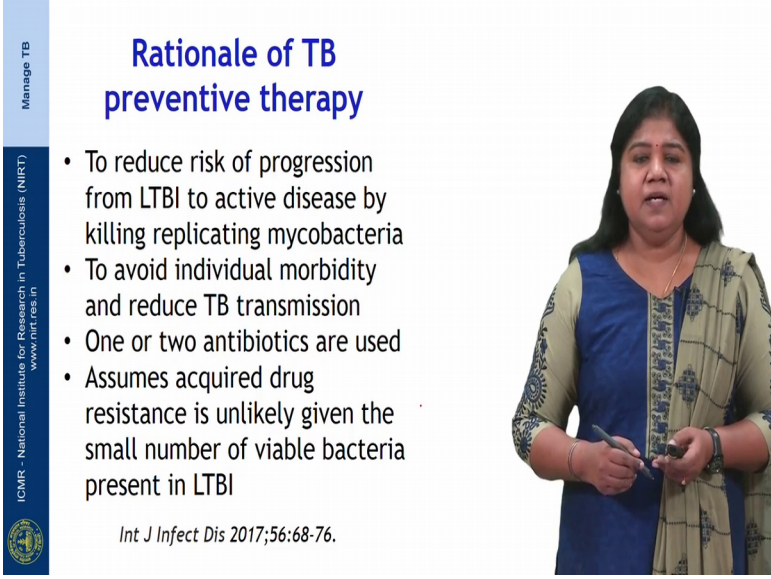


Manage TB_NIRT
Dr. V.V. Banu Rekha
National Institute for Research in Tuberculosis, Chennai

Lecture – 57
Management of Latent TB Infection (Session 2)

Welcome back to the second session on Management of Latent TB Infection. So, in this session we will talk about TB preventive therapy and its importance.

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The slide features a vertical blue bar on the left with the text 'Manage TB' at the top, 'ICMR - National Institute for Research in Tuberculosis (NIRT)' in the middle, and 'www.nirt.res.in' at the bottom. The main title is 'Rationale of TB preventive therapy'. The bullet points are: 'To reduce risk of progression from LTBI to active disease by killing replicating mycobacteria', 'To avoid individual morbidity and reduce TB transmission', 'One or two antibiotics are used', and 'Assumes acquired drug resistance is unlikely given the small number of viable bacteria present in LTBI'. A citation at the bottom reads 'Int J Infect Dis 2017;56:68-76.' To the right of the text is a photograph of Dr. V.V. Banu Rekha, a woman with dark hair wearing a blue and green patterned sari, holding a small object in her hands.

So, what is a rationale for TB preventive therapy? This is very important to reduce risk of progression from LTBI to active TB disease by killing the replicating mycobacterium. This is very important to avoid individual morbidity from TB disease and reduce TB transmission because of active pulmonary TB disease. 1 or 2 antibiotics are used for preventive therapy and light treatment in which we use a minimum of 4 to 5 drugs in the intensive phase of therapy.

This assumes that acquired drug resistance is unlikely given the smaller number of viable bacteria present in the latent TB infection.

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Populations at risk of developing active TB

- Adults, adolescents and children living with HIV
- Infants aged < 12 months living with HIV who are in contact with a case of TB
- HIV-negative household contacts aged <5 years of bacteriologically confirmed pulmonary TB patients

should be given TB preventive therapy

Latent tuberculosis infection: WHO guidelines, 2018



So, the populations at risk of developing TB include adults, adolescents and children living with HIV, infants aids less than 12 months living with HIV, who are in contact with a case of TB, HIV negative household contacts, age less than 5 years of bacteriologically confirmed pulmonary TB patients. And these people should be given TB preventive therapy according to the WHO guidelines 2018 which is talking about the management of latent TB infection.

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Populations to be tested and treated for LTBI

Persons who are

- initiating anti-TNF treatment
- receiving dialysis
- preparing for an organ or haematological transplant
- with silicosis


should be tested and treated for LTBI

Latent tuberculosis infection: WHO guidelines, 2018



The populations to be tested and treated for LTBI include persons who are initiating anti TNF treatment, who are receiving dialysis preparing for an organ or hematological transplant and those with silicosis. So, the test we have already seen in the first session that it can be TST or IGRA.

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Manage TB

**Low TB incidence countries
- Populations to be tested
and treated for LTBI**

- Low TB incidence countries (Estimated TB incidence <100/100000)
- Adults, adolescents and children who are household contacts of people with bacteriologically confirmed pulmonary TB
- Prisoners, health workers, immigrants from countries with a high TB burden, homeless people and people who use illicit drugs

should be tested and treated for LTBI

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Latent tuberculosis infection: WHO guidelines, 2018

In low TB incident countries which is actually the estimated TB incidence to be less than 100 per lakh population the populations to be tested and treated for LTBI include adults, adolescents and children who are household contacts of people with bacteriologically confirmed pulmonary TB, prisoners, health workers, immigrants from countries with a high TB burden, homeless people and people who use illicit drugs. So, these groups should be tested and treated for latent TB infection.

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High TB incidence countries - Populations for TB preventive treatment

- High TB incidence countries (Estimated TB incidence $\geq 100/100000$)
- Children aged ≥ 5 years, adolescents and adults who are household contacts of bacteriologically confirmed pulmonary TB

may be given TB preventive therapy

Latent tuberculosis infection: WHO guidelines, 2018



In case of high TB incident countries where the estimated TB incidence is more than or equal to 100 per lakh population; the populations for TB preventive treatment include children aged more than or equal to 5 years, adolescents, adults who are household contacts of bacteriologically confirmed pulmonary TB patients. So, they may be given TB preventive therapy.

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TB preventive therapy regimens recommended by WHO

High / Low TB incidence countries	High TB incidence countries*	Low TB incidence countries**
Isoniazid monotherapy for 6 months for treatment of LTBI in both adults and children	Alternative to 6 months of Isoniazid • Rifampicin plus isoniazid daily for 3 months for children and adolescents aged < 15 years • Rifapentine and isoniazid weekly for 3 months for both adults and children	Alternative to 6 months of Isoniazid for treatment of LTBI • 9 months of isoniazid • 3-month regimen of weekly rifapentine plus isoniazid • 3-4 months of isoniazid plus rifampicin • 3-4 months of rifampicin alone

*Estimated TB incidence $\geq 100/100000$ **Estimated TB incidence $< 100/100000$

- In settings with high TB incidence and transmission, adults and adolescents living with HIV who have an unknown or a positive TST should receive at least 36 months of IPT.
- People with a negative TST should not receive 36 months of IPT.
- Rifampicin and rifapentine-containing regimens should be prescribed with caution to people living with HIV who are on ART because of potential drug-drug interactions.

LTBI : WHO guidelines, 2018

So, what does the regimen which is recommended by WHO for TB preventive therapy? In both high and low TB incidence countries WHO recommends isoniazid mono therapy


for a duration of 6 months for treatment of LTBI in both adults and children. In high TB incidence countries that is where the estimated TB incidence is more than or equal to 100 per lakh population; alternatively to the 6 months of isoniazid rifampicin plus isoniazid daily for 3 months for children and adolescent age less than 15 years is recommended.

Rifapentine and isoniazid once weekly for 3 months for both adults and children is the other regimen which is recommended. We must remember that India is one of the high TB incidence countries, because the estimated TB incidence is more than 200 per lakh population. Rifapentine currently is not available in our country and this may be available in the near future.

Low TB incidence countries that is where the estimated TB incidence is less than 100 per lakh cases alternatively to the 6 months of isoniazid WHO recommends 9 months of isoniazid daily or 3 month regimen of weekly rifapentine plus isoniazid, 3 to 4 months of isoniazid plus rifampicin or 3 to 4 months of rifampicin alone. So, these are the regimens which are recommended as alternatives to the 6 months isoniazid daily treatment. In settings with high TB incidence and transmission adults and adolescents living with HIV who have an unknown or positive tuberculin skin test should receive at least 36 months of isoniazid preventive therapy.

This is based on previously published studies people with a negative TST should not receive 36 months of isoniazid preventive therapy. And it is important to bear in mind that rifampicin and rifapentine containing at regimens should be prescribed with caution to people living with HIV who are on ART because of potential drug drug interactions.

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Manage TB

Isoniazid Preventive Therapy (IPT) in India

- Children aged <6 years who are close contacts of TB patient
- HIV infected children aged >12 months and adults
- Children with HIV successfully completed TB treatment - INH for additional 6 months
- TST positive children receiving immunosuppression therapy
- A child born to mother who had TB during pregnancy

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Technical and Operational guidelines, RNTCP, 2016

So, what is India use for preventive therapy? It is basically isoniazid preventive therapy or IPT in India, the children is less than 6 years who are close contacts of TB patients are to be given IPT. So, there is a difference between the WHO and Indian guidelines; the WHO guidelines recommends for children less than 5 years, while the Indian guidelines recommend for children age less than 6 years.

The HIV infected children age more than 12 months and adults. Children with HIV successfully who are successfully completed treatment can be given INH for an additional 6 months. The TST positive children receiving immunosuppressive therapy and a child born to a mother who had TB during pregnancy after continental TB is ruled out in a child. So, isoniazid preventive therapy should be given in all these groups of patients.

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TB prevention in People living with HIV (PLHIV)

- ART Reduces the risk of TB by 65% to 70% in PLHIV
- 76% reduction in TB risk among patients receiving both ART and IPT - Study from Brazil
- IPT has benefit independent of ART in reducing TB and mortality - TEMPRANO trial
- IPT was found to be effective in reducing TB incidence by almost 50%, under programme conditions in India - NIRT study

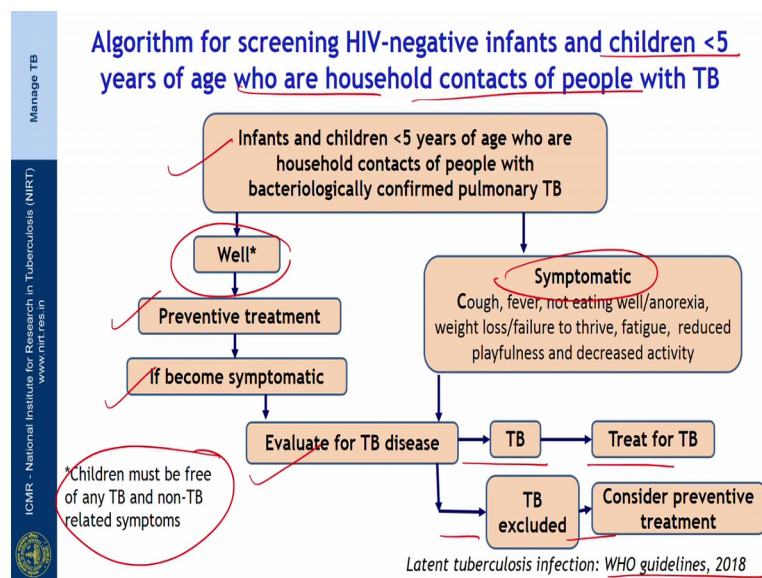
PLoS Med 9(7): e1001270; Thorax 2017;0:1-17; AIDS 2007;21(11):1441-1448; NEJM 2015; 373: 808-22



TB prevention in people living with HIV; antiretroviral therapy reduces the risk of TB by 65 percent to 70 percent in PLHIV's.

A study from Brazil showed that there is 76 percent reduction in TB risk among patients receiving both ART and isoniazid preventive therapy. The temprano trial has shown that isoniazid preventive therapy has benefit independent of art in reducing TB and mortality in PLHIVs. IPT was found to be effective in reducing TB incidents by almost 50 percent under program conditions in a study from India which was from NIRT.

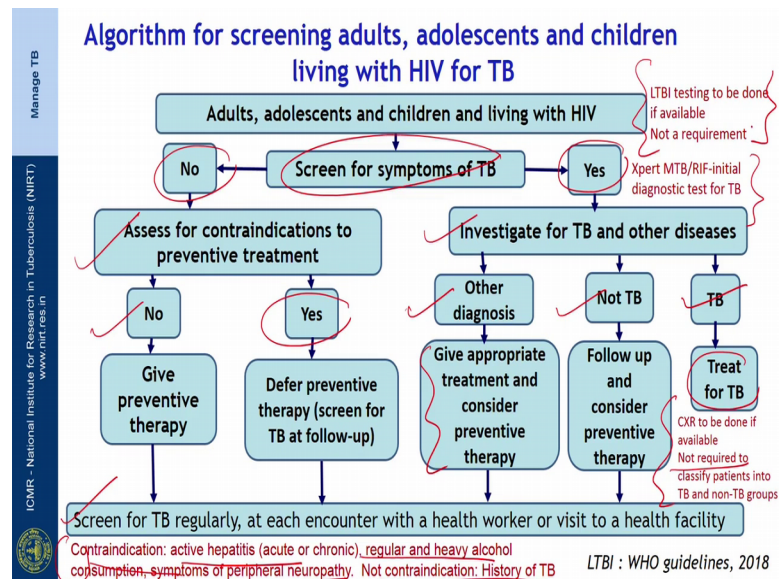
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So, the algorithm for screening HIV negative infants and children less than 6 years of age who are household contacts of people with TB; according to the WHO guidelines this is the screening strategy. So, these category of patients if they are well by well we mean the children must be free of any TB and non-TB related symptoms. So, you can give preventive therapy to them and if they become symptomatic evaluate them for TB disease; in case of TB, treat for TB and if TB is excluded consider preventive treatment.

If the child is symptomatic you are supposed to evaluate for TB disease and the subsequent management whether TB is present or TB is excluded.

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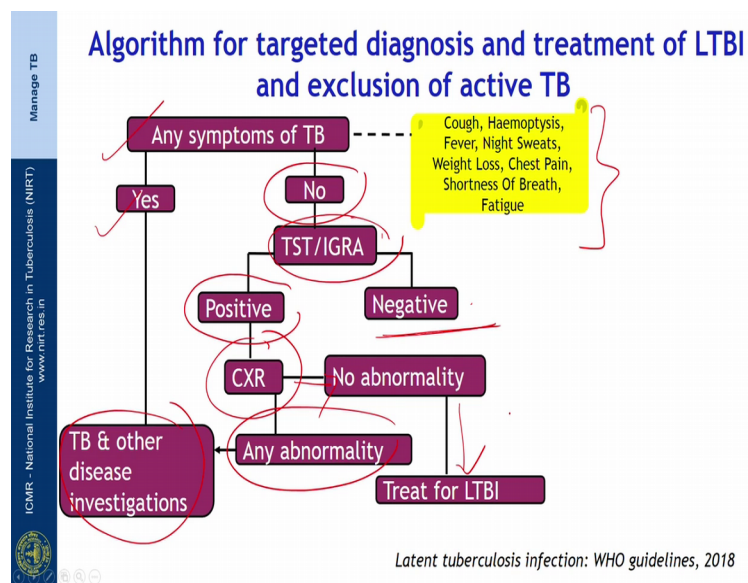


The algorithm for screening adults, adolescents and children living with HIV is as follows. First you screen them for symptoms of TB if they do not have symptoms of TB one has to assess them for contracting indications to preventive treatment. So, what are the contraindications to preventive treatment? It includes active hepatitis, regular and heavy alcohol consumption, symptoms of peripheral neuropathy; however, history of TB and pregnancy is not a contraindication.

So, if they do not have contraindications for preventive therapy give preventive therapy; however, if they have contraindications defer preventive therapy and screen for TB at follow up and closely monitor these patients. Once preventive therapy is given they must be screened for TB regularly at each encounter with the health co worker or during a visit to a health facility.

In case the patients have symptoms suggestive of TB one has to investigate them for TB and other diseases. The expert MTB rifampin is used as the initial diagnostic test for TB and chest X-ray to be done if available, but it is not a requirement to classify patients into TB and non-TB group. If the diagnosis of TB is established one has to treat them for TB, if the diagnosis is not TB follow up and consider preventive therapy, if there is other diagnosis established you give appropriate treatment for that condition and then consider preventive therapy for TB in these patients. So, latent TB infection testing can be done if available; however, it is not a requirement to start preventive therapy in PLHIV's.

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So, what is the algorithm for targeted diagnosis and treatment for LTBI an exclusion of active TB? So, any symptoms suggestive of TB has to be inquired in the patient which may be cough, haemoptysis, fever, night sweats, weight loss, chest pain, shortness of breath or fatigue; if the patient reports any symptoms they have to be evaluated for TB and other diseases; if there they report no symptoms then TST or a IGRA has to be done for this patient.

If the TST or IGRA is negative there NC algorithm if the TST or IGRA is positive a chest X-ray has to be taken. In case of any abnormality they have to be evaluated for TB and other disease conditions if there are no abnormality then the patient has to be treated for latent TB infection.

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Manage TB

Administration of IPT

Adult and Adolescent with HIV: Isoniazid 300mg + Pyridoxine 50mg (Vitamin B6) daily
Children with HIV aged > 12 months: Isoniazid 10mg/kg + Pyridoxine 25 mg (Vitamin B6) daily
Duration : 6 months

Isoniazid dosage (100mg)		
Body weight (kg)	Dosage (mg)	Number of tablets
< 5	50	Half
5.1 to 9.9	100	One
10 to 13.9	150	One and a half
14 to 19.9	200	Two
20 to 24.9	250	Two and a half
>25	300	Three
Adults	300	Three

Pyrdoxine dosage (50mg)	
Body weight (kg)	Number of tablets
1 - 13.9	Quarter
14 - 25	Half
>25	One
Adults	One

- IPT to be administered after ruling out active TB
- Closely monitored for TB symptoms, adverse events

CTD and NACO, 2016

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The administration of isoniazid preventive therapy according to the central TB division and a NACO guidelines is the adolescent and adults with HIV has to be given isoniazid 300 milligram plus pyridoxine 50 milligram which is vitamin B 6 to reduce a peripheral neuropathy daily. Children with HIV who are aged more than 12 months have to be given isoniazid at the dosage of 10 milligram per kilogram along with pyridoxine 25 milligram daily and the duration of IPT is for 6 months.

So, this is a dosage of drugs the isoniazid is available as 100 milligram tablets and the dosage is as per body weight; for adults it is 300 milligram daily or 3 tablets. Pyridoxine is available as the 50 milligram tablet which is also given based on the body weight of the child and in adults it is 1 tablet to be taken along with isoniazid. The isoniazid preventive therapy has to be always administered after ruling out active TB in this population they should be closely monitored for TB symptoms and adverse events.

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IPT for child contacts of TB patients

- RNTCP currently recommends 6 months of IPT for child contacts aged <6 years of TB patients after ruling out active TB
- IPT to be given irrespective of BCG/nutritional status
- Dosage of INH - 10mg/kg bodyweight daily for a minimum period of six months
- Contacts should be closely monitored for TB symptoms

Technical and Operational guidelines, RNTCP, 2016



The isoniazid preventive therapy for child contacts of TB patient; the revised national TB control program currently recommends 6 months of isoniazid preventive therapy for child contacts age less than 6 years of age of TB patients after ruling out active TB. The isoniazid preventive therapy to be given irrespective of BCG and nutritional status; the dosage of isoniazid is 10 milligram per kilogram body weight daily for a minimum period of 6 months and these contact should be closely monitored for symptoms of tuberculosis.

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Preventive treatment for contacts of MDR-TB

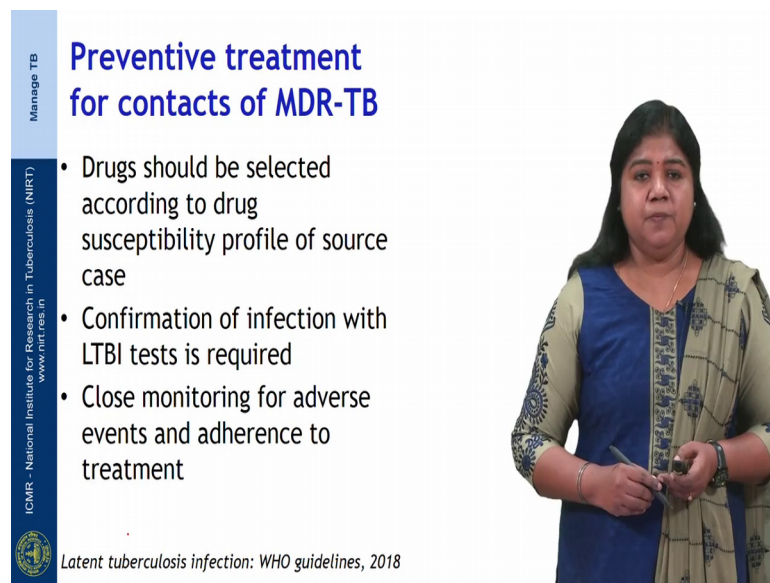
- In selected high-risk household contacts of patients with MDR-TB, preventive treatment may be considered based on individualised risk assessment and sound clinical justification.
- Preventive treatment should be given to household contacts at high risk (e.g. children, people receiving immunosuppressive therapy and people living with HIV).

Latent tuberculosis infection: WHO guidelines, 2018



So, what do we do for contacts of multi drug resistant tuberculosis? According to the WHO guidelines and selected high risk household contacts of patients with MDR-TB preventive treatment may be considered based on individualized risk assessment and sound clinical justification. Preventive treatment should be given to household contacts, who are at high risk for TB which include children people living receiving immunosuppressive therapy and people living with HIV.

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The slide features a vertical blue bar on the left with the text 'Manage TB' at the top, 'ICMR - National Institute for Research in Tuberculosis (NIRT)' in the middle, and 'www.nirt.res.in' at the bottom. The main title is 'Preventive treatment for contacts of MDR-TB'. The bullet points are: '• Drugs should be selected according to drug susceptibility profile of source case', '• Confirmation of infection with LTBI tests is required', and '• Close monitoring for adverse events and adherence to treatment'. At the bottom right of the slide, it says 'Latent tuberculosis infection: WHO guidelines, 2018'. On the right side of the slide, a woman in a blue and green patterned sari is standing and presenting.

Drugs should be selected according to the drug susceptibility profile of the source case and there should be confirmation of infection with LTBI test which is a requirement. They should be close monitoring for adverse events and adherence to treatment.

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Prevention of TB in contacts of drug resistant TB in RNTCP

- Monitor closely for signs & symptoms of active TB
- No consensus on choice of drug or duration of treatment
- Prompt treatment of MDR-TB - most effective way of preventing spread of infection to others

Technical and Operational guidelines, RNTCP, 2016




The revised national TB control program; however, recommends monitoring closely for signs and symptoms of active TB among the contacts of drug resistant TB patients. There is no consensus yet on the choice of drug or the duration of treatment, prompt treatment and diagnosis of MDR-TB is the most effective way for preventing spread of infection to others.

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Key messages

- Management of LTBI is a crucial part of the WHO's End TB strategy
- Active screening of persons at risk for TB is essential
- Either TST or IGRA can be used to detect LTBI
- TST and IGRA cannot be used to diagnose active TB disease
- Preventive therapy reduces the risk of progression from LTBI to active disease



So, what are the key messages of this session? The management of latent TB infection is very important and it is an integral part of the WHO's end TB strategy with target's TB elimination and eradication.

The active screening of persons at risk for TB is very important to identify TB early and provide appropriate treatment. Either the TST or the IGRA can be used to detect latent TB infection; the TST and IGRA cannot be used to diagnose active TB disease. Preventive therapy reduces a risk of progression from LTBI to active TB disease.

Thank you for your attention of the session on Management of Latent TB Infection.