New regimens in latent tuberculosis treatment

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Natural history of TB infection

- **Exposure**
- **Infection**
- **Dendritic Cell (innate response)**
- **T Cell (adaptive response)**
- **Initial immune control of bacteria**
- **Granuloma**
- **Latent TB**
- **Elimination of bacteria**
- **Lifelong containment**
- **Reactivation**
- **Macrophage**
- **Onward transmission**
- **Active TB**
- **Inability to control bacteria**
- **Active TB**
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.

Treatment efficacy

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.

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)

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

  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)
  

- 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-Related Tuberculosis 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.

Risk of RIF resistance

- No difference in risk of resistance among incident TB cases (0.1% vs 0.09%, risk ratio 1.12 CI 95% 0.41-3.08).

- No statistically significant increased risk of rifamycin resistance after LTBI treatment with rifamycin-containing regimens compared to non-rifamycin-containing regimens (RR 3.45, CI 95% 0.72-16.56; P = 0.12) or placebo (RR 0.20, CI 95% 0.02-1.66; P = 0.13).

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
<table>
<thead>
<tr>
<th>Drug regimen</th>
<th>Formula</th>
<th>Dose per body weight</th>
<th>Comment</th>
</tr>
</thead>
</table>
| **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 Rifampicin but with 5 times longer half-life  
Intake with food. DOT  |
<table>
<thead>
<tr>
<th>Drug</th>
<th>Common (&gt;1/100)</th>
<th>Uncommon (&lt;1/100)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Peripheral neuropathy (4-17%)</td>
<td>Depression, psychosis. Convulsions. Hepatitis.</td>
<td>Always combine with Pyridoxine (vit B6) 40mg OD (max 240mg OD)</td>
</tr>
<tr>
<td></td>
<td>Fatigue, headache, joint ache, vertigo, nausea, dyspepsia, rash. Elevated liver enzymes.</td>
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<td></td>
<td></td>
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<tr>
<td>Rifapentine</td>
<td>Specific for RPT: Fluelike symptoms (ca 3%)</td>
<td>Specific for RPT: Hypotension/syncope (0,1%)</td>
<td></td>
</tr>
</tbody>
</table>
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 for 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 rifamycin-based 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


- 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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Estimated efficacy (%)</th>
<th>Estimated stop due to AE (%)</th>
<th>Estimated completion rate (%)</th>
<th>Estimated TB cases prevented (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No tx</td>
<td>0</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>PZA/FQ</td>
<td>90</td>
<td>66</td>
<td>31</td>
<td>134</td>
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<tr>
<td>PZA/EMB</td>
<td>62</td>
<td>25</td>
<td>75</td>
<td>223</td>
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<tr>
<td>FQ</td>
<td>62</td>
<td>8</td>
<td>81</td>
<td>241</td>
</tr>
<tr>
<td>FQ/EM</td>
<td>76</td>
<td>1</td>
<td>100</td>
<td>288</td>
</tr>
</tbody>
</table>

FQ 6m 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.


Thank you!