Multidrug-resistant Tuberculosis: Tools for Tackling a New Face of an Old Foe

Accessible Version: https://youtu.be/YrLP9UE-6Kk
In 2010, I was diagnosed with Multidrug-resistant Tuberculosis (MDR TB)
Un treated, each person with TB will infect on average between 10-15 people each year.
Only 42% of MDR TB patients in South Africa are cured

Side effects of treatment may include hearing loss, neurologic, and psychiatric symptoms
- Treatment for MDR TB involves highly toxic, injectable drugs which cause severe side effects

- Every day I had to put up an IV infusion for myself and for 18 months I had to take 30 pills a day

- 10 of these pills were to combat side effects of the anti-tuberculosis medications
Bedaquiline is the first new drug to treat TB to be approved by the U.S. Food and Drug Administration in over 40 years.

I was cured of MDR TB one year after being granted “compassionate” use of bedaquiline.
For more information:

vimeo.com/album/2646660/video/68639600
Tuberculosis

- Ancient disease dating to ~3400 BC
  - *Mycobacterium tuberculosis* discovered by Robert Koch in 1882
- Can cause latent TB infection (LTBI) and TB disease
- Primary involvement in lungs
- Airborne transmission by respiratory droplets
  - Highest risk in congregate settings, poor ventilation, or prolonged exposure
  - HIV infection an important contemporary risk factor
- Diagnosis by sputum smear microscopy
- First anti-TB drugs developed in 1940s
Tuberculosis: Global Health Importance

- 8.6 million new TB cases each year worldwide
- More than 95% cure rate
  - Combination (4-drug) standard therapy
  - Uninterrupted 6-month treatment under directly observed therapy
- Case notification and cure rates under program conditions below targets
  - 66% (5.7 million) case notification rate
  - 87% treatment success rate

Drug-resistant Tuberculosis

- Development of resistance can occur spontaneously in large replicating bacterial populations (once in $10^6$–$10^8$ bacteria)
- Drug resistance largely caused by nonstandard treatment regimen or incomplete adherence to treatment
- Spread of drug-resistant strains through person to person transmission

Adapted from: CDC. *Antibiotic Resistance Threats in the United States, 2013.*
Global Burden of Drug-resistant TB

8.6 million TB Cases

Any resistance ~1 million

Multidrug-resistant (MDR) TB 450,000

Extensively drug-resistant (XDR) TB 43,200

Global Emergence of XDR TB

**World TB Day — March 24, 2006**
World TB Day is March 24. This annual event commemorates the date in 1882 when Robert Koch announced his discovery of Mycobacterium tuberculosis.


Countries that had notified at least one case of extensively drug-resistant tuberculosis by the end of 2012

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Drug-resistant TB a serious threat in United States and globally

Among 10,528 U.S. TB cases in 2011, 9.9% had drug resistance

- 124 cases of MDR TB = 1.2% of TB cases
- 6 cases of XDR TB = 4.8% of MDR TB cases

Highest Burden of Global MDR TB in India, Russia and China

Number of multidrug-resistant tuberculosis cases estimated to occur among notified pulmonary TB cases, 2012

Diagnostic Challenges for Drug-resistant TB

Drug-resistant TB cannot be diagnosed by smear microscopy

- **Diagnosis requires culture and drug-susceptibility testing or molecular testing**

- **Key barriers**
  - Inadequate laboratory infrastructure, investment, and capacity
  - Limited patient access to adequate testing facilities
    - <5% of TB patients have access to diagnosis of drug resistance
  - Policies that limit who can be tested, and when
    - Due to resource limitations

Underdiagnosis of Drug-resistant TB

- **20% of total estimated MDR TB cases detected in 2012**
  - Case detection even lower in India (6%) and China (3%)
  - Limited data on children; case detection lower than for adults

- **Only 5% of new cases and 9% of previously treated cases are tested for drug resistance**
  - Testing capability for XDR TB even more limited

- **In 2009, World Health Assembly called for universal access to TB culture and drug-susceptibility testing**
  - Achieving this goal will require massive laboratory and health system strengthening
  - CDC is involved in global initiatives to address this critical need

Treatment Challenges in Drug-resistant TB

Compared to drug-susceptible TB, treatment of MDR TB is

- Less effective
- More toxic
  - 90% experience side effects, some severe (e.g., hearing loss, neuropathy, or psychosis)
- Lengthier
  - Up to 2 years vs. 6 months
- More costly
  - 10–100 times more costly ($2500 and up)

Source: Médecins San Frontières

Treatment Challenges in Drug-resistant TB

Among the minority of those who are treated:

- Low cure rates (48%-54%)
- Low treatment completion rates due to:
  - Loss to follow-up (14%-23%)
  - Death (15%)
  - Treatment failure (8%-9%)

Drug-resistant TB (MDR and XDR TB) causes extensive morbidity and mortality globally
CDC considers drug-resistant TB to be a serious health threat
Major challenges with diagnosis and treatment
High-burden countries including India, China, and Russia face substantial economic, logistic, and policy barriers to improving diagnosis and treatment
New diagnostics and new drugs offer promise
Rapid Diagnosis of MDR TB: A Laboratory Systems-based Approach

Thomas M. Shinnick, PhD
Associate Director for Global Laboratory Activities
Division of Tuberculosis Elimination
National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention
Lack of Laboratory Services is a Barrier to the Control of TB and Drug-resistant TB

- Only ~53% of new cases and 63% of new smear-positive cases are detected
- In high HIV prevalence settings, AFB smear-based testing is less sensitive
- Only 19% of estimated MDR TB cases laboratory confirmed
- Many XDR TB cases are not detected due to the lack of second-line DST

- Molecular diagnostics may help solve the challenge

AFB: acid-fast bacilli
DST: drug susceptibility testing
WHO-Endorsed Molecular Tests for TB

- **Molecular Line Probe Assay (LPA)**
  - Regional or national-level laboratory
  - Smear-positive sputum or MTB cultures

- **Cepheid Xpert® MTB/RIF test**
  - Sub-district or district hospital level laboratory
  - Smear-positive or negative pulmonary and extra-pulmonary specimens from adults and children

MTB: Mycobacterium tuberculosis
A Single Xpert® MTB/RIF Test

- Is about as sensitive and specific as one culture on solid media
- Can increase TB case detection by 40% over direct smear microscopy alone
- Takes only 2 hours to complete, compared to weeks for culture
- Uses simple sputum processing steps
- Detects presence of MTB and rifampicin resistance simultaneously
- Does not require sophisticated BSL-3 facilities or specialized expertise

**Sample** → **Cartridge** → **Module** → **4 Module Instrument**

MTB: Mycobacterium tuberculosis
BSL-3: Biosafety level 3
Rifampicin resistance (RIF-R) is a marker for MDR TB

- >85% of RIF-R strains are MDR strains in most countries
- WHO recommended treatment of RIF-R TB is similar to MDR TB

Strong recommendation by WHO to use Xpert® MTB/RIF as the initial diagnostic test in individuals suspected of having MDR TB

- Excellent sensitivity (95%) and specificity (98%) for detecting rifampicin resistance
- Implementing Xpert® MTB/RIF will cost less than conventional culture and DST to meet diagnostic targets for MDR TB

DST: drug susceptibility testing
Lessons from Early Implementers of Xpert® MTB/RIF Testing

- Clinical and public health impact varies with the epidemiologic setting, target population, laboratory testing algorithm, and treatment algorithms
  - Can increase detection of bacteriologically confirmed and rifampicin-resistant cases, as well as decrease time to diagnosis in resource-limited settings
  - Has less impact in settings where clinicians initiate TB treatment in the absence of bacteriological confirmation
- Private sector must be engaged
- Diagnostic and treatment capacity need to be matched
Realizing the Potential of Xpert® MTB/RIF to Treat More People with MDR TB More Quickly

- A systems approach is needed to strengthen all steps in the process
- Testing must be linked to drug access and program capacity
Impact of Xpert® MTB/RIF Testing on Time To Treatment

Xpert® MTB/RIF may reduce the median time to treatment

- For culture-diagnosed cases, from 56 days to 5 days
- For MDR TB, from 86 days to 5 days

Scale-up of PMDT in Parallel with Xpert<sup>®</sup> MTB/RIF Scale-up

- **Laboratory capacity**
  - Conventional culture and DST
  - Other molecular methods (e.g., line-probe assays)
  - Specimen referral and reporting of results

- **Treatment capacity**
  - Hospital based and ambulatory care
  - Patient support and palliative care
  - Infection control

- **Second-line drug management**
  - Forecasting and ordering

PMDT: programmatic management of drug-resistant tuberculosis
DST: drug susceptibility testing
Summary

- Lack of laboratory services is a crucial barrier to an effective response to TB and MDR TB
- Molecular diagnostics may revolutionize TB lab services
- Xpert® MTB/RIF should be used as the initial diagnostic test in individuals suspected of having MDR TB
- Xpert® MTB/RIF should increase detection of TB and MDR TB cases and shorten the time to begin treatment
- Need to scale-up PMDT program in parallel with increased use of Xpert® MTB/RIF, so that the anticipated increased number of cases can be treated more effectively

PMDT: programmatic management of drug-resistant tuberculosis
Rational Use of New Drugs for Treatment of MDR TB: Context and Challenges

Christian Lienhardt, MD, MSc, PhD
Senior Research Advisor
Global TB Programme
World Health Organization
Geneva, Switzerland
Global TB Drug Pipeline

No TB drugs currently in phase I trials
New Drugs: Bedaquiline (BDQ)

- Novel target: ATP synthase inhibitor
- Chemical class: diarylquinoline
  - First new TB drug class in over a generation
- Phase IIb data: placebo-controlled trial of BDQ in combination with background MDR TB therapy (BT)
  - Primary endpoint: time to sputum culture conversion and proportion with sputum culture conversion at 6 months
  - Showed greater efficacy of BT with BDQ, than BT with placebo

- Approved by FDA (accelerated procedure) in December 2012 “as part of combination therapy to treat adults with multi-drug resistant TB when other alternatives are not available”

ATP: adenosine triphosphate
June 2013 - BDQ recommended for use in MDR TB treatment under five strict conditions:

- Treatment under close monitoring
- Proper patient selection
- Patient informed consent required
- Treatment design based on WHO recommendations
- Active pharmacovigilance (drug safety monitoring)
New Drugs: Delamanid (DLM)

- Chemical class: nitroimidazole

- Phase Ib data: placebo-controlled trial of Delamanid in combination with optimized background therapy (OBT)
  - 2 test arms: (i) Delamanid (100mg bid) + OBT
    (ii) Delamanid (200mg bid) + OBT
  - Primary endpoint: 2-month sputum culture conversion
  - Showed greater efficacy of OBT with DLM, than OBT with placebo

- Phase III trial launched in September 2011

Delamanid: Regulatory Status

- Approved in December 2013 by the European Medicines Agency (EMA) "as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability."
- Not yet approved by FDA
- Planned review by WHO in April 2014
Public Health Challenges of Introduction of New TB Drugs in Countries

- Determine optimal regimens for use of newly developed or re-purposed drugs for treatment of drug-susceptible and DR TB under programmatic conditions
- Evaluate patient eligibility requirements
- Assess programmatic feasibility
- Evaluate cost-effectiveness
Public Health Challenges of Introduction of New TB Drugs in Countries

- **Ensure proper surveillance and pharmacovigilance**
  - Especially in case of accelerated approval
  - Safety monitoring, especially for Bedaquiline

- **Ensure responsible use**
  - Appropriate indication, doses, drug combinations, and treatment duration
  - Prevent unwarranted off-label use and emergence of resistance

- **Encourage equitable access**
Other New Treatment Regimens Involving Previously Approved Drugs

- **Short course regimen for treatment of MDR TB**
  - Treatment series in Bangladesh with various combinations and durations of treatment
  - Best outcome with 9 months duration regimen
    - Minimum 4 months of 7 drug combination (KmCfzGfxEHZPto) prolonged if necessary until culture negative
    - Followed by 5 months of 4 drug combination (GfxEZCfz)

\[\text{Km}=\text{kanamycin} \]
\[\text{Cfz}=\text{clofazimine} \]
\[\text{Gfx}=\text{gatifloxacin} \]
\[\text{E}=\text{ethambutol} \]
\[\text{H}=\text{high-dose isoniazid} \]
\[\text{Z}=\text{pyrazinamide} \]
\[\text{Pto}=\text{prothionamide} \]

Outcome (regimen 6):
- Cure 82.5%
- Completion 5.3%
- Death 5.3%
- Default 5.8%
- Failure 0.5%
- Relapse 0.5%

Proportion of patients with a successful outcome in the treatment of multidrug-resistant tuberculosis

(Clo = clofazimine; Gati = gatifloxacin; INH = isoniazid; Oflo = ofloxacin; Pth = prothionamide)

Treatment Options for XDR TB
Remain Limited

- Lack of evidence for the best drug regimens for treating patients with XDR TB

- Recent review of treatment outcomes did not find any associations between specific drugs or treatment regimens and successful outcomes
  - However, success highest if at least 6 drugs used in intensive phase and 4 in continuation phase

- Successful treatment is possible, but requires
  - Early and accurate diagnosis of resistance to second-line drugs
  - Availability of multiple classes of second-line drugs
  - Access to clinicians who have special expertise in treating such cases

Pediatric Formulations of Current Drugs and Trials of New Drugs are Urgently Needed

- Few estimates on burden of disease in children
  - Estimated to be 6%-10% of adult burden
  - Does not include children exposed to DR TB
- Current diagnostics limited; Xpert® shown to be useful
- Limited pharmacokinetic data, few child-friendly formulations
- TB treatment programs often separate from child health programs
- Lack of capacity and expertise among providers
- Limited funding
- Small proportion of children actually treated, although those treated have excellent outcomes
  - Among 315 patients, 81% success rate

Becerra et al., 2012, Ettehad et al., 2012, Hesseling et al, 2013; Furin et al., 2013, Graham et al., 2012
Preventive Therapy for Contacts of MDR and XDR TB Cases

- Robust evidence to support the efficacy of INH preventive therapy (PT) to reduce the risk of disease progression in child and adult contacts of drug-susceptible TB
  - 11 randomized controlled trials (RCT) involving over 73,000 persons

- No RCT comparing preventive regimens for contacts of MDR TB

- Pediatric cohort of MDR TB contacts in Cape Town, South Africa
  - Treated with INH + ethambutol + ofloxacin
  - Among 168 children treated, regimen well-tolerated and only 3.2% developed active TB

INH: isoniazid
Preventive Therapy for Contacts of MDR and XDR TB Cases

- **Outbreak investigation in Chuuk, Micronesia**
  - 5 MDR TB cases and 119 infected adult and child contacts
  - All contacts offered preventive therapy (PT) for 12 months (FQ alone or with another agent)
  - None of the 104 contacts who received PT developed TB, but 3 of 15 untreated contacts progressed to disease

- **RCT study “TB-CHAMP” in late stages of development to assess preventive therapy with INH or levofloxacin in children exposed to drug-resistant TB in South Africa**

Seddon et al., 2013
INH: isoniazid
FQ: fluoroquinolone
Conclusions

- Two newly approved medications for the treatment of MDR TB are Bedaquiline (FDA approved) and Delamanid (EMA approved)
- Multiple scientific and program challenges remain as these drugs are used more widely
  - Need for data collection under “real world” conditions
- New combinations of existing and repurposed medicines show potential for treatment shortening of MDR TB
- Areas requiring additional investigation include XDR TB treatment, pediatric regimens to treat MDR TB, and preventive therapy for contacts of both MDR and XDR TB cases

Tom Kenyon, MD, MPH

Director

Center for Global Health
Centers for Disease Control and Prevention
How Did We Get Here?  
A Brief History of Drug-susceptible TB

- 19th century: Microscopy, culture, tuberculin skin testing, radiology
- 20th century: Stepwise improvements in these diagnostics
- 1940s-1960s: Effective, safe TB drugs discovered, multidrug therapy established by extensive clinical trials
- 1970s-1980s: Systematic 5-part TB control strategy based on diagnosis by microscopy and standard short-course treatment elaborated
- 1990s to date: Systematic 5-part TB control strategy implemented and expanded worldwide
Global Progress in TB Care and Control, 2000-2012

Global incidence decreased 15%

Global mortality decreased 40%

<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence (per 100,000 population per year)</th>
<th>Prevalence (per 100,000 population)</th>
<th>Mortality (per 100,000 population)</th>
<th>Case detection rate (%)</th>
<th>Treatment success rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>148</td>
<td>263</td>
<td>22</td>
<td>42</td>
<td>69</td>
</tr>
<tr>
<td>2012</td>
<td>122</td>
<td>169</td>
<td>13</td>
<td>66</td>
<td>87</td>
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</tbody>
</table>

World Health Organization. *Global Tuberculosis Report 2013*
## Progress Toward 2015 Millennium Development Goals Related to TB as of 2012

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Target</th>
<th>Global Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>Falling incidence rate</td>
<td><strong>Target met</strong></td>
</tr>
<tr>
<td>Prevalence</td>
<td>50% decrease compared with 1990</td>
<td>Not on track to meet target</td>
</tr>
<tr>
<td>Mortality</td>
<td>50% decrease compared with 1990</td>
<td><strong>On track to meet target</strong></td>
</tr>
<tr>
<td>Case Detection</td>
<td>70% of estimated number of cases</td>
<td>66%</td>
</tr>
<tr>
<td>Treatment Success</td>
<td>85% among new sputum smear-positive cases</td>
<td>87%</td>
</tr>
</tbody>
</table>
How Did We Get Here?  
A Brief History of Drug-resistant TB

- 1947: Emergence of drug-resistant TB documented
- 1955: First nationwide survey documented widespread drug resistance in the United Kingdom
- 1980s-1990s: Worldwide outbreaks of MDR TB
- 1990s-present: WHO and IUATLD Global Project on anti-TB Drug Resistance Surveillance
- 1990s-2000s: Pilot testing services for DR TB in middle- and low-income countries

IUATLD: International Union Against Tuberculosis and Lung Disease
Streptomycin Committee, Central Office Veterans Administration. Am Rev Tuberc, 1947
Global Scale-up of Services for Drug-resistant TB

- **2009:** World Health Assembly resolution declaring that all TB cases should be appropriately diagnosed and treated

- **Unprecedented pace of scale-up; among 450,000 incident cases of MDR TB worldwide:**
  - 2009: ~5% of MDR TB cases detected and treated worldwide
  - 2013: ~20% of MDR TB cases detected and treated worldwide

- **Shortfalls in progress toward 2015 Goals for case detection and treatment success**
  - Case detection target 100%, current status 20%
  - Treatment success target 75%, current status 48%

WHO. *Global Tuberculosis Report 2013*
Global Plan to Stop TB. Available at: www.stoptb.org/global/plan/
Rapid Scale-up of Services for Drug-resistant TB

- **Unprecedented leadership and political commitment**
  - World Health Assembly, World Health Organization
  - Public and private sectors worldwide

- **Unprecedented economic support**
  - The Global Fund to Fight AIDS, Tuberculosis, and Malaria (Global Fund); UNITAID; PEPFAR; BMGF; USAID

- **New technology**
  - Gene Xpert® and other rapid molecular methods
  - Rapid expansion and implementation worldwide

- **Better treatment**
  - Global Drug Facility: quality-assured anti-TB drugs at reduced prices
  - New drugs (Bedaquiline, Delamanid) and drugs with new indications (e.g., linezolid)

PEPFAR: President’s Emergency Fund for AIDS Relief
BMGF: Bill and Melinda Gates Foundation
USAID: US Agency for International Development
As of 30 September 2013, a total of 1,843 GeneXpert instruments (comprising 9,625 modules) and 4,214,990 Xpert MTB/RIF cartridges had been procured in the public sector in 95 of the 145 countries eligible for concessional pricing.
Prevention and Control of Drug-resistant TB

- **Primary Prevention**
  - Strengthen basic TB control services to detect and cure all drug-susceptible TB cases
    - Don’t create new cases of DR TB
  - Detect and treat existing drug-resistant TB cases
    - Prevent transmission to others
  - Infection control
    - Prevent transmission

- **Secondary Prevention**
  - Detect and treat contacts of DR TB cases
    - Prevent progression from LTBI to active disease

LTBI: latent tuberculosis infection
Obstacles to Detect and Treat Existing Cases of MDR TB

- **Case Detection and Diagnosis**
  - Need to strengthen laboratories to provide classic culture and susceptibility testing
  - Rapid molecular methods not yet widely available

- **Effective treatment**
  - Limited quality assured second-line drug supply
  - Paucity of evidence from clinical trials
  - Need for data on use of new drugs
### Rates of Baseline and Acquired XDR TB

<table>
<thead>
<tr>
<th>Total number baseline MDR TB isolates</th>
<th>Baseline isolate XDR n (%)</th>
<th>Baseline isolate simple MDR TB</th>
<th>Acquired XDR TB n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>832</td>
<td>66 (7.9%)</td>
<td>766</td>
<td>68 (8.9%)</td>
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<table>
<thead>
<tr>
<th>Green Light Committee*</th>
<th>Acquired XDR TB, %</th>
<th>Risk Ratio (95% CI) unadjusted</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLC-approved</td>
<td>3.7</td>
<td>0.27 (0.16, 0.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-GLC</td>
<td>15.6</td>
<td>Referent</td>
<td></td>
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*The GLC serves as a technical advisory body to the Stop TB Partnership and the World Health Organization

Cegielski JP, et al., 2014
GLC: Green Light Committee
Importance of Infection Control: Estimating Global Role of Transmission

- **WHO**: 74% of MDR TB cases globally arise from transmission rather than acquired resistance

- **China**: 78% of MDR TB due to transmission

- **Meta-analysis of 31 cohorts**: 90% of XDR TB cases with no history of MDR TB treatment
  - Initially infected with XDR TB strains

Zhao et al. NEJM 2012
Falzon et al. Eur Resp J 2013
WHO 2010 Drug-Resistance Report
Transmission of XDR TB, 2005-2009, Tugela Ferry, South Africa

- Largest XDR TB cluster reported worldwide
- Total of 516 cases culture confirmed
- Genotyping revealed that >85% of cases had single predominant genetic fingerprint
- Epidemiologic investigation and social network analysis demonstrated up to 5 generations of transmission in hospital

Red line = single chain of transmission

Gandhi et al. J Inf Dis 2013
CDC / USAID Partnership

- Technical assistance for MDR TB scale-up in countries with underperforming Global Fund grants
  - Phase 1 (starting 2013): six countries (Philippines, Bangladesh, Vietnam, Mozambique, Uganda, Nigeria)
  - Phase 2 (starting 2014): eight more countries (India, Kenya, Haiti, Lesotho, Swaziland, Botswana, Tanzania, Zambia)

- “New model” of technical assistance – long term strengthening of local human resources instead of “fly-in, fly-out” short term assistance
Additional CDC Contributions

- **Antimicrobial Resistance Initiative**
  - CDC report: Antimicrobial Resistance Threats
    - White House and Congressional Support
  - WHO and IUATLD reports: Global Anti-TB Drug Resistance Surveys

- **Global Health Security Agenda**
  - MDR TB and XDR TB
  - Prevent – Detect – Respond model applies to TB, both as endemic disease and in outbreak settings
  - Example of Uganda, 2013
    - Enhanced communications
    - Enhanced laboratory capacity and specimen referral systems
    - Improved outbreak response capacity
Looking Past the Millennium Development Goals: Three Pillars of the Post-2015 Strategy

- Integrated, patient-centered TB care and prevention

- Bold policies and supportive systems
  - Example: global recommendation for using Xpert® MTB/RIF as a primary diagnostic test for RIF-resistance simultaneous with the diagnosis of TB itself, leading to numerous initiatives for rapid worldwide scale-up

- Intensified research and innovation
Multidrug-resistant Tuberculosis: Tools for Tackling a New Face of an Old Foe