NATIONAL TUBERCULOSIS ELIMINATION PROGRAMME

Guidance document of implementation of 3RH (3months of daily rifampicin and isoniazid) TB Preventive Treatment regimen

Forward:

This is a technical and operational guidance document regarding shorter 3RH TPT regimen implementation in 0-15years of age group. The guidance is presented as an addendum to the Guidelines for Programmatic Management of TB Preventive Treatment in India 2021. Nevertheless, this guidance document should be referred in context of Guidelines of Programmatic Management of TB Preventive Treatment in India 2021.

Evidence for 3RH:

- A systematic review updated in 2017 showed that the efficacy and safety profile of 3–4 months' daily rifampicin plus isoniazid were similar to those of 6 months' isoniazid[1] [2].
- A new review to compare the effectiveness of rifampicin plus isoniazid daily for 3 months with isoniazid for 6 or 9 months in children identified one RCT and two observational studies. The RCT reported no clinical disease in either group and used new radiographic findings suggestive of active TB as a proxy for clinical disease. Fewer participants given daily rifampicin plus isoniazid than those given 9 months of isoniazid developed radiographic changes (RR 0.49, 95% CI 0.32; 0.76). The authors reported lower risk for adverse events (RR 0.33, 95% CI 0.20; 0.56) and higher adherence rate (RR 1.07, 95% CI 1.01; 1.14) among children given daily rifampicin plus isoniazid (22). Similar findings were reported in the observational studies.

[1] Stagg HR, Zenner D, Harris RJ, Muñoz L, Lipman MC, Abubakar I. Treatment of Latent Tuberculosis Infection. Ann Intern Med. 2014 Sep 16;161(6):419–28.

[2] Spyridis NP, Spyridis PG, Gelesme A, Sypsa V, Valianatou M, Metsou F, et al. The effectiveness of a 9-month regimen of isoniazid alone versus 3- and 4-month regimens of isoniazid plus rifampin for treatment of latent tuberculosis infection in children: results of an 11-year randomized study. Clin Infect Dis. 2007 Sep 15;45(6):715–22.

TPT target group, strategy, and treatment options:

Target population	Strategy	Treatment option
• **People living with HIV** ○ PLHIV adults and children >12 months irrespective of ART initiation status ○ Child living with HIV age <12 months in contact with active TB • **Household contact below 5 years** of pulmonary* TB patients	TPT to all after ruling out active TB disease	• 3HP (3 months of weekly isoniazid and rifapentine – 12 dosages) in person older than 2 years Or • 6H (6 months of daily isoniazid – 180 dosages) Or • **3RH (3 months of daily rifampicin and isoniazid - 84 dosages) in age group <15years**
• **Household contacts 5 years and above** of pulmonary* TB patients (testing would be offered whenever available)	TPT among TBI positive[#] after ruling out TB disease	
• **Other risk group** ○ Children/adult on initiation of immunosuppressive therapy or anti-TNF treatment, ○ Person with silicosis, ○ Patient on dialysis, ○ Person considered for organ or haematologically transplantation	TPT after ruling out TB disease among TBI positive	

** bacteriologically confirmed pulmonary TB patients will be prioritized for enumeration of the target population for TPT*

[#] Chest Xray (CXR) and testing for TB infection would be offered wherever available, but TPT must not be deferred in their absence

Recommended dosages of 3RH

Regimen	Dose by age and weight band
3RH – three months of daily rifampicin and isoniazid	**Isoniazid:** Age 10 years & older: 5 mg/kg/day[d] Age <10 years: 10 mg/kg/day (range, 7–15 mg) **Rifampicin**: Age 10 years & older: 10 mg/kg/day Age <10 years: 15 mg/kg/day (range, 10–20 mg) **Weight band**

Weight band	4-7 kg	8-11 kg	12-15 kg	16-24 kg	≥25 kg
RH 75/50 mg (FDC)	1	2	3	4	Use adult formulation

Comparison of TPT treatment options

	6H	3HP	3RH
Medicines	Isoniazid	Isoniazid + Rifapentine	**Isoniazid + Rifampicin**
Duration	6 months	3 months	**3 months**
Interval	Daily	Weekly	**Daily**
Number of doses	180	12	**84**
Pill burden per dose (total number of pills for an average adult)	1 (180 pills)	9 pills with loose drugs (108 pills) 3 pills of FDC (36 pills)	**3 (252 pills)**
Pregnancy	Safe to use	Not known	**Safe for use**
Interaction with ART	No restriction	Contraindicated with – All PIs, NVP/NNRTIs, TAF Can use with – TDF, EFV (600mg), DTG, RAL (without dose adjustment)	**Contraindicated: All PIs, NVP/most NNRTIs@** **Use with caution: TAF** **Adjust dose: RAL** **Use: TDF, EFV (600 mg), double dosing of DTG**
Adverse Drug Reactions	Hepatotoxicity (more), Peripheral Neuropathy, Rash, GI upset	Flu- like syndrome, Hypersensitivity reactions, GI upset, Orange discolouration of body fluids, rash, hepatotoxicity (less)	**Hypersensitivity reactions, hepatotoxicity, rash, GI upset, hypoprothrombinaemia, orange discoloration of body fluids**
Absorption	Best absorbed on empty stomach (Up to 50 % reduction in peak concentration with a fatty meal)	Peak concentration is increased with given with a meal. Oral Rifapentine bioavailability is 70%;	**Rifampicin absorption is rapid but may be delayed or decreased by high-fat meals**

Special situation and 3RH

- **Babies born to mothers with TB disease:** TPT with 3RH cannot be given along with nevirapine prophylaxis since rifamycins decrease nevirapine levels and may result in increased mother-to-child transmission of HIV.
- **TPT among people who use drugs:** people taking 3HP, 3RH or 4R with OST should be closely monitored for signs of opiate withdrawal and other adverse events. Increasing the dose of methadone or buprenorphine when taking rifamycins can lessen the risk of withdrawal.

Management of interruptions in 3RH

3RH treatment interruptions should be managed same as interruptions during 6H, 6Lfx and 4R

TPT regimen	Duration of interruption	Management steps
6H, **3RH,** 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 3RH missed 3 days of treatment, continue TPT for a total duration of 3 months + 3 days from the date of start)
	More than 2 weeks	• If treatment interruption occurred after more than 80% of doses expected in the regimen were taken, 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 the expected time for completion, consider restarting the full TPT course.

Treatment outcomes:

- **Treatment completion with 3RH:** 80% of recommended dose (68/84) consumed within 133% of planned TPT duration (120 days) for 3RH

Regimen	Total duration in months	Expected number of dosages	80% of recommended dosages (days)	Extended time for treatment completion (days) (treatment duration + 33% additional time)
3RH (daily)	3	84	68	120

- There is no difference in definitions of treatment failed, died, loss-to-follow-up, TPT discontinuation due to toxicity and not evaluated. Refer Guidelines for Programmatic Management of TB Preventive Treatment in India 2021