Preventive treatment of Latent TB infection

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Controversies in LTBI treatment

- Apart from the ones mentioned by Christoph
  1. How long? E.g. 6 – 9 – 12 – 36 months isoniazid
  2. Isoniazid and/or rifampicin-containing regimens?
  3. Prolonged treatment in immunosuppressed persons?
## Isoniazid 12 months

Several RCTs in the 1950s by the United States Public Health Service (USPHS):

<table>
<thead>
<tr>
<th>Groups studied</th>
<th>N</th>
<th>Reduction</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children with asymptomatic primary TB (Mount, 1961)</td>
<td>2,750</td>
<td>80%</td>
<td>Complications</td>
</tr>
<tr>
<td>Household contacts (regardless TST) (Ferebee, 1962)</td>
<td>25,033</td>
<td>70%</td>
<td>morbidity over 2 yrs</td>
</tr>
<tr>
<td>Inmates of mental institutions (Ferebee, 1963)</td>
<td>25,210</td>
<td>63%</td>
<td>morbidity over 2 yrs</td>
</tr>
<tr>
<td>Alaskan community trials (Bethel) (Comstock, 1967)</td>
<td>6,054</td>
<td>59%</td>
<td>morbidity over 6 yrs</td>
</tr>
<tr>
<td>Persons with “inactive” lesions (Ferebee, 1970)</td>
<td>4,575</td>
<td>60%</td>
<td>morbidity over 5 yrs</td>
</tr>
</tbody>
</table>

Isoniazid 3, 6 and 12 months

International Union Against Tuberculosis (IUAT) trial in Eastern Europe, TST reactors with healed TB (28,000 persons)

• 3-months regimen resulted in 22% reduction of TB morbidity, 6 months in 65% and 12 months in 75%.

• Reduction in compliant persons (>80% pill intake) was 69% in 6-months regimen versus 93% in 12-months regimen.

• 12 months was more effective than 6 months in persons with larger X-ray abnormalities (89% versus 67%).

➤ 6 months INH adequate for persons with normal X-rays.

How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults?

G. W. Comstock

“Optimal treatment duration = 9-10 months”
11 RCTs; 90,000 people

Benefit of longer treatment was marginal (RR of 0.38 for 12 months and 0.44 for 6 months).

In high-risk individuals, however, the difference in effectiveness between 6 and 12 month regimens may be clinically important.
Isoniazid versus rifampicin

Double-blind placebo-controlled trial (679 men) in silicosis patients in Hong Kong (1981-1987); (most) with TST ≥ 10mm

- 6 months isoniazid
- 3 months rifampicin
- 3 months rifampicin and isoniazid

• Disease reduction of about 50% in treatment groups (5 yrs follow-up), no differences between Rx series.
• Adverse effects were similar in four series.
• Hepatotoxicity less in the placebo and the rifampicin-only group.

Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB (Review)

Sharma SK, Sharma A, Kadhiravan T, Tharyan P

• 10 RCTs; 10,717 people
  • 3-4R vs 6H
  • 3HR vs 6H
  • 2RZ vs 6H
  • 3 INH-RPT weekly-DOT vs 9H
Rifampicin (3 to 4 months) compared to isoniazid (6 to 9 months) for preventing active TB in HIV-negative people

Patient or population: HIV-negative people at risk of TB infection
Intervention: Rifampicin for 3 to 4 months
Comparison: Isoniazid for 6 to 9 months

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>150 per 1000 (70 to 210)</td>
<td>RR 0.81 (0.47 to 1.4)</td>
<td>332 (1 study)</td>
<td>□□□□□ very low^2,3,4,5</td>
</tr>
<tr>
<td>Active TB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up: 5 years</td>
<td>121 per 1000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adherence^6</td>
<td>690 per 1000 (697 to 884)</td>
<td>RR 1.19 (1.01 to 1.3)</td>
<td>1768 (5 studies)</td>
<td>□□□□□ moderate^2,7,8,9</td>
</tr>
<tr>
<td>Treatment-limiting adverse events</td>
<td>93 per 1000 (21 to 93)</td>
<td>RR 0.48 (0.23 to 1)</td>
<td>1674 (4 studies)</td>
<td>□□□□□ very low^10,11,12</td>
</tr>
<tr>
<td>Hepatotoxicity: Grade 3 and 4 toxicity</td>
<td>46 per 1000 (3 to 16)</td>
<td>RR 0.15 (0.07 to 0.4)</td>
<td>1774 (5 studies)</td>
<td>□□□□□ moderate^10</td>
</tr>
</tbody>
</table>
### Ritampicin plus isoniazid (3 months) compared to isoniazid (6 to 9 months) for preventing active TB in HIV-negative people

**Patient or population:** HIV-negative people at risk of TB infection  
**Intervention:** Rifampicin plus isoniazid for 3 months  
**Comparison:** Isoniazid for 6 to 9 months

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>has assumption</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Active TB</strong></td>
<td><strong>INH</strong> 150 per 1000</td>
<td><strong>Rifampicin plus INH</strong> 162 per 1000</td>
<td><strong>RR 1.08</strong> (0.65 to 1.79)</td>
<td><strong>328</strong> (1 study)</td>
</tr>
<tr>
<td><strong>Follow-up: 5 years</strong></td>
<td><strong>(97 to 268)</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>Adherence</strong></td>
<td><strong>INH</strong> 758 per 1000</td>
<td><strong>Rifampicin plus INH</strong> 812 per 1000</td>
<td><strong>RR 1.07</strong> (0.98 to 1.17)</td>
<td><strong>524</strong> (2 studies)</td>
</tr>
<tr>
<td><strong>Treatment-limiting adverse events</strong></td>
<td><strong>INH</strong> 114 per 1000</td>
<td><strong>Rifampicin plus INH</strong> 133 per 1000</td>
<td><strong>RR 1.16</strong> (0.74 to 1.82)</td>
<td><strong>536</strong> (2 studies)</td>
</tr>
<tr>
<td><strong>Hepatotoxicity</strong></td>
<td><strong>INH</strong> 55 per 1000</td>
<td><strong>Rifampicin plus INH</strong> 49 per 1000</td>
<td><strong>RR 0.88</strong> (0.43 to 1.81)</td>
<td><strong>536</strong> (2 studies)</td>
</tr>
</tbody>
</table>
### Rifapentine plus isoniazid weekly for 3 months (12 doses) compared to isoniazid daily for 9 months (270 doses) for preventing active TB in HIV-negative people with LTBI

**Patient or population:** HIV-negative people at risk of TB infection

**Intervention:** Rifapentine (900 mg) plus isoniazid (900 mg) weekly for 3 months (12 doses)

**Comparison:** Isoniazid (300 mg) daily for 9 months (270 doses)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
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<tr>
<td>Isoniazid</td>
<td>4 per 1000 (1 to 4)</td>
<td>RR 0.44 (0.18 to 1.07)</td>
<td>7731 (1 study)</td>
<td>Moderate</td>
<td>2,3,4</td>
</tr>
<tr>
<td>Ritapentine plus isoniazid</td>
<td>2 per 1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active TB</td>
<td>Follow-up: 33 months after enrolment</td>
<td></td>
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</tr>
<tr>
<td>Adherence</td>
<td>690 per 1000 (801 to 842)</td>
<td>RR 1.19 (1.16 to 1.22)</td>
<td>7731 (1 study)</td>
<td>Moderate</td>
<td>5,6</td>
</tr>
<tr>
<td>Treatment-limiting adverse events</td>
<td>37 per 1000 (40 to 61)</td>
<td>RR 1.32 (1.07 to 1.64)</td>
<td>7731 (1 study)</td>
<td>Moderate</td>
<td>7,8,9</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>Follow-up: 5 months to 11 months</td>
<td>RR 0.16 (0.1 to 0.27)</td>
<td>7799 (1 study)</td>
<td>High</td>
<td>7,10</td>
</tr>
<tr>
<td></td>
<td>27 per 1000 (3 to 7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 per 1000</td>
<td></td>
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</tbody>
</table>
Open-label randomized noninferiority trial

- 7/3986 in INH-RPT (0.19%) and 15/3745 in INH-only (0.43%) developed TB.
- 82% completed in INH-RPT and 69% in INH-only group.
- 4.9% discontinued treatment in INH-RPT versus 3.7% in INH (side effects INH-RPT: hypersensitivity; hypotension).
- 0.4% drug-related hepatotoxicity in INH-RPT versus 2.7% in INH-only
HIV-infected persons
12 RCTs; 8,578 people

- Preventive therapy gave a 32% reduction
- For TST-positive the effect was 62%
- No difference in efficacy of different regimens (regardless duration of treatment)
- More discontinuation in short-course chemotherapy compared to INH
New Regimens to Prevent Tuberculosis in Adults with HIV Infection

Neil A. Martinson, M.B., B.Ch., M.P.H., Grace L. Barnes, B.S.N., M.P.H., Lawrence H. Moulton, Ph.D., Reginah Msandiwa, R.N., Harry Hausler, M.D., Ph.D., Malathi Ram, Ph.D., James A. McIntyre, M.B., B.Ch., Glenda E. Gray, M.B., B.Ch., and Richard E. Chaisson, M.D.

- Open-label randomized trial. Inclusion: HIV-positive with CD4 > 200 without antiretroviral therapy (1148 persons)
  - Rifapentine 900 mg + INH 900 mg weekly, 12 weeks
  - Rifampicine 600 mg + INH 900 mg twice weekly, 12 weeks
  - INH 300 mg daily for the duration of the study (6 yrs)
  - Control: INH 300 mg daily for 6 months

- All regimens effective, none was superior to 6 INH.
- Serious adverse effects more common in continuous INH group.
To evaluate relative efficacies and adverse events.

Method: Network meta-analysis (Bayesian hierarchical models) allows indirect comparison between different treatment regimens, so-called Mixed-treatment comparisons (MTCs).
Stagg et al. Treatment LTBI, Annals

- 53 RCTs met inclusion criteria
  - All 31 RCTs in the Cochrane Reviews of Smieja, Sharma and Akolo were included.
  - 15 regimens were included in the network
  - 45 with extractable data on progression to active TB
  - 25 with extractable data on hepatotoxicity
Figure 2. Comparison of odds ratios for active tuberculosis obtained from random-effects pairwise meta-analysis, with a corresponding estimate from the mixed treatment comparison model.
Table 5. Summary of evidence to support recommendations
(data taken only from published randomized trials)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration</th>
<th>Completion</th>
<th>Adverse events</th>
<th>Efficacy*</th>
</tr>
</thead>
</table>
| INH (Daily)                  | 12 months | 68%\textsuperscript{63}  
69%\textsuperscript{64}  
85%\textsuperscript{66}  
6%\textsuperscript{65}  
5.2%\textsuperscript{53}  
6.1%\textsuperscript{54}  | 67%\textsuperscript{65}  
93%\textsuperscript{63}  |
|                              | 9 months  | 57%\textsuperscript{67}  
60%\textsuperscript{68}  
62%\textsuperscript{63}  
69%\textsuperscript{69}  
86%\textsuperscript{70}  | 0\textsuperscript{170}  
3.7%\textsuperscript{69}  
4.0%\textsuperscript{68}  | 90%\textsuperscript{71}  |
|                              | 6 months  | 63%\textsuperscript{61}  
65%\textsuperscript{72}  
73%\textsuperscript{13}  
75%\textsuperscript{73}  
78%\textsuperscript{63}  
84%\textsuperscript{74}  | 0.6%\textsuperscript{73}  
1.9%\textsuperscript{74}  
2.8%\textsuperscript{61}  
3.6%\textsuperscript{63}  
7%\textsuperscript{72}  
8%\textsuperscript{13}  | 67%\textsuperscript{63}  
68%\textsuperscript{73}  |
| INH (Twice weekly)           | 6 months  | 55%\textsuperscript{175}  
72%\textsuperscript{76}  | 0\textsuperscript{75}  
3%\textsuperscript{76}  | Eq2RMP/PZA\textsuperscript{75}  
40%\textsuperscript{76}  |
| RMP (Daily)                  | 4 months  | 76%\textsuperscript{13}  
80%\textsuperscript{68}  
86%\textsuperscript{77}  | 0\textsuperscript{13}  
1.5%\textsuperscript{68}  | 63%\textsuperscript{13}  |
| INH/RMP (Daily or twice weekly) | 3 months  | 63%\textsuperscript{67}  
69%\textsuperscript{72}  
75%\textsuperscript{73}  
76%\textsuperscript{13}  
95%\textsuperscript{174}  
97%\textsuperscript{78}  | 0\textsuperscript{170}  
2.3%\textsuperscript{73}  
3.8%\textsuperscript{74}  
5%\textsuperscript{13}  
7%\textsuperscript{78}  
10%\textsuperscript{67}  
18%\textsuperscript{72}  | 64%\textsuperscript{73}  
Eq6INH\textsuperscript{13,72,74}  
Eq9INH\textsuperscript{67}  
Eq12INH\textsuperscript{76}  |
| INH/RPT** (Once weekly)      | 3 months  | 82%\textsuperscript{169}  
95%\textsuperscript{179}  
96%\textsuperscript{174}  | 1.0%\textsuperscript{79}  
1.8%\textsuperscript{74}  
4.9%\textsuperscript{69}  | Eq 2RMP/PZA\textsuperscript{79}  
Eq 6INH\textsuperscript{74}  
Eq 9INH\textsuperscript{69}  |

From Canadian TB Standards, 2014.
### Guidelines

#### The Netherlands
- 6H
- 3HR
- HIV/TNF-α
- 9H
- 4HR

#### CDC, USA
- 9H
- 6H
- 3INH-RPT
- 4R
- HIV
- 9H

#### Canada
- 9H
- 6H
- 3-4HR
- (4R)
- (3INH-RPT)

#### UK
- 6H
- 3HR
The following treatment options are recommended for the treatment of latent TB infection:

- 6 months isoniazid (6H)
- 9 months isoniazid (9H)
- 3 months regimen of weekly rifapentine plus isoniazid (3HP)
- 3 to 4 months isoniazid plus rifampicin (3-4HR)
- 3 to 4 months rifampicin alone (3-4R)

(Strong recommendation, moderate to high quality of evidence)

With permission of Alberto Matteelli, Global TB Programme, WHO, Geneva to share this information.
Rifapentine availability
(email Isabelle Cieren-Puiseux, Sanofi, with permission to share)

Rifapentine (Priftin™) is registered and marketed in the USA since 1999 for active DS TB but the approved regimen seems to be not optimal and new regimen (daily and higher rifapentine dose) will be studied in the very near future.

With regards to latent TB indication, following S26 study results (Sterling, New Engl J of Med, 2011), Sanofi has decided to apply for a supplemental New Drug Application (NDA). The e submission has been done on May 30, 2014 and the claimed indication is Treatment of LTBI in combination with INH (3RPT/INH once-weekly regimen) in patients > 2 years at high risk of progression to TB disease. FDA agreed for a priority review and the user fee goal date is November 30, 2014.

Concomitantly some countries have shown a great interest in the new regimen and express their willingness to have it in their local guidelines and to have Rifapentine registered locally; some clinical studies are in progress in UK, Taiwan, Australia. Moreover Sanofi plans to register the product outside USA.

We are in the process of regulatory assessment for a submission as outside USA Rifapentine is considered as a new chemical entity meaning that a whole Common Technical Document (CTD) dossier is to be submitted in addition to the clinical part recently submitted to the FDA.

This means that the initial dossier (built in the 80) need to be electronically built and updated in order to be in accordance with state of the art rules. For Europe we are currently assessing work to be done in order to define future timelines.

Reviews
Treatment of Latent TB infection
