Goals of TB Treatment

- Reduce further morbidity and prevent mortality
  - Get better as quickly as possible
- Reduce contagiousness
  - Reduce bacillary load quickly
- Prevent emergence of drug resistance
- Prevent relapse (long term cure)
Features of current standard therapy

• Initial intensive phase
  – Two months duration
  – Four drugs; HRZE
• Continuation phase
  – Four months duration
  – Two drugs: HR
• Fully ambulatory and intermittent

Initial intensive phase - early bactericidal activity

Reduction in bacillae in first 2 days of treatment

Drugs Given (in-vitro)

Log reduction in bacilli

INH EMB RIF STREP PZA SHRZ
## Duration of Rifampin and Relapse

<table>
<thead>
<tr>
<th>Rifampin duration</th>
<th>Arms (N)</th>
<th>Pooled event rate</th>
<th>95% Conf Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Rifampin</td>
<td>43</td>
<td>11.8%</td>
<td>8.8 – 15</td>
</tr>
<tr>
<td>1-2 months</td>
<td>66</td>
<td>11.6%</td>
<td>8.9 – 14</td>
</tr>
<tr>
<td>3-5 months</td>
<td>22</td>
<td><strong>6.2%</strong></td>
<td>4.2 – 8.2</td>
</tr>
<tr>
<td>6-7 months</td>
<td>131</td>
<td>5.5%</td>
<td>4.8 – 6.3</td>
</tr>
<tr>
<td>8+ months</td>
<td>25</td>
<td>1.1%</td>
<td>0.3 – 1.9</td>
</tr>
</tbody>
</table>

## Duration of Rifampin and Treatment outcomes

(from multivariate meta-regression)

<table>
<thead>
<tr>
<th>Duration of RIF</th>
<th>Failure IRR (95% CI)</th>
<th>Relapse IRR (95% CI)</th>
<th>Acquired drug resistance IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Months</td>
<td>2.2 (0.7 – 7.2)</td>
<td><strong>18.6 (7.4 – 47)</strong></td>
<td>7.9 (2.4 – 26)</td>
</tr>
<tr>
<td>3 – 5 months</td>
<td>2.5 (0.7 – 8.4)</td>
<td><strong>9.4 (3.3 – 26)</strong></td>
<td>3.2 (0.7 – 14)</td>
</tr>
<tr>
<td>6 Months</td>
<td>0.6 (0.2 – 1.7)</td>
<td><strong>6.6 (2.7 – 16)</strong></td>
<td>2.0 (0.7 – 6.0)</td>
</tr>
<tr>
<td><strong>≥ 8 Months</strong></td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
</tbody>
</table>
# Association of Number of drugs in regimen and Treatment outcomes (from multivariate meta-regression)

<table>
<thead>
<tr>
<th></th>
<th>Failure IRR (95% CI)</th>
<th>Relapse IRR (95% CI)</th>
<th>Acquired drug resistance† IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial phase ≤ 3</strong></td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td><strong>Initial phase ≥ 4</strong></td>
<td><strong>0.4 (0.2 – 0.7)</strong></td>
<td>0.9 (0.6 – 1.3)</td>
<td><strong>0.4 (0.2 – 0.7)</strong></td>
</tr>
<tr>
<td><strong>Continuation = 2</strong></td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td><strong>Continuation ≥ 3</strong></td>
<td><strong>0.5 (0.3 – 0.9)</strong></td>
<td>0.9 (0.7 – 1.2)</td>
<td><strong>0.5 (0.3 – 0.9)</strong></td>
</tr>
</tbody>
</table>

---

## Intermittent therapy

- Possible because of long half life of drugs
- And slow growth of M TB
- Intermittent therapy does work
- What is the lowest frequency?
- How early can it start?
## Intermittent regimens and Failure

<table>
<thead>
<tr>
<th>Administration of drugs</th>
<th>Arms (N)</th>
<th>Pooled event rate</th>
<th>95% Conf Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily – all</td>
<td>173</td>
<td>2.6%</td>
<td>1.8 – 3.4</td>
</tr>
<tr>
<td>Daily – then intermittent</td>
<td>76</td>
<td>2.0%</td>
<td>0.4 – 3.7</td>
</tr>
<tr>
<td>Intermittent all – thrice weekly</td>
<td>53</td>
<td>2.7%</td>
<td>0.1 – 4.4</td>
</tr>
<tr>
<td>Intermittent all – twice weekly</td>
<td>17</td>
<td><strong>8.8%</strong></td>
<td>1.5 – 16</td>
</tr>
</tbody>
</table>

## Intermittent regimens and Relapse

<table>
<thead>
<tr>
<th>Administration of drugs</th>
<th>Arms (N)</th>
<th>Pooled event rate</th>
<th>95% Conf Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily – all</td>
<td>149</td>
<td>6.7%</td>
<td>5.4 – 8.0</td>
</tr>
<tr>
<td>Daily – then intermittent</td>
<td>65</td>
<td>7.0%</td>
<td>5.1 – 8.9</td>
</tr>
<tr>
<td>Intermittent all – thrice weekly</td>
<td>52</td>
<td>6.8%</td>
<td>5.6 – 8.1</td>
</tr>
<tr>
<td>Intermittent all – twice weekly</td>
<td>17</td>
<td><strong>10.7%</strong></td>
<td>7.2 – 14.3</td>
</tr>
</tbody>
</table>
Summary points - current therapy

• Initial intensive phase
  – Two months duration is optimal
  – Minimum 3 drugs (4 is better)
  – INH - most potent bactericidal agent
  – RIF - second most potent, least resistance
  – PZA - allows total therapy to be 6 mos only
  – EMB - protects against resistance

• Continuation phase - Four months duration is sufficient
  – If Drug-sensitive organisms
  – If HRZ given in first 2 months
  – If INH&RIF given, but PZA not needed
  – Some advantage to 3 drugs vs 2 drugs

• If No Rifampin (INH/EMB or INH/Thiac) then at least 6 months required
Summary points - current therapy

- Intermittent regimens facilitates DOT
  - Once weekly unacceptable
  - Twice weekly is minimum
  - Thrice weekly - better
    - One advantage - when doses are missed

- If Intermittent within first month – worse outcomes if twice weekly from outset
  - Best is daily therapy in first two months
  - Then switch to intermittent

Drug resistance
Emergence of resistance
Therapy with one drug (First ever TB trial)

• In 1950 first TB trial was conducted in Britain.
• 109 patients received Streptomycin only
  – Only drug available at the time
• Resistance developed rapidly in these patients
  – First detected after three weeks
  – 60% resistant after two months
  – 80% resistant after three months

Emergence of resistance to streptomycin and/or PAS para-aminosalicylic acid given alone or in combination

From Reider, Interventions for TB control, IUATLD.
The “fall and rise” phenomenon – patients given INH alone

From Toman, Case Finding and Chemotherapy

Rate of spontaneous mutations of M Tuberculosis to anti-TB drugs

- **Streptomycin**: $10^{-6}$
- **Isoniazid**: $10^{-6} - 10^{-7}$
- **Rifampin**: $10^{-8} - 10^{-9}$
- **Ethambutol**: $10^{-7} - 10^{-8}$
- **INH&Rif**: $10^{-14}$
Total number of bacilli – in different lesions

- Latent TB: $10^3$
- Infiltrates: $10^6 - 10^7$
- Cavity (one): $10^8 - 10^9$
- Multi-cavities: $10^{10} - 10^{12}$
- Death: $10^{13}$

Probability of developing resistance during therapy

<table>
<thead>
<tr>
<th>Number of Drugs</th>
<th>Total number of bacilli</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$10^4$</td>
</tr>
<tr>
<td>One</td>
<td>1%</td>
</tr>
<tr>
<td>Two</td>
<td>0</td>
</tr>
<tr>
<td>Three</td>
<td>0</td>
</tr>
</tbody>
</table>
Transient drug resistance during therapy with two or more drugs (effect of default)

Drug resistance - prevention and therapy

• To prevent resistance:
  – Minimum two drugs
  – Give at least 3 when bacillary load is high
  – 4 drugs offer better protection

• Therapy if resistance known
  – Tailor to specific resistance pattern

• IF failure or relapse, while waiting…
  – Always give two new drugs
  – Usually Quinolone and injectable
## Association of Initial drug resistance with Treatment outcomes
(from multivariate meta-regression)

<table>
<thead>
<tr>
<th></th>
<th>Failure IRR (95% CI)</th>
<th>Relapse IRR (95% CI)</th>
<th>Acquired drug resistance IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan Sensitive</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Initially SDR</td>
<td>12 (7 – 20)</td>
<td>2.3 (1.7 – 3.0)</td>
<td>7 (4.5 – 12)</td>
</tr>
<tr>
<td>Initially PDR</td>
<td>47 (22 – 103)</td>
<td>2.3 (1.3 – 4.2)</td>
<td>29 (15 – 58)</td>
</tr>
</tbody>
</table>

## Drug resistance - therapy

- **If INH resistance:**
  - RIF/PZA/EMB – 2 months, RIF/EMB - 10 mos
  - Or, RIF/PZA/EMB – 6-9 mos
- **If RIF resistance:**
  - INH/PZA/Quin/EMB/Injectable – 2-6 mos
  - Then INH/EMB ??Quin – total 18 mos
- **If PZA resistance:**
  - INH/RIF/EMB – 2 mos, INH/RIF – 7 mos
Multi-Drug resistance - therapy

• MDR = Resistance to INH & RIF
• High rates of failure & relapse (20%)
• High mortality (10-20%)
• Success rates: average 60%

Rational selection of MDR-TB regimen

Group 1: Isoniazid, Ethambutol, Rifampin, Pyrazinamide
Group 2: Streptomycin, Amikacin, Kanamycin, Capreomycin
Group 3: Ofloxacin, Moxifloxacin, Levofloxacin, Gatifloxacin
Group 4: Ethionamide, Cycloserine, Thioacetazone, P-aminosalicylic acid, Protionamide, Terizidone
Group 5: Clofazimine, Amoxacillin/Clavulanate, Macrolides, Imipenem, Linezolid
TB drugs: Serious adverse effects

- INH – Hepatitis, Rash, Neuropathy (B6)
- RIF – Rash, Drug Interactions, Hematologic, Hepatitis
- PZA – Rash, Hepatitis, Arthralgias, Uric acid (gout)
- EMB – Optic neuritis, rash
- Injectables – Renal, oto-toxicity
Serious adverse effects - management

• Step 1: Stop all possible drugs
• Step 2: Immediately start enough new drugs to ensure adequate therapy (minimum 2 drugs at all times)
• Step 3: When effect resolves re-introduce in reverse order of probability of causation

Serious adverse effects - management

• Cause of rash: PZA>RIF>INH>EMB
• So – start with INH or RIF
  – If no rash add second, etc
  – Speed – every 3-4 days
• Cause of hepatitis: PZA>INH>RIF
• So – start with RIF, then INH
  – Speed – every 2 weeks (much slower)
  – If no hepatitis with INH/RIF do not give PZA
Thanks/Merci