Latent tuberculosis infection

Updated and consolidated guidelines for programmatic management
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 manifest active TB. There is no gold standard test for LTBI. The WHO guidelines on LTBI consider the probability of progression to active TB disease in a specific risk group, the epidemiology and burden of TB, the availability of resources and the likelihood of a broad public health impact. Two fragmented recommendations have been made for the management of LTBI, which resulted in a number of guideline documents, posing a challenge to implementation. Therefore, several WHO Member States requested consolidated guidelines on LTBI management.

The updated, consolidated guidelines in this document respond to that request. They provide a comprehensive set of WHO recommendations for programmatic management of LTBI and the basis and rationale for national guidelines. These guidelines supersede previous WHO policy documents on the management of LTBI in people living with HIV and household contacts of people with TB and other at-risk groups. The guidelines were prepared in accordance with the requirements and recommended process of the WHO Guideline Review Committee. Seven systematic reviews were conducted to update the recommendations and make new ones. The Guideline Development Group considered the quality of the evidence, benefits and harms, values and preferences, equity, costs, acceptability and feasibility of implementation in formulating the recommendations and determining their strength.

The recommendations are presented logically according to the cascade of care for managing LTBI: identification of at-risk populations (adults and children living with HIV, HIV-negative adult and child contacts and other HIV-negative at-risk groups), ruling out active TB disease, testing for LTBI, providing treatment, monitoring adverse events, adherence and completion of treatment and monitoring and evaluation. The recommendations are categorized as: existing ones previously approved by the review committee and published, which are still valid; updated recommendations that were previously approved by the review committee but for which the evidence was reviewed, discussed with the Guidelines Development Group (GDG) and updated (including for clarity); and new recommendations. There are 10 existing, 7 updated and 7 new recommendations.

In general, the GDG reviewed the evidence from the systematic reviews and discussed each population risk group identified in detail for the prevalence of LTBI, the risk for progression to active TB and the incidence of active TB as compared with that in the general population. The GDG used the guiding principle that individual benefit outweighs risk as the mainstay of recommendations on LTBI testing and treatment. The GDG found clear evidence for the benefit of systematic testing and treatment of LTBI for people living with HIV and infants and children under 5 years of age who are household contacts of pulmonary TB patients, in all settings, regardless of the background epidemiology of TB. Similarly, they concluded that HIV-negative groups at clinical risk, such as patients initiating anti-TNF treatment, receiving dialysis, preparing for organ or haematological transplantation and those with silicosis would also benefit from testing and treatment of LTBI, regardless of the background TB epidemiology, because of their increased risk of progression to active TB disease.

The specific recommendations are given below.

A. Identification of at-risk populations for LTBI testing and treatment

*Adults, adolescents, children and infants living with HIV*

- Adults and adolescents living with HIV, with unknown or a positive tuberculin skin test (TST) and are unlikely to have active TB should receive preventive treatment of TB as part of a comprehensive package of HIV care. Treatment should be given to these individuals irrespective of the degree of immunosuppression.
and also to those on antiretroviral treatment (ART), those who have previously been treated for TB and pregnant women. (Strong recommendation, high-quality evidence. Existing recommendation)

- Infants aged < 12 months living with HIV who are in contact with a case of TB and are investigated for TB should receive 6 months of isoniazid preventive treatment (IPT) if the investigation shows no TB disease. (Strong recommendation, moderate-quality evidence. Updated recommendation)

- Children aged ≥ 12 months living with HIV who are considered unlikely to have TB disease on the basis of screening for symptoms and who have no contact with a case of TB should be offered 6 months of IPT as part of a comprehensive package of HIV prevention and care if they live in a setting with a high prevalence of TB. (Strong recommendation, low-quality evidence. Existing recommendation)

- All children living with HIV who have successfully completed treatment for TB disease may receive isoniazid for an additional 6 months. (Conditional recommendation, low-quality evidence. Existing recommendation)

**HIV-negative household contacts**

- HIV-negative children aged < 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have active TB on an appropriate clinical evaluation or according to national guidelines should be given TB preventive treatment. (Strong recommendation, high-quality evidence. Updated recommendation)

- In countries with a low TB incidence, adults, adolescents and children who are household contacts of people with bacteriologically confirmed pulmonary TB should be systematically tested and treated for LTBI. (Strong recommendation, high–moderate-quality evidence. Existing recommendation)

- In countries with a high TB incidence, children aged ≥ 5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have active TB by an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment. (Conditional recommendation, low-quality evidence. New recommendation)

**Other HIV-negative at-risk groups**

- Patients initiating anti-TNF treatment, patients receiving dialysis, patients preparing for an organ or haematological transplant and patients with silicosis should be systematically tested and treated for LTBI. (Strong recommendation, low–very low-quality evidence. Updated recommendation)

- In countries with a low TB incidence, systematic testing for and treatment of LTBI may be considered for prisoners, health workers, immigrants from countries with a high TB burden, homeless people and people who use illicit drugs. (Conditional recommendation, low–very low-quality evidence. Existing recommendation)

- Systematic testing for LTBI is not recommended for people with diabetes, people with harmful alcohol use, tobacco smokers and underweight people unless they are already included in the above recommendations. (Conditional recommendation, very low-quality evidence. Existing recommendation)

**B. Algorithms to rule out active TB disease**

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

- Chest radiography may be offered to people living with HIV and on ART and preventive treatment given to those with no abnormal radiographic findings. (Conditional recommendation, low-quality evidence. New recommendation)

- Adults and adolescents living with HIV who are screened for TB according to a clinical algorithm and who report any of the symptoms of current cough, fever, weight loss or night sweats may have active TB
and should be evaluated for TB and other diseases that cause such symptoms. (Strong recommendation, moderate-quality evidence. Updated recommendation)

- Infants and children living with HIV who have poor weight gain, fever or current cough or who have a history of contact with a case of TB should be evaluated for TB and other diseases that cause such symptoms. If the evaluation shows no TB, these children should be offered preventive treatment, regardless of their age. (Strong recommendation, low-quality evidence. Updated recommendation)

- The absence of any symptoms of TB and the absence of abnormal chest radiographic findings may be used to rule out active TB disease among HIV-negative household contacts aged ≥ 5 years and other at-risk groups before preventive treatment. (Conditional recommendation, very low-quality evidence. New recommendation)

C. Testing for LTBI

- Either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) can be used to test for LTBI. (Strong recommendation, very low-quality evidence. New recommendation)

- People living with HIV who have a positive test for LTBI benefit more from preventive treatment than those who have a negative LTBI test; LTBI testing can be used, where feasible, to identify such individuals. (Strong recommendation, high-quality evidence. Existing recommendation)

- LTBI testing by TST or IGRA is not a requirement for initiating preventive treatment in people living with HIV or child household contacts aged < 5 years. (Strong recommendation, moderate-quality evidence. Updated recommendation)

D. Treatment options for LTBI

- Isoniazid monotherapy for 6 months is recommended for treatment of LTBI in both adults and children in countries with high and low TB incidence. (Strong recommendation, high-quality evidence. Existing recommendation)

- Rifampicin plus isoniazid daily for 3 months should be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for children and adolescents aged < 15 years in countries with a high TB incidence. (Strong recommendation, low-quality evidence. New recommendation)

- Rifapentine and isoniazid weekly for 3 months may be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for both adults and children in countries with a high TB incidence. (Conditional recommendation, moderate-quality evidence. New recommendation)

- The following options are recommended for treatment of LTBI in countries with a low TB incidence as alternatives to 6 months of isoniazid monotherapy: 9 months of isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or 3–4 months of isoniazid plus rifampicin, or 3–4 months of rifampicin alone. (Strong recommendation, moderate–high-quality evidence. Existing recommendation)

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

E. Preventive treatment for contacts of patients with multidrug-resistant-TB

- In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualised risk assessment and a sound clinical justification. (Conditional recommendation, very low-quality evidence. New recommendation)
Important additional considerations

Adverse events monitoring
The risk for adverse events during preventive treatment must be minimized. Individuals receiving treatment for LTBI should be monitored routinely and regularly at monthly visits to health care providers. The prescribing health care provider should explain the disease process and the rationale for the treatment and emphasize the importance of completing it. People receiving treatment should be urged to contact their health care providers if they develop symptoms between visits, such as anorexia, nausea, vomiting, abdominal discomfort, persistent fatigue or weakness, dark-coloured urine, pale stools or jaundice. If a health care provider cannot be consulted at the onset of such symptoms, the patient should immediately stop treatment.

Adherence and completion of preventive treatment
Adherence to the full course and completion of treatment are important determinants of clinical benefit, both to the individual and to the success of the programme. Interventions should be tailored to the specific needs of the risk groups and to the local context to ensure adherence and completion of treatment.

Programmatic management, monitoring and evaluation
The national programme should prepare a national plan for programmatic management of LTBI, including prioritizing groups identified as being at high risk on the basis of local epidemiology and the health system. They should create a conducive environment for the policy and the programme, including national and local policies and standard operating procedures to facilitate implementation of the recommendations in these guidelines. Programmatic management of LTBI should include monitoring and evaluation systems that are aligned with national systems for patient monitoring and surveillance. Appropriate recording and reporting tools should be developed, with standardized indicators.