TB Prevention: Let’s Move Beyond Only Using INH for Prevention

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PITCA, September 13, 2017
Disclosures

• I will be presenting on investigational or off-label use of rifabutin for LTBI treatment.
Objectives

• Identify three treatment regimens for tuberculosis infection.

• Identify common side effects and monitoring with rifampin in order to improve patient outcomes.

• Identify common drug-drug interactions with rifampin in order to improve patient safety.
Span of TB Control Activities in San Francisco 2014- update for PI or delete

- 114 San Franciscans with TB Disease
- Over 400 TB suspect cases
- 1,100 Contacts to TB Cases
- 78,000 San Franciscans with TB Infection
- 850,000 San Franciscans

TB Control

TB Elimination
How far are we from elimination?- update for PI or delete

<table>
<thead>
<tr>
<th>TB elimination: &lt;1 case per million</th>
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<tbody>
<tr>
<td><strong>United States, 2013</strong></td>
</tr>
<tr>
<td>30 cases per million (all)</td>
</tr>
<tr>
<td>12 cases per million (U.S. born)</td>
</tr>
<tr>
<td>156 cases per million (foreign-born)</td>
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</tbody>
</table>

| **San Francisco, 2013**            |
| 1360 cases per million (all)       |
| 23 cases per million (U.S. born)   |
| 3510 cases per million (foreign-born) |

[www.cdc.gov](http://www.cdc.gov), Reported Tuberculosis in the United States, 2013
Incidence Projections to 2060 - simplify slide

- Cut in transmission
- Increase LTBI treatment, 2x or 4x more

Reduce FB arrivals with LTBI by 50%
Reduce FB arrivals with LTBI by 75%

Hill et al., Epidemiol Infect, 2012
INH + Rifapentine (3HP)

- INH + Rifapentine, Qweek x 12 weeks
- Recommended as an equal alternative to INH x 9 mo in healthy patients ≥12 yo and HIV-infected patients not on ART.
- Not recommended in the following:
  - Children <2yo
  - HIV-infected patients on any ART
  - Pregnant or planning to become pregnant
  - Contact to INH/RIF resistant cases
  - Prior adverse events / hypersensitivity to INH/RIF

Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection. MMWR 2011;60:1650–1653
## Dosing- 3HP

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>15 mg/kg rounded to nearest 50/100 mg in patients ≥ 12 years</td>
<td>900 mg</td>
</tr>
<tr>
<td></td>
<td>25 mg/kg rounded to the nearest 50/100 mg in patients 2-11 years</td>
<td></td>
</tr>
<tr>
<td>Rifapentine</td>
<td>10.0 – 14.0 kg = 300 mg</td>
<td>900 mg</td>
</tr>
<tr>
<td></td>
<td>14.1 – 25.0 kg = 450 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25.1 – 32.0 kg = 600 mg</td>
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<tr>
<td></td>
<td>32.1 – 49.9 kg = 750 mg</td>
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</tbody>
</table>

Rifapentine tablets can be crushed and administered with semi-solid food for children unable to swallow pills

DOT- 3HP

• Current CDC recommendations: DOT for 3HP

• Recent CDC-sponsored study (TBTC Study 33, data still to be published) suggests self-administered treatment (SAT) is non-inferior to DOT in the US

• Study design for SAT: some pts received SMS reminders, not all doses were SAT (first dose and monthly visits were witnessed when able), only 4 SAT doses were dispensed at a time
Side effects - 3HP

- Possible hypersensitivity (3.8%)
- Rash (0.8%)
- Hepatotoxicity (0.4%)
- Thrombocytopenia (rare)
- Other toxicities (3.2%)

- Monitoring - similar to INH or RIF
- RFP drug-drug interactions similar to RIF

### Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

<table>
<thead>
<tr>
<th></th>
<th>INH-RPT</th>
<th>INH</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>3,986</td>
<td>3,745</td>
</tr>
<tr>
<td>Administration</td>
<td>Directly-observed therapy</td>
<td>Self-administered therapy</td>
</tr>
<tr>
<td>Frequency</td>
<td>Weekly</td>
<td>Daily</td>
</tr>
<tr>
<td>Duration</td>
<td>12 weeks</td>
<td>9 months</td>
</tr>
</tbody>
</table>

## Prevent TB Study Results

<table>
<thead>
<tr>
<th></th>
<th>INH-RPT</th>
<th>INH</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effectiveness</strong></td>
<td>1.9 per 1,000</td>
<td>4.3 per 1,000</td>
<td>Non-inferior</td>
</tr>
<tr>
<td><strong>Completion rate</strong></td>
<td>82.1%</td>
<td>69.0%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td><strong>Hepatotoxicity</strong></td>
<td>0.4%</td>
<td>2.7%</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Which of the following are reasons to choose rifampin for LTBI treatment in a patient?

A. Exposure to INH-resistant TB
B. Allergy to INH
C. INH-induced hepatotoxicity
D. RIF more effective than INH
E. All of the above
F. A, B, and C only
Current recommendations

• Consider 4 month regimen of RIF (4R) in*:
  • Patients with INH intolerance
  • Contacts to INH-resistant TB
  * 6 months for pediatrics

• Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. MMWR 2000; 49 (No. RR-6)
Monitoring

ATS/CDC LTBI guidelines, 2000

• Routine baseline / follow-up laboratory testing
  ➔ Not needed

• Except for:
  • HIV infection
  • Pregnancy / Early postpartum (<3mo)
  • History of liver disease / hepatitis
  • Regular EtOH use
Also consider for: Statin/other hepatotoxic meds, age >50
Which one of these is NOT a common side effect of Rifampin?

A. Orange discoloration of urine
B. Rash
C. Gout
D. Elevated bilirubin
Adverse Effects

• Hepatotoxicity
  • Rare severe hepatitis, more common when combined with other medications
• Asymptomatic hyperbilirubinemia (0.6%)
• Dermatologic: Pruritis, rash (up to 6%)
• Hypersensitivity reaction (0.07-0.3%)
• GI: nausea, anorexia, abdominal pain
• Immune-mediated: thrombocytopenia, TTP, hemolytic anemia (<0.1%)
• Orange discoloration of body fluids
Monitoring

Evaluate **monthly** for:

• Adherence

• Symptoms of hepatitis or other side effects
  • Anorexia, nausea, vomiting, or abdominal pain in right upper quadrant
  • Fatigue or weakness
  • Dark urine
  • Rash
  • Persistent numbness in hands or feet
Management of side effects: Drug-induced liver injury

- Review hepatotoxic meds (tylenol, statins, etc), ETOH use, prior hepatitis risk/screen
- HOLD Treatment if:
  - AST/ALT > 3 times the upper limit of normal + symptoms of hepatotoxicity
  - AST/ALT > 5 times the upper limit of normal + asymptomatic
- If less than parameters above, continue treatment with plan to repeat labs in 1-4 weeks.
- Depending on above, consider alternate therapy with close LFT monitoring.
Management of Side Effects: Derm

- Fixed drug eruption
- Rash, itching (1-5%, RIF)
- Pemphigoid reaction
- DRESS
- Anaphylaxis, urticaria

- **Mild**: anti-histamine, topical steroids, f/u visit
- **Mild-moderate**: hold meds and above, consider re-challenge once resolves
- **Mod-severe**: hold meds and above, emergency care / derm consult as needed. Consider alternate therapy once resolves
ARS: 65 yo HIV+ M with HTN, diabetes, hypothyroidism. Which of these diseases may have treatments with rifampin drug-drug interactions?

A. HTN
B. Diabetes
C. Hypothyroidism
D. HIV
E. All of the above
Drug-Drug Interactions

Requires re-dosing or alternate:
- Coumadin
- Opioids (e.g. Methadone)
- Antiretrovirals
- OCP’s
- Proton-pump Inhibitor
- Chemotherapy
  - Cyclosporine
  - Tacrolimus
  - Tamoxifen

Monitor and titrate:
- Endo:
  - Levothyroxine
  - Corticosteroids
  - sulfonylureas
- CNS
  - Benzodiazepines
  - Phenytoin, lamotrigine
  - SSRI
- Cardiac
  - Statins
  - Anti-HTN: b-blocker, ACE-I, ARB, Ca-channel blockers
Rifamycin: Drug-drug Interaction

• Rifabutin is a less potent potent inducer of CYP3A4 than rifampin. Thus, can be considered in certain cases with close monitoring (methadone, anti-coagulation, anti-retrovirals)

Resources:
• Lexicomp / Micromedex Drug Interaction Look-up
Do you use rifampin for LTBI treatment in your practice/program?

A. Yes
B. Yes, but we only use it in combo (RIF+INH) or in cases of INH resistance/intolerance
C. No
D. I don’t know
## Pros / Cons Rifampin

<table>
<thead>
<tr>
<th>Potential Benefit</th>
<th>Potential Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shorter duration</td>
<td>Development of resistance</td>
</tr>
<tr>
<td>Decreased hepatotoxicity</td>
<td>Increased immune phenomenon (anemia, rash)</td>
</tr>
<tr>
<td>Cost</td>
<td>Cost</td>
</tr>
<tr>
<td></td>
<td>Efficacy data limited</td>
</tr>
</tbody>
</table>
Need for more data

• Cost
• Efficacy
• Adherence
• Adverse events
• Development of resistance
• HIV
• Pediatrics
Efficacy of 3R in silicosis

- RCT, n= 679
- Silicosis, PPD+
  - PI- placebo
  - HR3- INH/RIF x 3 mo
  - H6- INH x 6 mo
  - R3- RIF x 3 mo

- Active pulmonary TB more frequent in placebo vs chemoprophylaxis groups (p<0.01)
- No significant difference between 3 chemoprophylaxis regimens

Efficacy of 3R in silicosis

- Limitations- regimens self-administered
- Serum ALT significantly higher in H6 and HR3 compared to R3 (p<0.001)
- Similar freq adverse effects in all 4 groups
- No evidence of development of drug resistance


Normal ALT <28 IU/L)
Epidemic of INH/SM-resistance in Boston’s homeless, 1984
204 TST converters eligible for LTBI treatment
Mean follow-up periods ranged from 23.5-31.2 months for the 4 groups
3 cases of active in INH group were INH-resistant

Efficacy: Phase 3 RCT

- Multi-center Phase 3 RCT: 4R vs 9H
- Results expected in 2017
- Study sites: Canada, Australia, Benin, Brazil, Ghana, Guinea, Indonesia, Korea, Saudi Arabia

Objectives:
- Effectiveness- incidence of confirmed active TB within 28 months post-randomization
- Efficacy- incidence of confirmed active TB in those who took at least 80% of doses within allowed time
- Serious adverse events

Menzies, D. 4 Months of Rifampin for the Treatment of LTBI. As presented at National TB Controller’s Association Conference, Atlanta, GA, June 11, 2014
Cost-effectiveness

- Costs estimated based on open-label RCT (visits, labs, meds)

- If 4R efficacy > 74%: 4R would be cheaper and would prevent more cases than INH

- If 4R efficacy > 65%: 4R would be cheaper than INH

Cost-effectiveness

• Computerized model: 4R could be up to 17% less efficacious than INH and still be cost saving and more effective (Holland, et al)

• Decision-analysis model from multicenter RCT: if 4R efficacy ≥ 69%, then 4R is more cheap and effective compared to INH (Esfahani, et al)

<table>
<thead>
<tr>
<th>Study design</th>
<th>Treatment Completion: RIF vs INH</th>
<th>Adverse events: RIF vs INH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lardizabal, et al, 2006 Retrospective New Jersey N=474</td>
<td>80.5 vs 53.1 % (p&lt;0.0001)</td>
<td>3.1% vs 5.8 % (p&gt;0.05)</td>
</tr>
<tr>
<td>Page, et al, 2006 Retrospective Maryland N=2255</td>
<td>71.6 vs 52.6% (p&lt;0.001)</td>
<td>Adverse events: 1.9 vs 4.6% (p&lt;0.001) Hepatotoxicity: 0.08 vs 1.8% (p&lt;0.001)</td>
</tr>
<tr>
<td>Menzies, et al, 2008 Randomized, open-label, multicenter (Canada, Saudi Arabia, Brazil) N=847</td>
<td>78 vs 60% (CI 12-24%, p&lt;0.001)</td>
<td>Grade 3/4 hepatitis: 0.7 vs 3.8% (p=0.03) Decreased platelet/WBC: RIF&gt;INH</td>
</tr>
<tr>
<td>Fresard, et al, 2011 Retrospective Switzerland N=624</td>
<td>83 vs 74% (p=0.02)</td>
<td>Hepatotoxicity: 2.0 vs 6.1% (p=0.03)</td>
</tr>
</tbody>
</table>
Hepatotoxicity: Favors RIF > INH

Adherence: Favors RIF > INH

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Rifampicin</th>
<th>INH</th>
<th>Risk Ratio</th>
<th>M.H. Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>1.3.1 Rifampicin 3 to 4 months versus INH 6 to 9 months (in adults with silicosis or LTBI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chan 2012 (1)</td>
<td>163</td>
<td>160</td>
<td>142</td>
<td>133</td>
</tr>
<tr>
<td>HKCS 1992</td>
<td>142</td>
<td>165</td>
<td>123</td>
<td>167</td>
</tr>
<tr>
<td>Menzies 2004</td>
<td>53</td>
<td>58</td>
<td>44</td>
<td>55</td>
</tr>
<tr>
<td>Menzies 2008</td>
<td>328</td>
<td>420</td>
<td>255</td>
<td>427</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>833</td>
<td>835</td>
<td>80.8%</td>
<td>1.19 [1.10, 1.30]</td>
</tr>
<tr>
<td>Total events</td>
<td>686</td>
<td>564</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 6.63, df = 3 (P = 0.08); I² = 55%</td>
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<td></td>
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<tr>
<td>Test for overall effect: Z = 4.20 (P &lt; 0.0001)</td>
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</tbody>
</table>

1.3.2 Rifampicin 4 months versus INH 6 months (in children)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Rifampicin</th>
<th>INH</th>
<th>Risk Ratio</th>
<th>M.H. Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Magdoff 1994</td>
<td>43</td>
<td>50</td>
<td>47</td>
<td>50</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>50</td>
<td>50</td>
<td>19.2%</td>
<td>0.91 [0.80, 1.04]</td>
</tr>
<tr>
<td>Total events</td>
<td>43</td>
<td>47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.32 (P = 0.19)</td>
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</tbody>
</table>

| (1) Treatment of prisoners in this trial was by direct observation (except when on parole) |

Sharma SK, et al. Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB. Cochrane Database Syst Rev. 2013 Jul5;7:CD007545.
Summary

• Compared to INH, rifampin appears to:
  • Be cost-effective
  • Have higher rates of treatment completion
  • Reduced rates of hepatotoxicity / adverse events

• Additional data is needed on:
  • Efficacy
  • Development/risk of resistance
  • Use in special populations (pediatrics, HIV, immunocompromised, etc)

• Results of Phase 3 clinical trial is upcoming
Treatment Completion / Adverse Events References


• Fresard I, Bridevaux PO, Rochat T, Janssens JP. Adverse effects and adherence to treatment of rifampicin 4 months vs isoniazid 6 months for latent tuberculosis: a retrospective analysis. Swiss Med Wkly. 2011 Aug 15;141:w13240.