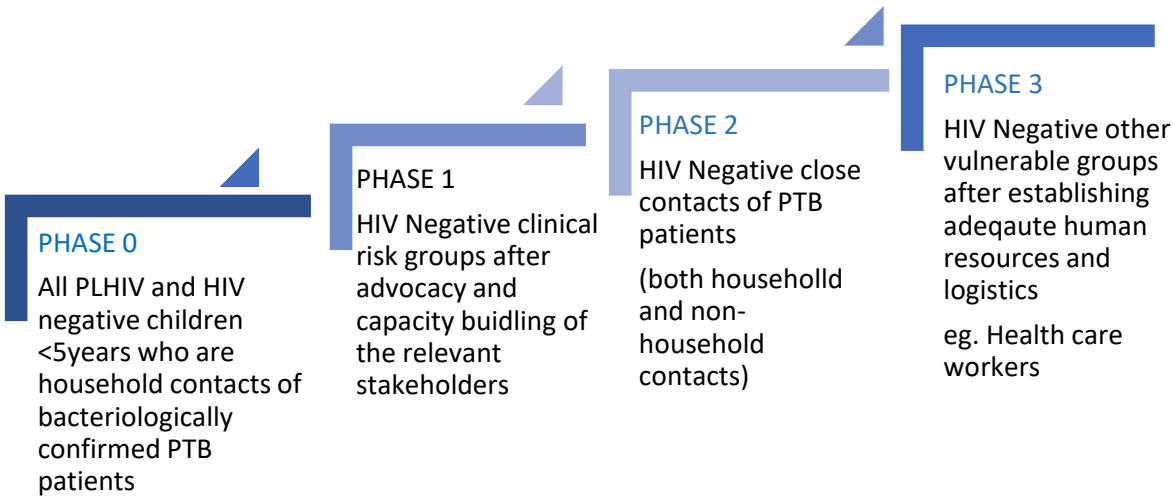


Figure 9: Schematic representation of scaling up of LTBI screening programme

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ANNEXURE

Annex I: LTBI 01 - LTBI Screening Record

National Programme for Tuberculosis Control and Chest Diseases — LTBI – 01

LTBI Screening Record

Chest Clinic		Date of Screening	

GENERAL INFOMRATION			
District LTBI screening no/Standard card no:			
Name of patient:			
Date of birth:		Age:	
Sex:	Male ☐ Female ☐	Contact number:	
Complete address			
Past TB history:			

Presumptive LTBI category			
HIV positive		PLHIV	☐
HIV negative	Close contacts	Close contact of TB patient – (Age <5 years)	☐
		Close contact of TB patient – (Age >5 years)	☐
		If close contact, DTB no of index TB patient	
	Clinical risk groups	Patient on treatment with anti-TNF alpha	☐
		Patient on treatment with non-anti-TNF alpha biologics	☐
		Patient receiving dialysis	☐
		Patient preparing for solid organ transplantation	☐
		Patient preparing for Hematopoietic stem cell transplantation	☐
		Patients with silicosis	☐
	Other vulnerable groups	Healthcare workers	☐
		Prisoners	☐

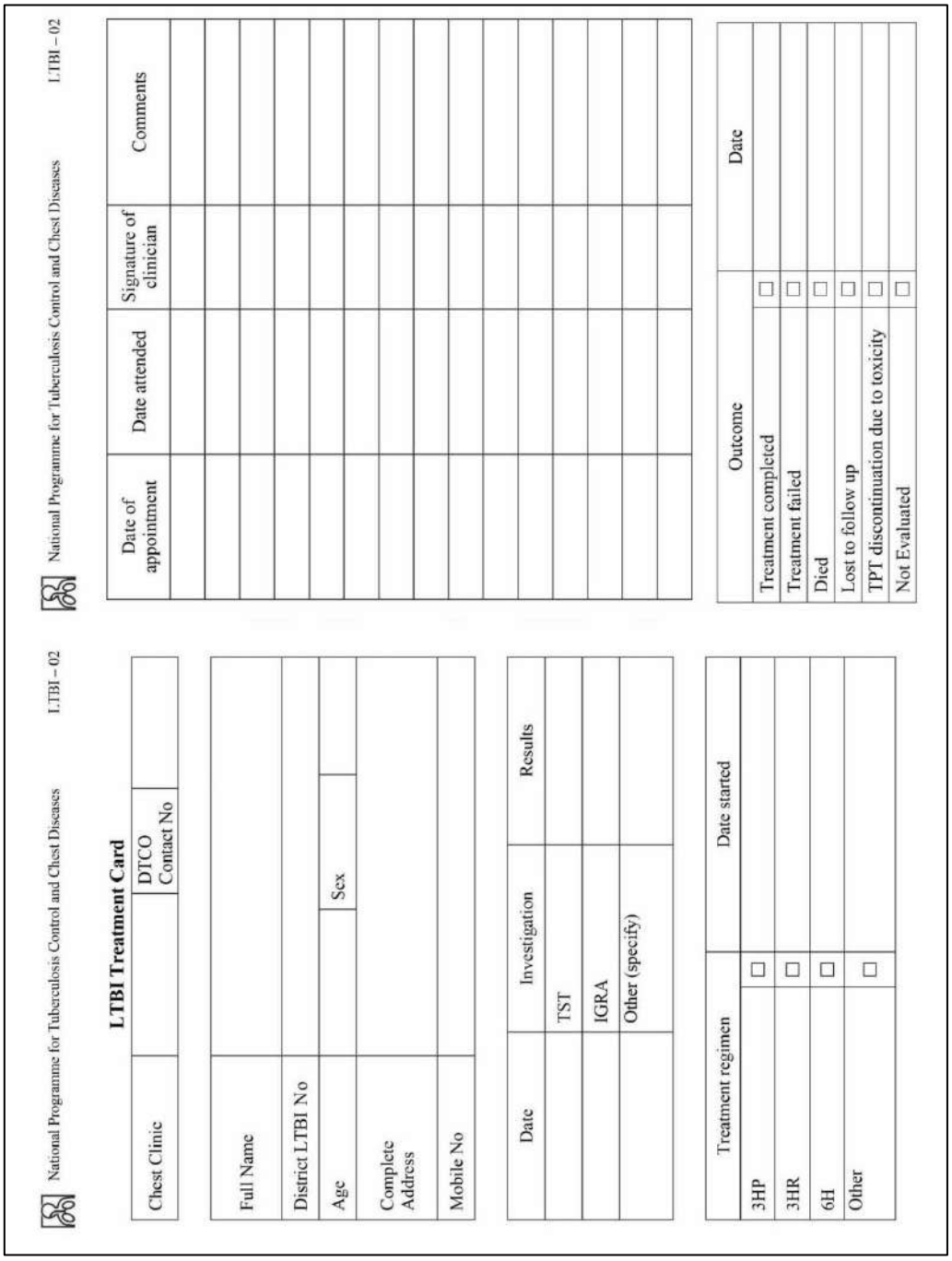
CLINICAL FEATURES	
Symptoms (If any)	
Signs (If any)	

INVESTIGATIONS				
Investigation	**Report number**	**Results**	**Date test done (dd/mm/yyyy)**	**Date of results (dd/mm/yyyy)**
TST				
IGRA		Positive/Negative/Indeterminate		
CXR				
Sputum AFB				
GeneXpert				
Any other (specify)				

SCREENING OUTCOME		
Active TB	Positive	☐
	Negative	☐
LTBI	Positive	☐
	Negative	☐

MANAGEMENT			
Action		**Date**	**DTB/LTBI No**
Registered for TB Treatment	☐		
Registered for LTBI Treatment	☐		
Other (Specify)	☐		

Annex II: LTBI 02 - LTBI Treatment Card



National Programme for Tuberculosis Control and Chest Diseases LTBI – 02

LTBI Treatment Card

Chest Clinic		DTCO Contact No	

Full Name	
District LTBI No	
Age	Sex
Complete Address	
Mobile No	

Date	Investigation	Results
	TST	
	IGRA	
	Other (specify)	

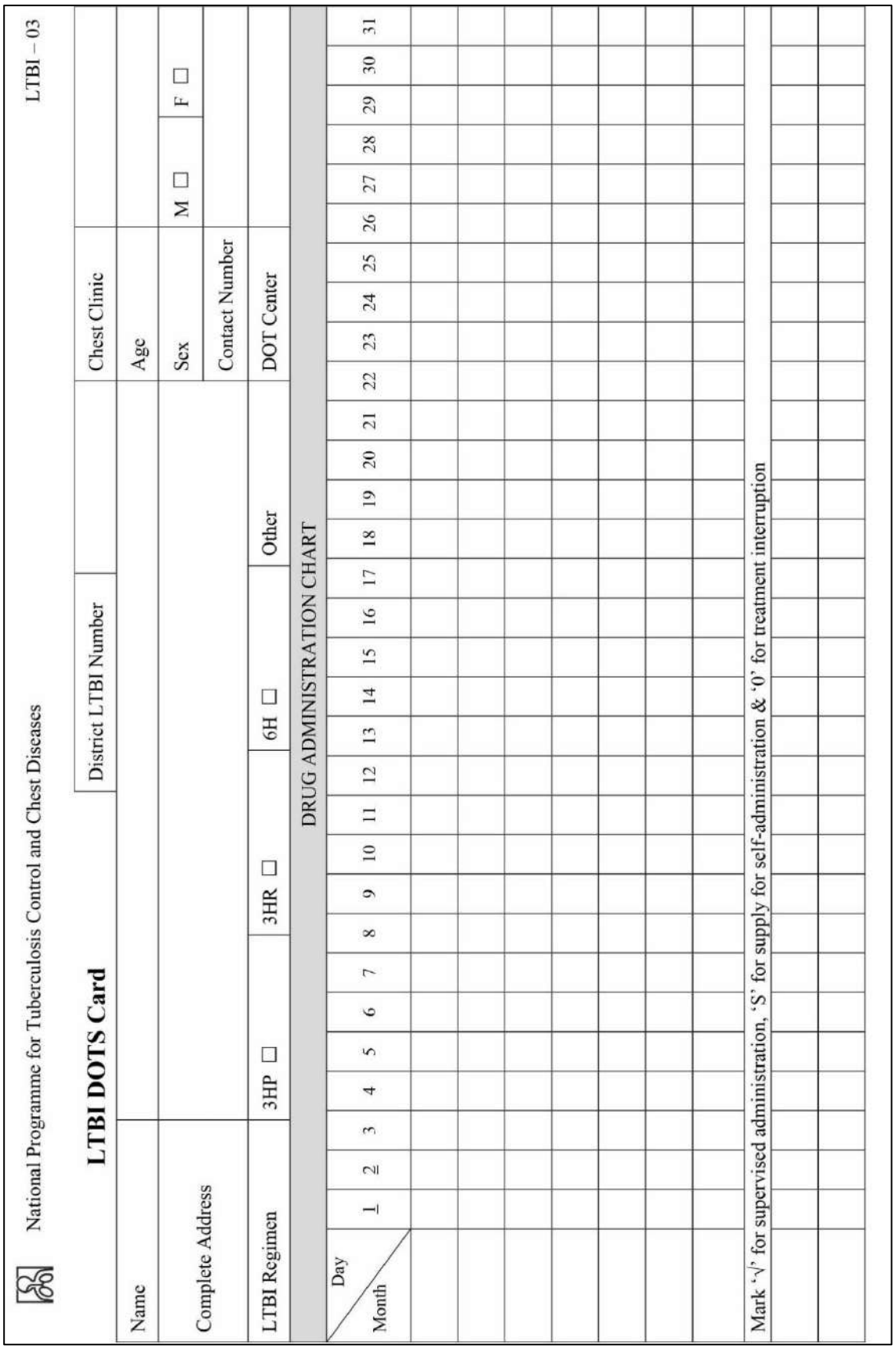
Treatment regimen		Date started
3HP	☐	
3HR	☐	
6H	☐	
Other	☐	

National Programme for Tuberculosis Control and Chest Diseases LTBI – 02

Date of appointment	Date attended	Signature of clinician	Comments

Outcome		Date
Treatment completed	☐	
Treatment failed	☐	
Died	☐	
Lost to follow up	☐	
TPT discontinuation due to toxicity	☐	
Not Evaluated	☐	

Annex III: LTBI 03 - LTBI DOTS Card



National Programme for Tuberculosis Control and Chest Diseases

LTBI – 03

LTBI DOTS Card

District LTBI Number

Chest Clinic

Name

Age

Complete Address

Sex M ☐ F ☐

Contact Number

LTBI Regimen 3HP ☐ 3HR ☐ 6H ☐ Other

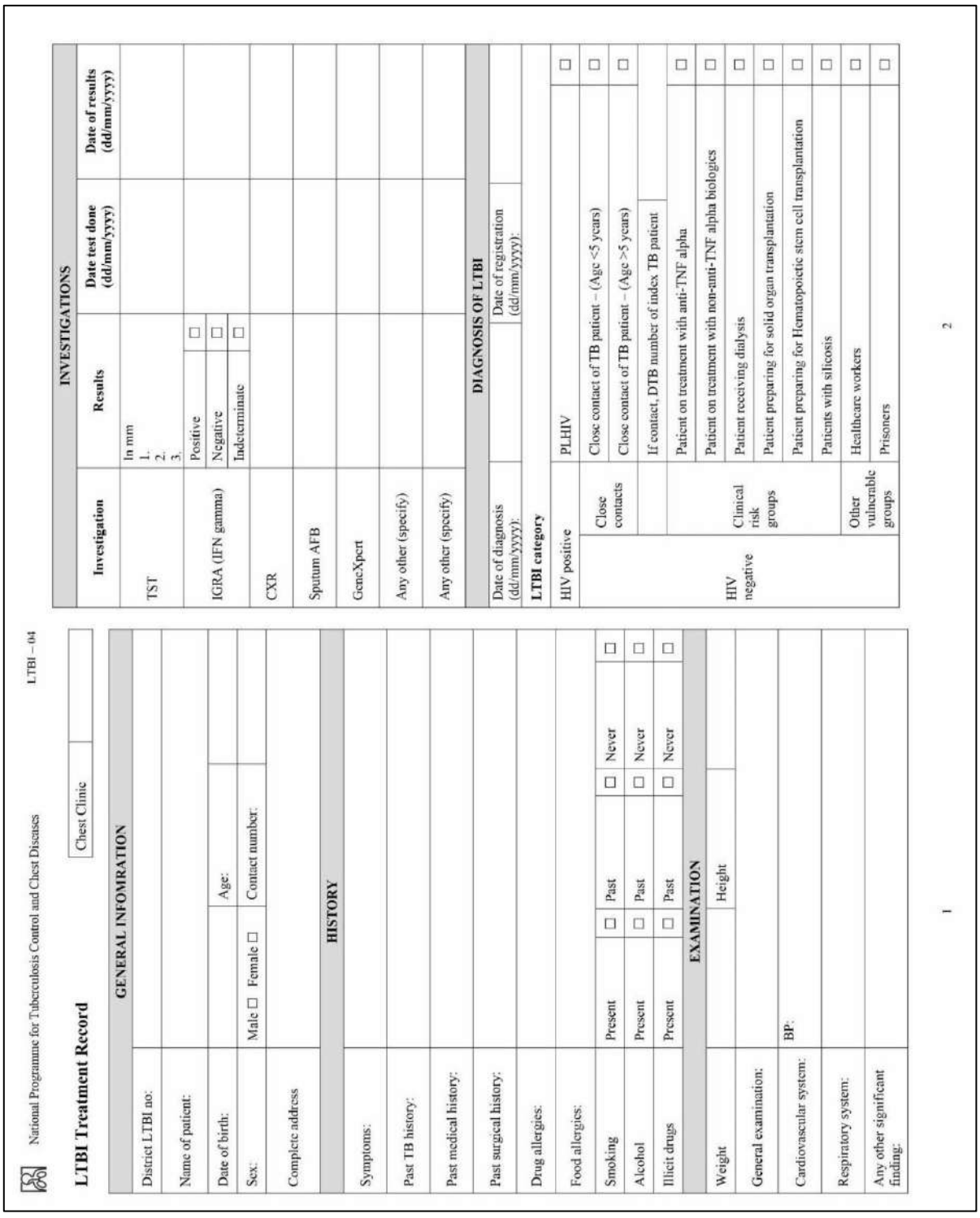
DOT Center

DRUG ADMINISTRATION CHART

Month \ Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

Mark '√' for supervised administration, 'S' for supply for self-administration & '0' for treatment interruption

Annex IV: LTBI 04 - LTBI Treatment File



National Programme for Tuberculosis Control and Chest Diseases — LTBI – 04

LTBI Treatment Record — Chest Clinic: ☐

GENERAL INFOMRATION

District LTBI no:	
Name of patient:	
Date of birth:	Age:
Sex:	Male ☐ Female ☐ — Contact number:
Complete address	

HISTORY

Symptoms:					
Past TB history:					
Past medical history:					
Past surgical history:					
Drug allergies:					
Food allergies:					
Smoking	Present	☐	Past	☐	Never ☐
Alcohol	Present	☐	Past	☐	Never ☐
Illicit drugs	Present	☐	Past	☐	Never ☐

EXAMINATION

Weight	Height		
General examination:			
Cardiovascular system:	BP:		
Respiratory system:			
Any other significant finding:			

1

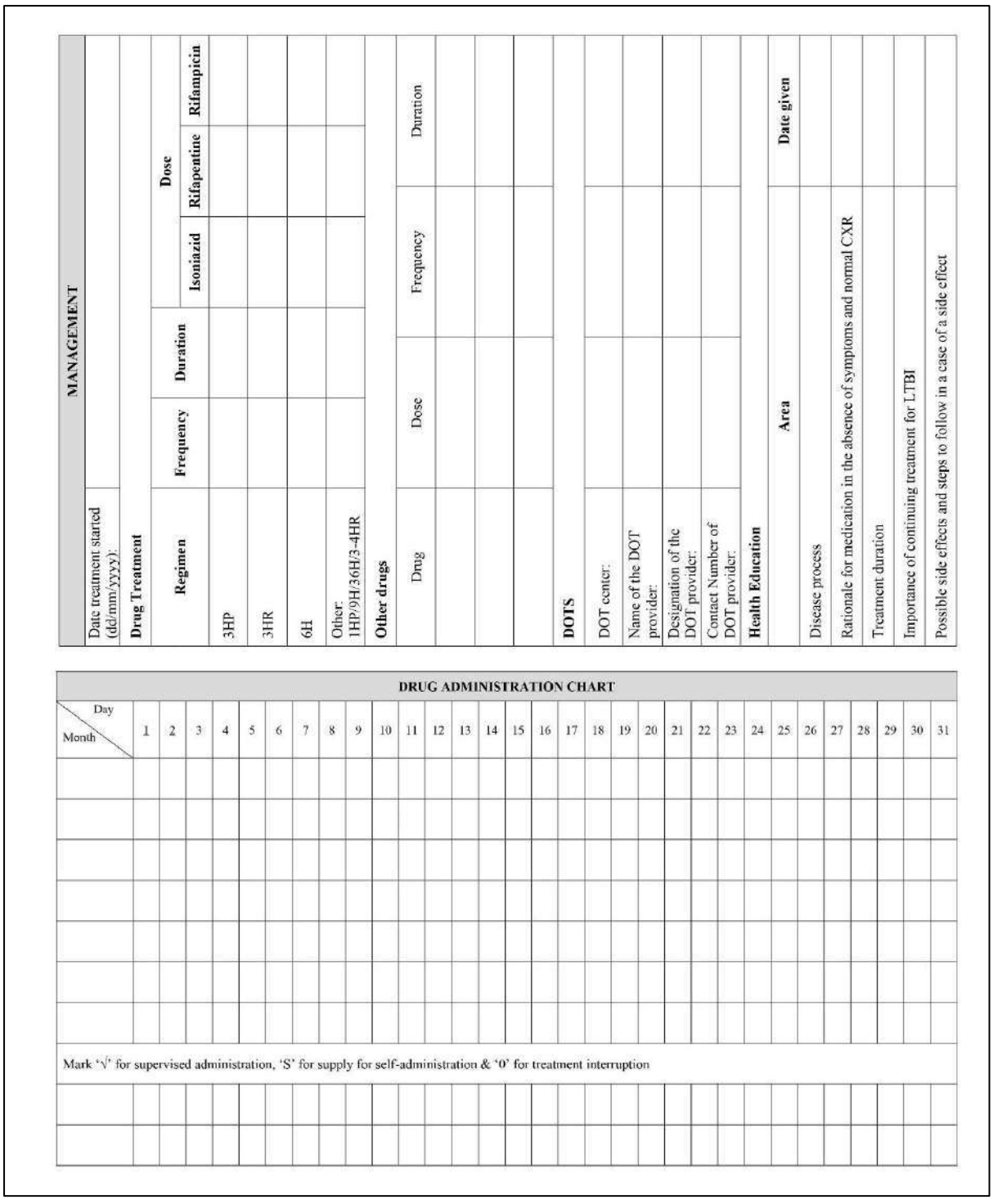
INVESTIGATIONS

Investigation		Results	Date test done (dd/mm/yyyy)	Date of results (dd/mm/yyyy)
TST		In mm 1. 2. 3.		
IGRA (IFN gamma)		Positive ☐ Negative ☐ Indeterminate ☐		
CXR				
Sputum AFB				
GeneXpert				
Any other (specify)				
Any other (specify)				

DIAGNOSIS OF LTBI

Date of diagnosis (dd/mm/yyyy):		Date of registration (dd/mm/yyyy):	
LTBI category			
HIV positive		PLHIV	☐
HIV negative	Close contacts	Close contact of TB patient – (Age <5 years)	☐
		Close contact of TB patient – (Age >5 years)	☐
		If contact, DTB number of index TB patient	
	Clinical risk groups	Patient on treatment with anti-TNF alpha	☐
		Patient on treatment with non-anti-TNF alpha biologics	☐
		Patient receiving dialysis	☐
		Patient preparing for solid organ transplantation	☐
		Patient preparing for Hematopoietic stem cell transplantation	☐
		Patients with silicosis	☐
	Other vulnerable groups	Healthcare workers	☐
		Prisoners	☐

2



MANAGEMENT

Date treatment started (dd/mm/yyyy):

Drug Treatment

Regimen	Frequency	Duration	Dose		
			Isoniazid	Rifapentine	Rifampicin
3HP					
3HR					
6H					
Other: 1HP/9H/36H/3-4HR					

Other drugs

Drug	Dose	Frequency	Duration

DOTS

DOT center:

Name of the DOT provider:

Designation of the DOT provider:

Contact Number of DOT provider:

Health Education

Area	Date given
Disease process	
Rationale for medication in the absence of symptoms and normal CXR	
Treatment duration	
Importance of continuing treatment for LTBI	
Possible side effects and steps to follow in a case of a side effect	

DRUG ADMINISTRATION CHART

Month \ Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

Mark '√' for supervised administration, 'S' for supply for self-administration & '0' for treatment interruption

FOLLOW UP VISITS			
Due Date:		Date attended:	
Complaints if any:			
Symptoms suggestive of TB disease		**Duration**	
Cough	☐		
Low grade fever	☐		
Loss of appetite	☐		
Malaise	☐		
Any other (specify)	☐		
Signs suggestive of TB disease			
General examination:			
Respiratory system examination:			
Investigation Results			
Investigation	**Date**	**Result**	
Adverse Effects			
Effect	**Possible Drug**	**Action**	
Investigation Requests		**Prescriptions**	
Remarks:			

5

TREATMENT OUTCOME			
Outcome		**Date**	**Comments**
Treatment completed (Completed the treatment within due period)	☐		
Treatment failed (Development of active TB while on TPT)	☐		
Died (Death due to any reason while on LTBI treatment)	☐		
Lost to follow up (2 consecutive months for H, one month for HP and HR)	☐		
TPT discontinuation due to toxicity	☐		
Not Evaluated (Please mention reason)	☐		

Remarks:	

6

Annex V: LTBI 05 - District LTBI Screening Register

LTBI - 05

District LTBI Screening Register

Date of screening	LTBI Screening No/ Standard Card No	Full name	Complete address	Age	Sex	Latent TB screening category					Investigations for active TB				Active TB screening outcome[4]	Investigations for latent TB		Latent TB screening outcome[5]	Remarks[6]
						PLHIV	Close contact[1]	If close contact, DTB no of index patient	Clinical risk group[2]	Other vulnerable group[3]	Sputum	CXR	Xpert MTB-RIF	Other (specify)		TST	IGRA		

1: Enter "H" for household close contacts and "NH" for non -household close contacts
2: Enter "TNF" for patients on treatment with anti-TNF alpha, "NTNF" for patients on treatment with non-anti-TNF alpha, "HD" for patients receiving dialysis, "SOT" for patients preparing for solid organ transplantation, "HSCT" for patient preparing for hematopoietic stem cell transplantation, "SIL" for patients with silicosis
3: Enter "H" for health care workers and "P" for prisoners
4. Enter "P" for positive and "N" for negative
5. Enter "P" for positive and "N" for negative
6. Enter DTB no where TB treatment started and DLTBI no where LTBI treatment started

Annex VI: LTBI 06 - District LTBI Treatment Register

LTBI - 06

District LTBI Treatment Register

Date of registration	District LTBI No	Patil name	Complete address	Age	Sex	Latent TB category					Treatment Regimen[4]				Outcome of LTBI treatment[5]						Remarks[6]
						PLHIV	Close contact[1]	If close contact, DTB no of index patient	Clinical risk group[2]	Other vulnerable group[3]	3HP	3HR	6H	Other (specify)	Treatment completed	Treatment failed	Died	Lost to follow up	Discontinued due to toxicity	Not Evaluated	

1: Enter "H" for household close contacts and "NH" for non-household close contacts
2: Enter "1NF" for patients on treatment with anti-TNF alpha; "2NF" for patients on treatment with non-anti-TNF alpha; "HD" for patients receiving dialysis; "SOT" for patients preparing for solid organ transplantation; "HSCT" for patient preparing for hematopoietic stem cell transplantation; "SIL" for patients with silicosis
3: Enter "HF" for health care workers and "P" for prisoners
4. Enter Date treatment started in the relevant regime column
5. Enter Date of outcome in the relevant outcome column
6. Enter Reasons for not evaluated

National Programme for Tuberculosis Control and Chest Diseases

Quarterly return on LTBI screening and case finding

LTBI 07

District		Patients Registered During	Quarter		Date of Completion of Report	
			Year			
Name of DTCO					Signature	

			Number of persons screened for LTBI							Number of persons started on LTBI treatment						
			0-4		5-14		>=15		Total	0-4		5-14		>=15		Total
			M	F	M	F	M	F		M	F	M	F	M	F	
HIV positive		PLHIV[1]							0							0
HIV negative	Close contacts	Close contact of TB patient[2]							0							0
	Clinical risk groups	On treatment with anti-TNF alpha							0							0
		On treatment with non-anti-TNF alpha biologics							0							0
		Receiving dialysis							0							0
		Preparing for solid organ transplantation							0							0
		Preparing for Hematopoietic stem cell transplantation							0							0
		With silicosis							0							0
	Other vulnerable groups	Healthcare workers							0							0
		Prisoners							0							0
Total			0	0	0	0	0	0	0	0	0	0	0	0	0	0

1- For PLHIV age <5years, mention the total number as all are eligible for LTBI treatment
2- For contacts age <5years, mention the total number as all are eligible for LTBI treatment

Annex VIII: LTBI 08 - Quarterly return on treatment outcome of LTBI treatment of patients registered 12-15 months earlier

National Programme for Tuberculosis Control and Chest Diseases

Quarterly return on treatment outcome of LTBI treatment of patients registered 12-15 months earlier

LTBI 08

District | Patients Registered During | Quarter | Date of Completion of Report

Name of DTCO | Year | Signature

			Number started on LTBI treatment			Outcome																				Total		
						Treatment completed			Treatment failed			Died			Lost to follow up			Discontinued due to toxicity			Not Evaluated					
			0-4	5-14	>=15	0-4	5-14	>=15	0-4	5-14	>=15	0-4	5-14	>=15	0-4	5-14	>=15	0-4	5-14	>=15	0-4	5-14	>=15	0-4	5-14	>=15
HIV positive	PLHIV																							0	0	0
HIV negative	Close contacts	Close contacts																						0	0	0
	Clinical risk groups	On treatment with anti-TNF alpha																						0	0	0
		On treatment with non-anti-TNF alpha biologics																						0	0	0
		Receiving dialysis																						0	0	0
		Preparing for solid organ transplantation																						0	0	0
		Preparing for hematopoietic stem cell transplantation																						0	0	0
		With silicosis																						0	0	0
	Other vulnerable groups	Healthcare workers																						0	0	0
		Prisoners																						0	0	0
Total			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Annex IX: Monitoring indicators of programmatic management of LTBI

Coverage area	Indicator	Numerator	Denominator
1. TB evaluation of the target groups for TPT initiation	1.1 Proportion of children under 5 years who are household/close contacts of TB cases who have completed investigation for TB	Number of children under 5 years who are household/close contact who completed investigation for TB	Total number of children under 5 years who are household/close contacts of PTB
	1.2 Proportion of contacts ≥ 5 years who are household contacts of TB cases who have completed investigation for TB	Number of contacts ≥ 5 years who are household contacts of TB cases who have completed investigation for TB	Total number of contacts ≥ 5 years years who are household contacts of PTB
	1.3 Proportion of eligible PLHIV enrolled in HIV care who have completed investigation for TB	Number of eligible PLHIV enrolled in HIV care who have completed investigation for TB	Total number of eligible PLHIV enrolled in HIV care
2. Coverage of TPT initiation	2.1 Proportion of children under 5 years who are household/close contacts of TB cases who are eligible for TPT and have started TPT	Number of children under 5 years who are household/close contacts of TB cases who are eligible for TPT and have started TPT	Total number of children under 5 years who are household/close contacts of TB cases who are eligible for TPT
	2.2 Proportion of contacts ≥ 5 years who are household/close contacts of TB cases (according to national guideline) who are eligible for TPT and have started TPT	Number of contacts ≥ 5years who are household/close contacts of TB cases who are eligible for TPT and have started TPT	Total number of contacts ≥ 5years who are household/close contacts of TB cases who are eligible for TPT
	2.3 Proportion of eligible PLHIV enrolled in HIV care and started on TPT	Number of PLHIV who are eligible for TPT and have started TPT	Number of PLHIV who are eligible for TPT

	2.4 Proportion of eligible individuals in at risk populations (as defined by national guidelines) with a positive LTBI test who are eligible for TPT and have started TPT	Number of at-risk individuals (clinical risk groups and other vulnerable groups) who are eligible for TPT and have started TPT	Number of at-risk individuals (clinical risk groups and other vulnerable groups) who are eligible for TPT
3. Coverage of TPT completion	3.1 Proportion of children under 5 years who are household contacts of TB cases (according to national guideline) who have completed a course of TPT	Number of children under 5 years who are household/close contacts of TB cases who have completed TPT	Number of children under 5 years who are household/close contacts of TB cases who are eligible for TPT and have started TPT
	3.2 Proportion of contacts ≥ 5 years who are household contacts of TB cases (according to national guideline) who have completed a course of TPT	Number of contacts ≥ 5years who are household/close contacts of TB cases who have completed TPT	Number of contacts ≥ 5years who are household/close contacts of TB cases who are eligible for TPT and have started TPT
	3.3 Proportion of eligible PLHIV who completed course of TPT	Number of PLHIV who are eligible for TPT and have completed TPT	Number of PLHIV who are eligible for TPT and have started TPT
	3.4 Proportion of eligible individuals in at-risk populations (as defined by national guidelines) with a positive LTBI test who have started TPT and completed the course	Number of at-risk individuals (clinical risk groups and other vulnerable groups) who have completed TPT	Number of at-risk individuals (clinical risk groups and other vulnerable groups) who are eligible for TPT and have started TPT