New TB regimens and the need for new approaches to drug susceptibility testing

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Outline

• TB Alliance and the drug development pipeline
• Resistance and DST algorithms
• Turning theory into diagnostic development
TB Alliance Vision

Current Treatment

6-30 Months

New Treatments in Development

2-4 Months

Our Vision

7-10 Days

Success will require novel drug combinations
## Current Therapy and Unmet Needs

<table>
<thead>
<tr>
<th>Current Therapy</th>
<th>Unmet Needs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Sensitive TB</strong></td>
<td>4 drugs taken for 6 or more months</td>
</tr>
<tr>
<td><strong>M(XDR)-TB</strong></td>
<td>Injections and drugs taken for more than 2 years, poorly tolerated</td>
</tr>
<tr>
<td><strong>TB/HIV co-infection</strong></td>
<td>Drug-drug interactions with ARVs</td>
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<tr>
<td><strong>Latent TB Infection</strong></td>
<td>9 months of isoniazid</td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td>Formulations not adequately dosed</td>
</tr>
</tbody>
</table>

No new drugs for TB in more than 40 years
Timeline for country availability of new TB drugs and regimens

• 2013+: Bedaquiline (TMC-207; Janssen/Tibotec) and delamanid (OPC-67683; Otsuka) for MDR-TB
  – Based on Phase II results: adding new drug for 6 months on top of existing MDR-TB regimen
  – Phase III trial will take several years
• 2014+: Dispersible first-line (HRZE) FDCs for pediatric use
• 2015: REMoxTB regimens (moxifloxacin) for drug-sensitive TB
• 2018+: PaMZ for drug-sensitive TB AND some MDR-TB
Phase 3 REMox TB Trial Design

Randomized, Double-blind; Non-inferiority

<table>
<thead>
<tr>
<th>Treatment Duration (months)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensive</td>
<td>Continuation</td>
<td></td>
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<tr>
<td>630 participants</td>
<td>HRZE</td>
<td>HR</td>
<td></td>
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<tr>
<td>Standard Regimen</td>
<td>Placebos</td>
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<tr>
<td>630 participants</td>
<td>HRZM</td>
<td>HRM</td>
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<tr>
<td>Moxifloxacin for Ethambutol</td>
<td>Placebos</td>
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<tr>
<td>630 participants</td>
<td>MRZE</td>
<td>MR</td>
<td></td>
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<tr>
<td>Moxifloxacin for Isoniazid</td>
<td>Placebos</td>
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</tbody>
</table>

All participants followed for 12 months post-treatment

H = isoniazid; M = moxifloxacin; R = rifampin; Z = pyrazinamide; E = ethambutol

1931 patients enrolled in China, India, Kenya, Malaysia, Mexico, South Africa, Tanzania, Thailand, Zambia
Benefits of REMox Regimen

Shorten Treatment from 6 to 4 months

• Treatment outcome benefits (potentially higher effective cure rates & less emergence of MDR-TB)
  – Increased adherence/reduced drop-out
  – Less resistance to drugs in regimen (e.g. isoniazid or ethambutol)

• Health Systems benefits
  – Reduced cost in healthcare utilization (at any one time in Bangladesh, ~53,000 active patients instead of 80,000)

• Patient benefits
  – Reduced out of pocket costs (fewer visits)
  – Less time exposed to side effects
Timeline for REMox TB
Clinical, Regulatory and Market Access activities in brief

2012
• Enrollment completed
• Patient treatment completed

2013
• Complete trial
• Initiate data analysis
• Secure funding for demonstration studies

2014
• Complete data analysis
• File & receive FDA approval
• Seek & receive WHO policy approval
• Secure policy commitment in priority countries

2015
• Launch in demonstration countries
• Receive approval to import in priority countries
• File in priority countries & EMA

TB ALLIANCE
Value Proposition of PaMZ

Potential benefits from PaMZ

• TIME
  – Reduce treatment duration from 6 months (first line) or 18-24 months (MDR-TB) to 4 months.

• TREATMENT OUTCOMES
  – Eliminate interaction with ARVs with removal of R from regimen
  – Treat some (10-67%) of MDR patients with shorter, safer, cheaper, more efficacious regimen with fewer side effects and no injections

• SUPPLY MANAGEMENT
  – Single weight band for all patients
  – No technical barrier to being made into FDC
  – All oral, no refrigeration

• COST
  – For DS-TB: Tradeoff similar to REMoxTB, i.e., higher drug costs but reduced cost of delivery
  – For MDR-TB: Drug costs and delivery costs both dramatically reduced
  – Patient out of pocket costs reduced
Questions for Adoption

What countries may need to know about drug resistance

• What is the background, *population-based* resistance to drugs in the combination?

• Based on modeling, what *individual* drug susceptibility testing (DST) – with what kind of sensitivity and specificity – will be needed?

• What is the likely availability of those DST diagnostics?
  – Developed
  – In field use
  – At national & district levels

Current DST is focused on the needs of the current regimen – **but** what will be needed for the future?
Resistance exists: the question is how to deal with it

- H resistance among new cases of 15% is not unusual.
- R resistance among new cases: 3% is typical.
- Z resistance among non-MDR-TB cases: around 3%.
- FQ resistance among non-MDR-TB cases appears to be ~1-2%, though data here are particularly sparse.
- Resistance to FQ and Z appears to be higher in Asia than in Africa – possibly due to the more extensive private sector TB drug use in Asia.
- Z resistance rates among MDR-TB range from 33-90%.
Test everybody for everything?
It’s not that simple

• Xpert uptake not just for DST ability, but often for TB detection
• Many high burden countries have insufficient resources to do DST on all suspects or patients
• If resistance prevalence is low, false positives (and need for confirmatory testing) would be high
• Trade-off:
  – DST increases knowledge of patient’s clinical status
  – But DST increases burden on health system and patient
• If DST results in greater travel costs, multiple visits and diagnostic delays, it will reduce patient retention and may result in worse outcomes.
Current treatment algorithm: many countries

- **HRZE**
  - **cure**
  - **fail**
    - **Xpert (R)**
      - **Rs**
      - **Rr**
        - **HRZE**
        - **Hain sl**
          - **MDR24**
Current treatment algorithm: Some high HIV-burden countries

Assess HIV status

HIV-

HRZE

HIV+

Xpert (R)

Sm+

Rs

Rr

Confirm R + Hain sl

Sm-

HRZE

2-3mo smear

MDR24

HRZE
Current treatment algorithm: South Africa

Xpert (R)

- Rs 95%
- Rr 5%

HRZE

Confirm R + Hain sl

MDR24
Potential algorithms for PaMZ

1) Test all for R & M; or 2) presumptive treatment for all

(1) New Z + M diagnostic
   - Zs, Ms
   - Zr or Mr
     - Xpert (R); Confirm Z + M
       - Rs
       - Rr
         - HRZE
         - MDR24

Safe but expensive, complex and difficult logistics

(2) PaMZ
   - Cure
   - Fail
     - DST for R, Z and M
       - Zs, Ms
       - Zr or Mr, but Rs
       - PaMZ
       - Zr or Mr, plus Rr
         - HRZE
         - MDR24

Cheaper, simpler, but more risk of resistance generation
Potential algorithm for PaMZ (cont)

Before M/Z DST, do triage based on R DST

• Prioritizes Z and M testing for those at higher risk;
• Presumptive PaMZ treatment is now for “DS-TB” (non-MDR-TB) cases, rather than for “new” cases.
• But still a risk that M has only 1 active companion drug.

Cheaper, simpler, and safer, but still risk of M resistance generation
Conclusions on DST algorithms

• For M:
  – Upfront DST may not be needed or advisable in sub-Saharan Africa, if they have M resistance in new cases of ~1%
  – This may be a closer call in Asia, if they have higher prevalence of M resistance among new cases.

• For Z:
  – Baseline resistance among new cases may be ~3% everywhere (i.e., somewhat higher than for M). This, plus concern about exposing M to an inadequate regimen, may increase pressure for upfront Z DST.
  – How low would Z resistance have to be in new cases (algorithm #2) or non-MDR-TB cases (algorithm #3) for presumptive PaMZ treatment to be OK?

• For both:
  – Fast test = molecular test. Achieving a high PPV with a molecular test may be more challenging for M and Z than it is currently for R (not all mutations known, or known to be specific to resistant strains). If PPV is low, either reserve DST for high risk subpopulation and/or need confirmatory testing of positives.
What diagnostics developers need

• Specifications:
  – which drugs;
  – surveillance, screening or stand-alone test;
  – what sensitivity and specificity required;
  – What decentralization required.

• Market size/demand:
  – What resistance prevalence is the cut-off for adoption; therefore which countries adopt
  – Where the diagnostic is placed in algorithms – therefore what percentage of TB suspects or patients get tested
Two-fold challenge in predicting demand

• Prediction
  – Predicting new regimen adoption is hard;
  – Predicting new DST adoption is hard;
  – Predicting new regimen + new DST adoption is much harder.

• Chicken and egg
  – Diagnostic companies only willing to develop new DST if new regimens are adopted.
  – But adoption of new regimens relies on availability of new DST assays
Pathway for action

• Enabling science
  – Define which mutations correlate with in vitro resistance and have clinical impact
  – Establish a strain bank to use for testing of new assays

• Surveillance
  – Establish more baseline values for fluoroquinolone resistance among new patients, and Z resistance among new and MDR-TB patients

• Modeling impact
  – Model trade-offs between speed, accuracy, price, and technical specs of DST assays
  – Model different DST algorithms (e.g., DST for all, DST for retreatment/failure cases only, or use of novel regimens without DST). Above what threshold of resistance prevalence would more widespread DST be advisable?

• Assay development
  – Finalize target product profiles, so developers have a clear pathway forwards
  – Use both existing platforms (e.g., FQr via Xpert) and new platforms

Co-development of drugs and diagnostics is the way forwards!