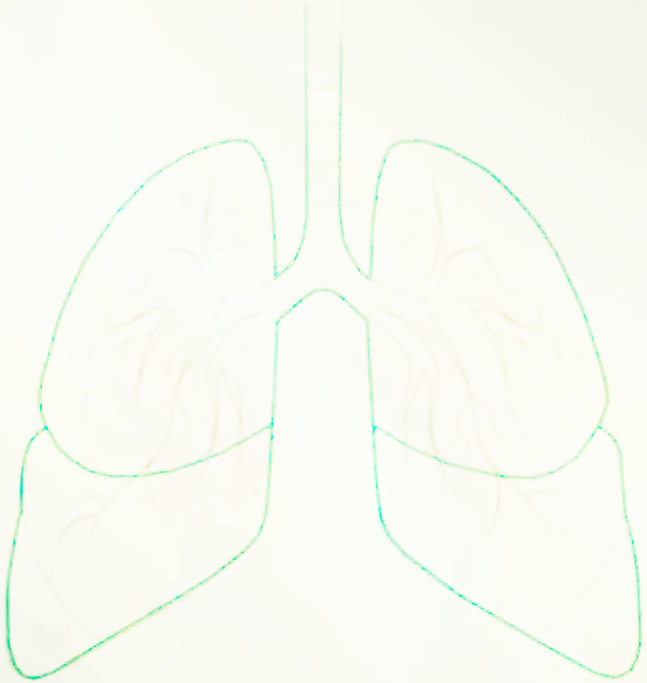
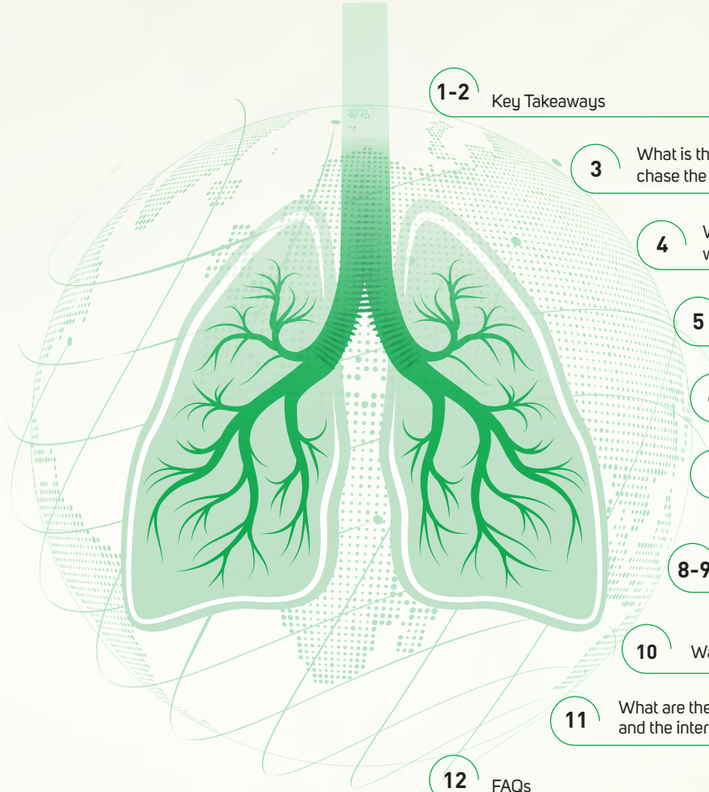


Joint
Effort for
Elimination of
Tuberculosis

DECODING LTBI, ONE QUESTION AT A TIME

Treat to Beat
In India's fight to eliminate TB



Joint
Effort for
Elimination of
Tuberculosis

KEY TAKEAWAYS

NEED OF THE HOUR

A combined assault on transmitted and latent infections is synergistic and the need of the hour to eliminate the Tuberculosis (TB) burden from India. TB reactivation rates can be substantially reduced by up to 90%, if Latent Tuberculosis Infection (LTBI) patients take preventative treatment.

Reference: Kiazyk, S, and T B Ball. "Latent tuberculosis infection: An overview." Canada communicable disease report = Releve des maladies transmissibles au Canada vol. 43,3-4 62-66. 2 Mar. 2017, doi:10.14745/ccdr.v43i34a01

WHICH PATIENT CATEGORIES ARE AT HIGH-RISK AND WORTH FOCUSSING ON

High risk patient categories which need closer observation -

1. HouseHold Contacts (HHC's) of Pulmonary TB patients
2. Patients with chronic renal failure requiring hemodialysis or organ transplant,
3. Patients on immunosuppressants,
4. Patients with silicosis
5. HIV patients
6. Patients treated with tumour necrosis factor alpha (TNF-α) inhibitors
7. Patients planning or already undergone any organ transplant

Other important patient segments - (i) Diabetic patients (ii) Alcohol, Tobacco users

TREATMENT COURSE WITH PROVEN SUCCESS

A systematic review of randomized control trials (RCTs) involving PLHIV in 2009 showed that **TPT reduces overall risk for TB by 33% (RR 0.67; 95% CI 0.51;0.87), and the preventive efficacy reached 64% for people with a positive TST** (RR 0.36; 95% CI 0.22;0.61)

Reference: Akolo C et al

DOES TUBERCULOSIS PREVENTIVE TREATMENT (TPT) AFFECT DRUG RESISTANCE IN PATIENTS?

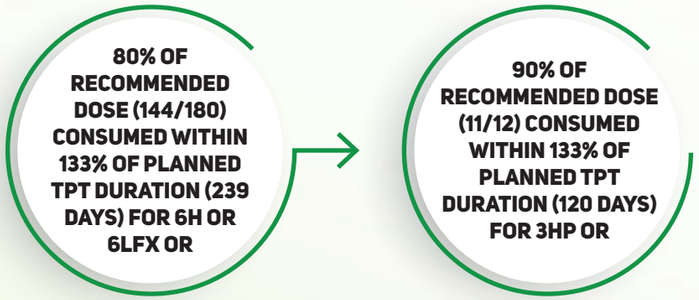
There is no evidence of significant association between development of resistance to H or R with use of these drugs for TPT. However, TB disease must be ruled out before TPT is initiated, along with regular follow-up to rule out development of active TB disease. Rapid molecular Drug susceptibility test (DST) must be offered to all patients if TB disease is detected before, during or any time post TPT.

HOW LONG DOES TPT REMAIN EFFECTIVE FOR?

Preventative treatment remains effective for a duration of (3-7 years) as per multiple researches done across the world

HOW TO MEASURE TREATMENT COMPLETION OF TPT?

Treatment completion: A person initiated on TPT who completed at least:



Regimen	Total duration in months	Expected number of doses	80% of recommended doses (days)	Extended time for treatment completion (days) (treatment duration +33% additional time)
6H (daily)	6	180	144	239
3HP (weekly)	3	12	11*	120

* 90% of recommended number of doses

References:
1. Golub JE, Cohn S, Saraceni V, et al. Long-term protection from isoniazid preventive therapy for tuberculosis in HIV-infected patients in a medium-burden tuberculosis setting: the TB/HIV in Rio (THRio) study. Clin Infect Dis. 2014;60(4):639-45. 2. Anani Badje et.al. Effect of isoniazid preventive therapy on risk of death in west African, HIV-infected adults with high CD4 cell counts: long-term follow-up of the Temprano ANRS 12136 trial 3. Semu, M., Fenta, T.G., Medhin, G. et al. Effectiveness of isoniazid preventive therapy in reducing incidence of active tuberculosis among people living with HIV/AIDS in public health facilities of Addis Ababa, Ethiopia: a historical cohort study. BMC Infect Dis. 17, 5 (2017) doi:10.1186/s12879-016-2109-7

SPECIFIC RESEARCH STUDIES

1) WHAT IS THE WAY TO APPROACH TBI IN ORDER TO CHASE THE TARGET OF ELIMINATING THE TB BURDEN?

To force case incidence down more quickly, we must not only cut transmission but also neutralize the reservoir of latent infection, both among people who have not yet suffered an episode of TB and among those who have recovered from illness but who still carry live bacilli

Achieving TB elimination requires a direct attack on the reservoir of latent infection, with a drug or a vaccine (or both) that is effective against established infection. For instance, if 14% of people infected with M. tuberculosis are fully and permanently protected each year, incidence would fall to 20 per million by 2050 with no other intervention

The combined assault on transmitted and latent infections is synergistic. Incidence in 2050 is 3.5 times lower than it would be if the two interventions acted independently

Consequently, elimination should be carried out not as a sequential, two-step process-first interrupt transmission and then remove the latent reservoir-**but rather as a simultaneous attack on two components of the M. tuberculosis life cycle**

THE INDIA CONTEXT OF ELIMINATING TB

- **Elimination by 2050 in India is not unimaginable,** but it requires far more than improved case management. Most effectively, India would need mass preventive therapy, both for infected people to prevent first episodes of TB and for cured cases to prevent relapse.
- However, whereas TPT for HIV-infected people in South Africa is already recommended [along with Antiretroviral therapy (ART)], **mass preventive therapy in India, would be a radical departure from current practice.**
- **Achieving high coverage of and adherence to TPT is likely to require biomarkers to target those who are most at risk of progressing from subclinical to active TB,** plus short drug regimens (three months or less) that are safe and that can eliminate latent infection.

Reference: Prospects for Tuberculosis Elimination Christopher Dye, Philippe Glaziou, Katherine Floyd, Mario Raviglione. Annual Review of Public Health. 2013 34:1, 271-286

2) WHICH ARE THE HIGH-RISK CATEGORIES OF PATIENTS WHO SHOULD BE OBSERVED WITH A KEEN EYE?

The understanding of the underlying reasons for TBI reactivation is incomplete, but it does include bacterial, host and environmental factors. While the lifetime risk for reactivation among otherwise healthy individuals with documented TBI is quoted as approximately 5% to 15% various comorbidities and risk factors are associated with increased risk and hence elevated rates of developing active TB.

The most potent risk factor is human immunodeficiency virus (HIV) infection. Those with HIV and latent TB co-infection have more than a 100-fold increased risk of developing active TB disease. Even after successful antiretroviral therapy, the risk remains significantly elevated.

Other comorbidities and conditions associated with TBI reactivation are categorized as high, moderate, slightly increased, low and very low risk, depending on their associated risk factors.

IN THE HIGH-RISK CATEGORY ARE

(i) Patients with chronic renal failure requiring hemodialysis transplant

(ii) Patients on immunosuppressants and

(iii) Patients with silicosis

(iv) Household contacts of Pulmonary TB patients are also classified in the high-risk category

AT MODERATE RISK ARE

(i) Patients treated with tumour necrosis factor alpha (TNF-α) inhibitors (used for many autoimmune and inflammatory conditions) or glucocorticoids,

(ii) Patients with diabetes (all types) and recently infected children under the age of four.

Those who abuse alcohol, smoke cigarettes or are underweight or malnourished are at slightly increased risk for TBI reactivation.

TB incidence is higher among these groups than within the general population. A commonality among the majority of these conditions leading to increased reactivation risk is suppressed immunity.

TB reactivation rates can be substantially reduced by up to 90%, if TBI patients take preventative therapy.

Latent tuberculosis infection: An overview
Reference: Kiazyk, S, and T B Ball. "Latent tuberculosis infection: An overview." Canada communicable disease report = Releve des maladies transmissibles au Canada vol. 43,3-4 62-66. 2 Mar. 2017, doi:10.14745/ccdr.v43i34a01

3) WHAT KIND OF PREVENTATIVE TREATMENT HAS BEEN FOUND TO BE MORE EFFECTIVE?

Recently, a 12-dose once-weekly regimen of isoniazid plus rifapentine (commonly known as 3HP), administered by directly observed therapy, has been shown to be as effective as the standard INH9, and has also resulted in reduced hepatotoxicity and higher compliance rates

No significant difference in the incidence of active TB between participants given a 3HP and 6H (RR 0.73, 95% CI 0.23; 2.30)

The reactivation of TB from untreated TBI is a major source of new active TB infections and transmission. In order to meet TB elimination goals, targeted TBI testing and treatment of marginalized and hard-to-access groups and those with high-risk for TB reactivation is a priority

The 3HP regimen is associated with a higher completion rate in all subgroups (adults with HIV: RR 1.25, 95% CI 1.01; 1.55; adults without HIV: RR 1.19, 95% CI 1.16; 1.22; children and adolescents: RR 1.09, 95% CI 1.03; 1.15) (https://apps.who.int/iris/handle/10665/260233)

Shorter and efficacious preventative treatment regimens (3HP), more sensitive TBI diagnostics and novel tests to identify those individuals at the highest risk for TB reactivation will all help to reach the TB elimination goals.

Target population	Regimen

• People living with HIV (+ ART)
  • Adults and children >12 months
  • Infants <12 months with HIV in contact with active TB
• HHC below 5 years of pulmonary TB patients
	• 6-months daily isoniazid (6H)
	• 3-month weekly Isoniazid and Rifapentine (3HP) in persons older than 2 years

• HHC 5 years and above of pulmonary TB patients	• 3-month weekly Isoniazid and Rifapentine (3HP) • 6-months daily isoniazid (6H)
• Children/adult on immunosuppressive therapy, silicosis, anti-TNF treatment, dialysis, transplantation	• 3-month weekly Isoniazid and Rifapentine (3HP) • 6-months daily isoniazid (6H)

Latent tuberculosis infection: An overview
Reference: Kiazyk, S, and T B Ball. "Latent tuberculosis infection: An overview." Canada communicable disease report = Releve des maladies transmissibles au Canada vol. 43,3-4 62-66. 2 Mar. 2017, doi:10.14745/ccdr.v43i34a01

Latent tuberculosis infection: Opportunities and challenges
Reference: Chee CBE, Reves R, Zhang Y, Belknap R. Latent tuberculosis infection: Opportunities and challenges. Respirology. 2018 Oct;23(10):893-900. doi: 10.1111/resp.13346. Epub 2018 Jun 14. PMID: 29901251.

4) HOW LONG WILL THE TPT TREATMENT REMAIN EFFECTIVE?

Preventative treatment (TPT) remains effective for a duration of (3-7 years) as per multiple researches done across the world. Although there is no conclusive evidence for India, TPT should not be repeated for a particular patient (who has been given TPT before) before a minimum period of 2 years.

In Brazil (Thrio study), TPT in **TST + PLHIV reduced incidence by 92% and reduces the TB risk over 7 years**

Temprano ANRS 12136 trial Côte d'Ivoire (159 per 100 000) TPT showed 37% reduction in mortality independent of ART and baseline CD4 and **Sustained benefits up to 6 years**

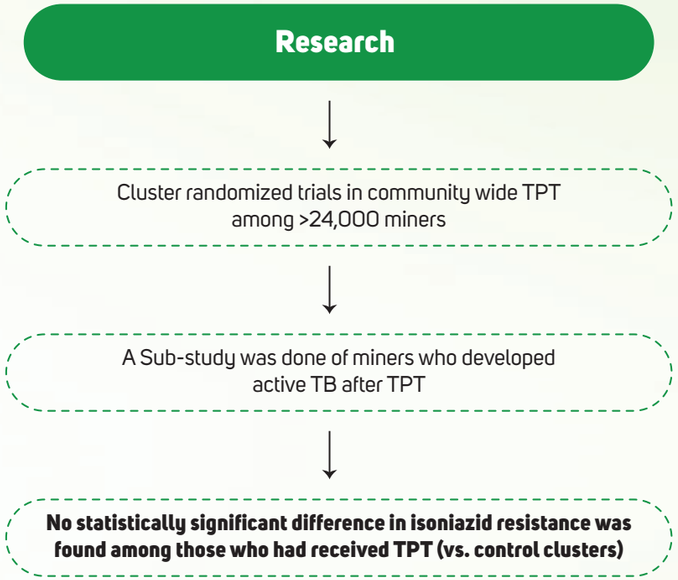
Study in Ethiopia reduced incidence by 96.3% and offered sustained **protection against occurrence of active TB for 3 years among people living with HIV/AIDS**

References:
1. Golub JE, Cohn S, Saraceni V, et al. Long-term protection from isoniazid preventive therapy for tuberculosis in HIV-infected patients in a medium-burden tuberculosis setting: the TB/HIV in Rio (THRio) study. Clin Infect Dis. 2014;60(4):639-45. 2. Anani Badje et.al. Effect of isoniazid preventive therapy on risk of death in west African, HIV-infected adults with high CD4 cell counts: long-term follow-up of the Temprano ANRS 12136 trial 3. Semu, M., Fenta, T.G., Medhin, G. et al. Effectiveness of isoniazid preventive therapy in reducing incidence of active tuberculosis among people living with HIV/AIDS in public health facilities of Addis Ababa, Ethiopia: a historical cohort study. BMC Infect Dis. 17, 5 (2017) doi:10.1186/s12879-016-21

5) WILL TPT INCREASE DRUG RESISTANCE IN THE PATIENTS?

Multiple studies have shown no statistically significant increase in drug resistance. However, it is unclear whether large scale programmatic scaleup will differ and limited data exists on Rifamycins

There is no evidence of significant association between development of resistance to H orR with use of these drugs for TPT. However, TB disease must be ruled out before TPT is initiated, along with regular follow-up to rule out development of active TB disease. Rapid molecular DST must be offered to all patients if TB disease is detected before, during or any time post TPT.
The takeaway is that Benefits of TPT outweigh the risks involved.



Reference: Thibela TB study (INH resistance after TPT. No difference)

6) HOW TO MANAGE AND GUIDE PATIENTS WHO HAVE MISSED SOME OF THEIR PRESCRIBED DOSES.

TPT regimen	Duration of interruption	Management steps
6H, 6Lfx, 4R	Less than 2 weeks	• Resume TPT 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 6H missed 3 days of treatment, continue TPT for a total duration of 6 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, continue and complete the remaining treatment doses in the course. • If less than 80% of doses expected in the regimen were taken, and the treatment course can still be completed within the expected time for completion, i.e. treatment duration + 33% additional time, , continue and complete the remaining treatment doses in the course. • If less than 80% of doses expected in the regimen were taken, and the treatment course cannot be completed within expected time for completion, consider restarting full TPT course.

TPT regimen	Duration of interruption	Management steps
3HP	Weekly schedule of up to 3 doses missed	• If the missed dose is remembered within 2 days of scheduled day, the person can take the dose immediately and continue to take remaining doses following the same schedule to complete the course. • If the missed dose is remembered after 2 days, 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 two weekly doses being taken less than 4 days apart. • If between 1-3 weekly doses are missed, treatment is continued until all 12 doses are taken, thus prolonging the treatment duration to a maximum of 16 weeks.
	More than 3 weekly doses of 3HP missed	• If 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.

7) WAYS TO INCREASE ADHERENCE TO TPT

- Poor adherence or early cessation of TPT can potentially increase the risk of the individual developing TB disease including drug-resistant TB.
- **Efficacy of TPT is greatest if at least 80% of the doses are taken within 133% of the duration of the regimen.** Total number of doses taken is a key determinant of the extent of TB prevention.
- Success of the TPT strategy is based on adherence to the treatment.

FOLLOW-UP ASSESSMENT- MAINTAINING REGULAR CONTACT WITH PERSONS ON TPT AND THEIR FAMILY

- The health worker of healthcare facility and TBHV/STS concerned are responsible to maintain regular contact and review the persons on TPT and their family along with the index TB patient on at least monthly basis
- Contact can be made either at healthcare facility or during home visits or tele/video call and assess:

I. Assess adherence of every dose of TPT using digital tools or counting empty blister or refill monitoring if treatment supporter is a family member; (Consider Use of digital platforms (tele/video calls, 99DOTS/MERM).

II. Check for any signs and symptoms of TB emerging while on TPT.

III. Check for any adverse events of TPT drugs and arrange for its prompt management.

IV. Arrange for clinical assessment by the doctor at HF (including CHO) on a monthly basis.

V. Conduct biochemical assessments (LFT etc.), as indicated.

VI. Undertake periodic counselling.

8) WHAT ARE THE LIMITATIONS OF TUBERCULIN SKIN TEST (TST) AND THE INTERFERON GAMMA RELEASE ASSAY (IGRA) TO DIAGNOSE TBI?

The tuberculin skin test (TST) and the interferon gamma release assay (IGRA) are currently used to establish the diagnosis of TBI. However, neither TST nor IGRA is useful to discriminate between active and latent tuberculosis. **Moreover, these tests cannot be used to predict whether an individual with TBI will develop active tuberculosis (TB) or whether therapy for TBI could be effective to decrease the risk of developing active TB.**

The TST has been the most broadly used technique for the diagnosis of TBI because of its simplicity and the in vivo evidence it provides for an antimycobacterial cellular immune response. **However, it has the inconvenience of being positive in the BCG-vaccinated individual.**

The further introduction of IGRAs has added higher specificity, while the new version **QTF-Plus looks promising in differentiating between active TB and TBI.** Despite this progress, the search for a reliable biomarker of TBI and evaluating the efficacy of drug therapy in patients with TBI remains open.

One of the strategies/ targets/ immunological markers that have been proposed over the last decade for the differential diagnosis between TBI and active TB and for evaluating the effectiveness of treatment of TBI includes the analysis of cellular profile such as the proportion of TNF-α-only TEFF with an effector memory phenotype CD45RA–CCR7–CD127–, which has been associated with a higher risk of progression to active TB in immunocompetent adults

The challenges ahead include the validation of these tests in groups of individuals representative of distinct populations and their practicality in low-income countries, where tuberculosis is still a major public health problem. Such challenges, once overcome, may pave the way to a whole new way to deal with the disease.

Reference:
Diagnosis for Latent Tuberculosis Infection: New Alternatives.
Claudia Carranza1, Sigifredo Pedraza-Sanchez2, Eleane de Oyarzabal-Mendez1 and Martha Torres.

Notes

Notes

FAQ

1. Can patients treated for TB be put on TPT?

In patients previously treated for TB, post-treatment TPT has been considered in view of the 5-7 times higher risk of recurrence of TB among PLHIV and nearly 90% of these due to re-infection (11). In addition to post-treatment TPT, ensuring completion of the initial course of TB treatment and effective infection control measures in clinical and community settings frequently visited by PLHIV would reduce recurrence of TB. Thus, all CLHIV/PLHIV who had successfully completed treatment for TB disease earlier should receive a course of TPT after completing treatment of TB.

2. Why are health care providers are not included in high-risk group ?

They are high-risk but relative risk as compared to other patient categories considered in the high-risk group of this category is low.

3. Is there any window period of TBI where we miss them during testing?

Window period is more pertinent for the TB disease and not for TBI. Majority of TBI (Infection) patients will break into TB disease within a 2 year period. Therefore, all efforts should be made immediately after an index patient has been identified to track all household contact and test them for TBI and subsequently, administer them treatment.

4. Which is the best approach to test and treat or treat all?

The most important step is to exclude TB disease before testing for TBI. The guiding principle is not to undertreat any patient.