New regimens in latent tuberculosis treatment

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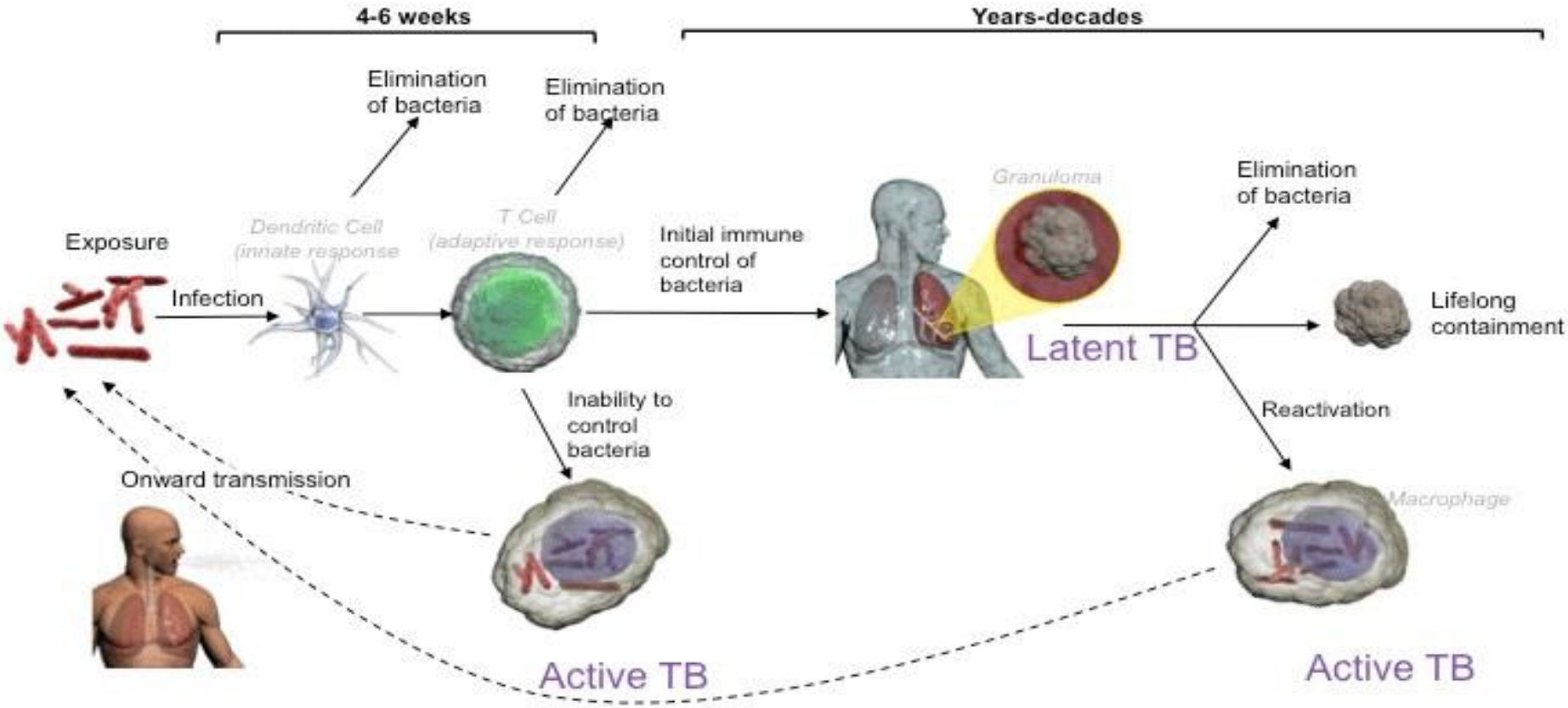
Natural history of TB infection



Prioritized groups for screening and treatment WHO 2018 (2020)

Strong recommendation

- Adults, adolescents and children living with HIV
- HIV negative adult and child household contacts (high and low endemic settings)
- Individuals prior to or ongoing immunosuppression (anti-TNF, dialysis, transplant candidates and silicosis)

Conditional recommendation

- Migrants from high endemic areas.
- Prisoners
- Health care workers
- Homeless people
- IV drug users

Prioritized groups for screening and treatment Stockholm county 2019

According to WHO (strong recommendation) and:

- Migrants from TB high endemic countries (>100/100 000)
- Pregnant women from high endemic countries or known TB contact
- Individuals with hematologic malignancies
- Individuals planned for high dose steroids (>15 mg prednisone/day> 1 month)

INH protective efficacy by duration of treatment

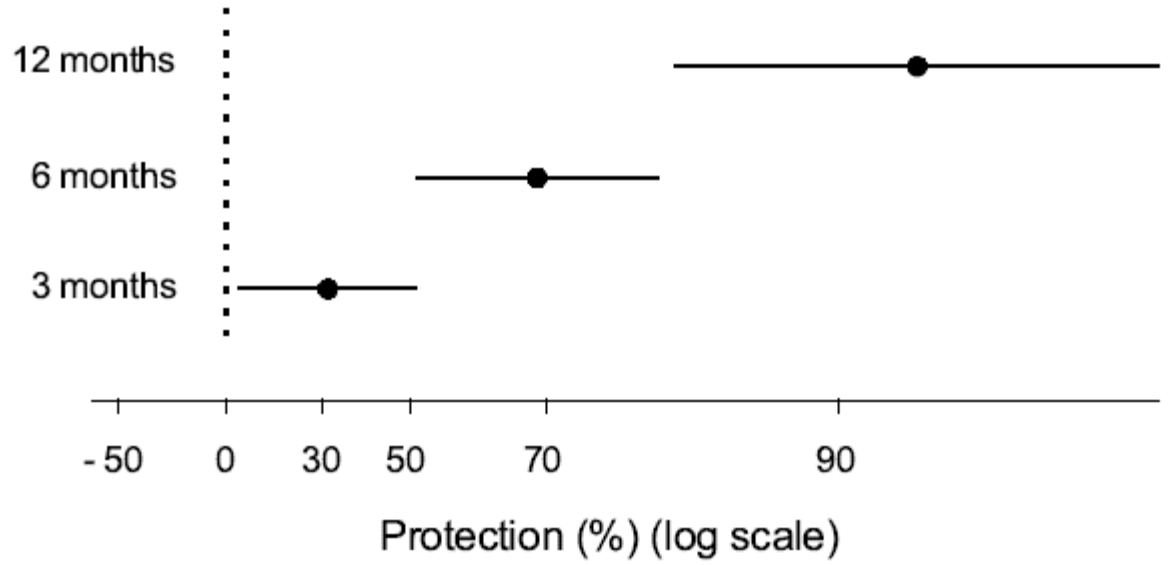
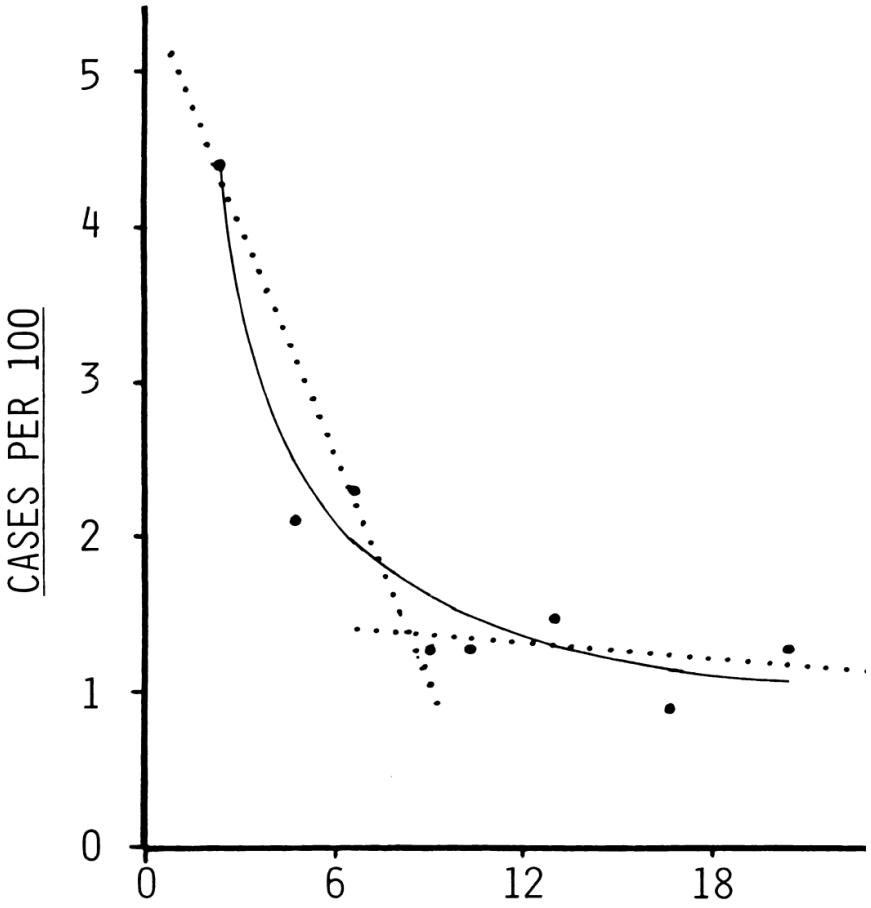


Figure 83. Impact of duration of intake of isoniazid preventive therapy on protective efficacy.[123]

Rieder HL. Interventions for TB control and elimination. Int Union against TB and Lung Dis. 2002

INH treatment –optimal duration?



- Immunocompetent adults: 6 months of preventive treatment does not give optimal protection;
- More than 12 months of preventive treatment is not necessary;
- 9–10 months appears to be the optimal duration;
- Total duration of preventive treatment may be more important than its continuity.

Comstock GW et al. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? Int J Tuberc Lung Dis. 1999 Oct;3(10):847-50

Treatment efficacy

Table 1. ORs and Treatment Rankings for the Prevention of Active TB, Derived From the Network Meta-analysis

Regimen	OR vs. Placebo (95% CrI)	OR vs. No Treatment (95% CrI)	Rank (95% CrI)
No treatment	1.62 (1.06-2.47)	1.00 (reference)	16 (14-16)
Placebo	1.00 (reference)	0.62 (0.41-0.94)	13 (11-15)
INH 3-4 mo	0.93 (0.55-1.50)	0.57 (0.31-1.02)	13 (8-15)
INH 6 mo	0.65 (0.50-0.83)	0.40 (0.26-0.60)	10 (7-12)
INH 9 mo	0.75 (0.35-1.62)	0.46 (0.22-0.95)	11 (4-15)
INH 12-72 mo	0.50 (0.41-0.62)	0.31 (0.21-0.47)	6 (4-10)
RFB-INH	0.30 (0.05-1.50)	0.18 (0.03-0.95)	3 (1-15)
RFB-INH (high)	0.30 (0.05-1.52)	0.19 (0.03-0.98)	3 (1-15)
RPT-INH	0.58 (0.30-1.12)	0.36 (0.18-0.73)	8 (3-14)
RMP	0.41 (0.19-0.85)	0.25 (0.11-0.57)	5 (1-12)
RMP-INH 1 mo	1.05 (0.37-2.77)	0.65 (0.23-1.71)	14 (4-16)
RMP-INH 3-4 mo	0.53 (0.36-0.78)	0.33 (0.20-0.54)	7 (4-11)
RMP-INH-PZA	0.35 (0.19-0.61)	0.21 (0.11-0.41)	3 (1-8)
RMP-PZA	0.53 (0.33-0.84)	0.33 (0.18-0.58)	7 (3-12)
INH-EMB	0.87 (0.32-2.36)	0.54 (0.19-1.56)	12 (4-16)
INH-EMB 12 mo	0.20 (0.04-0.82)	0.12 (0.02-0.54)	2 (1-11)

CrI = credible interval; EMB = ethambutol; INH = isoniazid; OR = odds ratio; PZA = pyrazinamide; RFB = rifabutin; RMP = rifampicin; RPT = rifapentine; TB = tuberculosis.

Meta-analysis: Randomized, controlled trials that evaluated LTBI treatment in humans and recorded at least 1 of 2 pre-specified end points (preventing active TB or hepatotoxicity).

Purpose: To evaluate the comparative efficacy and harms of LTBI treatment regimens aimed at preventing active TB among adults and children.

Ann Intern Med. 2017 Aug 15;167(4):248-255.Treatment of Latent Tuberculosis Infection: An Updated Network Meta-analysis. Zenner D, Beer N, Harris RJ, Lipman MC, Stagg HR, van der Werf MJ.

INH vs rifamycins alone or in combinations

- **INH+RIF 3m vs INH 6m:**
  → Adherence was similar and no difference was detected for treatment-limiting adverse events or hepatotoxicity.

- **INH/Rifapentine once weekly for 12 weeks vs INH 9m:**
  → INH/Rifapentine non-inferior to INH 9m for the incidence of active TB (0.2% vs 0.4%, RR 0.44, CI95% 0.18-1.07).
  → INH/Rifapentine less hepatotoxicity (0.4% vs 2.4%; RR 0.16, CI95% 0.10-0.27) but treatment-limiting adverse events more frequent (4.9% vs 3.7%; RR 1.32, CI95%1.07-1.64)

Rifamycins compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB. Sharma SK et al. Evid.-Based Child Health 9:1: 169–294 (2014)

INH vs rifamycins alone or in combinations

- 3443 adults randomised

  Efficacy: 4 RIF non-inferior to 9 H

- Better safety (all AEs)

  2.8 vs 5.8% (Risk difference -3.0 (- 4.1 vs -2.0))

- Higher treatment completion rate

  78.7 % vs 62% (Risk difference 15.6% (13.4%-17.8%))

  - Similar results seen in children

Menzies D et al N Engl J Med. 2018 Aug 2;379(5):440-453. doi

INH/RPT 12 weeks (3HP)

- 3HP has proven as effective as 9H, but with a higher completion rate (82.1% vs 69.0%, p<0.001)

  Sterling, T.R *et al.* 2011. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med *365*, 2155-2166.

- Review including 2 studies comparing 3HP to INH 6 or 9 months among HIV+ adults, 1 in HIV-negative adults and 1 in HIV-negative children and adolescents.

- Risk of active TB was not significantly different between 3HP and 6/9H
  in adults with HIV (risk ratio [RR] 0.73, 95%CI 0.23–2.29)
  in adults without HIV (RR 0.44, 95%CI 0.18–1.07
  in children and adolescents (RR 0.13, 95%CI 0.01–2.54)

INH/RPT 12 weeks (3HP)

- Risk of hepatotoxicity was significantly lower in the 3HP group among
  → adults with HIV (RR 0.26, 95%CI 0.12–0.55)
  → adults without HIV (RR 0.16, 95%CI 0.10–0.27).

- 3HP was also associated with a higher completion rate in all subgroups.

Hamada Y et al. 2018. Three-month weekly rifapentine plus isoniazid for tuberculosis preventive treatment: a systematic review Int J Tuberc Lung dis 22(12);1422-1428, 2018

INH/Rifapentine 1 month

- Randomized, open-label, phase 3 non-inferiority trial comparing efficacy and safety of 1-month daily HP vs 9H alone in 3000 HIV-infected adults living in areas of high TB prevalence or who had evidence of LTBI.

- Primary end points: first diagnosis of TB, death from TB or unknown cause. Follow-up 3.3 years

- Median CD4+ count 470 cells per cubic millimeter, half the patients were receiving ART.

Swindells S et al. 2019. One Month of Rifapentine plus Isoniazid to Prevent HIV-RelatedTuberculosis NEJM

INH/Rifapentine 1 month

- Primary end point reported in 32 of 1488 patients (2%) in 1 HP and in 33 of 1498 (2%) in the 9H. Non-inferiority achieved.
- Serious adverse events: 6% of the patients in 1 HP and in 7% of those in 9H (P = 0.07).
- The percentage of treatment completion was significantly higher in 1HP than in 9H (97% vs. 90%, P<0.001).

Swindells S et al. 2019. One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis NEJM

Recommended drug regimens (WHO 2018/update 2020)

High endemic

- INH 6 (9) months
- RIF/INH 3 months < 15 years old
- RPT/INH once/week 12 weeks

Low endemic

- INH 6 (9) months
- RIF/INH 3 months
- RIF 4 months
- RPT/INH once/week 12 weeks

Choice of treatment TB centre Karolinska 2019

- RIF 4m or INH/RPT once weekly/12 weeks
  - Contacts (if sensitive resistance pattern of index patient known)
  - Migrants
  - Post-partum (not INH/RPT)

- INH 9m
  - When increased risk of developing RIF resistance
  - Immunosuppressive treatment (increased risk of asymptomatic active M.tb)
  - Pulmonary chest x-ray indicating previous TB

Risk of INH or RIF drug resistance development

- INH 6-12 months: No difference in the risk of resistance among incident TB cases (risk ratio 1.45 CI95% 0.85-2.47). HIV-infected and HIV-uninfected populations were comparable.

WHO Guidelines on LTBI 2018.

Risk of RIF resistance

- No difference in risk of resistance among incident TB cases (0,1% vs 0,09%, risk ratio 1.12 CI95% 0.41-3.08).

  WHO Guidelines on LTBI 2018.

- No statistically significant increased risk of rifamycin resistance after LTBI treatment with rifamycin-containing regimens compared to non-rifamycin-containing regimens (RR 3.45, CI95% 0.72-16.56; P = 0.12) or placebo (RR 0.20, CI95% 0.02-1.66; P = 0.13).

  Rifampicin resistance after treatment for latent tuberculous infection: a systematic review and meta-analysis. den Boon S et al. Int J Tuberc Lung Dis. 2016 Aug;20(8):1065-71.

Contraindications

Absolute

- Suspected/confirmed active TB
- Non-compensated liver failure

Relative

- Liver disease
- Age >35yrs
- Alcohol or other drug abuse
- Expected non-adherence
- Exposure to MDR-TB
- Frequent travels and/or migration to high endemic area
- Rifapentine: Pregnancy or breastfeeding

Drug regimens dosing (WHO 2018)

Drug regimen	Formula	Dose per body weight	Comment
Isoniazid OD 9 months	Tabl Tibinide 300mg Oral solution (ex tempore) Isoniazid 10mg/ml or 20mg/ml	Adults = 5 mg/kg Children = 10 mg/kg Max 300 mg (>50kg)	Intake on empty stomach. Combine with Pyridoxine (vit B6) Kidney failure: GFR<10ml/min or HD reduce INH to 200mg
Rifampicin OD 4 months	Caps Rimactan 150, 450, 600mg Oral solution Rifadin 20mg/ml	Adults/children = 10 mg/kg Max 600 mg (>50kg)	Obs! Do not miss active TB Intake on empty stomach. Kidney failure: GFR<10ml/min or HD reduce RIF to 450mg
Isoniazid + Rifampicin OD 3 months	See above	As above	Intake on empty stomach
Isoniazid + Rifapentine once weekly for 12 weeks	Tabl Tibinide 300mg Tabl Priftin 150mg	Adults/children Isoniazid = 15 mg/kg Max 900 mg Rifapentine 10.0–14.0 kg = 300 mg 14.1–25.0 kg = 450 mg 25.1–32.0 kg = 600 mg 32.1–49.9 kg = 750 mg ≥50.0 kg = 900 mg Max 900 mg	Rifapentine as effective as Rifampicine but with 5 times longer half-life Intake with food. DOT

WHO Guidelines on LTBI 2018.

Side effects

Drug	Common (>1/100)	Uncommon (<1/100)	Comment
Isoniazid	Peripheral neuropathy (4-17%) Fatigue, headache, joint ache, vertigo, nausea, dyspepsia, rash. Elevated liver enzymes.	Depression, psychosis. Convulsions. Hepatitis.	Always combine with Pyridoxine (vit B6) 40mg OD (max 240mg OD)
Rifampicin	Fatigue, headache, joint ache, vertigo, nausea, dyspepsia, rash. Elevated liver enzymes.	Haemolytic anaemia, leukopenia, trombocytopenia. Hepatitis, porfyria. Haematuria, nefritis, kidney failure.	Red coloured urin, breast milk. Interaction with anticonceptives, ART, antifungal, anticonvulsive, warfarin, antidiabetics, corticosteroids
Rifapentine	Specific for RPT: Fluelike symptoms (ca 3%)	Specific for RPT: Hypotension/syncope (0,1%)	

Ongoing trials to further shorten TB preventive Treatment (TPT)

2R2 trial (Dick Menzies PI)

Aim

- to determine if RIF at double or triple the standard dose fro 2 months is as safe and effective as 4R

Design

- 1:1:1 randomised
- Phase 2 b, partially blinded, controlled trial
- The two higher doses (intervention arms) will be administered double blind: participants and providers will be blinded to dose (i.e. 20 or 30 mg/kg/day)

Ongoing trials to shorten TB preventive Treatment (TPT)

Asteroid trial (Tim Sterling)

Aim

- To compare the safety and effectiveness of daily RPT 6 weeks with 12-16 weeks of rifamycinbased treatment. RIF

Design

- RCT
- 1:1 randomisation

The future: Microshort regimens?

Activity of a Long-Acting Injectable Bedaquiline Formulation in a Paucibacillary Mouse Model of Latent Tuberculosis Infection.

- Effect of one injection of the long acting BDQ intramuscular lasted 12 weeks, comparable to oral BDQ, RTP/INH and RIF regimens

  Kaushik A et al, AAV 2019 Mar 27;63(4). pii: e00007-19. doi: 10.1128/AAC.00007-19. Print 2019 Apr.

- TPT with one or two injections of long acting drugs could be transformative.

- Possible problems with AEs, long halftime. Start with oral BDQ to evaluate AEs before longlasting injection suggested.

LTBI treatment after MDR exposure

Treatment	Estimated efficacy (%)	Estimated stop due to AE (%)	Estimated completion rate (%)	Estimated TB cases prevented (n)
No tx				0
PZA/FQ	90	66	31	134
PZA/EMB	62	25	75	223
FQ	62	8	81	241
FQ/EMB	76	1	79	288
4R/3HP (n=12)	89	0	100	331

Clin Infect Dis. 2017 Jun 15;64(12):1670-1677. Systematic Review, Meta-analysis, and Cost-effectiveness of Treatment of Latent Tuberculosis to Reduce Progression to Multidrug-Resistant Tuberculosis. Marks SM, Mase SR, Morris SB.

- FQ-om preventive therapy to household contacts to MDR-TB resulted in
- substantial health system savings
- reduced mortality
- reduced incidence of MDR-TB
- reduced incidence of acquired FQ-resistant disease
- improved quality of life
- substantial health system savings.

Am J Respir Crit Care Med. 2015 Jul 15;192(2):229-37. Fluoroquinolone Therapy for the Prevention of Multidrug-Resistant Tuberculosis in Contacts. A Cost-Effectiveness Analysis.
Fox GJ, Oxlade O, Menzies D.

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Thank you!