MANAGEMENT OF LATENT TUBERCULOSIS:

SPECIAL FOCUS ON INDIA

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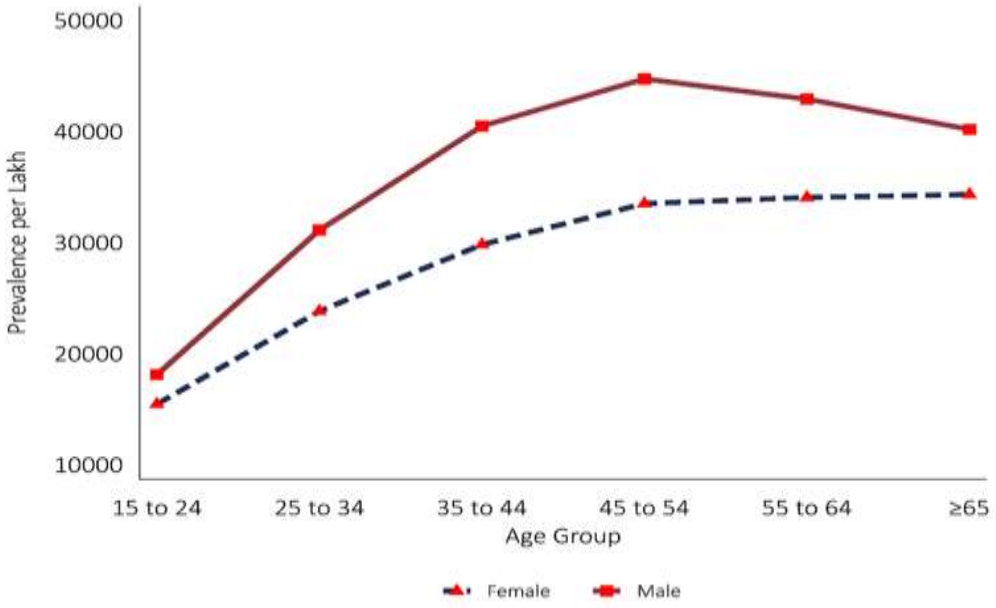
SR

QUESTIONS

- What is the burden of latent tuberculosis
- What is the rationale to treat it
- What are the benefits and risks associated-evidence
- What do the guidelines say
- Current status of treatment of TBI in India
- Practical aspects of treating TBI in India

BURDEN



TB infection:
A persistent state of immunological response to stimulation by M. tuberculosis antigens without any evidence of clinically manifest tuberculosis disease.

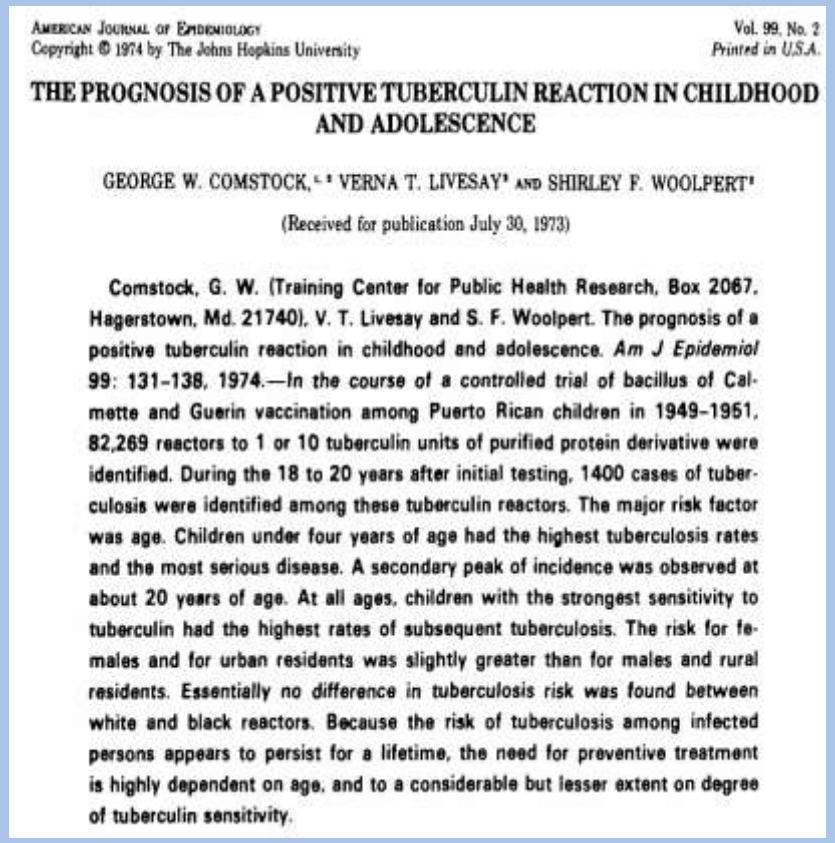
- 35-40 crore Indians are estimated to have TB infection
- 18-36 lakhs of them are expected to develop tuberculosis disease each year
- Globally 200 crore people have TBI

- As per national tuberculosis prevalence survey (2019-2021) prevalence of TB infection in India among adults (>15 years) is 31.3% (crude prevalence; basis: IGRA)(1)
- More recent meta-analysis has detected the prevalence to be 36% in general population (excluding high risk groups) and 40% in the population with high-risk groups included(2)

1. National TB prevalence survey (2019-2021)
2. Chauhan A, Parmar M, Dash GC, Solanki H, Chauhan S, Sharma J, et al. The prevalence of tuberculosis infection in India: A systematic review and meta-analysis. Indian J Med Res. 2023;157(2&3):135-51.

RISK OF TB DISEASE

- A study performed over 20 years on Puerto Rican children
- 82,269 children tested positive to TST (either initial 1 TU or subsequent 10 TU;)
- Positivity was taken as >6 mm induration after 72 hours
- 1400 subjects developed tuberculosis during the follow up period
- Younger age of testing positive for TST was associated with higher risk of TB disease
- Larger induration was also associated with a higher risk of developing disease in the ensuing 2 decades



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THE PROGNOSIS OF A POSITIVE TUBERCULIN REACTION IN CHILDHOOD AND ADOLESCENCE

GEORGE W. COMSTOCK,[1,2] VERNA T. LIVESAY[2] AND SHIRLEY F. WOOLPERT[2]

(Received for publication July 30, 1973)

Comstock, G. W. (Training Center for Public Health Research, Box 2067, Hagerstown, Md. 21740), V. T. Livesay and S. F. Woolpert. The prognosis of a positive tuberculin reaction in childhood and adolescence. *Am J Epidemiol* 99: 131–138, 1974.—In the course of a controlled trial of bacillus of Calmette and Guerin vaccination among Puerto Rican children in 1949–1951, 82,269 reactors to 1 or 10 tuberculin units of purified protein derivative were identified. During the 18 to 20 years after initial testing, 1400 cases of tuberculosis were identified among these tuberculin reactors. The major risk factor was age. Children under four years of age had the highest tuberculosis rates and the most serious disease. A secondary peak of incidence was observed at about 20 years of age. At all ages, children with the strongest sensitivity to tuberculin had the highest rates of subsequent tuberculosis. The risk for females and for urban residents was slightly greater than for males and rural residents. Essentially no difference in tuberculosis risk was found between white and black reactors. Because the risk of tuberculosis among infected persons appears to persist for a lifetime, the need for preventive treatment is highly dependent on age, and to a considerable but lesser extent on degree of tuberculin sensitivity.

Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. Am J Epidemiol. 1974;99(2):131-8.

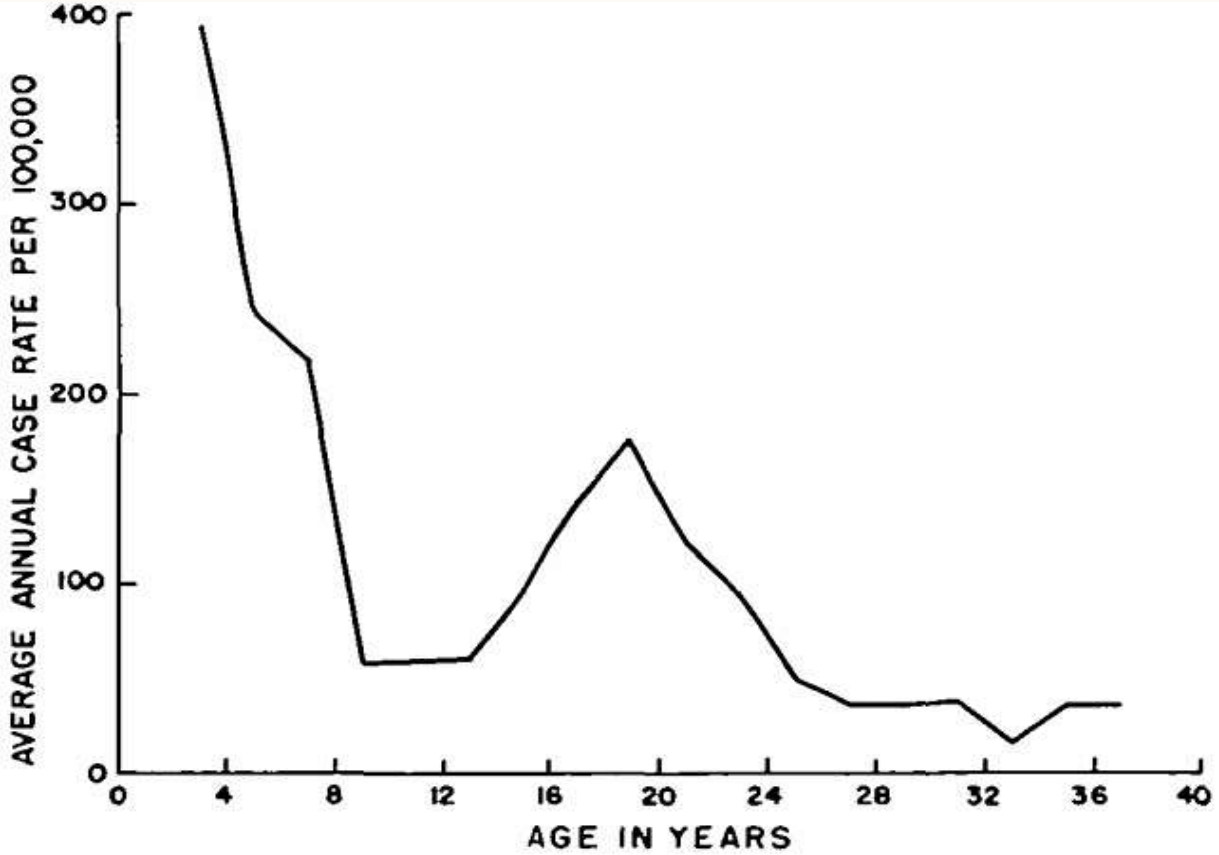


FIGURE 1. Incidence of tuberculosis among initial reactors to tuberculin, by age when tuberculosis was first diagnosed.

RISK OF TB DISEASE

- Generally, 5-15% of subjects with TB infection develops TB disease in their lifetime (1)
- Highest risk of contracting infection is house-hold/close contact with active pulmonary TB patients
- Globally, people with certain ailments are at a higher risk of TBI progression to active disease
- Children < 5 years are most vulnerable amongst all groups

High Risk Groups (1)			
Compromised immunity	Drugs/interventions	High risk occupation/ habit	Habitat
HIV	Organ transplant/haematologic transplant	Silicosis	Prisoners
Diabetes	Glucocorticoids, TNF-alpha-i	HCW	Homeless adults
Elderly	Haemodialysis/ESRD	IVDU	Recent immigrants

1. Getahun H, Matteelli A, Chaisson RE, Raviglione M. Latent Mycobacterium tuberculosis infection. N Engl J Med. 2015;372(22):2127-35.

RISK OF TB DISEASE

Table 1. Incidence of Active Tuberculosis and Prevalence of Latent Tuberculosis Infection in Selected High-Risk Groups, According to Published Studies.*

High-Risk Group	Incidence of Active Tuberculosis	Prevalence of Latent Tuberculosis Infection†		
		QuantiFERON-TB Gold In-Tube	T-SPOT.TB	Tuberculin Skin Test
	median rate per 1000 population (range)	*median percentage (range)*		
Persons with HIV infection	16.2 (12.4–28.0)	14.5 (2.7–21.5)	11.3 (4.3–67.6)	19.2 (2.1–54.8)
Adult contacts of persons with tuberculosis	0.6‡	21.1 (6.6–55.1)	48.0 (29.6–59.6)	26.3 (1.8–82.7)
Patients receiving tumor necrosis factor blockers	1.4‡§	11.8 (4.0–22.3)	20.0 (12.9–25.0)	18.6 (11.3–68.2)
Patients undergoing hemodialysis	26.6 (1.3–52.0)	33.4 (17.4–44.2)	43.6 (23.3–58.2)	21.9 (2.6–42.1)
Patients undergoing organ transplantation	5.1‡	21.9 (16.4–23.5)	29.5 (20.5–38.5)	7.7 (4.4–21.9)
Patients with silicosis	32.1‡	46.6‡	61.0‡	—
Prisoners	2.6 (0.03–9.8)	—	—	45.5 (23.1–87.6)
Health care workers	1.3 (0.4–4.1)	14.1 (0.9–76.7)	5.2 (3.5–28.7)	29.5 (1.4–97.6)
Immigrants from countries with a high tuberculosis burden	3.6 (1.3–41.2)	30.2 (9.8–53.8)	17.0 (9.0–24.9)	39.7 (17.8–55.4)
Homeless persons	2.2 (0.1–4.3)	53.8 (18.6–75.9)	—	45.6 (20.5–79.8)
Illicit-drug users	6.0‡	63.0 (1.4–66.4)	45.8 (34.1–57.5)	85.0 (0.3–86.7)
Elderly persons	—	16.3‡	—	31.7‡

* Data are from studies in countries with a low incidence of tuberculosis (<1 per 1000 population). The search for the incidence of active tuberculosis covered the period from January 1, 2004, to August 30, 2014, and data were restricted to articles published in English. The search for the prevalence of latent tuberculosis covered the period from January 1, 2009, to August 30, 2014, and data were restricted to articles published in English, Spanish, or French. The list of included studies and specific values for each risk group are provided in Tables S1 and S2, respectively, in the Supplementary Appendix. Dashes denote no data.

† The QuantiFERON-TB Gold In-Tube assay (Cellestis) and the T-SPOT.TB assay (Oxford Immunotec) are interferon-γ release assays. In response to the tuberculin skin test, indurations that measured at least 5 mm in diameter were used to compute prevalence.

‡ Data are from a single study.

§ Patients received treatment with infliximab.

Getahun H, Matteelli A, Chaisson RE, Raviglione M. Latent Mycobacterium tuberculosis infection. N Engl J Med. 2015;372(22):2127-35.

HOUSEHOLD AND CLOSE CONTACTS

Close contacts:

A person who is not in the household but

1. shared an enclosed space, such as at a social gathering, workplace or facility
2. for extended periods during the day with the index TB patient
3. during the three months before commencement of the current TB treatment episode.

House-hold contacts

A person who

1. shared the same enclosed living space as the index TB patient
2. for one or more nights or for frequent or extended daytime periods
3. during the three months before the start of current TB treatment.

EVIDENCE OF RISK

Meta-Analysis > Lancet. 2020 Mar 21;395(10228):973-984. doi: 10.1016/S0140-6736(20)30166-5.

The risk of tuberculosis in children after close exposure: a systematic review and individual-participant meta-analysis

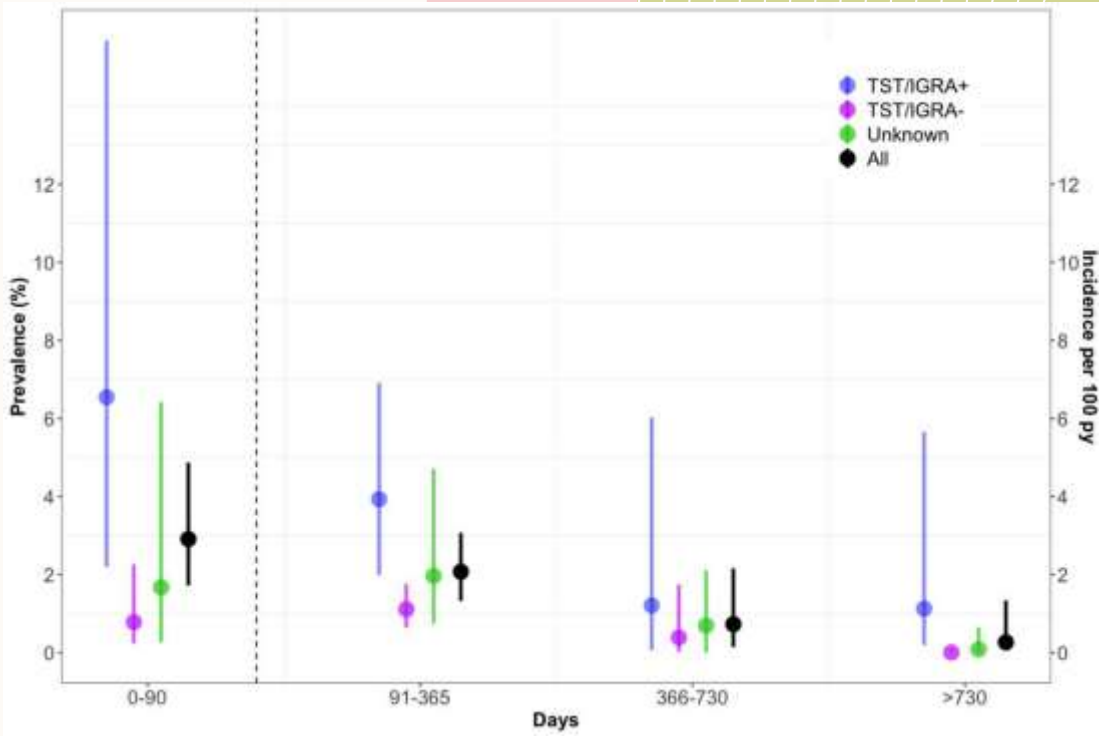
Leonardo Martinez [1], Olivia Cords [2], C Robert Horsburgh [3], Jason R Andrews [2]; Pediatric TB Contact Studies Consortium

- In 2020 a systematic review by Martinez et al evaluated the risk of TB prevalence and incidence among children exposed to microbiologically or radiologically diagnosed TB patients (close and house-hold contacts
- They also evaluated the effectiveness of preventive therapy on risk of contracting TB disease
- The review included studies across 34 countries (quality- majority good)
- They found that on 2 years follow up the rate of developing TB was highest during the first 90 days, and it was higher among children with baseline IGRA/TST positivity (6.5% vs 0.8%) [these subjects did not receive preventive therapy of any kind)

Martinez L, Cords O, Horsburgh CR, Andrews JR. The risk of tuberculosis in children after close exposure: a systematic review and individual-participant meta-analysis. Lancet. 2020;395(10228):973-84.

CONTINUED..

- 61% developed TB within first 90 days (overall)
- 82% IGRA/TST positive children developed TB within this time (all age)
- 96% IGRA/TST positive under-5 children developed TB within first 90 days after exposure
- Children living with HIV had higher risk of prevalent (Adjusted Odds Ratio [AOR], 2.80, 95% CI, 1.62–4.85) and incident (Adjusted Hazard Ratio [AHR], 5.31, 95% CI, 2.39–11.81) disease



ROLE OF PREVENTIVE THERAPY

- Effectiveness of preventive therapy 63% overall
- Effectiveness was greater in TST/IGRA positive children (AHR- 0.09 vs 0.66)
- BCG vaccination protective against all forms of TB in < 5 years children
- No protective effect of BCG vaccination in children above 5 years

GUIDELINES: WHO TO TREAT?

- Guidelines for programmatic management of TB preventive treatment in India 2021

Target population	Strategy
• 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	TPT to all after ruling out active TB disease
• HHC 5 years and above of pulmonary* TB patients#	TPT among TBI positive# after ruling out TB disease

Target population	Strategy
Individuals who are: • on immunosuppressive therapy • having silicosis • on anti-TNF treatment • on dialysis • preparing for organ or hematologic transplantation	TPT after ruling out TB disease among TBI positive

GUIDELINES: WHO TO TREAT?

LATENT TUBERCULOSIS INFECTION: UPDATED AND CONSOLIDATED GUIDELINES FOR PROGRAMMATIC MANAGEMENT : WHO 2018

Risk groups	Members
Adults, adolescents, children and infants living with HIV	All adults and adolescents living with HIV including pregnant women (positive or unknown TST reports) (irrespective of degree of immunosuppression)
	Children >12 months living with HIV irrespective of contact
	Infants <12 months with h/o contact with TB patients
	All patients living with HIV who have been treated for tuberculosis
HIV-negative HHC	Children <5 years exposed to active TB
	In low-prevalence countries children, adults and adolescents years exposed to active TB
	In high prevalence countries children>5 years, adults and adolescents exposed to active TB

Risk groups	Members
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 prisoners, health workers, immigrants from countries with a high TB burden, homeless people and people who use illicit drugs (in low prevalence countries)

- Patients with diabetes mellitus, smokers, chronic alcoholics and low BMI patients need not undergo screening routinely for LTBI

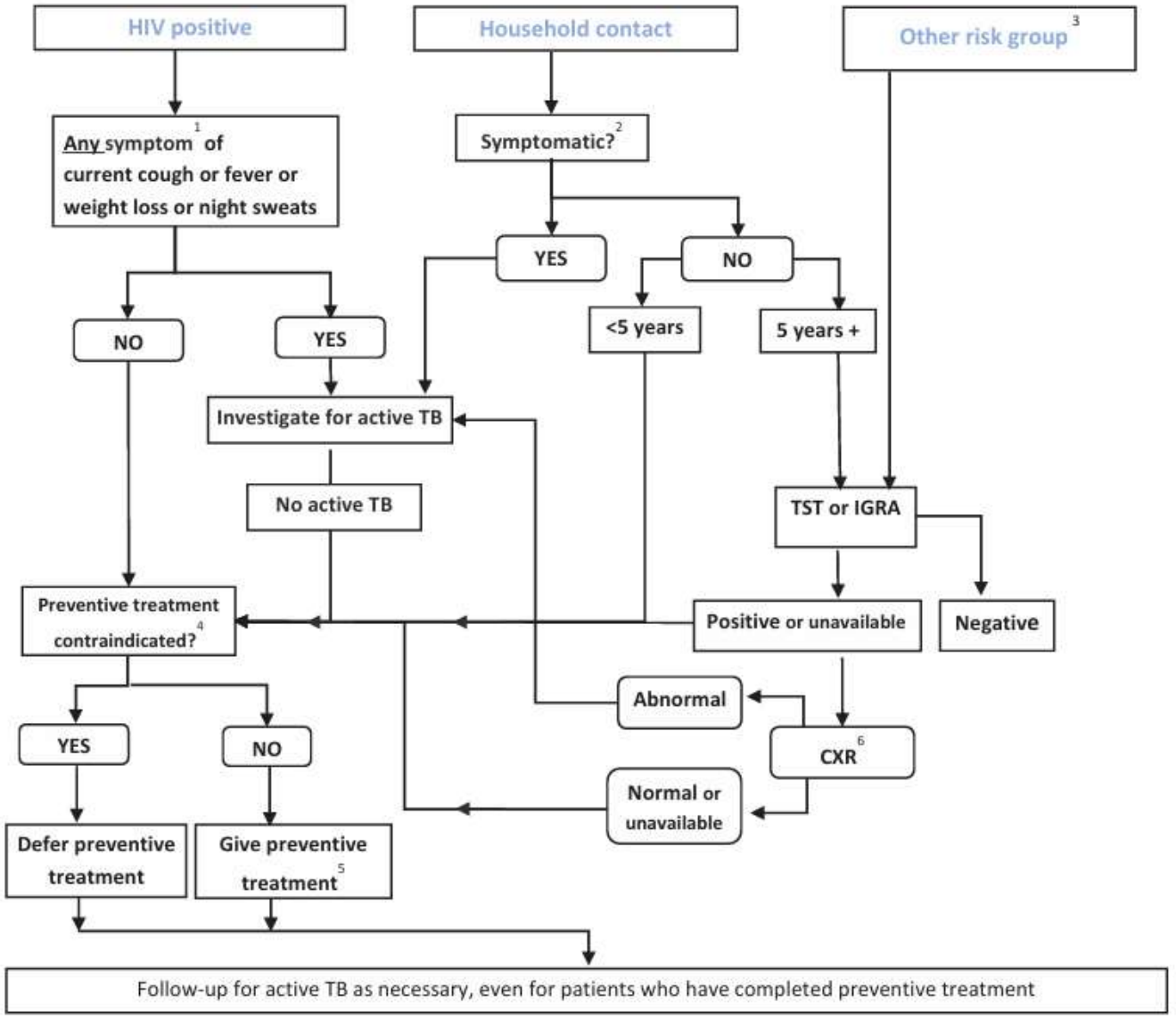


Figure 4.1 Algorithm for TB screening and TPT in India

ALGORITHM FOR DIAGNOSING TBI

TREATMENT OPTIONS

- Isoniazid for 6 months (for all ages, in both high and low prevalence countries)
- Rifampicin+isoniazid for 3 months (<15 years of age, in high prevalence studies)
- Rifapentin+Isoniazid weekly for 3 months (for high prevalence countries)
- PLHIV should receive 36 months of IPT in high prevalence settings

Alternatives in low prevalence settings:

1. INH for 9 months
2. 3HP
3. INH+R for 3 months
4. 4R

REGIMENS RECOMMENDED IN INDIA

Target population	Treatment option
• People living with HIV (adults and children >12 months) • Infants <12 months 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 (testing would be offered whenever available)	• 3-month weekly Isoniazid and Rifapentine (3HP) • 6-months daily isoniazid (6H)
b. Other risk groups expansion	
• Children/adult on immunosuppressive therapy, silicosis, anti-TNF treatment, dialysis, transplantation	• 3-month weekly Isoniazid and Rifapentine (3HP) • 6-months daily isoniazid (6H)

PREREQUISITES

- Rule out contraindications
- Explain the need for initiation and completion of tpt
- inform about the common side effects, drug interactions
- Educate about the signs and symptoms of active tb disease
- Give contact of nikshay help-line/assistance
- Pre-treatment assessment

CONTRAINDICATIONS

- Any evidence of active tb
- Acute or chronic hepatitis
- Regular heavy alcohol consumption
- Concurrent use of other hepatotoxic drugs
- Evidence of neuropathy
- Known hypersensitivity to drugs in the regimen

PREGNANCY AND PREVIOUS USE OF ATD ARE NOT CONTRAINDICATIONS

PRE-TREATMENT ASSESSMENT

- PERSONAL HISTORY
- HISTORY OF MEDICATION
- LIVER FUNCTION TESTS

(encouraged for patients at high risk of deranged liver function)

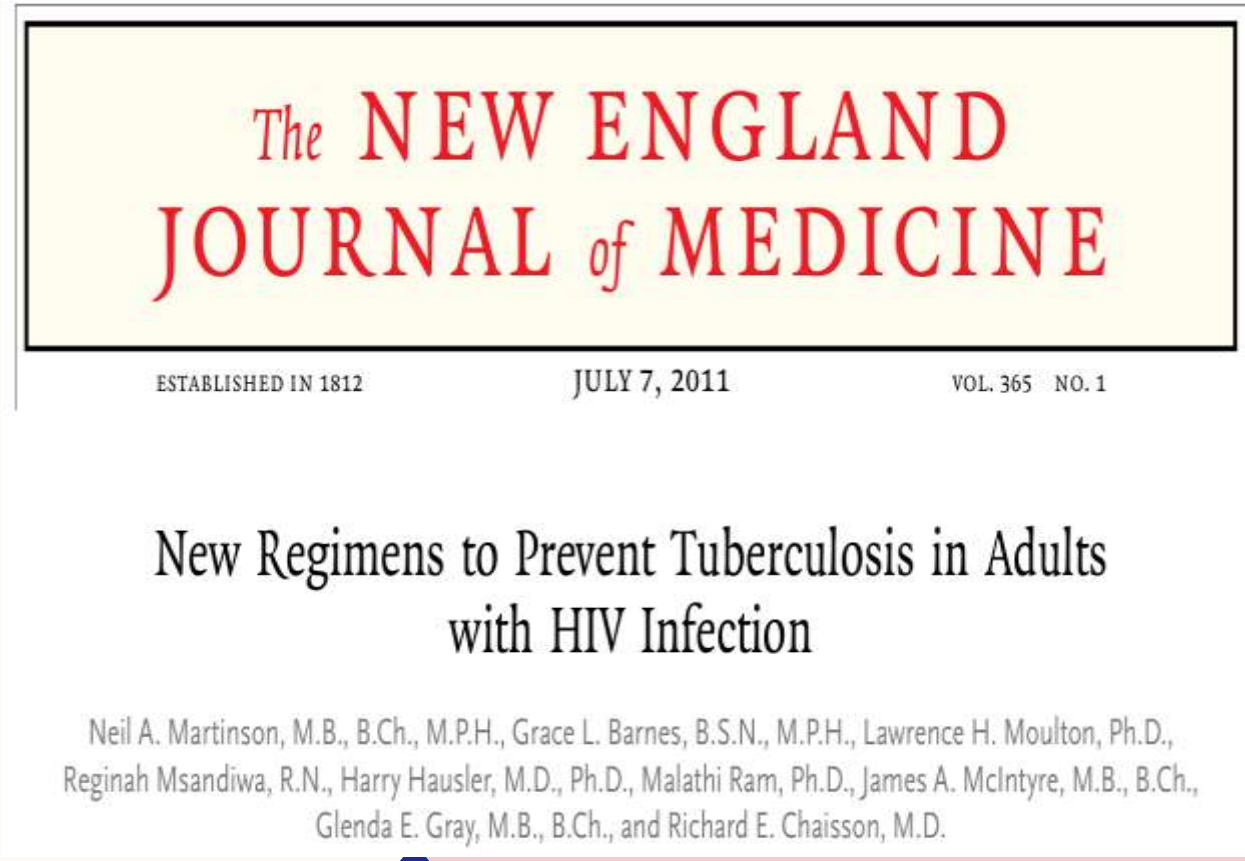
- SOCIAL AND FINANCIAL SITUATIONS

CONCERNS REGARDING TPT

- Is their an actual risk of TB disease in the future without it?
- Benefits outweigh the risk?
- Unnecessary risk of serious adverse effects?
- Risk of emergence of drug resistance TB with monotherapy regimens?

EVIDENCE OF BENEFITS

- In 2011, an RCT was performed to compare the efficacies of different regimens among PLHIV not on ART, but with positive TST (>5mm)
- As secondary outcomes they also studied adherence and adverse effects along with emergence of DRTB
- They excluded patients with active TB, pregnant/breastfeeding, CD4 count< 200



Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, et al. New regimens to prevent tuberculosis in adults with HIV infection. N Engl J Med. 2011;365(1):11-20.

- The patients were allocated to four treatment arms with a 2:2:2:1 block randomization to

1. Rifapentin(900 mg)-INH(900 mg) q1wk (3HP)
2. Rifampin(600)-INH(900) twice weekly (3HR)
3. Isoniazid (300) daily for 6 months (6H)
4. Isoniazid (300) daily continuously for study period

- The groups were followed up intermittently for almost 4 years for development of active TB

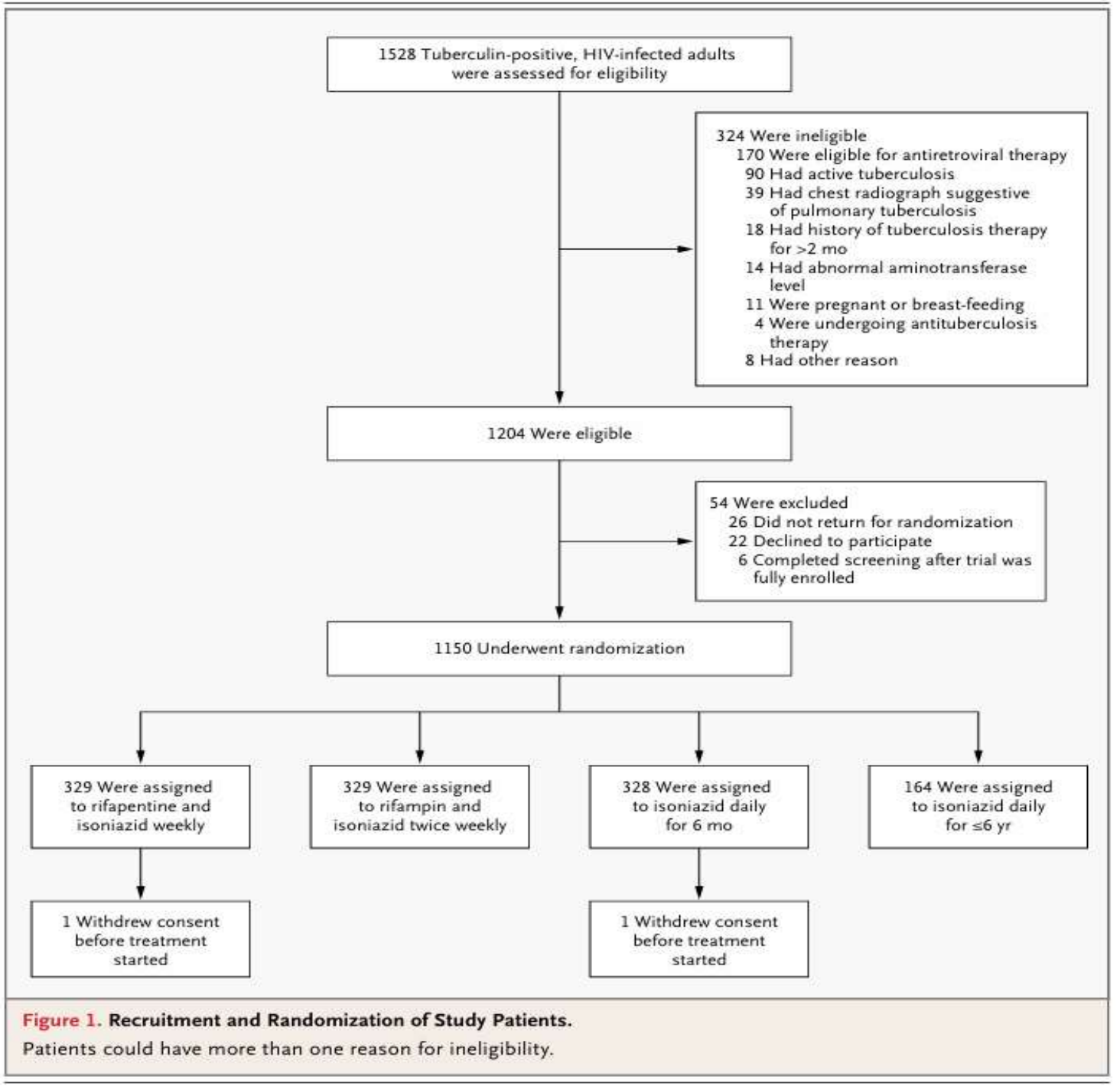


Figure 1. Recruitment and Randomization of Study Patients.
Patients could have more than one reason for ineligibility.

RESULTS: CONCLUSION

- Study did not show any superiority of one regimen over the other
- New regimens non-inferior to 6 months INH regimen
- Better adherence to 3HP and 3HR
- Less chance of hepatotoxicity with newer regimens
- Emergence of DR-TB is not a concern

- The baseline CD4 count for all groups was considerably high
- Largely female patients
- About 18% was started on ART during the study but they were not excluded from the analysis
- Any patient who received 2 months of preventive therapy was included in ITT population

Table 1. Baseline Characteristics of the Study Patients, According to Treatment Group.

Characteristic	Rifapentine with Isoniazid Weekly for 12 Wk (N=328)	Rifampin with Isoniazid Twice Weekly for 12 Wk (N=329)	Isoniazid Daily for ≤6 Yr (N=164)	Isoniazid Daily for 6 Mo (N=327)	All Patients (N=1148)
Female sex — no. (%)	277 (84.5)	267 (81.2)	139 (84.8)	273 (83.5)	956 (83.3)
Age — yr					
Median	30.3	30.5	30.2	30.4	30.4
Interquartile range	26.3–35.0	27.0–34.3	25.4–34.2	26.3–34.9	26.4–34.7
Black race — no. (%)*	325 (99.1)	327 (99.4)	163 (99.4)	327 (100.0)	1142 (99.5)
≥12 Yr of schooling — no. (%)	93 (28.4)	102 (31.0)	61 (37.2)	117 (35.8)	373 (32.5)
Formal employment — no. (%)	40 (12.2)	34 (10.3)	12 (7.3)	39 (11.9)	125 (10.9)
Imprisoned before enrollment — no. (%)	48 (14.6)	52 (15.8)	21 (12.8)	40 (12.2)	161 (14.0)
Diameter of induration from tuberculin skin test — mm					
Median	14.5	15.0	15.0	15.0	15.0
Interquartile range	12–19	12–19	12–19	11–18	12–19
CD4 count — cells/mm^3					
Median	471	498	476	490	484
Interquartile range	352–666	353–696	346–644	340–670	350–672
Viral load — $\log_{10}$ copies/ml					
Median	4.3	4.0	4.2	4.2	4.2
Interquartile range	3.6–4.8	3.4–4.7	3.6–4.7	3.6–4.7	3.6–4.7
Body-mass index					
Median	25.0	24.7	25.3	24.9	24.9
Interquartile range	21.8–29.2	21.9–28.4	22.6–29.3	22.1–29.5	22.1–29.0

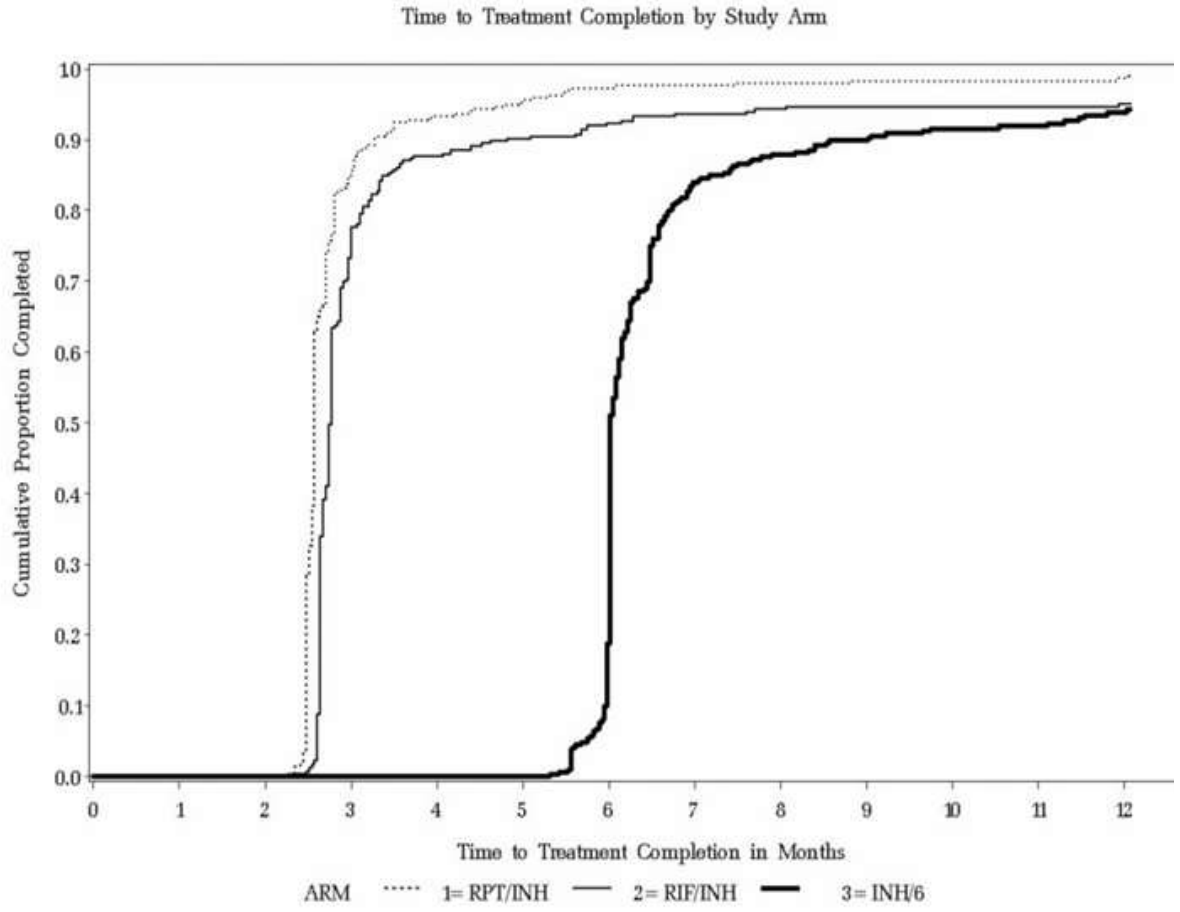
* Black race was self-reported.

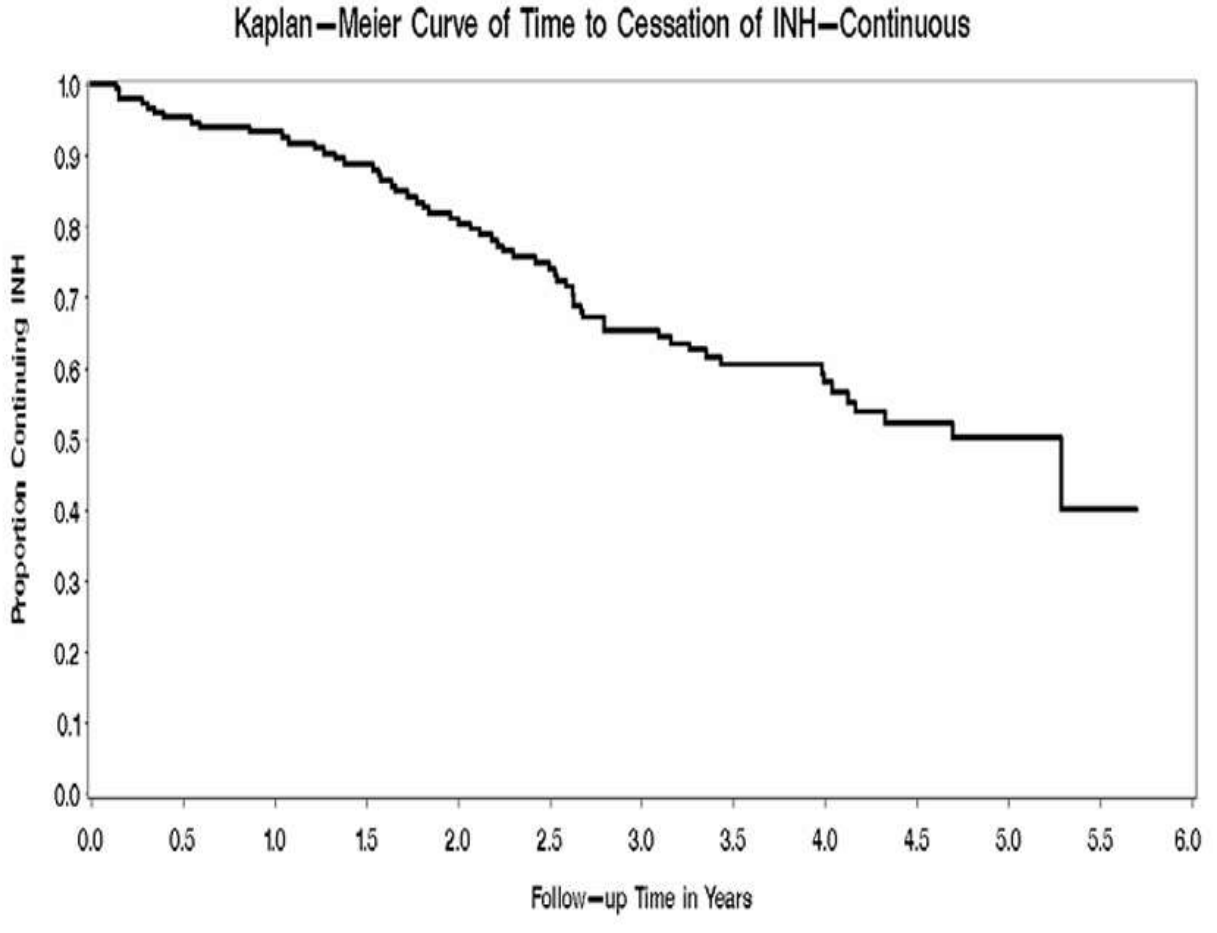
- Compared with 6H, all regimens show similar rate of active TB disease ($p > 0.05$)
- Continuous INH has the lowest incidence of active TB, TB death or both (non-significant difference)
- The benefit of continuous INH was lost once patient defaulted

Table 2. Rates of Study End Points According to Treatment Group.*

End Point	Rifapentine–Isoniazid	Rifampin–Isoniazid	Continuous Isoniazid	6-Mo Isoniazid	All
Tuberculosis					
No. of cases	24	24	8	22	78
Person-yr of follow-up	1187.5	1219.7	561.0	1143.9	4112.1
Incidence rate per 100 person-yr	2.0	2.0	1.4	1.9	1.9
Death					
No. of cases	17	16	8	25	66
Person-yr of follow-up	1223.6	1269.8	574.2	1180.0	4247.6
Incidence rate per 100 person-yr	1.4	1.3	1.4	2.1	1.6
Death or tuberculosis					
No. of cases	37	35	15	41	128
Person-yr of follow-up	1187.5	1219.7	561.0	1143.9	4112.1
Incidence rate per 100 person-yr	3.1	2.9	2.7	3.6	3.1
Tuberculosis					
Crude incidence-rate ratio (95% CI)	1.05 (0.56–1.97)	1.02 (0.55–1.91)	0.74 (0.29–1.73)	Reference 1.0	
P value	0.87	0.94	0.48		
Death					
Crude incidence-rate ratio (95% CI)	0.66 (0.33–1.26)	0.59 (0.30–1.16)	0.66 (0.26–1.50)	Reference 1.0	
P value	0.18	0.10	0.31		
Death or tuberculosis					
Crude incidence-rate ratio (95% CI)	0.87 (0.54–1.39)	0.80 (0.50–1.29)	0.75 (0.38–1.38)	Reference 1.0	
P value	0.54	0.34	0.34		

* P values are for the comparison with the 6-month regimen of isoniazid. CI denotes confidence interval.





- Most of the users of the newer regimens reached >90% dose completion by there scheduled time period
- Continuous INH arm showed a drop in number of users over time

- Overall side effects profile was similar
- Grade 3 and 4 side effects were more common in continuous INH group
- Commonest was hepatotoxicity which did not result in any death
- Treatment discontinuation was more common with continuous INH group

Table 3. Adverse Events, Including Those Occurring after Discontinuation of Study Medications, and Status of Study Medications after the Adverse Events.

Event	Rifapentine–Isoniazid (N=328)	Rifampin–Isoniazid (N=329)	Continuous Isoniazid (N=164)	6-Mo Isoniazid (N=327)	Total (N=1148)
Adverse event — no. (rate per 100 enrolled patients)*					
Hospitalization	95 (29.0)	89 (27.1)	38 (23.2)	104 (31.8)	326 (28.4)
Pregnancy†	81 (24.7)	74 (22.5)	31 (18.9)	49 (15.0)	235 (20.5)
Death	17 (5.2)	16 (4.9)	8 (4.9)	25 (7.6)	66 (5.7)
Grade 3 toxic effect	17 (5.2)	15 (4.6)	35 (21.3)	17 (5.2)	84 (7.3)
Grade 4 toxic effect	4 (1.2)	9 (2.7)	18 (11.0)	14 (4.3)	45 (3.9)
Other	3 (0.9)	7 (2.1)	7 (4.3)	7 (2.1)	24 (2.1)
Total	217 (66.2)	210 (63.8)	137 (83.5)	216 (66.1)	780 (67.9)
Treatment status after event — no. (% of total no. with adverse event)					
Treatment discontinued					
Temporarily	5 (2.3)	7 (3.3)	39 (28.5)	15 (6.9)	66 (8.5)
Permanently	4 (1.8)	8 (3.8)	50 (36.5)	4 (1.9)	66 (8.5)
Not receiving study regimen at time of event	207 (95.4)	195 (92.9)	17 (12.4)	183 (84.7)	602 (77.2)
Treatment uninterrupted	1 (0.5)	0	29 (21.2)	12 (5.6)	42 (5.4)
Treatment restarted	0	0	2 (1.5)	2 (0.9)	4 (0.5)

* Note that rates are not in person-years. Because some patients had more than one event, rates are reported instead of proportions.
† Pregnancy was considered an adverse event because rifapentine and rifampin have not been proven safe for use in pregnancy (FDA Category C).

- Risk of emergence of drug resistant strains (by selection) unlikely
- Negligible isolates showed drug resistance
- Concern: small sample size

Table 4. Cases of Tuberculosis, Culture-Confirmed Cases, and Drug-Resistant Isolates, According to Treatment Group.

Tuberculosis Cases	Rifapentine–Isoniazid	Rifampin–Isoniazid	Continuous Isoniazid	6-Mo Isoniazid	Total
			number of cases		
All cases*	24	24	8	22	78
Culture-confirmed cases	21	18	5	18	62
Drug-resistant isolate					
Total tested	21	16	5	16	58
Resistant					
To isoniazid†	1	0	1	0	2
To rifampin†	2	0	1	0	3
To both	1	0	1	0	2

* The numbers include possible, probable, and confirmed cases of tuberculosis.
† The numbers include multidrug-resistant cases.

RECENT EVIDENCES

Study	Participants	Endpoints/outcomes	Results	Conclusions	Comments
Systematic review 2011, Akolo C et al (1)	HIV patients irrespective of TST status	Active TB/death from TB	Any anti-TB drug regimen reduced the risk of active TB by 32% overall (in comparison to placbo, for INH RR-0.67) and by 62% if TST is positive (1.5-3 years follow up) Mortality benefit with INH-monotherapy in TST+ve patients	TB preventive therapy reduces risk of active TB and death in HIV patients, more so if TST positive	No difference between different anti-TB drug regimens; In the meta-analysis that included all regimens there was no difference in mortality even with placebo.
Metaanalysis 2023, Panida Youpetch et al (2)	TB infected patients	Treatment efficacy Treatment completion Adverse reactions (in comparison to 6H)	Efficacy: placebo increased risk of active TB. All other regimens were comparable; Completion: 3HP and 4R had higher completion rates A/E: 3HP, 4R and 9H showed lower rates	3HP can be considered a more tolerable and equally efficacious preventive regimen for latent TB	Difference between HIV and non-HIV patients not considered; Additionally showed all treatment regimens more effective than placebo in preventing active TB.

1. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database Syst Rev. 2010;2010(1):Cd000171.

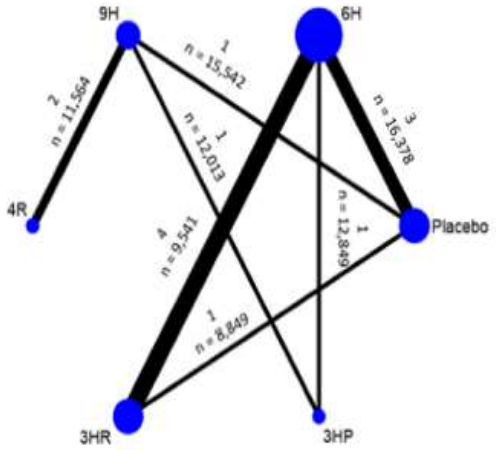
2. Yoopetch P, Anothaisintawee T, Gunasekara ADM, Jittikoon J, Udomsinprasert W, Thavorncharoensap M, et al. Efficacy of anti-tuberculosis drugs for the treatment of latent tuberculosis infection: a systematic review and network meta-analysis. Sci Rep. 2023;13(1):16240.

Efficacy of anti-tuberculosis drugs for the treatment of latent tuberculosis infection: a systematic review and network meta-analysis

Panida Yoopetch[1], Thunyarat Anothaisintawee[1,2], Agampodi Danushi M. Gunasekara[1,3], Jiraphun Jittikoon[4], Wanvisa Udomsinprasert[4], Montarat Thavorncharoensap[1,5], Sitaporn Youngkong[1,5], Ammarin Thakkinstian[2] & Usa Chaikledkaew[1,5]

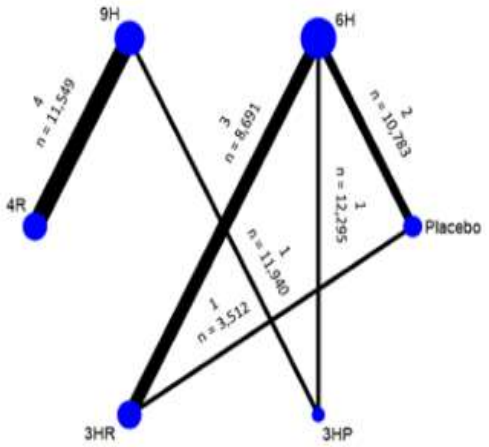
- Included studies across the globe and over 40 years
- Definition of active tuberculosis varied widely
- Did both paired comparisons and network meta-analysis to identify “risk differences” (RD) and also assigned SUCRA ranks to regimens

(a) Efficacy; 11 studies (33,262 participants)



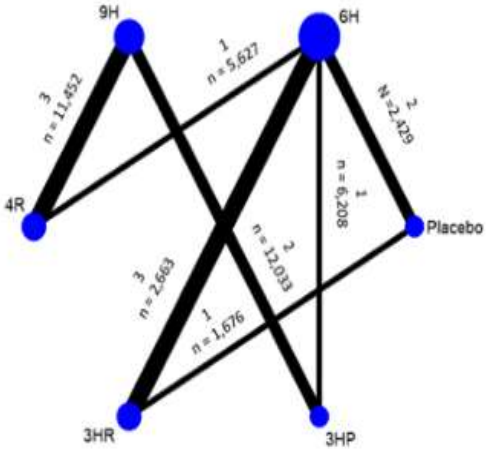
n = 33,262

(b) Treatment completion; 10 studies (27,356 participants)



n = 27,356

(c) Adverse events; 11 studies (19,336 participants)



n = 19,336

EFFICACY AND ADVERSE EFFECTS

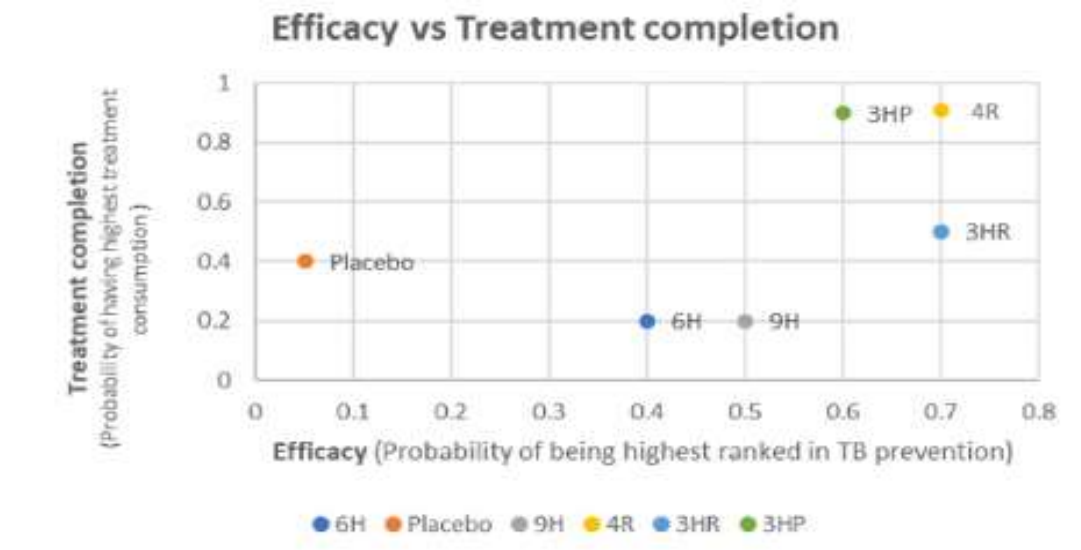
(a) Efficacy

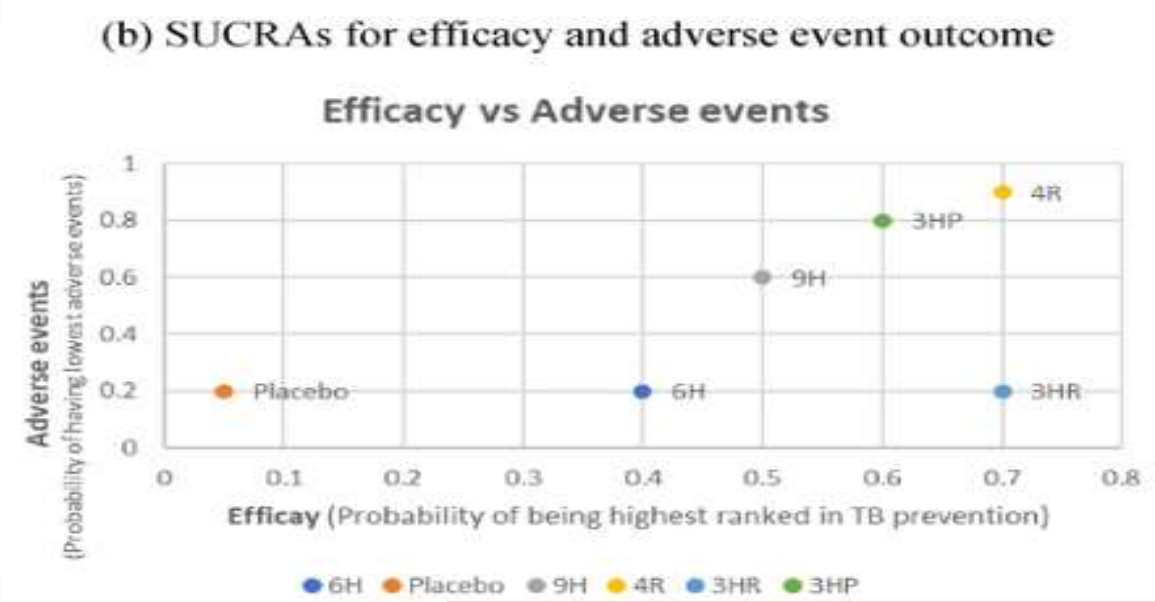
3HP					
0.0006583 (-0.0128619, 0.0141785)	4R				
-0.0176925 (-0.0434772, 0.0080923)	-0.0183507 (-0.044872, 0.0081706)	Placebo			
0.0021779 (-0.0263171, 0.0306729)	0.0015196 (-0.0277625, 0.0308017)	**0.0198704 (0.005332, 0.0344087)**	3HR		
-0.0014805 (-0.0120684, 0.0091074)	-0.0021388 (-0.0105466, 0.006269)	0.0162119 (-0.0089413,0.0413652)	-0.0036584 (-0.0317076, 0.0243908)	9H	
-0.0049024 (-0.031043, 0.0212382)	-0.0055607 (-0.0325699, 0.0214486)	**0.0127901 (0.0033555 0.0222246)**	-0.0070803 (-0.0188358, 0.0046752)	-0.0034219 (-0.0290892, 0.0222454)	6H

(c) Adverse events

3HP					
-0.0013635 (-0.0131669, 0.0104398)	4R				
-0.0452655 (-0.0767056, -0.0138255)	**-0.043902 (-0.0755113, -0.0122927)**	Placebo			
-0.0446328 (-0.0759612, -0.0133044)	**-0.0432693 (-0.0747675, -0.0117711)**	0.0006327 (-0.0048038, 0.0060692)	3HR		
-0.0075437 (-0.0184554, 0.003368)	**-0.0061802 (-0.0108313, -0.0015291)**	**0.0377218 (0.006127, 0.0693166)**	**0.0370891 (0.0056054, 0.0685728)**	9H	
-0.0453212 (-0.0762876, -0.0143548)	**-0.0439577 (-0.0750958, -0.0128195)**	-0.0000557 (-0.0054929, 0.0053815)	-0.0006884 (-0.0054374, 0.0040606)	**-0.0377775 (-0.068901, -0.006654)**	6H

- All regimens equally effective
- 4R and 3HR had the highest SUCRA rank for preventing active TB
- 3HP, 4R and 9H all had lower side effect rates than 6H





- As per SUCRA ranks, 4R regimen had the highest efficacy and lowest risk of side effects
- 4R regimen also has the best treatment completion rate along with 3HP
- Cumulatively it is the most effective, tolerable and the safest

RISK-BENEFIT

Regimen	Incremental risk (adverse events)	Incremental benefit (TB prevention)	IRBR
6H	Reference	Reference	Reference
Placebo	−0.0001	−0.0128	0.004
9H	−0.0378	0.0034	−11.040
4R	−0.0440	0.0056	−7.905
3HR	−0.0007	0.0071	−0.097
3HP	−0.0453	0.0049	−9.245

- All newer regimens had a better Risk-benefit ratio than 6H
- 3HP,4R and 9H were the most efficacious and the safest

NEWER REGIMENS

- A non-inferiority trial to show that a 1-month daily rifapentine+INH regimen was effective as 9 month long daily isoniazid

- 3000 patients with HIV (majority not on ART) randomized 1:1 to the two arms
- Outcome was development of active TB and a non-inferiority margin of 1.25 events per 100 person-years was kept

Swindells S, Ramchandani R, Gupta A, Benson CA, Leon-Cruz J, Mwelase N, et al. One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis. N Engl J Med. 2019;380(11):1001-11.

- The difference in events was <1.25 events per 100 person-years
- Results were similar for MITT and per-protocol groups
- TST positivity and ART therapy did not change the outcome significantly

Table 2. Univariate Analysis of Risk Factors for the Primary End Point.*

Variable	1-Month Group		9-Month Group		Difference in Incidence Rate (95% CI)†
	no. of events/ person-yr	*incidence rate/ 100 person-yr*	*no. of events/ person-yr*	*incidence rate/ 100 person-yr*	
All patients	32/4926	0.65	33/4896	0.67	−0.02 (−0.35 to 0.30)
Per-protocol analysis	31/4876	0.64	29/4718	0.61	0.02 (−0.30 to 0.34)
Status on tuberculin skin test or IGRA					
Positive	10/1110	0.90	11/1137	0.97	−0.07 (−0.87 to 0.73)
Negative or unknown	22/3815	0.58	22/3759	0.59	−0.01 (−0.35 to 0.34)
Receipt of antiretroviral therapy at entry					
Yes	13/2381	0.55	15/2387	0.63	−0.08 (−0.52 to 0.35)
No	19/2545	0.75	18/2508	0.72	0.03 (−0.44 to 0.50)
Screening CD4+ count					
≤250 cells/mm^3	12/621	1.93	8/628	1.28	0.66 (−0.75 to 2.06)
>250 cells/mm^3	20/4304	0.47	25/4268	0.59	−0.12 (−0.43 to 0.19)
Sex					
Male	11/2303	0.48	15/2293	0.65	−0.18 (−0.61 to 0.26)
Female	21/2623	0.80	18/2603	0.69	0.11 (−0.36 to 0.58)

* The primary end point was a diagnosis of tuberculosis or death from tuberculosis or an unknown cause.
† This difference is the incidence rate in the 1-month group minus the rate in the 9-month group, so negative values indicate a lower risk in the 1-month group.

- All adverse events were similar among the two groups
- Grade 3-5 serious adverse events were commoner in the 9-month group (significant)
- Hepatic dysfunction and neuropathies were commoner in the 9-month group
- Neutropenia was commoner in 1-month group

Table 3. Adverse Events of Grade 3 or Greater.*

Adverse Event	1-Month Group (N=1488)				9-Month Group (N=1498)			
	Grade 3	Grade 4	Grade 5	Grades 3–5	Grade 3	Grade 4	Grade 5	Grades 3–5
	number of patients (percent)							
Targeted adverse event†	34	9	1	44 (3)	32	20	0	52 (3)
Serious adverse event	41	22	12	75 (5)	49	25	19	93 (6)
Any systemic event	101	9	1	111 (7)	123	12	0	135 (9)
Any adverse event	198	47	5	250 (17)	213	59	2	274 (18)
Hematologic event	41	22	0	63 (4)	36	21	0	57 (4)
Thrombocytopenia	0	3	0	3 (<1)	4	1	0	5 (<1)
Anemia	6	14	0	20 (1)	8	18	0	26 (2)
Neutropenia	28	8	0	36 (2)	16	2	0	18 (1)
Hepatic event	19	9	0	28 (2)	24	18	0	42 (3)
Gastrointestinal event	29	1	1	31 (2)	22	2	0	24 (2)
Dermatologic event	8	0	0	8 (1)	11	0	0	11 (1)
Neurologic event	12	2	0	14 (1)	25	4	1	30 (2)

* There was a significant between-group difference in neutropenia and in neurologic events (P=0.02 for both comparisons) at an alpha level of 0.05 with no adjustment for multiple comparisons.
† Targeted adverse events included nausea and vomiting, rash, drug-associated fever, elevated liver-enzyme levels, and peripheral neuropathy.

CONCLUSIONS:

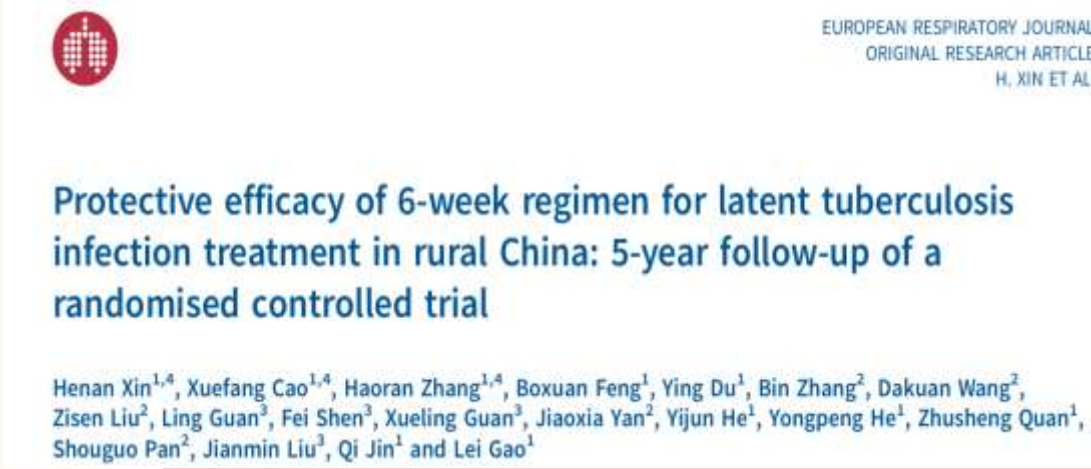
- One-month long HP regimen can be used as TB preventive therapy for HIV-infected patients (expected better adherence)
- It will also have lower incidence of side effects associated with long term isoniazid use

Concerns:

- Majority had a good CD4 count
- Study did not allow PI-based ARTs beyond 1 month

6-WEEK REGIMEN

- 5 year follow-up study on patients who were treated with a 6 week-long twice weekly H+P regimen to find out its protective efficacy in comparison to untreated population
- In the original study patients were randomized in 3 groups, one receiving (finally) 2HP regimen, one receiving 6 weeks-long twice weekly HP and one untreated
- In the original study group 1 showed 37% protection and group 2 showed 69% protective efficacy



Xin H, Cao X, Zhang H, Feng B, Du Y, Zhang B, et al. Protective efficacy of 6-week regimen for latent tuberculosis infection treatment in rural China: 5-year follow-up of a randomised controlled trial. Eur Respir J. 2022;60(1).

CONCLUSIONS

- The 6 weeks regimen offered a >60% protection against active TB
- Baseline IGRA levels correlated with higher risk of developing TB in untreated group
- Of the active TB cases, majority was clinicoradiologically diagnosed
- The study had only a power of 76% to detect said difference (retrospectively)
- The patients with fibrotic lesions on CXR was not evenly distributed between two groups

The results of this study should be interpreted carefully

More studies are needed to validate the findings

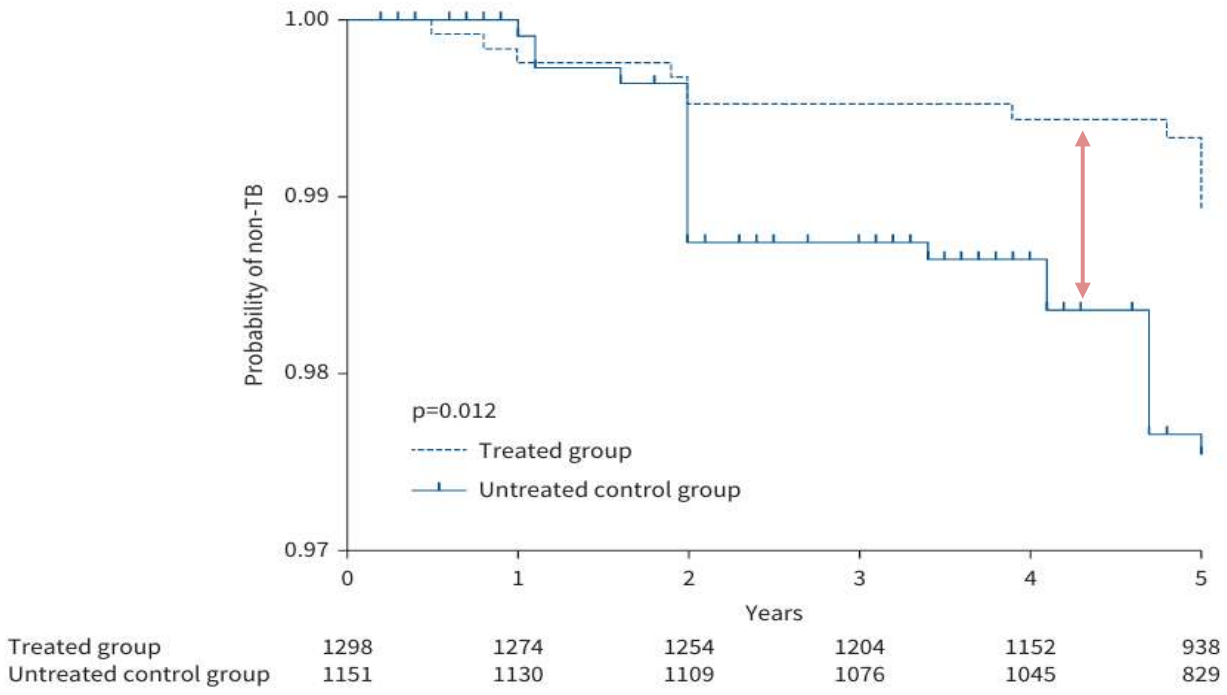


FIGURE 2 Kaplan–Meier curve analysis of time to tuberculosis (TB) by study arm. Numbers of participants who remained without disease are listed by study arm. Most of the cases were identified in yearly examinations with chest radiography screening-based active case finding. The Kaplan–Meier curves demonstrate that participants in the untreated group had an increased risk of developing active TB compared with the treated control group.

TABLE 2 Incidence of active tuberculosis in the study groups

	Treated group[#]	Untreated control group
Intention-to-treat analysis		
Subjects	1298	1151
Person-years	5876	5337
Incident cases	12	26
Cumulative incidence (% (95% CI))	0.92 (0.40–1.45)	2.26 (1.40–3.12)
Protection rate[¶] (%)	59.29	
Incidence rate per 100 person-years (95% CI)	0.20 (0.09–0.32)	0.49 (0.30–0.67)
Protection rate[+] (%)	59.18	
Adjusted hazard ratio (95% CI)[§]	0.41 (0.20–0.84)	Reference
Per-protocol analysis		
Subjects	1012	1151
Person-years	4654	5337
Incident cases	9	26
Cumulative incidence (% (95% CI))	0.89 (0.31–1.41)	2.26 (1.40–3.12)
Protection rate[¶] (%)	60.62	
Incidence rate per 100 person-years (95% CI)	0.19 (0.07–0.32)	0.49 (0.30–0.67)
Protection rate[+] (%)	61.22	
Adjusted hazard ratio (95% CI)[§]	0.39 (0.17–0.88)	Reference

Data are presented as n, unless otherwise stated. [#]: completed 6 weeks of twice-weekly rifapentine plus isoniazid (both with a maximum dose of 600 mg); [¶]: calculated using the cumulative incidence; [+]: calculated using the incidence rate per 100 person-years; [§]: adjusted for age, body mass index, baseline interferon-γ and presence of pulmonary fibrotic lesions.

MANAGEMENT OF CONTACTS OF DR-TB

- Levofloxacin for 6 months: for Rif-resistant
- Rifampicin for 4 months: for H-mono/poly

REGIMENS

Available guidelines on the preventive therapy for DR-TB contacts.

Source	Year of Publication	Population Addressed	Recommendation to Treat	Watchful Observation Approach	Drug	Ancillary Drugs	Treatment Duration
WHO	2020	General	Yes	Consider	Lfx	E, Eth	6 months
ECDC	2012	General	Yes	Consider	Lfx	No	6 months
ATS/CDC/ ERS/IDSA	2019	General	Yes	Not recommended	Lfx	No	6–12 months
MSF	2022	Pediatric	Yes	Consider	Lfx	No	6 months

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Abbreviations: WHO, World Health Organisation; ECDC, European Centre for Disease Prevention and Control; ATS, American Thoracic Society; CDC, U.S. Centers for Disease Control and Prevention; ERS, European Respiratory Society; IDSA, Infectious Diseases Society of America; MSF, Doctors Without Borders; Lfx, levofloxacin, E, ethambutol and Eth, ethionamide.

SYSTEMATIC REVIEW

Reference	Setting	Population	Intervention(s)	Control(s)	Outcome definition	Proportion of participants who developed TB disease
Studies of TPT including child and adolescent HHCs of patients with MDR-TB						
Gureva et al. (2022) *(4)*	Arkhangelsk Region, Russian Federation	Household contacts aged < 18 years (n=72)	9MFX (n=55)[a]	Child contacts with caregivers who refused TPT (n=14)	People with culture-confirmed TB within 2 years of follow-up	MFX: 0/55 Refused TPT: 1/14
Malik et al. (2021) *(5)*	Karachi, Pakistan	Household contacts of all ages (n=799)	6-month FQ (Lfx/MFX) + ETH/EMB (n=172)	Refused TPT (n=43) Considered ineligible for TPT (n=574)	People with culture-confirmed TB within 2 years of follow-up	Any TPT: 2/172 Refused TPT: 0/43 Ineligible: 0/574
Studies of TPT among close adult contacts of MDR-TB						
Bedini et al. (2016) *(6)*	Penitentiary in Modena, northern Italy	Incarcerated adults in close contact with MDR-TB (n=17)	6-month Lfx + PZA (n=12)	Refused TPT (n=5)	People with incident TB disease during 24 months of follow-up	Lfx + PZA: 0/12 Refused TPT: 0/5

- Good quality studies were lacking, and most studies had several bias
- These few studies did not show any benefit of levofloxacin over placebo in preventing TB disease in DR TB contacts
- Other studies have tried INH and EMB but current WHO guidelines do not recommend them

META-ANALYSIS 2024

- Zhou et al examined 8 studies comparing treated and non-treated contacts of DR-TB for development of active TB
- They found that treatment of contacts has benefits in preventing active DR-TB
- The knowledge about sensitivity pattern of index patient gives additional benefit
- Adverse events and treatment discontinuation rates were acceptably low.

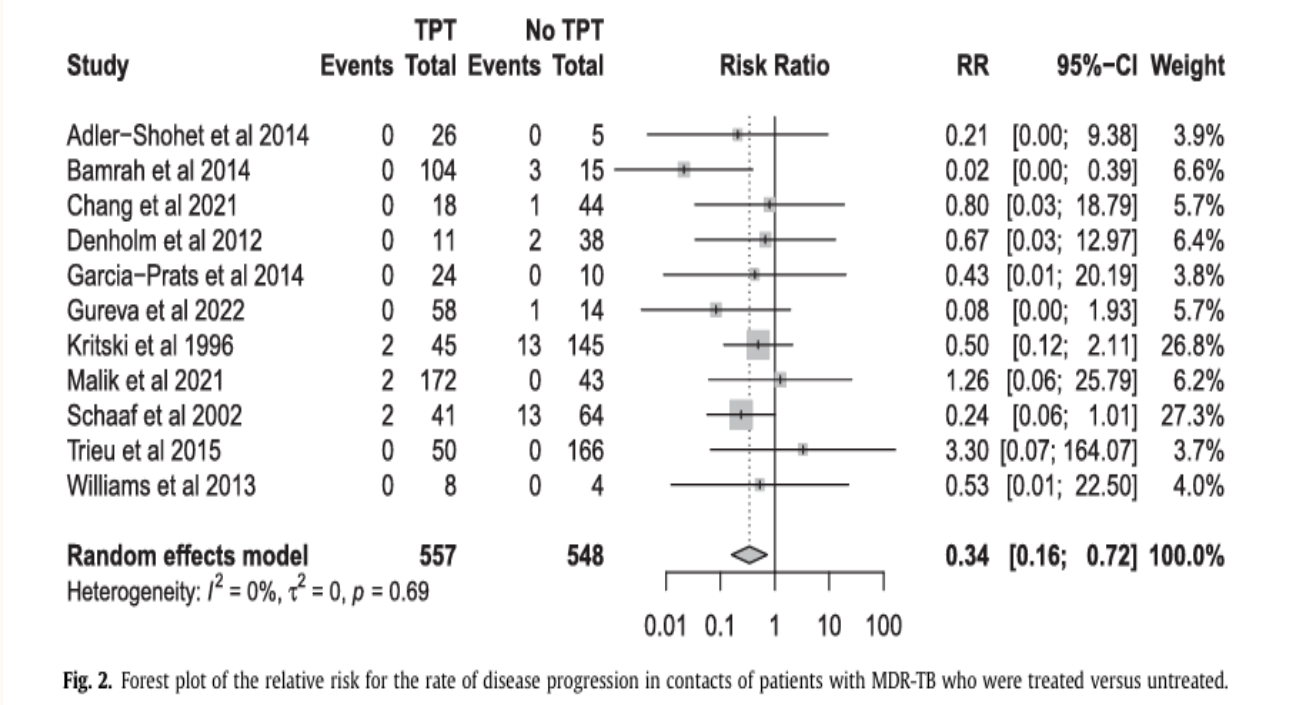


Fig. 2. Forest plot of the relative risk for the rate of disease progression in contacts of patients with MDR-TB who were treated versus untreated.

Zhou G, Luo S, He J, Chen N, Zhang Y, Cai S, et al. Effectiveness and safety of tuberculosis preventive treatment for contacts of patients with multidrug-resistant tuberculosis: a systematic review and meta-analysis. Clin Microbiol Infect. 2024;30(2):189-96.

Variable	Cohorts	Individuals	RR (95% CI)	I^2 (%)	p[a]
All studies	11	557/548	0.34 (0.16–0.72)	0	—
Participants (n)					
>100	5	412/433	0.34 (0.10–1.12)	33	1
≤99	6	145/115	0.36 (0.09–1.45)	0	0.9211
Age group					
Children group	6	168/135	0.27 (0.09–0.76)	0	1
All-age group	5	389/413	0.44 (0.10–1.88)	32	0.5054
Definition of close contact					
Close contacts were well-defined	6	235/271	0.28 (0.12–0.67)	0	1
Close contacts were poorly defined	5	322/277	0.60 (0.13–2.69)	0	0.3973
Treatment regimen					
Drug-resistant profile-guided regimen[b]	4	174/161	0.22 (0.06–0.84)	18	1
Uniform treatment regimen[c]	7	383/387	0.49 (0.17–1.35)	0	0.3204
Study design					
Prospective cohort	5	425/302	0.23 (0.05–1.01)	33	1
Retrospective cohort	6	132/246	0.51 (0.18–1.45)	0	0.3026
TB burden of study area[d]					
0–100 per 100 000	8	320/431	0.35 (0.13–0.89)	0	1
More than 101 per 100 000	3	237/117	0.34 (0.10–1.15)	0	0.9685
Year of publication					
1996–2019	8	309/447	0.32 (0.14–0.74)	0	1
2020–2022	3	248/101	0.45 (0.07–2.70)	0	0.7406
Quality					
Moderate	9	412/469	0.52 (0.21–1.32)	0	1
High	2	145/79	0.10 (0.01–0.99)	54	0.1213

EVIDENCE: TPT FOR DR-TB

Table 3

Trial landscape on preventive therapy for DR-TB contacts.

Study	Status	Population Type	Structure	Duration of Treatment	Country	Total Population Size (N)	Duration of Follow-Up
V-QUIN	Enrolment completed	Adults > 15 years	Lfx vs. Placebo	6 months	Vietnam	3344	30 months
TB-CHAMP	Enrolment ongoing	Children < 5 years	Lfx vs. Placebo	6 months	South Africa	1556	24 weeks
PHOENIx	Enrolment ongoing	Adults > 15 years	Dlm vs. H	6 months	International	5610	26 weeks

STUDY	PARTICIPANTS	INTERVENTION	ENDPOINTS	RESULTS
TB-CHAMP	Predominantly children< 5 years who had contact with DR TB, but did not have active TB, and TST/IGRA positive (if > 5 years); excluded pregnant+ breast-feeding	Levoflox vs placebo	TB disease at 48-54 weeks follow up Adverse events	Active TB found in 1.6% patient in Lfx group vs 3% in placebo group (HR 0.44, P=0.121 Adverse events in levoflox group not significantly higher than placebo
V-QUIN	Any age patients (last 6 months included only < 15 years) with positive TST/IGRA; Excluded pregnant+ breast feeding	Levoflox vs placebo	TB disease Adverse events Completion rates	Lfx reduced the risk of active TB by 45% at the end of 30 months Safety was comparable to placebo but completion rate was lower

WHO RECOMMENDATIONS

- WHO recommends levofloxacin for 6 months in subjects exposed to DR TB patients
- Concerns regarding administration in children has not been supported by study results
- Administration in pregnant and breast feeding should depend upon individual risk-benefit analysis; studies did not show increased birth defects with levofloxacin;

DOSE AND DURATION

Target population	Treatment option
• People living with HIV (adults and children >12 months) • Infants <12 months 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 (testing would be offered whenever available)	• 3-month weekly Isoniazid and Rifapentine (3HP) • 6-months daily isoniazid (6H)
b. Other risk groups expansion	
• Children/adult on immunosuppressive therapy, silicosis, anti-TNF treatment, dialysis, transplantation	• 3-month weekly Isoniazid and Rifapentine (3HP) • 6-months daily isoniazid (6H)

DOSE AND SCHEDULE

Regimen	Dose by age and weight band					
6 months of daily isoniazid monotherapy (6H)	Age 10 years & older: 5 mg/kg/day[d] Age <10 years: 10 mg/kg/day (range, 7–15 mg)					
Three months of weekly rifapentine plus isoniazid (12 doses) (3HP)	**Age 2-14 years[c]**					
	Medicine, formulation	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg
	Isoniazid, 100 mg[a]	3	5	6	7	7
	Rifapentine, 150 mg	2	3	4	5	5
	Isoniazid + rifapentine FDC (150 mg/150 mg)[b]	2	3	4	5	5
	Age >14 years[c]					
	Medicine, formulation	30–35 kg	36–45 kg	46–55 kg	56–70 kg	>70 kg
	Isoniazid, 300 mg	3	3	3	3	3
	Rifapentine, 150 mg	6	6	6	6	6
	Isoniazid + rifapentine FDC (300 mg/300 mg)[b]	3	3	3	3	3

a. *300 mg formulation can be used to reduce the pill burden*
b. *Expected to become available in the near future*
c. *Dosage may differ among adults and children in overlapping weight-bands*
d. *Maximum dose of H if given daily would be 300 mg/day*

	6H	3HP
Medicines	Isoniazid	Isoniazid + rifapentine
Duration (months)	6	3
Interval	Daily	Weekly
Doses	182	12
Pill burden per dose (total number of pills for an average adult)	1 (182 pills)	9 pills with loose drugs (108 pills) 3 pills of FDC (36 pills)
Pregnant women	Safe for use	Not known
Interaction with ART	No restriction	Contraindicated: All PIs, NVP/NNRTIs, TAF Use: TDF, EFV (600 mg), DTG, RAL (without dose adjustment)
Toxicity	Hepatotoxicity (more), peripheral neuropathy, rash, gastrointestinal (GI) upset	Flu-like syndrome, hypersensitivity reactions, GI upset, orange dis-coloration of body fluids, rash, hepatotoxicity (less)
Absorption	Best absorbed on an empty stomach; up to 50% reduction in peak concentration with a fatty meal	Oral rifapentine bioavailability is 70% (not HP); peak concentration increased if given with a meal

ADVERSE EVENTS AND HOW TO MANAGE

Adverse event	Stop and consider reintroduction with caution	Stop and do not reintroduce
Flu-like syndrome (attacks of fever, chills and malaise, sometimes with headache, dizziness or bone pain)	If mild and not increasing, continue treatment and observe closely	If moderate to severe symptoms, consider alternative TPT options without a rifamycin (such as 6H)
Drug-associated fever only	Consider reintroduction if fever settles below 39·C, but stop permanently if fever recurs	If fever > 39·C after previous episode of drug-associated fever
Persistent nausea, frequent vomiting and/or persistent episodes of unformed watery stools	Administer antiemetic or anti diarrhoeal medication Consider reintroducing 3HP with caution once the symptoms have resolved	If there is nausea, vomiting or diarrhoea which requires aggressive rehydration
Cutaneous reactions	Diffuse rash (no vesicles) Diffuse rash with limited vesicles	If there are extensive bullous lesions/ulceration of mucous membranes/Stevens Johnson or toxic epidermal necrolysis, contact a specialist and use steroids
Other hypersensitivity reactions (hypotension, acute bronchospasm, conjunctivitis, thrombocytopenia)	Assess the clinical severity of the symptoms and if severe consider alternative TPT options without a rifamycin (6H)	
Hepatitis (early symptoms weakness, fatigue, loss of appetite, persistent nausea)	Alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) < 5 times the upper limits of normal and absence of symptoms	ALT/AST >5 times (Upper limit of normal in the absence of symptoms) ALT/AST is ≥ 3 times (the upper limit of normal in the presence of symptoms)
Psychosis	Psychiatric evaluation, antipsychotic therapy, pyridoxine	Attributable to isoniazid
Seizures	Withhold isoniazid pending resolution of seizures, evaluate possible causes of seizures	Attributable to isoniazid

STUDIES: ADVERSE EVENTS

- A small study with 100 patients (prospective cohort) examined the adverse events of 9-month long INH therapy
- Only 56 patients developed one adverse effect at some point during therapy
- Only 6 of them had grade 3-4 adverse events
- The main adverse effects were gastro-intestinal, followed by neuropsychiatric and dermatological
- Despite side effects 85% completed their doses (by 12 months)

Adverse effect	Number of patients	Grade 3–4 severity
Any adverse effect	56	6
Any gastrointestinal	21	2
Hepatitis	5	1
Any dermatologic	15	1
Any rash	15	1
Acne	8	1
Alopecia	0	0
Any neuropsychiatric	19	1
Lethargy	7	0
Cognitive impairment	9	0
Peripheral neuropathy	4	0
Headache	2	0
Sleep disturbance	1	0
Depression	1	0

Conclusion: even in 9-month long INH regimen adverse events were not very common or severe

Denholm JT, McBryde ES, Eisen DP, Penington JS, Chen C, Street AC. Adverse effects of isoniazid preventative therapy for latent tuberculosis infection: a prospective cohort study. Drug Healthc Patient Saf. 2014;6:145-9.

STUDIES: ADVERSE EVENTS

- A systematic review and meta-analysis by Peas et al examined studies that compared adverse events with different regimens
- Only included studies examining patients with TST/IGRA positive result
- Different regimens included 3HP, 6H, 9H, 3/4HR, 3/4R
- Side effects was graded from one to four with four meaning life-threatening

Pease C, Hutton B, Yazdi F, Wolfe D, Hamel C, Barbeau P, et al. A systematic review of adverse events of rifapentine and isoniazid compared to other treatments for latent tuberculosis infection. Pharmacoepidemiol Drug Saf. 2018;27(6):557-66.

Regimen	No. of Studies	No. of Total Patients	Median Experiencing Adverse Event % (Min-Max)
No. of experiencing any adverse event			
INH-6	6[15,17,18,21,24,33]	1098	36.1% (6.0%-63.4%)
INH-9	4[5,13,16,20]	4482	17.6% (0.18%-71.8%)
INH/RPT-3	4[5,12,18,23]	4991	11.5% (1.9%-41.5%)
RMP 3-4	4[16,20,33,62]	838	20.0% (0.2%-57.4%)
INH/RMP 3-4	4[15,18,21,30]	745	29.7% (12.2%-41.3%)
No. of experiencing grade 3-4 adverse event			
INH-6	3[17,18,31]	880	8.2% (0.0%-9.5%)
INH-9	5[5,13,16,20,22]	4714	3.3% (0.0%-6.5%)
INH/RPT-3	2[5,18]	5787	6.0% (1.3%-8.9%)
RMP 3-4	3[16,17,20]	788	1.7% (1.7%-2.1%)
INH/RMP 3-4	1[22]	1023	2.3% (N/A)
No. of withdrawing from study because of adverse event			
INH-6	8[17,18,21,24-26,28,31]	1738	3.8% (0.0%-12.0%)
INH-9	6[5,13,16,19,20,22]	5304	6.4% (0.0%-16.8%)
INH/RPT-3	3[5,18,23]	5993	1.70% (0.5%-4.9%)
RMP 3-4	4[16,19,20,62]	846	2.8% (1.7%-10.1%)
INH/RMP 3-4	6[12,18,21,22,28,30]	1797	2.2% (0.0%-7.3%)

Grade 3 adverse event = medically significant but not imminently life-threatening event; grade 4 adverse event = life-threatening event.

Abbreviations: INH-6, isoniazid daily for 6 months; INH-9, isoniazid daily for 9 months; RMP 3-4, rifampin daily for 3 to 4 months; INH/RMP 3-4, isoniazid and rifampin daily for 3 to 4 months; INH/RPT-3, isoniazid and rifapentine once weekly for 3 months; N/A, not applicable.

Incidence of hepatotoxicity

Regimen	Randomized Trials		Nonrandomized Studies	
	No. of Studies (No. of Patients)	Median % (Min-Max)	No. of Studies (No. of Patients)	Median % (Min-Max)
No. of experiencing hepatotoxicity				
INH-6	9[15,18,21,24-28,33] (1997)	2.7% (0.8%-44.4%)	9[44,45,51-53,56,60,66,70] (1817)	6.3% (0%-13.3%)
INH-9	6[6,12,16,19,20,22] (4707)	5.6% (2.7%-23.5%)	16[34,38,41,43,44,47,49,50,54,57,62,68,74,75,85,86,88] (8432)	3.1% (0%-9%)
INH/RPT-3	3[5,18,23] (4520)	1.0% (0.4%-1.5%)	7[37,43,83,84,86-88] (2826)	1.1% (0.0%-3.9%)
RMP 3-4	3[19,20,33] (526)	2.0% (0.7%-8.6%)	7[46,47,49,54,56,81,85] (2346)	0.01% (0%-2.0%)
INH/RMP 3-4	7[12,15,18,21,22,28,30] (3349)	6.8% (0%-29.4%)	5[44,45,54,56,81] (1000)	5.1% (1.0%-20.0%)

Abbreviations: INH-6, isoniazid daily for 6 months; INH-9, isoniazid daily for 9 months; RMP 3-4, rifampin daily for 3 to 4 months; INH/RMP 3-4, isoniazid and rifampin daily for 3 to 4 months; INH/RPT-3, isoniazid and rifapentine once weekly for 3 months.

Incidence of death

Regimen	No. of Studies	No. of Total Cases	No. of Total Patients	Median % (Min-Max)
INH-6[a]	2[18,31]	97	697	13.6% (7.6%-19.5%)
INH-9	5[5,13,16,20,22]	43	4714	0.2% (0%-2.3%)
INH/RPT-3	3[5,18]	49	5316	0.7% (0.01%-5.2%)
RMP 3-4	2[16,20]	0	598	0% (0%-0%)
INH/RMP 3-4	3[18,22,30]	22	1092	4.8% (0%-8.7%)

Abbreviations: INH-6, isoniazid daily for 6 months; INH-9, isoniazid daily for 9 months; RMP 3-4, rifampin daily for 3 to 4 months; INH/RMP 3-4, isoniazid and rifampin daily for 3 to 4 months; INH/RPT-3, isoniazid and rifapentine once weekly for 3 months.

[a]Both studies were undertaken in untreated HIV patients in developing countries.

CONCLUSIONS & CONCERNS

- 3HP regimen has fewer rate of side effects
- The deaths in 3HP group (or any group) were not attributed to the drugs
- The higher rates of deaths were observed in patients with advanced HIV infection or other underlying diseases
- Very few studies reported flu-like symptoms or other side effects (indicating they were not very common);
- There was almost no case of hypersensitivity and angio-oedema in any of the studies

TPT DURING PREGNANCY

- A pharmacokinetic study by Jyoti et al (2021) found that clearance of rifapentine was 28% lower among non-HIV patients during pregnancy in comparison to post-partum
- Clearance of rifapentine was 30% higher in HIV infected mothers than non-HIV subjects but INH clearance was no different between two groups
- But despite these pharmacokinetic effects, efficacy in prevention of active TB was not reduced and there was no serious adverse events

Gupta A, Montepiedra G, Aaron L, Theron G, McCarthy K, Bradford S, et al. Isoniazid Preventive Therapy in HIV-Infected Pregnant and Postpartum Women. N Engl J Med. 2019;381(14):1333-46.

TPT DURING PREGNANCY

- A study by theron et al examined adverse pregnancy outcomes among PLHIV mothers on 28 weeks IPT
- The adjusted odds of fetal demise, preterm delivery (PTD), low birth weight (LBW), or a congenital anomaly were 1.63 times higher among women on immediate IPT compared to those who deferred IPT (95% CI, 1.15–2.31).
- The odds of fetal demise, PTD, LBW, or neonatal death within 28 days were 1.62 times higher among women on immediate IPT (95% CI, 1.14–2.30).
- The odds of early neonatal death within 7 days, fetal demise, PTD, or LBW were 1.74 times higher among women on immediate IPT (95% CI, 1.22–2.49).

Theron G, Montepiedra G, Aaron L, McCarthy K, Chakhtoura N, Jean-Philippe P, et al. Individual and Composite Adverse Pregnancy Outcomes in a Randomized Trial on Isoniazid Preventative Therapy Among Women Living With Human Immunodeficiency Virus. Clin Infect Dis. 2021;72(11):e784-e90.

Outcome	Immediate INH, n/N (%)	Deferred INH, n/N (%)	Unadjusted OR (95% CI), by study arm	Adjusted OR (95% CI), by study arm
Composite 1: fetal demise, PTD, LBW, or congenital anomaly	106/449 (23.6)	78/460 (17.0)	1.51 (1.09–2.10)	1.63 (1.15–2.31)
Composite 2: fetal demise, PTD, LBW, or neonatal death (<28 days)	105/450 (23.3)	78/459 (17.0)	1.48 (1.07–2.06)	1.62 (1.14–2.30)
Composite 3: fetal demise, PTD, LBW, or early neonatal death (<7 days)	105/450 (23.3)	73/459 (15.9)	1.61 (1.15–2.24)	1.74 (1.22–2.49)
Perinatal death 1: fetal demise or neonatal death	23/459 (5.0)	20/466 (4.3)	1.18 (.64–2.17)	1.32 (.69–2.53)
Perinatal death 2: fetal demise or early neonatal death	21/459 (4.6)	13/466 (2.8)	1.67 (.83–3.38)	1.84 (.87–3.85)
LBW: <2500 grams at birth	62/430 (14.4)	46/446 (10.3)	1.46 (.97–2.20)	1.58 (1.02–2.46)
PTD: <37 weeks gestation at delivery	48/442 (10.9)	40/458 (8.7)	1.27 (.82–1.98)	1.35 (.85–2.15)

Multivariable model for composite outcomes by study arm.

Abbreviations: CI, confidence interval; LBW, low birth weight; OR, odds ratio; PTD, preterm delivery.

Covariates associated with adverse pregnancy outcomes

Outcome[a]	Adjusted OR (95% CI)						
	HBsAG positive vs negative	Normal MUAC	Noninfectious pregnancy complication vs none	Infectious pregnancy complication vs none	Twin gestation vs singleton	Current smoker vs never/previous smoker	HIV RNA < LLOQ vs ≥ LLOQ
Composite 1: fetal demise, PTD, LBW, or congenital anomaly	2.32 (1.01–5.30)	.92 (.87–.96)	2.06 (1.34–3.17)	.46 (.22–1.00)	14.43 (3.35–62.08)	…	…
Composite 2: fetal demise, PTD, LBW, or neonatal death (<28 days)	…	.91 (.87–.96)	2.13 (1.39–3.28)	…	14.51 (3.38–62.29)	…	…
Composite 3: fetal demise, PTD, LBW, or early neonatal death (<7 days)	…	.91 (.87–.96)	2.06 (1.33–3.19)	…	15.02 (3.50–64.38)	…	…
Perinatal death 1: fetal demise or neonatal death	…	…	6.21 (3.14–12.31)	…	…	…	…
Perinatal death 2: fetal demise or early neonatal death	…	…	6.76 (3.18–14.36)	…	6.01 (1.08–33.55)	…	…
LBW: <2500 grams at birth	…	.88 (.83–.94)	…	…	19.09 (3.95–92.35)	3.18 (1.05–9.63)	…
PTD: <37 weeks gestation at delivery	…	.93 (.87–.99)	1.90 (1.08–3.34)	.29 (.09–.98)	…	…	.56 (.32–.97)

The multivariable model includes study arm and the following covariates: maternal age at delivery, CD4 quartiles, HIV RNA < LLOQ, timing of ART initiation, HBsAG status, MUAC, IGRA status, twin versus singleton pregnancy, current smoker, noninfectious pregnancy complications, infectious pregnancy complications, and maternal hospitalization.

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HBsAG, hepatitis B surface antigen; HIV, human immunodeficiency virus; IGRA, interferon-gamma release assay; LBW, low birth weight; LLOQ, lower limit of quantification; MUAC, mid-upper arm circumference; OR, odds ratio; PTD, preterm delivery.

[a]Estimates are shown if $P < .05$.

TPT: SAFE IN PREGNANCY?

- WHO examined the evidence of adverse pregnancy outcomes with IPT
- Few studies have found a higher rate of adverse pregnancy outcome, but the quality of the studies were questionable
- Also, especially in PLHIV mothers, risk of TB is higher during pregnancy and IPT can have more benefit than risk; 3HP is generally safe in pregnancy;
- Levofloxacin prophylaxis should be given after risk-benefit analysis

CURRENT STATUS: INDIA

- TBI testing services were established in 246 (32%) districts either as in-house facilities or linked with in-house or outsourced private facilities.

- 476 (62%) districts have expanded TPT in eligible HHC after ruling out active TB while awaiting establishment of TBI testing services

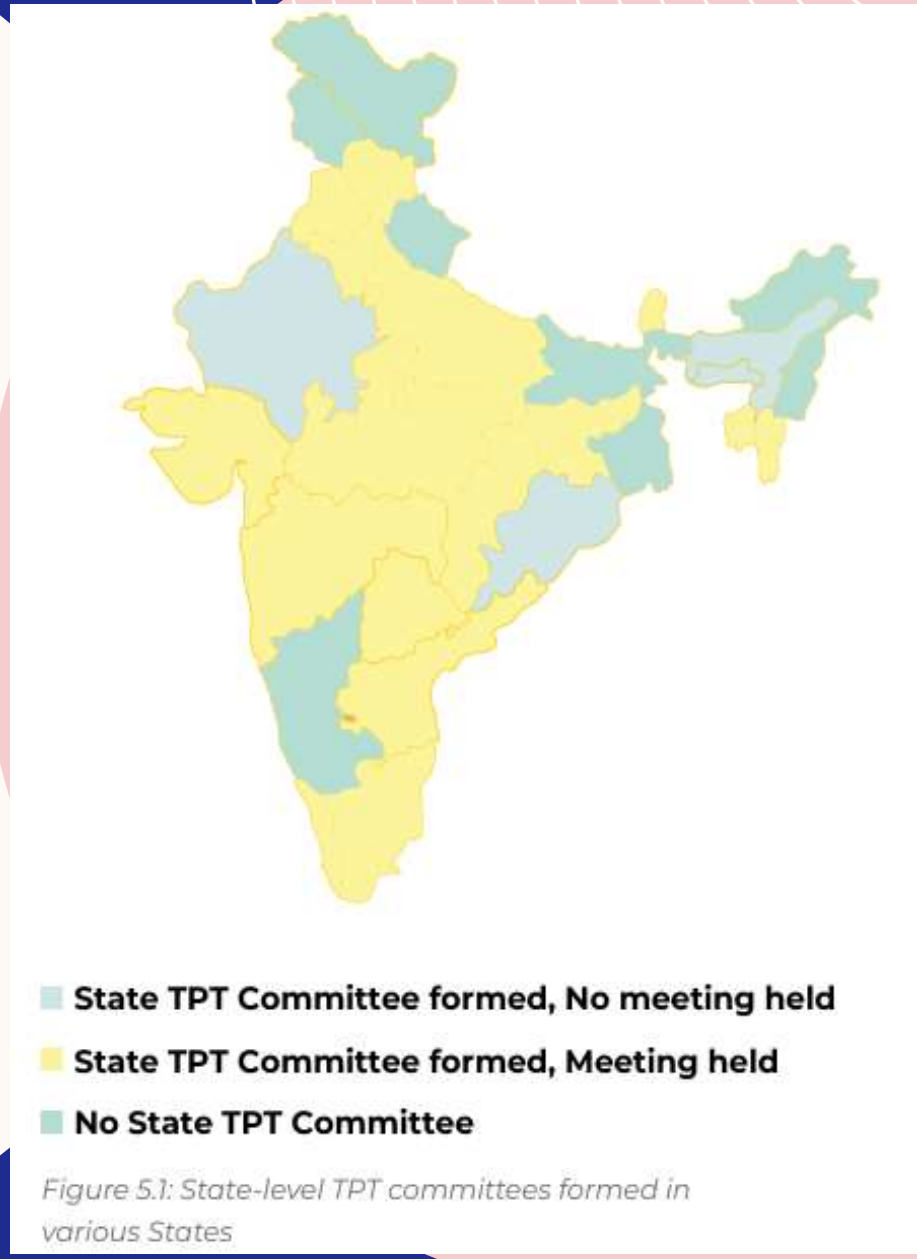
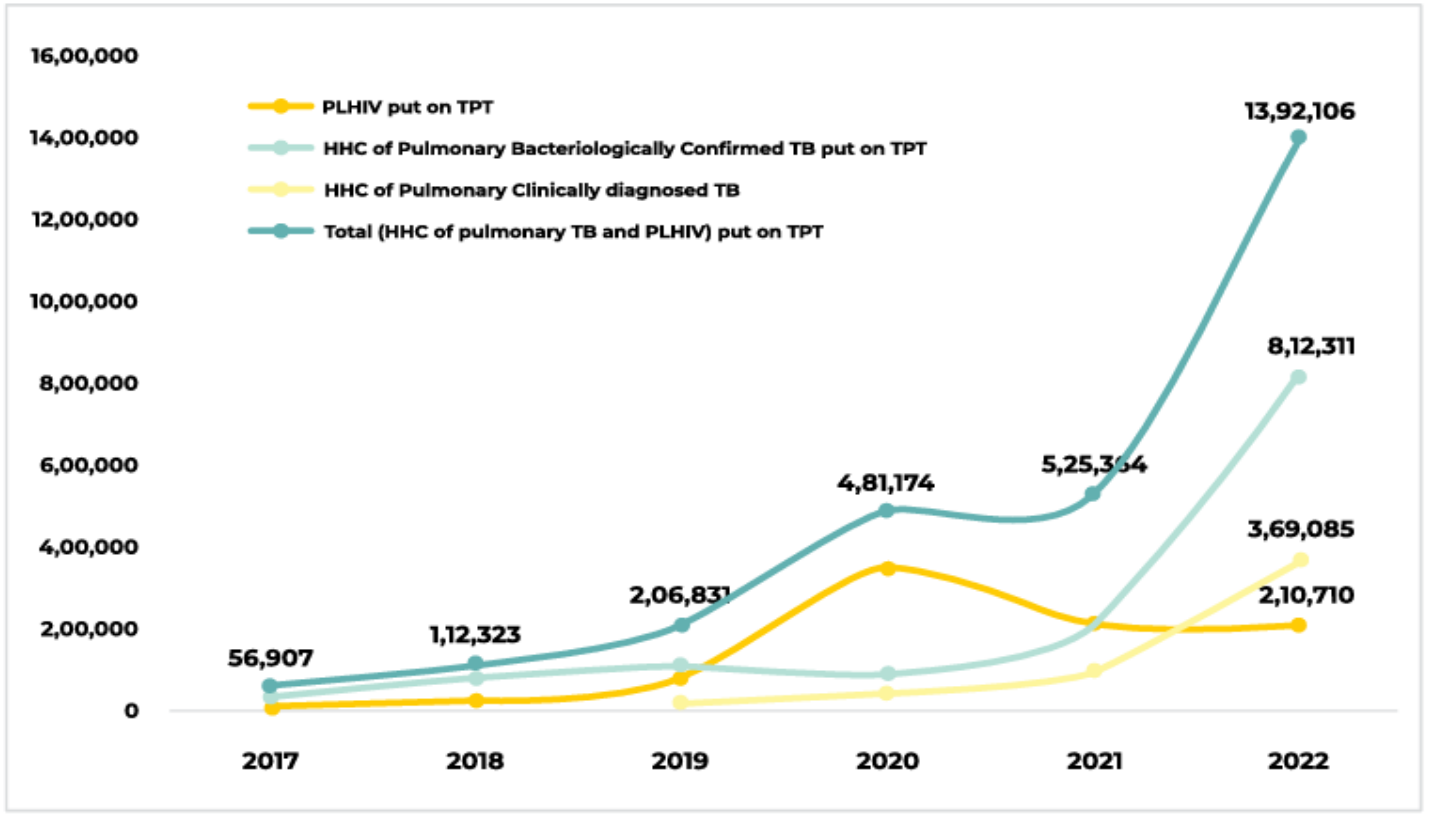


Figure 5.1: State-level TPT committees formed in various States

India TB report 2023

COVERAGE



Note: Expanded the TPT to all HHC (irrespective of age) of pulmonary TB (prioritized PBCT) and other risk groups from August 2021

Figure 5.2: A graph showing Achievement in programmatic management of TPT

- Rise in coverage of HHC
- Fall/plateauing of coverage of PLHIV

NEW REGIMENS

- Central TB division received 45,000 3HP doses from WHO-India and implemented them as TPT and in research
- Kerala used 3HR regimen for <5 years and 5-15 years HHCs
- Success in the pilot prompted implementation of the same in other states (Punjab, Gujrat, AP, MP, Odisha)

PERFORMANCES AND LACUNAE

States/UTs	No. of HHC <5years of PBCT	Screening, diagnosis and treatment of TB					Ruling out active TB and TPT initiation	
		No. of HHC <5years of PBCT screened for TB (%)	No. of HHC <5years of PBCT symptomatic for TB (%)	No. of HHC <5years of PBCT evaluated for TB (%)	No. of HHC <5years of PBCT diagnosed with TB (%)	No. of HHC <5years of PBCT put on TB treatment (%)	No. of HHC <5years of PBCT not diagnosed TB and eligible for TPT	No. of HHC <5years of PBCT initiated TPT (%)
Ladakh	72	70 (97%)	1 (1%)	1 (100%)	1 (100%)	1 (100%)	71 (99%)	62 (87%)
Lakshadweep	9	9 (100%)	0 (0%)	NA	NA	NA	9 (100%)	9 (100%)
Madhya Pradesh	25251	22305 (88%)	322 (1%)	224 (70%)	126 (56%)	75 (60%)	25125 (100%)	11097 (44%)
Maharashtra	14051	13114 (93%)	363 (3%)	296 (82%)	108 (36%)	99 (92%)	13943 (99%)	8312 (60%)
Manipur	426	388 (91%)	5 (1%)	0 (0%)	NA	NA	426 (100%)	163 (38%)
Meghalaya	2135	2009 (94%)	33 (2%)	25 (76%)	11 (44%)	11 (100%)	2124 (99%)	1335 (63%)
Mizoram	864	826 (96%)	4 (0%)	4 (100%)	2 (50%)	2 (100%)	862 (100%)	235 (27%)
Nagaland	546	388 (71%)	11 (3%)	7 (64%)	2 (29%)	2 (100%)	544 (100%)	335 (62%)
Odisha	8431	7910 (94%)	114 (1%)	87 (76%)	76 (87%)	69 (91%)	8355 (99%)	4660 (56%)
Puducherry	91	91 (100%)	13 (14%)	13 (100%)	0 (0%)	NA	91 (100%)	83 (91%)
Punjab	7835	7148 (91%)	107 (1%)	85 (79%)	36 (42%)	15 (42%)	7799 (100%)	4949 (63%)
Rajasthan	24054	22608 (94%)	315 (1%)	182 (58%)	72 (40%)	37 (51%)	23982 (100%)	12402 (52%)
Sikkim	98	66 (67%)	3 (5%)	2 (67%)	2 (100%)	2 (100%)	96 (98%)	59 (61%)
Tamil Nadu	5408	5166 (96%)	229 (4%)	213 (93%)	52 (24%)	47 (90%)	5356 (99%)	3485 (65%)
Telangana	4844	4571 (94%)	317 (7%)	280 (88%)	28 (10%)	6 (21%)	4816 (99%)	3159 (66%)
Tripura	347	326 (94%)	52 (16%)	49 (94%)	2 (4%)	0 (0%)	345 (99%)	165 (48%)
Uttar Pradesh	74997	70454 (94%)	436 (1%)	170 (39%)	125 (74%)	100 (80%)	74872 (100%)	47232 (63%)
Uttarakhand	4642	4163 (90%)	33 (1%)	12 (36%)	4 (33%)	5 (125%)	4638 (100%)	1668 (36%)
West Bengal	20001	19025 (95%)	231 (1%)	152 (66%)	30 (20%)	15 (50%)	19971 (100%)	12575 (63%)
India	**292945**	**269905 (92%)**	**4374 (2%)**	**3093 (71%)**	**1255 (41%)**	**903 (72%)**	**291690 (100%)**	**168665 (58%)**

State/UTs	No. of HHC ≥5years of PBCT	Screening, diagnosis and treatment of TB					Ruling out active TB, TBI testing and TPT initiation				
		No. of HHC ≥5years of PBCT screened for TB (%)	No. of HHC ≥5years of PBCT symptomatic for TB (%)	No. of HHC ≥5years of PBCT evaluated for TB (%)	No. of HHC ≥5years of PBCT diagnosed with TB (%)	No. of HHC ≥5years of PBCT put on TB treatment (%)	No. of HHC ≥5years of PBCT and TB not diagnosed (B-F)	No. of HHC ≥5years of PBCT tested for TB infection	No. of HHC ≥5years of PBCT positives for TB infection	No. of HHC ≥5 years of PBCT eligible for TPT (TBI positives + testing not done among TB not diagnosed (J+[H-I]))	No. of HHC ≥5years of PBCT initiated TPT (%)
Ladakh	648	610 (94%)	17 (3%)	14 (82%)	2 (14%)	2 (100%)	646 (100%)	2 (0.3%)	2 (100%)	646 (100%)	151 (23%)
Lakshadweep	34	31 (91%)	0 (0%)	NA	NA	NA	34 (100%)	1 (2.9%)	0 (0%)	33 (97%)	33 (100%)
Madhya Pradesh	196521	179064 (91%)	3488 (2%)	2596 (74%)	1294 (50%)	963 (74%)	195227 (99%)	33645 (17.2%)	10988 (32.7%)	172570 (88%)	62824 (36%)
Maharashtra	216585	203140 (94%)	5305 (3%)	4241 (80%)	740 (17%)	621 (84%)	215845 (100%)	7834 (3.6%)	3745 (47.8%)	211756 (98%)	40280 (19%)
Manipur	4246	3494 (82%)	32 (1%)	25 (78%)	14 (56%)	13 (93%)	4232 (100%)	0 (0%)	NA	4232 (100%)	16 (0%)
Meghalaya	13818	13219 (96%)	277 (2%)	234 (84%)	72 (31%)	69 (96%)	13746 (99%)	0 (0%)	NA	13746 (99%)	3785 (28%)
Mizoram	2972	2759 (93%)	15 (1%)	11 (73%)	9 (82%)	9 (100%)	2963 (100%)	12 (0.4%)	12 (100%)	2963 (100%)	990 (33%)
Nagaland	5783	4818 (83%)	39 (1%)	38 (97%)	24 (63%)	23 (96%)	5759 (100%)	1 (0%)	1 (100%)	5759 (100%)	1935 (34%)
Odisha	94585	91276 (97%)	1264 (1%)	940 (74%)	654 (70%)	633 (97%)	93931 (99%)	29 (0%)	0 (0%)	93902 (99%)	27026 (29%)
Puducherry	2184	2184 (100%)	349 (16%)	341 (98%)	3 (1%)	3 (100%)	2181 (100%)	9 (0.4%)	1 (11.1%)	2173 (99%)	701 (32%)
Punjab	91238	84153 (92%)	949 (1%)	737 (78%)	317 (43%)	284 (90%)	90921 (100%)	112 (0.1%)	5 (4.5%)	90814 (100%)	34645 (38%)
Rajasthan	226322	217136 (96%)	4252 (2%)	3287 (77%)	848 (26%)	398 (47%)	225474 (100%)	6 (0%)	1 (16.7%)	225469 (100%)	86285 (38%)
Sikkim	1752	1415 (81%)	19 (1%)	13 (68%)	5 (38%)	5 (100%)	1747 (100%)	139 (8%)	115 (82.7%)	1723 (98%)	134 (8%)
Tamil Nadu	125641	121690 (97%)	1746 (1%)	1461 (84%)	157 (11%)	129 (82%)	125484 (100%)	3512 (2.8%)	1027 (29.2%)	122999 (98%)	9169 (7%)
Telangana	87807	85301 (97%)	4586 (5%)	4116 (90%)	576 (14%)	364 (63%)	87231 (99%)	146 (0.2%)	89 (61%)	87174 (99%)	22048 (25%)
Tripura	5998	5652 (94%)	258 (5%)	241 (93%)	31 (13%)	11 (35%)	5967 (99%)	18 (0.3%)	18 (100%)	5967 (99%)	381 (6%)
Uttar Pradesh	770736	743179 (96%)	5727 (1%)	3439 (60%)	2590 (75%)	1894 (73%)	768146 (100%)	841 (0.1%)	575 (68.4%)	767880 (100%)	47592 (6%)
Uttarakhand	40512	37308 (92%)	451 (1%)	321 (71%)	213 (66%)	207 (97%)	40299 (99%)	5 (0%)	5 (100%)	40299 (99%)	4653 (12%)
West Bengal	183272	176028 (96%)	5727 (3%)	4821 (84%)	568 (12%)	417 (73%)	182704 (100%)	47 (0%)	2 (4.3%)	182659 (100%)	91189 (50%)
India	**3063327**	**2891117 (94%)**	**50747 (2%)**	**39141 (77%)**	**12920 (33%)**	**9498 (74%)**	**3050407 (100%)**	**37265 (1.2%)**	**14150 (38%)**	**3027292 (99%)**	**643646 (21%)**

State/UTs	No. of HHC of PBCT	Screening, diagnosis and treatment of TB					Ruling out active TB, TBI testing and TPT initiation			
		No. of HHC of PBCT screened for TB (%)	No. of HHC of PBCT symptomatic for TB (%)	No. of HHC of PBCT evaluated for TB (%)	No. of HHC of PBCT diagnosed with TB (%)	No. of HHC of PBCT put on TB treatment (%)	No. of HHC ≥5 years of PBCT tested for TB infection	No. of HHC ≥5 years of PBCT positives for TB infection	No. of HHC of PBCT eligible* for TPT	No. of HHC of PBCT provided TPT (%)
Lakshadweep	43	40 (100%)	0 (0%)	NA	NA	NA	1 (2.9%)	0 (0%)	42 (98%)	42 (100%)
Madhya Pradesh	221772	201369 (88%)	3810 (1%)	2820 (70%)	1420 (56%)	1038 (60%)	33645 (17.2%)	10988 (32.7%)	197695 (89%)	73921 (37%)
Maharashtra	230636	216254 (93%)	5668 (3%)	4537 (82%)	848 (36%)	720 (92%)	7834 (3.6%)	3745 (47.8%)	225699 (98%)	48592 (22%)
Manipur	4672	3882 (91%)	37 (1%)	25 (0%)	NA	NA	0 (0%)	NA	4658 (100%)	179 (4%)
Meghalaya	15953	15228 (94%)	310 (2%)	259 (76%)	83 (44%)	80 (100%)	0 (0%)	NA	15870 (99%)	5120 (32%)
Mizoram	3836	3585 (96%)	19 (0%)	15 (100%)	11 (50%)	11 (100%)	12 (0.4%)	12 (100%)	3825 (100%)	1225 (32%)
Nagaland	6329	5206 (71%)	50 (3%)	45 (64%)	26 (29%)	25 (100%)	1 (0%)	1 (100%)	6303 (100%)	2270 (36%)
Odisha	103016	99186 (94%)	1378 (1%)	1027 (76%)	730 (87%)	702 (91%)	29 (0%)	0 (0%)	102257 (99%)	31686 (31%)
Puducherry	2275	2275 (100%)	362 (14%)	354 (100%)	3 (0%)	NA	9 (0.4%)	1 (11.1%)	2264 (100%)	784 (35%)
Punjab	99073	91301 (91%)	1056 (1%)	822 (79%)	353 (42%)	299 (42%)	112 (0.1%)	5 (4.5%)	98613 (100%)	39594 (40%)
Rajasthan	250376	239744 (94%)	4567 (1%)	3469 (58%)	920 (40%)	435 (51%)	6 (0%)	1 (16.7%)	249451 (100%)	98687 (40%)
Sikkim	1850	1481 (67%)	22 (5%)	15 (67%)	7 (100%)	7 (100%)	139 (8%)	115 (82.7%)	1819 (98%)	193 (11%)
Tamil Nadu	131049	126856 (96%)	1975 (4%)	1674 (93%)	209 (24%)	176 (90%)	3512 (2.8%)	1027 (29.2%)	128355 (98%)	12654 (10%)
Telangana	92651	89872 (94%)	4903 (7%)	4396 (88%)	604 (10%)	370 (21%)	146 (0.2%)	89 (61%)	91990 (99%)	25207 (27%)
Tripura	6345	5978 (94%)	310 (16%)	290 (94%)	33 (4%)	11 (0%)	18 (0.3%)	18 (100%)	6312 (99%)	546 (9%)
Uttar Pradesh	845733	813633 (94%)	6163 (1%)	3609 (39%)	2715 (74%)	1994 (80%)	841 (0.1%)	575 (68.4%)	842752 (100%)	94824 (11%)
Uttarakhand	45154	41471 (90%)	484 (1%)	333 (36%)	217 (33%)	212 (125%)	5 (0%)	5 (100%)	44937 (100%)	6321 (14%)
West Bengal	203273	195053 (95%)	5958 (1%)	4973 (66%)	598 (20%)	432 (50%)	47 (0%)	2 (4.3%)	202630	103764 (51%)
India	**3356272**	**3161022 (92%)**	**55121 (2%)**	**42234 (71%)**	**14175 (41%)**	**10401 (72%)**	**37265 (1.2%)**	**14150 (38%)**	**3318982 (99%)**	**812311 (24%)**

State/UT	Microbiologist(IRL)		Microbiologist (EQA)		Senior Lab. Tech.		Technical Officer		Lab Technicians		Data Entry Operator		Lab Attendant	
	Sanc-tioned	In Place	Sanc-tioned	In Place	Sanc-tioned	In Place	Sanc-tioned	In Place	Sanc-tioned	In Place	Sanc-tioned	In Place	Sanc-tioned	In Place
Karnataka	2	2	2	1	20	14	0	0	6	0	5	5	5	5
Kerala	1	1	1	1	1	1	2	2	10	10	2	2	3	3
Lakshdweep	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Maharashtra	4	1	4	2	22	16	6	4	8	4	4	4	7	3
Manipur	1	1	1	1	1	1	0	0	4	0	1	1	2	2
Mizoram	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Meghalaya	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Madhya Pradesh	1	1	1	1	1	1	1	1	5	5	1	1	1	1
Nagaland	NA	NA	NA	NA	NA	NA	0	0	NA	NA	NA	NA	NA	NA
Odisha	2	1	1	1	1	1	1	0	6	4	2	2	4	3
Puducherry	1	1	1	1	1	1	1	0	5	4	1	1	1	1
Punjab	1	0	1	1	0	0	0	0	0	0	0	0	0	0
Rajasthan	1	1	1	1	1	1	0	0	19	8	3	2	8	4
Sikkim	1	1	1	0	1	1	1	1	7	7	1	1	1	1
Telangana	1	1	1	0	1	1	1	0	4	4	1	1	1	1
Tamil Nadu	2	2	2	2	1	1	0	0	9	9	3	1	8	4
Tripura	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Uttar Pradesh	8	6	5	1	29	4	0	0	5	4	6	5	6	4
Uttarakhand	1	1	1	1	1	1	0	0	7	7	1	1	3	3
West Bengal	1	0	2	1	6	3	0	0	1	1	1	1	0	0

- There is a clear lack of adequate manpower for implementation of the program

LACUNAE: WHAT MIGHT IMPROVE COVERAGE?

- Larger studies examining the safety of TPT in general population and among special groups
- Larger studies to examine emergence of drug resistance among recipients of TPT
- RCTs evaluating shorter and safer regimens

WHAT MIGHT IMPROVE COVERAGE?

- Recruitment of sufficient lab technicians and health-care-workers for implementation of policy

- Better IEC activity regarding the benefits of TPT and the incentives offered

CONCLUSIONS

- The chance of development of active TB from TB infection is substantial and may add to burden of TB treatment cost
- Certain populations are at a higher risk
- TB preventive treatment has proven effective against preventing development of active TB in infected individuals
- TB preventive therapy is largely safe, and the side effects are easily manageable

CONCLUSIONS

- For drug resistant TB contacts, the knowledge of resistance patterns of the index patient is important
- Upcoming researches may unfold shorter regimens with better adherence and lesser side effects

THANK YOU