Drug-resistant TB: Building a treatment regimen

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Example case:

21 year-old woman emigrated from India two years ago, no significant co-morbidities

- **History of prior treatment for TB** with “a handful of different pills” as a child, unclear duration??
- **Suggestive clinical presentation:** cough x 3 mo, 15 lbs. weight loss, & CXR biapical opacities
- Sputum x3 sent: smear, culture/DST, NAAT
- Started empirically on standard 4-drugs (HREZ)
Example case: Next steps

• Sputum: smear(+), culture & phenotypic DST pending, **NAAT**: Xpert MTB/RIF (**+Mtb** with RIF resistance)
  ➢ Phenotypic second-line tests & rapid molecular test for drug resistance ordered

• [If needed – expanded empiric regimen: add at least FQ & injectable agent – but many wait for rapid tests]

• **CDC Molecular Detection of Drug Resistance (MDDR) service** [tests for INH (**katG, inhA**); RIF(**rpoB**); FQ (**gyrA**); EMB (**embB**), PZA (**pncA**), injectables x3 (**rrs**), capreomycin (**tlyA**), kanamycin (**eis**)]
  – Found resistance to INH, RIF, EMB
How many drugs for MDR?

Goal: 4-6 likely effective drugs (& optimally at least 5)

• Recent studies suggest better outcomes with at least 5 drugs (we used to say “at least 4”)

• Expert input on 4-6 drug range:
  - Consider more if extensive disease and/or resistance
  - Four may be sufficient with limited disease and/or limited resistance

• [Note: WHO 2016 – at least 5 effective drugs including PZA]
Building an Individualized Regimen for MDR-TB

**STEP 1**

Begin with any first-line agents to which the isolate is susceptible

Add a fluoroquinolone and an injectable drug based on susceptibilities

<table>
<thead>
<tr>
<th>First-line drugs</th>
<th>Fluoroquinolones</th>
<th>Injectable agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrazinamide</td>
<td>Levofloxacin</td>
<td>Amikacin</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Moxifloxacin</td>
<td>Capreomycin</td>
</tr>
</tbody>
</table>

1. KM: Not available in U.S.
2. SM: use only if not previously used and if documented susceptibility
### STEP 1

**This case:** INH, RIF, EMB resistant

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<tr>
<td>Ethambutol</td>
<td>Moxifloxacin ✔</td>
<td>Capreomycin ✔</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kanamycin¹ ✔</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Streptomycin² ✔</td>
</tr>
</tbody>
</table>

1. Not available in U.S.
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Building an Individualized Regimen for MDR-TB

STEP 2

Add second-line drugs until you have 4-6 drugs (optimally at least 5) to which the isolate is susceptible (and preferably which have not been used to treat the patient previously)

Pick one or more of these

<table>
<thead>
<tr>
<th>Oral second-line drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>✔ Cycloserine</td>
</tr>
<tr>
<td>✔ Ethionamide</td>
</tr>
<tr>
<td>✔ PAS</td>
</tr>
<tr>
<td>✔ Linezolid(^3)</td>
</tr>
</tbody>
</table>

3. Although considered a third-line drug, many experts now use LZD as a second-line drug option
Consider use of these

<table>
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<tbody>
<tr>
<td><strong>Bedaquiline</strong></td>
</tr>
<tr>
<td><strong>Delamanid</strong>(^4)</td>
</tr>
<tr>
<td><strong>Clofazimine</strong></td>
</tr>
<tr>
<td><strong>Imipenem/Clavulanate</strong>(^5)</td>
</tr>
<tr>
<td><strong>Meropenem/Clavulanate</strong>(^5)</td>
</tr>
<tr>
<td><strong>High-dose INH</strong></td>
</tr>
<tr>
<td><strong>Clarithromycin</strong>(^6) (PAS(^6))</td>
</tr>
</tbody>
</table>

**STEP 3**

If there are not 4-6 drugs available in the above categories, consider third-line drugs in consultation with an MDR-TB expert.

4. Awaiting FDA approval
5. Available as amoxicillin-clavulanate
6. WHO 2016 removed macrolides and downgraded PAS
Additional Considerations: DR-TB Treatment

Seek expert consultation
CITC Warmline Consultation

Curry International Tuberculosis Center
1-877-390-NOTB  or  1-877-390-6682
www.currytbcenter.ucsf.edu
Or your own regional TB Center of Excellence
Additional Considerations: DR-TB Treatment

Seek expert consultation

When choosing drugs, consider:

• Cross-resistance [*Survival Guide table 2, page 76*]
• Potential side-effects
• Avoiding drugs used previously to treat patient’s TB
• Adjustments after phenotypic DST results

Never add a single drug to a failing regimen
Treatment Duration

• 2003 ATS/CDC/IDSA guidelines: 18-24 mo
• WHO 2011 (based on individual patient meta-analysis: 32 studies, over 9000 pts. Ahuja et al, PLoS Med 2012); Intensive phase at least 8 months
  – Total duration at least 20 months (if no prior rx for MDR; if prior MDR rx at least 24 months)

Survival Guide v3 – Expert consensus:
Utilize culture conversion to help guide minimum duration within U.S. high-resource setting
• Intensive phase: at least 6 mo beyond culture conversion for use of injectable agent
• Total duration: at least 18 months beyond culture conversion
Short course “Bangladesh” regimen

Nine (to twelve) month MDR regimen –
Endorsed for use in WHO 2016 guidelines:

• Intensive (4mo): Kanamycin, prothionimide, high-dose INH, gatifloxacin, clofazamine, EMB, PZA
• Continuation (5mo): gatifloxacin, clofazamine, EMB, PZA
• Treatment success 85% (n=515; 2005-2011)
  KJM Aung et al. Int J Tuberc Lung Dis 2014 ;18(10)
• Multi-country observational study treatment success 82%
  (substitutes MFX); Trebucq et al. IJTID ePub: Nov 17, 2017
• STREAM trial: randomized-controlled trial of 9 mo regimen
  (substitutes MFX^{HD}) vs “standardized” WHO regimen
Regimens for XDR-TB

In the face of quinolone and injectable drug resistance, treatment choices are limited

- Linezolid and/or Bedaquiline (and any remaining injectable) become the mainstay of treatment, along with whatever oral medications are left to which there is \textit{in vitro} susceptibility

- Duration \textbf{at least 24 mo post-culture conversion}

- Surgery if disease is localized

- [Few patients may not be treatable]
Other DR-TB Treatment considerations

• Use case management and DOT (7 days/wk optimal, but 5 days/wk acceptable)
• Use daily, not intermittent therapy
  – Exceptions: renal disease, injectable agents (post-culture conversion), HD-INH
• Drug-ramping (dose escalation) for cycloserine, ethionamide, and PAS to improve initial tolerance
• Helpful tools: Drug-o-gram, DR-TB flow charts
Patient-centered DOT

Patient-centered care: more than watching patients swallow their pills
Updated MDR Guidelines

- WHO 2016 Guidelines: Adds to WHO 2011 guide - additional meta-analysis of individual patient data (32 studies), >9000 patients
  http://www.currytbccenter.ucsf.edu
- New ATS/CDC/IDSA MDR-TB guideline in progress......
Management of Drug-Resistant TB

Summary:

• Treatment of MDR-TB is complex – and step-wise approach can be helpful (*and may change with upcoming new data/studies*)
• It is much easier to prevent than to treat
• Ask for help – obtain expert consultation when DR-TB is suspected

Preventable, Treatable, Curable