Introducing New TB Medicines and Regimens: Is Success Driven by Systems?

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Objectives

• Review key points on the global threat of drug resistant-TB
• Explore the importance of collaboration among stakeholders within a health system to ensure timely and rational introduction of new medicines
• Demonstrate application of health systems strengthening approaches through a practical case study
Outline

• Global burden of TB
• Challenges with TB medicines and regimens
• New TB medicines and novel regimens
• Intervention: Applying a systems strengthening approach to the introduction of new TB medicines in countries
• Real country example: Applying the systems strengthening approach to the introduction of new TB medicines in Swaziland
• Lessons learned and conclusions
Background TB Information
Global Burden of TB

205 countries reported on their response to TB, guided by WHO’s TB strategy

- 9.6 million people fell ill with TB in 2014
  - 5.4 million men
  - 3.2 million women
  - 1 million children

- 1.2 million people living with HIV developed TB in 2014
  - With 0.4 million associated deaths

- 480,000 people developed MDR-TB in 2014 with 190,000 multidrug-resistant TB (MDR-TB) deaths

Improved TB data from countries reveal that the burden of the disease is higher than previously estimated.

Adapted from the WHO Global Tuberculosis Report (2015)
MDR-TB is a Public Threat

480,000
estimated cases of MDR-TB in 2014

123,000
MDR/RR-TB cases detected in 2014

111,000
TB patients started on MDR-TB treatment in 2014

50%
of MDR/RR-TB cases started on treatment in 2012 with successful outcome

MDR-TB remains a crisis
WITH ONLY ONE IN FOUR MDR-TB CASES DETECTED AND ONLY ONE IN TWO CURED

Adapted from the WHO Global Tuberculosis Report (2015)
Economic Burden of DR-TB (US)

The Outsized Financial Toll of MDR and XDR TB
Cost increases with greater resistance:

A Major Human Cost
Of those treated for drug-resistant TB:

- 9% Die During Treatment
- 27% Stop Working
- 73% Hospitalized
- 37% Require Home Isolation

Source: U.S. Centers for Disease Control and Prevention

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# Pharmacological Treatment of TB (1)

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>First-line oral anti-TB drugs</td>
<td>Isoniazid, Rifampicin, Ethambutol, Pyrazinamide, Rifabutin, Rifapentine</td>
</tr>
<tr>
<td>2</td>
<td>Injectable anti-TB drugs (injectable agents or parenteral agents)</td>
<td>Streptomycin, Kanamycin, Amikacin, Capreomycin</td>
</tr>
<tr>
<td>3</td>
<td>Fluoroquinolones</td>
<td>Levofloxacin, Moxifloxacin, Gatifloxacin, Ofloxacin</td>
</tr>
</tbody>
</table>
## Pharmacological Treatment of TB (2)

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Oral bacteriostatic second-line anti-TB drugs</td>
<td>Ethionamide, Prothionamide, Cycloserine, Terizidone, $p$-aminosalicylic acid, $p$-aminosalicylate sodium, $p$-aminosalicylic acid sodium</td>
</tr>
<tr>
<td>5</td>
<td>Anti-TB drugs with limited data on efficacy and/or long-term safety in the treatment of drug-resistant TB (this group includes new anti-TB agents)</td>
<td>Bedaquiline, Delamanid, Linezolid, Clofazimine, Amoxicillin/clavulanate, Imipenem/cilastatin, Meropenem, High-dose isoniazid, Thioacetazone, Clarithromycin</td>
</tr>
</tbody>
</table>
Challenges with Current TB Regimens

- **Old** – Last approved new drug (before bedaquiline and delamanid) was over 40 years ago
- **Long** – Treatment takes 2 years
- **Complex** – Multiple tablets, 8 months of injectable agents, needs to be tailored to individual resistance patterns; hard to scale-up
- **Expensive** – Can cost up to $3,000 in drug costs alone
- **Toxic** – Side effects range from hearing loss to intractable nausea to psychosis
- **Inadequate** – High loss to follow-up, low cure rates, generates further resistance, no pediatric formulations
- **Unproven** – No randomized clinical trials or prospective trials exist for the current regimens
Global TB Drug Pipeline

Discovery

- Cyclopeptides
- Diarylquinolines
- DprE Inhibitors
- InhA Inhibitor, Indazoles
- LeuRS Inhibitors, Ureas Macrolides, Azaindoles
- Mycobacterial Gyrase Inhibitors
- Pyrazinamide Analogs
- Ruthenium(II) Complexes
- Spectinamides SPR-113
- Translocase-1 Inhibitors

Preclinical Development

- Early Stage Development
  - TBI-166
  - CPZEN-45*
  - SQ641*
  - 1599*
  - SEQ-9*
- GLP Tox.
  - PBTZ169*
  - TBA-354
  - Q203*

Clinical Development

- Phase I
  - Sutezolid (PNU-100480)
  - SQ109*
- Phase II
  - Rifapentine for DS-TB
  - High Dose Rifampicin for DS-TB
  - Bedaquiline-Pretomanid-Pyrazinamide Regimen
  - Levofloxacin with OBR for MDR-TB
- Phase III
  - Bedaquiline (TMC-207) with OBR for MDR-TB
  - Delamanid (OPC-67683) with OBR for MDR-TB
  - Pretomanid-Moxifloxacin-Pyrazinamide Regimen

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, New chemical class*

1 Details for projects listed can be found at http://www.newtbdrugs.org/pipeline.php and ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php

2 OBR = Optimized Background Regimen

www.newtbdrugs.org

Updated: September 2015
Activity Background

• USAID Bedaquiline Donation Program
  • GDF implementation in early 2015
  • 30,000 free courses of bedaquiline from 2015 to 2019
  • Criteria: Global Fund eligible countries

• KNCV and SIAPS to provide TA to countries to adopt bedaquiline

• WHO and partners have released several guidance documents for introducing new medicines
Using a Systems Strengthening Approach to Introduce New TB Medicines and Regimens
Key Terms

• Health system = people + institutions + resources + established policies to improve the health of the population they serve...

• Health system strengthening = identifying and implementing the changes in policy and practice in a country’s health system, so that the country can respond better to its health and health system challenges

Source: WHO Health Systems Strengthening Glossary
The Pharmaceutical System is a Subset of the Overall Health System
An Approach to Pharmaceutical Systems Strengthening

- Government
  - MOH, other ministries, regulators, policy makers

- Governance
- Service Delivery
- Human Resources
- Medical Products
- Financing
- Information

- Providers
  - public/private, NGO, commercial sector, professional associations

- Community
  - patients, consumers, caregivers, civil society

- Analysis
  - International health initiatives
  - Local context
  - Health status
  - Health systems

- Improved coverage & access of evidence-based interventions
- Sustainable Health Outcomes and Impact
  - aligned with:
  - Country Strategic Plans
  - USG/USAID Health-Specific Results

Monitor and Evaluate Performance
Pie Chart Analogy

Pharmaceutical system issues:
“symptoms of an underlying weak system”

Corresponding components to be strengthened, “the underlying disease state, i.e., a weak system”
From an Approach to Action (1)

1. Stakeholder coordination
   • Prevent parallel systems and duplication of effort by health care providers
   • Assign roles and responsibilities
   • Adopt a common approach
   • Discuss and ensure alignment of interests
   • Integrate services and technical assistance into other health programs, e.g., HIV and AIDS programs
Key Stakeholders

- MoH, NTP, CMS/RMS, PV unit, Ethics Committees, TWGs
- Doctors, pharmacists, nurses, other HCWs, labs
- USAID, WHO, PEPFAR, GDF, Global Fund
- SIAPS, KNCV, TRACK TB, MSF, endTB

Governmental bodies
Health care institutions
Donors/global bodies
Implementing partners
2. Governance
   • Develop policies, guidelines, SOPs, job aids
   • Create taskforce with oversight to ensure transparency and accountability

3. Financing
   • Assess financial barriers
   • Identify feasible solutions
   • Advocate for resources
4. Human resources
   • Build capacity and skills of health care providers
   • Continuous mentorship and supervisory visits

5. Service delivery
   • Supply chain management
   • Rational medicine use
   • Pharmacovigilance (PV)

6. Information for decision making
   • Implement appropriate tools
   • Monitor and evaluate
Country Case Study: Swaziland
Country Context: Swaziland

- Multiple stakeholders who were trying to access and use bedaquiline under different conditions (procurement from open market, compassionate use, study conditions)
- Limited clinical experience with the drug
- Delays in accessing the drugs in comparison to urgency of need
- Weak infrastructure and laboratory capacity to monitor the use of the drug
- High prices of bedaquiline and companion medicines
Pie Chart Analogy

Pharmaceutical system issues
“symptoms of an underlying weak system”

Corresponding components to be strengthened, “the underlying disease state, i.e., a weak system”

- Corruption, theft, no accountability
- Medicine use problems, safety problems
- Supply chain issues
- Staffing/mgmt issues
- Lack of or poor information
- Funding issues

- Governance
- Financing
- Human Resources (HR)
- Service delivery - ensuring rational use, safety, and quality
- Information for decision making
- Service delivery - SCM
Strengthening the System in Swaziland (1)

- Task force created to make decisions about bedaquiline
- National Implementation Plan approved
- Clinical guidelines and standard operating procedures approved

- Re-programmed unused funds to procure medicines
- Accessed free drug from donation program
- Addressed drug shipment costs
Strengthening the System in Swaziland (2)

- Held clinical training workshop
- Provided job aids
  - Clinical guidelines
  - Standard operating procedures
- Expanded existing M&E tools to collect bedaquiline-specific data
- Provided feedback from collection and analysis of adverse events from PV programs
Strengthening the System in Swaziland (3)

- Strengthened existing active-surveillance system for TB medicines
- Incorporated quantification and supply planning for future orders of bedaquiline
- Bedaquiline sent to central medical store for distribution to all facilities
Lessons Learned

• The importance of stakeholder coordination and prevention of parallel systems
• Meet the country where they are and then build upon existing processes, programs and systems
• View each public health intervention as an opportunity to strengthen the entire system
• Flexibility is key in implementing as each country situation is different
Conclusions

• New TB medicines expand management options for persons on DR-TB treatment
• However, the introduction of new TB medicines requires a systems strengthening approach to prevent misuse and premature resistance and ensure the monitoring of patient safety while using the medicines
For more information go to www.newtbdruginfo.org