Treatment of Latent TB Infection and BCG Vaccination

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Denver Metro Tuberculosis Control Program
Denver Public Health Department
Objectives

- Understand advantages/disadvantages of current treatment options for latent TB infection (LTBI)
- Understand efficacy of BCG vaccination & potential complications
Tuberculosis Screening

At-risk person

TST/IGRA + symptom review

Negative

Treatment not indicated

Positive

Chest x-ray

Normal

Potential candidate for LTBI treatment

Abnormal

Evaluate for active TB
26 yo woman refugee from Southeast Asia. Her IGRA is positive & chest radiograph is normal. What LTBI treatment would you select?

1. 6 months daily isoniazid
2. 9 months daily isoniazid
3. 4 months daily rifampin
4. 12 weekly doses of isoniazid/rifapentine
5. It depends – we need more information!
LTBI Treatment
Key considerations

✓ Efficacy
  - Ability to prevent disease among individuals adhering to medication

✓ Effectiveness (adherence)
  - Ability to prevent disease when used in public health practice

✓ Drug interactions & adverse events

✓ Monitoring requirements, cost, availability
## INH
The historical standard

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<td>9 months</td>
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<td>5mg/kg (300mg)</td>
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a Directly observed
## INH

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*a* Directly observed
INH
Bethel district Alaska

- RTC in 1957-1959
  - 1 year INH versus placebo
  - 69% reduction in TB
- Community-wide prophylaxis began in 1963
- 12-months INH recommended for LTBI treatment in 1970

INH

9 months or 6 months?

• IUAT trial
  – 28,000 adults with fibrotic pulmonary lesions followed 5y

IUAT Bull WHO 1982; 60:555
**INH**

9 months or 6 months?

- IUAT trial
  - 28,000 adults with fibrotic pulmonary lesions followed 5y

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<td>3 months INH</td>
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## INH

### 9 months or 6 months?

- **IUAT trial**
  - 28,000 adults with fibrotic pulmonary lesions followed 5y

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<td></td>
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* Not significantly different
**INH**

9 months or 6 months?

- IUAT trial
  - 28,000 adults with fibrotic pulmonary lesions followed 5y

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<td>21%</td>
<td>31%</td>
</tr>
<tr>
<td>6 months INH</td>
<td>65% *</td>
<td>69%</td>
</tr>
<tr>
<td>12 months INH</td>
<td>75% *</td>
<td>93%</td>
</tr>
</tbody>
</table>

* Not significantly different
9 months or 6 months?

- Lower TB rates among those who took 0-9 mo
- No significant increase among those who took >9 mo

Comstock Int J Tuberc Lung Dis. 1999 3; 10:847
Our refugee begins isoniazid...
She likely does not need laboratory monitoring

- Check baseline labs if:
  - HIV-infected
  - History of liver disease
  - Regular alcohol use
  - Pregnant or post-partum
  - H/o injection drug use
  - On liver-toxic medications

- Labs during follow-up only if baseline labs elevated or symptomatic
Our refugee begins isoniazid…
She needs clinical monitoring

• Monthly visits include
  – Education regarding purpose of treatment
  – Assessment of adherence
  – Education regarding drug-related symptoms
    ▪ Fever
    ▪ Headache
    ▪ Rash
    ▪ Nausea, RUQ pain
    ▪ Dark urine
    ▪ Numbness
One month later, another provider checked an ALT which was 105 (upper limit of normal = 45). She feels fine. Which of the following is not indicated?

1. Consider other causes of elevated ALT
2. Continue isoniazid – recheck ALT at intervals
3. Discontinue isoniazid immediately
Isoniazid
A spectrum of liver inflammation
Isoniazid
A spectrum of liver inflammation

“Adaptation” seen in 10-20%

- Increase in ALT
  - <3 x ULN with symptoms
  - <5 x ULN without symptoms
- Not an indicating for stopping Rx
- Generally normalizes despite continued Rx
Isoniazid
A spectrum of liver inflammation

Mild-moderate hepatocellular injury

- Increase in ALT
  - 3-10 x ULN with symptoms
  - 5-10 x ULN without symptoms
- Stop treatment – follow at weekly intervals
- 0.2% in patients <35 y/o; 1.8% in patients ≥ 35 y/o

Isoniazid
A spectrum of liver inflammation

- >10 x ULN ALT
- ↑ bilirubin, ↑ INR
- Hospitalize, monitor for fulminant hepatic failure

Severe hepatocellular injury
INH hepatotoxicity
CDC surveillance for severe hepatitis

• 17 persons treated for LTBI with INH during 2004-2008
  • All monitored according to guidelines
  • 5 transplants; 5 deaths
  • Among 15 adults, age ranged from 19-64
  • Symptom onset 1-7 months after initiating INH
  • 80% continued taking INH for more than a week after symptom onset

INH adverse events
Neuropathy

• Neurologic - interference in vitamin $B_6$ absorption
  – Higher risk in DM, renal insufficiency, alcoholism, malnutrition, HIV, pregnancy, seizure disorders
INH
“one of the preferred regimens”

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<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large body of evidence</td>
<td>Intermittent regimens must be directly observed</td>
</tr>
<tr>
<td>Regimen of choice for children aged 2-11 years</td>
<td>Adherence is poor</td>
</tr>
<tr>
<td>Efficacy shown in HIV + and -</td>
<td></td>
</tr>
<tr>
<td>Intermittent regimens useful for DOPT in high-risk children</td>
<td></td>
</tr>
</tbody>
</table>
## Self-administered rifampin

### A shorter option

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<th>Dose</th>
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<th>Time limit</th>
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</thead>
<tbody>
<tr>
<td>4 months</td>
<td>Daily</td>
<td>10 mg/kg (600mg)</td>
<td>120</td>
<td>Within 6 months</td>
</tr>
</tbody>
</table>

Self-administered rifampin
Efficacy for LTBI

• 679 patients with silicosis & LTBI in Hong Kong
• Randomized to:
  – Placebo - 27% developed TB within 5 years!
  – 6 months INH
  – 3 months INH/RIF
  – 3 months RIF
Self-administered rifampin
Efficacy for LTBI

H = isoniazid
R = rifampin
Pl = placebo

63% protection relative to placebo

Hong Kong Chest Service  Am Rev Resp Dis 1992;145:36
Self-administered rifampin Adherence & adverse events

- 847 adults with LTBI in Canada, Brazil & Saudi Arabia
- Randomized to:
  - 4 months RIF
  - 9 months INH
- Not designed to evaluate efficacy in preventing TB
Self-administered rifampin
Better adherence than INH

Menzies D, Ann Intern Med 2008; 149:689
Self-administered rifampin
Better tolerated than INH

<table>
<thead>
<tr>
<th></th>
<th>Rifampin 420 patients</th>
<th>INH 424 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>3.8%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Grade 3-4 Hepatotoxicity</td>
<td>0.7%</td>
<td>3.8%</td>
</tr>
</tbody>
</table>

Menzies D, Ann Intern Med 2008; 149:689
Self-administered rifampin

Adverse events

- Thrombocytopenia
- Hypersensitivity
Self-administered rifampin

Drug interactions

- Hormonal anti-contraceptives
- warfarin
- Thyroid hormone
- Anti-seizure agents
- Antihypertensives
- Antipsychotics
- Plus many more…
Self-administered rifampin

“An acceptable alternative”

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<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
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<tbody>
<tr>
<td>Better adherence</td>
<td>Evidence for efficacy less robust than for INH</td>
</tr>
<tr>
<td>No DOT required</td>
<td>Better tolerated than INH</td>
</tr>
<tr>
<td>Efficacy shown in HIV +/−</td>
<td>“An acceptable alternative”</td>
</tr>
</tbody>
</table>

Decision analysis: Even if 17% less efficacious RIF would be cheaper and more effective than INH
## Directly-observed INH/Rifapentine

### State of the art

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<th>Time limit</th>
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<tbody>
<tr>
<td>3 months</td>
<td>Once weekly</td>
<td>INH: 15 mg/kg (900mg)</td>
<td>12</td>
<td>Within 4 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Rifapentine</strong> 900mg for adults &gt;50kg</td>
<td></td>
<td></td>
</tr>
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Directly-observed INH/Rifapentine Study 26 - Prevent TB

• High risk LTBI in US, Canada, Brazil & Spain
• Randomized to:
  – 9 months daily self-administered INH (9H)
  – 12 weekly doses INH/Rifapentine (3HP)
• Outcome: TB over 33 months f/u
• A non-inferiority trial
Directly-observed INH/Rifapentine Study 26

- Screened: 11,637
- Randomized: 8,053
  - 9H: 3,908
    - Completed: 2,585 (69%)
      - Eligible for MITT analysis: 3,745
        - 15 TB cases
  - 3HP: N=4,145
    - Completed: 3,273 (82%)
      - Eligible for MITT analysis: 3,986
        - 7 TB cases
## Directly-observed INH/Rifapentine Study 26

<table>
<thead>
<tr>
<th></th>
<th>INH</th>
<th>Rifapentine INH</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Permanent discontinuation due</td>
<td>3.7%</td>
<td>4.6%</td>
<td>0.009</td>
</tr>
<tr>
<td>to drug toxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade III-IV events</td>
<td>3.0%</td>
<td>1.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>2.7%</td>
<td>0.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Possible hypersensitivity</td>
<td>0.5%</td>
<td>3.8%</td>
<td>&lt;0.001</td>
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Sterling NEJM 2011;365:2155
Systemic drug reactions with 3HP

- Flu-like syndrome
  - Fever, chills, fatigue, malaise, headache, myalgia, arthralgia
- Associated with being female, lower BMI, white
- Not a classic hypersensitivity reaction
- ~50% rechallenged without severe reactions
Directly-observed INH/Rifapentine
As effective as INH
Directly-observed INH/Rifapentine in children 2-12 y/o

- Efficacy equivalent to 9 months INH
- Higher completion rate
- Well tolerated

Directly-observed INH/Rifapentine In HIV infection with ARVs

- Efficacy equivalent to 9 months INH
- Higher completion rate
- Well tolerated
Self-administered INH/Rifapentine? iAdhere study

• Adherence trial with three arms:
  1. DOT
  2. SAT
  3. eSAT (with weekly text reminders)

• USA (75%), Spain, Hong Kong, South Africa

• Outcome: completion
  – Measured by self-report, pill count, MEMS

• 15% non-inferiority margin
## iAdhere results

<table>
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<tr>
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# iAdhere results

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<tr>
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<td>86.9%</td>
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<td>75.4%</td>
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- Overall
  - Non-inferiority not established for SAT or eSAT
- In US
  - iAdhere supports use of INH/rifapentine via SAT
Directly-observed INH/Rifapentine
“An equal alternative to INH”

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<tr>
<td>Well tolerated</td>
<td>Not for pregnant women</td>
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<td>Not for HIV + on ARVs</td>
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### Summary Efficacy & Completion

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<th>Regimen</th>
<th>Efficacy</th>
<th>Mean completion</th>
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<td>9 months INH</td>
<td>90-92%</td>
<td>53%</td>
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<tr>
<td>6 months INH</td>
<td>41-76%</td>
<td>49-79%</td>
</tr>
<tr>
<td>4 months Rifampin</td>
<td>Unknown</td>
<td>72%</td>
</tr>
<tr>
<td>3 months INH - Rifapentine</td>
<td>As good as 9 months INH!</td>
<td>High with DOT</td>
</tr>
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Adapted from Landry Int J Tubercl Lung Dis 2008; 12:1352
Special Situations
HIV-Infection in **high-resource** countries

- INH daily for 9-mo is optimal
- Rifampin interacts with many antiretrovirals
- Consult an expert
Special Situations
HIV-Infection in low-resource countries

- Cochrane Review of 12 trials with 8,578 subjects
- 32% reduction in TB risk with LTBI treatment
  - Benefit was only in TST positive patients
    - 62% reduction in among TST positive patients
    - No significant benefit among TST negative patients
- IPT does not increase risk of INH resistance

Akolo Treatment of latent tuberculosis infection in HIV infected persons
Cochrane Database Syst Rev 2010; 20
Special Situations
HIV-Infection in low-resource countries

- WHO strongly recommends at least 6 months of INH preventive therapy (IPT)
  - If no cough, fever, weight loss or sweats
  - TST and CXR not required
- Up to 36 months INH in high incidence settings with high transmission risk
- <2% of HIV-infected persons worldwide receive IPT

Harries Lancet 2010; 375:1906
Special Situations
Contact to MDR-TB

- No standard regimen
- Contact MDR-TB expert
- Follow for 2 years
Special Situations
Pregnancy and breastfeeding

- Pregnancy does not increase TB risk
- INH and Rifampin
  - Safe in pregnancy, no contraindication to breastfeeding
  - Higher hepatitis risk postpartum
Special Situations
Children

- INH x 9 months is regimen of choice
  - Intermittent regimens used for DOPT
- RIF if INH intolerant or exposed to INH resistance
  - 6 months recommended (scant evidence)
- INH-rifapentine may be considered if ≥ 2 years old
Special Situations
TNF-α antagonists

• Treat if
  – TST ≥ 5mm  --- or ---
  – Positive IGRA  --- or ---
  – Epidemiologic risk [even if TST and IGRA are negative]

• Initiate TNF--α inhibitor after one months of LTBI treatment
  – Based on expert opinion
BCG Vaccination
BCG Vaccines
Historical Perspective

• Bacillus of Calmette and Guerin
• Live attenuated *M. bovis* strain
  – Derived by serial passage (231 times during 1906-1919) until less virulent in animals
• First given to human in 1921
• Subsequently sub-cultured and distributed worldwide
  – >3 billion doses administered
BCG Vaccination
Cutaneous reactions

- Papule at 2-3 weeks
- Ulceration at 6-8 weeks
- Scar by 3 months
BCG Vaccines
High efficacy in children

- TB meningitis in children
  - 73% effective (95% CI: 67-79%)
- Miliary TB in children
  - 77% (95% CI: 58-87%)

Trunz Lancet 2006; 367:1173
BCG Vaccine Efficacy
Variable efficacy for adult pulmonary TB

Study Location
England
Native Americans
Chicago
Haiti
Puerto Rico
Mandanapalle, India
Georgia
Chingleput, India
Georgia
Illinois
England
Cameroon
Argentina
Indonesia
Papua New Guinea
Kenya
Colombia
Karonga, Malawi
BCG Vaccines
Why the Differences in Efficacy?

• A collection of different vaccines
  – Diversity of strains producing different antigens

• Geographic difference in NTM exposures
  – Exposure to environmental NTM may protect against TB
    --- or alternatively ---
  – Pre-existing immunity to NTM may interfere with BCG vaccine viability, reducing immune response

Behr MA Lancet Infect Dis 2002; 2: 86–92
BCG Vaccines
Why the Differences in Efficacy?

• Methodological flaws
• Differences between *M. tuberculosis* strains
• Differences between human populations
  – Genetics, environment, nutrition
BCG Vaccinations
Contraindications

- Immunosuppression
- Pregnant Women
http://www.bcgatlas.org/

157 of 180 countries surveyed recommend universal BCG vaccination
Thanks!