Epidemiology, Treatment and Prevention of MDR-TB

C. Robert Horsburgh, Jr.
Boston University School of Public Health

Objectives

• To document the extent of the global MDR-TB epidemic and suggest where it is headed
• To describe the drugs available for MDR-TB treatment and define their toxicities
• To provide guidance on using these drugs together in combination regimens
• To review potential strategies for prevention of MDR-TB and outline research needs

Outline

• What is MDR-TB and why does it threaten global TB control?
• Improving diagnosis of MDR-TB
• Improving treatment of MDR-TB
• New Drugs for MDR-TB treatment
• Prevention of MDR-TB
Multidrug-Resistant TB (MDR-TB)
Tuberculosis disease caused by *M. tuberculosis* resistant to Isoniazid and Rifampin (+/- other drugs)

![MDR-TB Diagnostic Trends Over Time](2015 Global TB Report)

MDR-TB Epidemiology

- Estimated 480,000 new cases last year
- Created by inappropriate treatment, interruption of drug supply and patient nonadherence
- Main mechanism is selection of naturally occurring mutations
- No evidence of transposition with other bacteria
- Also can be primary spread
Emergence of Additional DR on MDR-TB Treatment

- Cohort study of 832 patients with MDR-TB treated with WHO recommended regimens
- Of those without baseline resistance to specific SLDs:
  - 79 (11.2%) acquired fluoroquinolone (FQ) resistance
  - 56 (7.8%) acquired resistance to second-line injectable drugs (SLIs)
  - 68 (8.9%) acquired extensively drug-resistant (XDR) tuberculosis

Clin Infect Dis 2014;59:1049
Annual Incident Global MDR-TB

Can we Improve MDR-TB Diagnosis?

WHO Endorses GeneXpert MTB/RIF
December 2010

- Xpert MTB/RIF-molecular test, detects TB and rifampin resistance directly from sputum
- Provides diagnosis in < 2 hours
- Sensitivity
  - sm-pos: 98% (95% CI: 97%-99%)
  - sm-neg: 68% (95% CI: 61%-74%)
  - HIV-pos: 79% (95% CI: 70%-86%)
  - RIF-R: 95% (95% CI: 90%-97%)
WHO MDR-TB Treatment Recommendations

- 4 second-line antituberculosis drugs likely to be effective as well as PZA, should be included in the intensive phase
- 3rd generation FQ, ETO, CS preferred over PAS
- Intensive phase 8 months
- Drop injectable after intensive phase
- Total duration 20 months or 12 months after culture conversion

WHO MDR-TB Treatment Guidelines, 2011

Can we Improve MDR-TB Treatment Success?
Old and Repurposed Drugs for MDR-TB Treatment

- PZA
- Fluoroquinolones
- Clofazimine
- Linezolid
- Meropenem + Clavulinic acid

Pyrazinamide for MDR-TB

- Shortens duration of DS-TB therapy
- Synergistic with new and repurposed drugs in murine models
- Substantial hepatotoxicity
- 40-60% of MDR-TB isolates are resistant to PZA

“Third Generation” Fluoroquinolones

- Levofloxacin, Moxifloxacin and Gatifloxacin
- Gatifloxacin not widely available
- Moxifloxacin causes QT prolongation
- Optimal doses of Levofloxacin and Moxifloxacin for TB remain to be determined
- Global resistance to Levo and Moxi ~ 0-9% of MDR-TB
A 9-month regimen for MDR-TB in Bangladesh

<table>
<thead>
<tr>
<th>Medication</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanamycin</td>
<td>4-month intensive phase prolonged if still smear-positive after 4 months</td>
</tr>
<tr>
<td>Streptomycin</td>
<td></td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td></td>
</tr>
<tr>
<td>Clofazimine</td>
<td></td>
</tr>
</tbody>
</table>

Fixed 5-month continuation phase

AJRCCM 2010:182:684-92

---

**Bangladesh Regimen: Efficacy**

515 patients
- 435 Cures/completions (84.5%)
- 29 Deaths (5.6%)
- 40 Defaults (7.8%)
- 7 Failures (1.4%)
- 4 Relapses (0.8%)

IJTLD 2014:18:1180-8

---

**Bangladesh Regimen: Tolerability**

515 patients
- 111 Vomiting (21.6%)
- 8 Diabetes/glycosuria (1.5%)
- 50% completion in 9m; 95% in 12m
- Risk factors for failure: FQ or PZA resistance

IJTLD 2014:18:1180-8
STREAM Study

- Description: Modified Bangladesh regimen (with moxifloxacin in place of gatifloxacin) compared to "standard" MDR-TB regimen
- Regimens: 7-drug regimen (9 months)
  - 4-5 drugs (18-24 months)
- Sponsors: IUATLD, USAID
- Target population: smear+ MDR-TB, adults
- Outcome: Failure, relapse, default or death
- Size: 400 patients – 100% enrolled
- Sites: Ethiopia, Vietnam, South Africa
- Expected completion: 2017

Tolerability of Clofazimine

- Skin discoloration (75-100%)
- Gastrointestinal intolerance (40-50%)
- Eosinophilic enteritis
- Interstitial nephritis
- Rash, dry skin, ichthyosis
- QT prolongation

Clofazimine in TB Treatment

- Use for treatment of Leprosy since 1969
- Effective against *M. tuberculosis* in murine studies
- Early trials of use against TB were not successful
- Little activity in EBA study (days 1-14)
- Part of the “Bangladesh” regimen for MDR-TB
- Persists in tissues for 6-12 months after being given
Clofazimine in MDR-TB Treatment

![Graph showing the percentage of patients with positive sputum culture over time.](image)

Clofazimine Trial – Phase 3

- Description: WHO standard regimen +/- Clofazimine
- Regimens: WHO Standard + CFZ_{200mg} (20-24 months)
  - WHO Standard + Placebo (20-24 months)
- Sponsor: Novartis
- Target population: Xpert+ MDR-TB, adults, +/- HIV
- Outcomes: Time to negative sputum culture, cure, relapse
- Size: 380 patients
- Sites: Global
- Expected results: 2020

Prospective Study of Linezolid in XDR-TB Treatment

- 40 patients with XDR-TB in Korea
- Randomized to 300mg qd or 600mg qd
- Further randomized to immediate versus 2 month delayed linezolid (both with OBR)
- 36/40 converted sputum cultures (mean 90 days)
- 4 failures were all resistant to linezolid

NEJM 2012;367:1508-18
Tolerability of Linezolid in 72 Patients with MDR-TB*

- Peripheral neuropathy (40%)
- Anemia (25%)
- Optic Neuritis (10%)
- Thrombocytopenia (10%)
- GI disorders (8%)
- Neutropenia (2%)

*DOse < 600mg/day

Meropenem/Clavulinate

- Drug class: Carbapenem (beta-lactam)
- Mode of action: bacterial wall synthesis inhibitor; needs to be given with oral clavulanic acid
- Half life: 1 hour; renal excretion
- Toxicities: headache, diarrhea, nausea, thrombophlebitis
- Chemical Structure:
Efficacy and Tolerability of Meropenem

- 37 patients received meropenem 1 gm I.V. tid with clavulanate (125 mg p.o. tid) plus OBT including linezolid
- 61 comparison patients received OBT, most including linezolid
- Sputum-culture conversion in 31/37 (83.8%) versus 15/24 (62.5%) controls ($p=0.06$)
- 5/37 (13.5%) experienced diarrhea potentially attributed to meropenem–clavulanate
- Two of the five also experienced transient increased liver function tests

Eur J Resp Dis 2013;41:1386

New Drugs for MDR-TB Treatment
Bedaquiline (TMC-207)

- Drug class: diarylquinolone
- Mode of action: inhibits proton pump for ATP synthase
- Half life: 24 hours
- Toxicities: Nausea, QT prolongation
- Chemical Structure:

Bedaquiline Phase 2 Study

- Description: Addition of Bedaquiline to OBT for 6 months, followed by OBT for 18 months
- Regimens: OBT+Bedaquiline
  OBT+Placebo
- Sponsor: Janssen
- Target population: newly-diagnosed, smear+ MDR-TB, adults, CD4>300 if HIV+
- Outcome: Time to sputum culture conversion
- Size: 200 patients
Bedaquiline Phase 2 Study
Time to sputum culture conversion

Bedaquiline Phase 2 Study
Final results

<table>
<thead>
<tr>
<th></th>
<th>Bedaquiline+OBT</th>
<th>Placebo+OBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>79 patients</td>
<td>81 patients</td>
</tr>
<tr>
<td>Median Conversion</td>
<td>12 weeks</td>
<td>18 Weeks*</td>
</tr>
<tr>
<td>&quot;Cure&quot; at week 120</td>
<td>58%</td>
<td>32%*</td>
</tr>
<tr>
<td>Serious Adverse Events</td>
<td>23%</td>
<td>19%</td>
</tr>
</tbody>
</table>

*p<0.01

Tolerability of Bedaquiline

• QT prolongation: +15.4 msec in BDQ vs. +3.3 msec in Placebo
• Increased death at 120 weeks: 10/79 (13%) in BDQ vs. 2/81 (2%) in Placebo
• No other differences between BDQ and Placebo
WHO Bedaquiline Recommendations

- Use for patients with MDR-TB where isolate is resistant to FQ or injectable (or both)
- May also use if patient is intolerant of FQ or injectable
- Give only for first 6 months of regimen
- Continue other drugs for total of 20 months
- Do not use with delamanid

Delamanid (OPC-67683)

- Drug class: nitroimidazo-oxazole
- Mode of action: mycolic acid synthesis inhibitor
- Half life: 20-30 hours
- Toxicities: Nausea, QT prolongation
- Chemical Structure:
Delamanid Phase 2 Study

- Description: Addition of Delamanid (D) to OBT
- Regimens: OBT+D 100 mg bid
  - OBT+D 200mg bid
  - OBT+Placebo
- Target population: Adults with pulmonary MDR-TB, CD4>350 if HIV+
- Outcome: Sputum conversion at 8 weeks
- Size: 430 patients

Tolerability of Delamanid

- Increases in QTcF from baseline were 7.6 ms at 1 month and 12.1 ms at 2 months
- 3% of patients experienced an increase of 60 ms or greater
- 1 patient exhibited a QTcF interval > 500 ms
- No cases of Torsades de Pointes
WHO Delamanid Recommendations

- Use for patients with MDR-TB where isolate is resistant to FQ or injectable (or both)
- May also use if patient is intolerant of FQ or injectable
- Give only for first 6 months of regimen
- Continue other drugs for total of 20 months
- Do not use with bedaquiline

Pretomanid (PA-824)

- Drug class: nitroimidazo-oxazine
- Mode of action: mycolic acid synthesis inhibitor
- Half life: 16-20 hours
- Toxicities: QT prolongation?
- Chemical Structure:

Pretomanid/Moxi/PZA Regimen

Lancet March 18, 2015
MDR-TB Clinical Trials in Progress

- Delamanid - Phase 3
- Opti-Q – Phase 2 (Opti-Q)
- Pretomanid – Phase 3 (STAND)
- Pretomanid+Bedaquiline – Phase 2 (NC-005)
- Pretomanid+Bedaquiline – Phase 3 (NiX-TB)
- NEXT Trial – Phase 3 (BDQ+ oral OBT)

Constructing a new MDR-TB Regimen: Principles

- At least 3 new drug classes
- Avoid overlapping toxicities
- Strive for all-oral regimen
- Estimate duration based on 2 month sputum culture conversion

MDR-TB Drug Menu

<table>
<thead>
<tr>
<th>Class</th>
<th>Example Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diaryquinolone:</td>
<td>bedaquiline</td>
</tr>
<tr>
<td>Nitroimidazole:</td>
<td>delamanid, PA-824</td>
</tr>
<tr>
<td>Oxazolidinone:</td>
<td>linezolid, sutezolid?, others?</td>
</tr>
<tr>
<td>Fluoroquinolone:</td>
<td>levofloxacin, moxifloxacin, (gatifloxacin)</td>
</tr>
<tr>
<td>Riminophenazine:</td>
<td>clofazimine</td>
</tr>
<tr>
<td>Other:</td>
<td>PZA</td>
</tr>
</tbody>
</table>
MDR-TB Clinical Trials in Preparation

- STREAM Stage 2: 6 and 9-month BDQ regimens
- ACTG 5343: Bedaquiline/Delamanid DDI
- MDR-END: 9-month DLM+LZD+LFX+PZA Regimen
- TB-PRACTECAL: PRT+BDQ+LZD+PZA
- EndTB: BDQ, DLM and Combinations
- ACTG 5356: LZD dose optimization with DLM

MDR-TB Prevention

- Ensure that treatment of DS-TB is completed to prevent emergence of DR
- Find and promptly treat MDR-TB cases to reduce primary spread in the community
- Treatment of contacts with MDR-TB?

MDR-TB Household Contact Studies in Preparation

- V-QUIN (levofloxacin)
- TB-CHAMP (levofloxacin)
- Phoenix (delamanid)
Conclusions

- New TB drug classes may increase MDR-TB treatment responses, shorten treatment duration and decrease mortality
- Tolerability of a number of the new and repurposed agents remains to be defined, especially when used in combination
- Combination studies are underway to assess DDI between new agents, other TB drugs and ART

To follow developments in MDR-TB diagnosis and treatment:

RESIST-TB Website

www.resisttb.org