Tuberculosis in 2017: Searching for new solutions in the face of new challenges

6th TB Symposium – Ministry of Health of the Republic of Belarus, Republican Scientific and Practical Center for Pulmonology and Tuberculosis, and Médecins Sans Frontières

1-2 March, 2017, MINSK, BELARUS

The reasons why new treatments and approaches are needed, experience in new drugs and plans for future

Alena Skrahina

RSPC PT
RR/MDR-TB Belarus response

Notification and enrolment on treatment

<table>
<thead>
<tr>
<th>Year</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notified TB cases</td>
<td>6065</td>
<td>5756</td>
<td>5483</td>
<td>5511</td>
<td>5554</td>
<td>5118</td>
<td>5246</td>
<td>4859</td>
<td>4274</td>
</tr>
<tr>
<td>% new TB cases with drug susceptibility testing (DST) results</td>
<td>92%</td>
<td>94%</td>
<td>93%</td>
<td>96%</td>
<td>90%</td>
<td>94%</td>
<td>90%</td>
<td>95%</td>
<td>97%</td>
</tr>
<tr>
<td>Notified MDR/RR-TB cases</td>
<td>651</td>
<td>870</td>
<td>923</td>
<td>1433</td>
<td>1644</td>
<td>1637</td>
<td>1604</td>
<td>1386</td>
<td>1282</td>
</tr>
<tr>
<td>Patients started on MDR-TB treatment</td>
<td>200</td>
<td>1446</td>
<td>2478</td>
<td>2154</td>
<td>1903</td>
<td></td>
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</tr>
</tbody>
</table>
M/XDR-TB diagnostics in Belarus

**Pulmonary**

I. Image (Chest X-ray, CT)
II. Sampling
   1. Sputum
   2. Induced sputum
   3. Gastric aspirate (children)
   4. Other issue sampling: bronchoscopy, VATS
   5. Important: process via microbiology lab for TB tissue samples of any thoracic surgery

**EPTB**

I. Image (USE, X-ray, CT, MRI)
II. Sampling
   1. Cerebrospinal fluid
   2. Pleural fluid
   3. Joint fluid
   4. Peritoneal fluid
   5. Biopsy samples
   6. Tissue after surgery

**Microscopy**

- X-pert MTB/RIF
- LPA (MTC, FL, SL)

**Start treatment within 2-24 hours for:**
- DS-TB, Mono(H)R-TB
- MDR-TB, Pre-XDR-TB
- XDR-TB

**Culture**

- Liquid medium (BACTEC MGIT960)
- Solid medium (Lowenstein-Jensen)

**Treatment correction (weeks)**

Individualized based on full spectrum susceptibility and resistance

**Rapid tests**
M/XDR-TB treatment outcomes

**MDR-TB 2011-2013**

<table>
<thead>
<tr>
<th>Year</th>
<th>Cured</th>
<th>Completed</th>
<th>Failure</th>
<th>Death</th>
<th>LTFU</th>
<th>Not evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>41%</td>
<td>8%</td>
<td>21%</td>
<td>10%</td>
<td>12%</td>
<td>8%</td>
</tr>
<tr>
<td>2012</td>
<td>45%</td>
<td>10%</td>
<td>22%</td>
<td>11%</td>
<td>11%</td>
<td>1%</td>
</tr>
<tr>
<td>2011</td>
<td>43%</td>
<td>10%</td>
<td>24%</td>
<td>11%</td>
<td>11%</td>
<td></td>
</tr>
</tbody>
</table>

**XDR-TB 2013**

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment success</td>
<td>38%</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>33%</td>
</tr>
<tr>
<td>Death</td>
<td>7%</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>5%</td>
</tr>
<tr>
<td>Not evaluated</td>
<td>7%</td>
</tr>
</tbody>
</table>
Treatment

New Drugs for M/XDR-TB treatment

- Bedaquiline
- Delamanid

Repurposed
- Linezolid
- Clofazimine
- Moxifloxacin
- Imipenem/Cilastatin
- Meropenem
- Amoxicillin/clavulanic acid

Since June 2015
Treatment

Conditions for the use of new drugs

- Proper patient inclusion
- Adherence to the principles of designing a WHO-recommended MDR-TB regimen
- Treatment is closely monitored
- Pharmacovigilance / active Safety Monitoring and Management (aDSM)
- Patient informed consent obtained

Recent WHO documents on new drugs
Treatment

Early access to new TB drugs

- Funding and assistance: GF, WHO, MSF
- Special Resolution of the Council of Ministers
  - National guidelines new drug containing regimens
- BDQ, DLM, CFZ use without actual registration
- Import waiver
  - Single permission with batch quality control
- Treatment monitoring and active Drug Monitoring and Management
  - MoH order
Treatment

**MDR-TB Consilium (Expert Board)**

- Careful patient selection
- Ethic Committee approval
- Patient’s informed concern
- Designing treatment regimen in line with WHO recommendations
- Management of co-morbidities
- Active Drug Safety Monitoring and Management of Adverse Events
- Adherence issues
  - DOT, VOT
  - Alcohol and drug abuse
  - Mental health problems
  - Social support issues
- Surgery issues
## Treatment

**Design of new drugs containing regimens**

<table>
<thead>
<tr>
<th>Intensive phase</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em><em>Bdq</em> / DLM</em>**</td>
<td></td>
</tr>
<tr>
<td>Lzd</td>
<td>±</td>
</tr>
<tr>
<td>Cfz*</td>
<td></td>
</tr>
<tr>
<td>Trd</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Continuation phase</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lzd</strong></td>
<td>±</td>
</tr>
<tr>
<td><strong>Cfz</strong>*</td>
<td></td>
</tr>
<tr>
<td>Trd</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* DST to these drugs have not been conducted
Totally implantable central venous access ports
Totally implantable central venous access ports

Total - 54 in 52 patients

Approach:
- Subclavian right - 34
- left - 7
- Jugular right - 6
- left - 5
- Femoral right - 2
## Patients on treatment

<table>
<thead>
<tr>
<th>No</th>
<th>Age</th>
<th>Sex</th>
<th>DST</th>
<th>Treatment Regimen</th>
<th>Date of Treatment initiation</th>
<th>Baseline</th>
<th>Follow-up Month 1</th>
<th>Follow-up Month 2</th>
<th>Follow-up Month 3</th>
<th>Follow-up Month 4</th>
<th>Follow-up Month 5</th>
<th>Follow-up Month 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSF002</td>
<td>43</td>
<td>F</td>
<td>XDR</td>
<td>Dlm-Imp/Cln-Amx/Clv-Cfz-Lfx-Cs-PAS</td>
<td>12-Aug-15</td>
<td>1+12</td>
<td>P-15</td>
<td>1+12</td>
<td>P-15</td>
<td>1+12</td>
<td>Oct-15</td>
<td>N</td>
</tr>
</tbody>
</table>

### Total no. of patients

- **330**

### Incl. children and adolescents (BDQ)

- **15**

### BDQ

- **297**

### DLM

- **33**

### BDQ Interim results (> 6 mo. treatment)

- **208**

### Cure

- **2**

### Treatment completed

- **1**

### Treatment failed

- **1**

### LTFU

- **8**

### Died

- **3**

### Treatment continues

- **193**
## Adherence and LFTU

<table>
<thead>
<tr>
<th>Month of LFTU / DR</th>
<th>Risk factor/condition</th>
<th>Results of non-adherence</th>
<th>Further treatment if known</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,5 MDR</td>
<td>Alcohol abuse, brain injury consequences</td>
<td>Lost and found</td>
<td>Conventional care At home region</td>
</tr>
<tr>
<td>2 XDR</td>
<td>Alcohol abuse</td>
<td>transferred to compulsory treatment</td>
<td>Palliative care</td>
</tr>
<tr>
<td>3 XDR</td>
<td>multiple organ disorders: dwarfism, multiple urolithiasis, DM</td>
<td>Lost and found</td>
<td>Palliative care At home region</td>
</tr>
<tr>
<td>4 XDR</td>
<td>Alcohol abuse</td>
<td>transferred to compulsory treatment</td>
<td>Palliative care</td>
</tr>
<tr>
<td>4 XDR</td>
<td>Alcohol abuse</td>
<td>Lost and found</td>
<td>Palliative care At home region</td>
</tr>
<tr>
<td>6 XDR</td>
<td>Alcohol abuse former prisoners, imprisoned during treatment</td>
<td>transferred to prison</td>
<td>Conventional /palliative care?</td>
</tr>
<tr>
<td>7 XDR</td>
<td>Alcohol abuse</td>
<td>Lost and found</td>
<td>Conventional care At home region</td>
</tr>
<tr>
<td>12 pre-XDR</td>
<td>Job abroad (driver)</td>
<td>missing (m.i.a)</td>
<td>still missing</td>
</tr>
</tbody>
</table>
Death

• < 1 month of treatment XDR
  – XDR-TB/HIV/HCV → progression → disseminated disease (incl. CNS involvement)

• 4 months of treatment XDR
  – Acute heart failure, alcohol abuse (overdose) possible relations with treatment

• 11 months of treatment XDR – 3 mo. after BDQ finished
  – Sudden death – post mortem: mesenteric thrombosis, pulmonary embolism
Conclusions

• New TB drugs are vitally important to improve M/XDR-TB treatment outcomes
• Belarus demonstrated existence of necessary mechanisms for successful implementation of new TB drugs
• Safety and effectiveness showed in preliminary results provides a basis for further expansion
Thanks!