New and repurposed anti-TB drug introduction and active TB drug-safety monitoring and management

Alena Skrahina, NTP Belarus

WOLFHEZE WORKSHOPS 2017
REACHING OUT
To find, treat and cure more TB patients and address their co-morbidities
31 May-2 June, 2017
TB epidemiology

2016

<table>
<thead>
<tr>
<th>TB indicator</th>
<th>No. of patients</th>
<th>Per 100 000</th>
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<tbody>
<tr>
<td>Incidence</td>
<td>2864</td>
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<td>Prevalence</td>
<td>5481</td>
<td>57.7</td>
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<tr>
<td>Mortality</td>
<td>323</td>
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TB notification

Graph showing TB notifications from 2002 to 2015, with a decrease from approximately 5000 to 3115 in 2016.


Bar chart showing the distribution of MDR, pre-XDR (SLI), pre-XDR (FQ), and XDR.
Key strategic directions of NSP

1. Scale up of case finding and prophylaxis
2. Full scale-up of rapid molecular diagnostics
3. **Rapid uptake of new drugs and regimens**
4. Expanding people-centered models of care
5. Scale up TB research

Bedaquiline Delamanid
Linezolid Clofazimine
Moxifloxacin Carbapenems
Rapid uptake of new drugs and regimens

- 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 aDSM MoH order
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

1. The use of delamanid in the treatment of multidrug-resistant tuberculosis
   Interim policy guidance
2. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis
   Interim policy guidance
3. The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents
   Interim policy guidance
4. WHO treatment guidelines for drug-resistant tuberculosis
   2016 update
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
• aDSM
• Adherence issues
  • DOT, VOT
  • Alcohol and drug abuse
  • Mental health problems
  • Social support issues
• Surgery issues
Design of new drugs containing regimens

<table>
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<tr>
<th>Intensive phase</th>
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<tr>
<td>Bdq* / DLM*</td>
<td>Z</td>
</tr>
<tr>
<td>Lzd</td>
<td>Imp/Cilas* (Merop)* + Amx/Clv*</td>
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<tr>
<td>Cfz*</td>
<td>Lfx / Mfx</td>
</tr>
<tr>
<td>Trd</td>
<td>Pto/Eto</td>
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<tr>
<td></td>
<td>PAS</td>
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</table>

<table>
<thead>
<tr>
<th>Continuation phase</th>
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<tbody>
<tr>
<td>Lzd</td>
<td>Mfx/Lfx</td>
</tr>
<tr>
<td>Cfz*</td>
<td>AG(Cm/Am/Km) 3 time a week</td>
</tr>
<tr>
<td>Trd</td>
<td>Pto/Eto</td>
</tr>
<tr>
<td></td>
<td>PAS</td>
</tr>
<tr>
<td>±</td>
<td></td>
</tr>
</tbody>
</table>

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

“active and systematic clinical and laboratory assessment of patients on treatment with new TB drugs, novel MDR-TB regimens or XDR-TB regimens to detect, manage and report suspected or confirmed drug toxicities”

apps.who.int/iris/bitstream/10665/204465/1/WHO_HTM_TB_2015.28_eng.pdf
Cohort Event Monitoring. aDSM

Data analysis and database input

Vigibase
National database of ADR

National TB register

Analysis Report Recommendations
Enrollment form

### Patient data
- **Pre-conditions:**
  - Co-morbidity/
  - Risk factor/
  - Profile-modifying factors

### Monitoring site/HCP data
- **Clinical events before admission**
- **Microbiological and laboratory data**
  - (hematological, hepatological, renal, pancreatic, metabolic, immunological parameters)

### Drugs, traditional medicines, additives before admission

### Laboratory tests
- Lab results
- Test
  - Date
  - Result (ed.)
Treatment monitoring form

Patient ID

Patient data

Monitoring site/HCP data

Audiogramm, ECG, ophthalmologist, neurologist examination, X-ray

Laboratory data
(hematological, hepatological, renal, pancreatic, metabolic, immunological, electrolyte parameters)

New clinical events

Anti-TB treatment

Concomitant medication, traditional medicines etc.

DST

Outcomes

To capture:
1) SAE
2) AE of special interest
3) AE → treatment discontinuation or change in drug dosage
4) Other clinically significant AE
## Patients on NEW DRUGS
### May 15, 2017

<table>
<thead>
<tr>
<th>Total no. of patients</th>
<th>406</th>
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<tbody>
<tr>
<td>Incl. children and adolescents</td>
<td>23</td>
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<tr>
<td>BDQ</td>
<td>350</td>
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<tr>
<td>DLM</td>
<td>51</td>
</tr>
<tr>
<td>BDQ+DLM</td>
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</table>

### Interim results BDQ

<p>| &gt; 6 months of treatment | 208 |
| &gt; 12 months of treatment | 156 |
| Treatment failed | 1 |
| LTFU | 8 |
| Died | 3 |
| Treatment continues | 394 |</p>
<table>
<thead>
<tr>
<th>Month of LTFU / 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>
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<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>
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<tr>
<td>4 XDR</td>
<td>Alcohol abuse</td>
<td>transferred to compulsory treatment</td>
<td>Palliative care</td>
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<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>
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<tr>
<td>7 XDR</td>
<td>Alcohol abuse</td>
<td>Lost and found</td>
<td>Conventional care at home region</td>
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<tr>
<td>12 pre-XDR</td>
<td>Job abroad (driver)</td>
<td>missing (m.i.a)</td>
<td>still missing</td>
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</table>
Death

• < 1 month of treatment XDR
  • XDR-TB/HIV/HCV → progression → disseminated disease (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
Sputum conversion

- Culture positive: $n=201$, $n=3$
- Smear positive: $n=74$, $n=0$
Safety results

*QTcF-interval example*

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<th>ФИО</th>
<th>год рождения</th>
<th>пол</th>
<th>начало лечения</th>
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<th>2-я нед</th>
<th>разница QT</th>
<th>1-й мес</th>
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Safety of BDQ-containing regimens

Interim results

Most common AE:

- ↑ LFT
- ↓ K +
- ↓ Mg ++
- ↑ uric acid

Arrhythmia (ECG)
Nausea
Vomiting
Abdominal pain
Low platelet count
↓ creatinin clearance
Headache
Dizziness
Insomnia
Paraesthesia
Periph. polyneuropathy
Hearing loss
Candidiasis

n= 208

AE: 100% of patients, most AE - mild and moderate

SAE: death - 3, treatment discontinuation due to AE – 0

AE:
- ↑ LFT 29,3%
- ↓ K + 21,7%
- ↓ Mg ++ 17,4%
- ↑ uric acid 17,4%
- Arrhythmia (ECG) 69,1%
- Nausea 43,4%
- Vomiting 12,8%
- Abdominal pain 19,0%
- Low platelet count 19,0%
- Headache 50,5%
- Dizziness 50,5%
- Insomnia 50,5%
- Paraesthesia 36,9%
- Periph. polyneuropathy 36,9%
- Hearing loss 36,9%
- Candidiasis 36,9%

System:
- nervous system 21,7%
- blood & lymphatic system 29,3%
- metabolism & nutrition 73,3%
- electrolyte 50,5%

Other:
- cardiac 43,4%
- renal and urinary 22,8%
- ear & labyrinth 19,0%
- skin & subcutaneous tissue 19,5%

Diagnosis:
- hear disease 36,9%
- mental disorder 36,9%
- metabolic & nutrition disorder 36,9%
- bone & joint disorder 36,9%
- ear & labyrinth disorder 36,9%
- nervous system disorder 36,9%
- skin & subcutaneous tissue disorder 36,9%
- other disorder 36,9%
- congenital anomaly & birth defect 36,9%
Conclusions

- Belarus implemented regimens containing new and repurposed drugs to treat M/XDR-TB in programmatic settings
- aDSM, as a key component of new drugs and regimens use, was also implemented
- Our patient series will help increase the global knowledge base for M/XDR-TB patients treated with new drugs containing regimens under programmatic conditions
Thanks