Experience of M/XDR-TB treatment with Bedaquiline

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• New MDR TB cases – 5812 persons*

• Total number of MDR TB cases – 34778 persons*

Estimated number of XDR TB in RF – 3339 persons

*Form # 33
XDR-TB in 13 regions of RF, 2013

- Among new cases—2.7% (0 – 5.9%)
- Among relapses – 6.7% (0 – 15.6%)
- Among other retreatment cases – 7.8% (0 – 24.2%)

Circular

“TB situation in the areas of CTRI RAMS supervision, 2010-2013”. Moscow, 2014
Additional DR in MDR-TB patients (%) in 11 federal entities of the RF, 2013
n=1905

- New cases: 50.4% (E), 26.9% (Km/Am), 14.5% (Ofx)
- Relapses: 57.6% (E), 33.7% (Km/Am), 16.0% (Ofx)
- Retreatment cases: 57.6% (E), 37.7% (Km/Am), 28.5% (Ofx)
Favorable Ultimate Results of TB Standard Regimens chemotherapy (5 subjects of the RF):

- Susceptible TB – 91.3%
- Polyresistant TB – 76%
- MDR TB – 53.5%

Effective treatment (Tomsk oblast)

- XDR TB - 48.3%,
- MDR TB (non XDR) - 66.7%


Russian Phthisiatriists' Society (RFS)

Federal Clinical Recommendations (Protocols) on TB Diagnostics and Treatment
Regimens of chemotherapy

Main factor to choose regimen—DST result

Susceptible TB
- I / III regimen
  - No risk for MDR-TB

Polyresistant TB
- II regimen
  - 3 Km /Am [Cm] R Z Fq [E] [Pto/Eto] /
  - 6 R Z Fq [E] [Pto/Eto]
  - Only if there is a sensitivity to R

MDR-TB
- IV regimen
  - Risk for MDR-TB

XDR-TB
- V regimen

Regimens without DST results should be exception but not a rule
TB chemotherapy based on DST with molecular-genetic techniques

Development of treatment regimen based on results of molecular-genetic techniques

1. On the basis of individual DST results received with molecular-genetic techniques
   Sensitivity to anti-TB drugs - 1st regimen (for susceptible TB)
   Resistance to
   
   H   - 2nd regimen (for polyresistant TB)
   HR  - 4th regimen (for MDR TB)
   HR Fq - 5th regimen (for XDR TB)

2. On the basis of DST results to 1st and 2nd lines drugs using liquid or solid media techniques.
Development of chemotherapy regimen with bedaquiline for MDR/preXDR-TB when DST result for FLD and SLD are available

- Amino glycosides/polypeptides
  - Cm
  - Km/Am

- Fluoroquinolones
  - Lfx
  - Mfx - after treatment with BQ is over

- FLD

- Cycloserine/Terizidone

- Ethionamide/Prothionamide

- PAS

- Bedaquiline
Development of chemotherapy regimen with bedaquiline for XDR TB when DST result for FLD and SLD are available

- Capreomycin
- Levofloxacin -1.0
- Moxifloxacin
- Bedaquiline
- Pyrazinamide
- Cycloserine
- Ethionamide/Prothionamide
- Linezolid
- Imipenem
- Amox/Clav
- Clarithromycin
- PAS
- Imipenem
Prescription of Regimen with Bedaquiline

- **Within MDR TB chemotherapy regimen (IV) bedaquiline is prescribed:**
  - When it is impossible to provide the regimen of 5 first and second line drugs provided that the patient is sensitive to 3 and more TB drugs
  - As the 6th drug to basic chemotherapy regimen IV

- **For XDR TB chemotherapy regimen (V) bedaquiline is prescribed:** if there is sensitivity to 3 and more TB drugs out of the prescribed combination
  - Bedaquiline is not to be used along with moxifloxacin; levofloxacin in the dose of 1.0 is to be prescribed to the patient.
  - Under any other conditions prescription of bedaquiline is not allowed.
  - It is prohibited to add bedaquiline to ineffective chemotherapy regimen.
Range of mutations in *katG, inhA, ahpC* genes responsible for INH resistance (n=968)

Mutations in a gene *kat G* - a high degree of resistance to isoniazid
Treatment efficacy of XDR TB patients depending on drug regimen (n=174)

174 patients
Z(E) Cm (Km/Am) Cs/Trd (Pto) (PAS) +

34 patients +Ofx
64 patients +Mfx Clr Amx
56 patients +Mfx Lzd
20 patients +Lfx/Mfx Bq Lzd
The inclusion of linezolide and bedaquiline in the treatment regimen

TREATMENT EFFICACY OF XDR TB PATIENTS BY CULTURE NEGATIVATION DEPENDING ON DRUG REGIMEN (N=174)

- 1st group (Ofx) n=34
- 2nd group (Mfx+Clr+Amx) n=64
- 3rd group (Mfx+Lzd) n=56
- 4th group (Lzd+Bq) n=20

The chart shows the percentage of culture negativity over different treatment durations (2 to 12 months) for each group. The statistical significance (P values) are also indicated for the comparisons between groups.
## Factors increasing the treatment efficacy of XDR TB patients

<table>
<thead>
<tr>
<th>Factors</th>
<th>N</th>
<th>Culture negative to 12 months of treatment</th>
<th>Culture positive to 12 months of treatment</th>
<th>OR</th>
<th>CI95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid detection of XDR</td>
<td>77</td>
<td>70</td>
<td>7</td>
<td>8,3</td>
<td>3,26 – 22,03</td>
<td>&lt;0,05</td>
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<tr>
<td>Moxifloxacin</td>
<td>140</td>
<td>111</td>
<td>29</td>
<td>7,02</td>
<td>2,90-17,21</td>
<td>&lt;0,05</td>
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<tr>
<td>Linezolid</td>
<td>76</td>
<td>69</td>
<td>7</td>
<td>8,03</td>
<td>3,16-21,30</td>
<td>&lt;0,05</td>
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<tr>
<td>Bedaquilin</td>
<td>20</td>
<td>19</td>
<td>1</td>
<td>9,13</td>
<td>1,23-188,23</td>
<td>&lt;0,05</td>
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</table>
### Frequency of side effects during treatment of XDR TB

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>1 group (Ofx) n=34</th>
<th>2 group (Mfx+Clr+Amx) n=64</th>
<th>3 group (Mfx+Lzd) n=56</th>
<th>4 group (Lzd+Bq) n=20</th>
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</thead>
<tbody>
<tr>
<td>Pancreatitis</td>
<td>23.5</td>
<td>26.6</td>
<td>25.0</td>
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<tr>
<td>Gastritis</td>
<td>2.9</td>
<td>4.7</td>
<td>5.4</td>
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<tr>
<td>Diarrhea</td>
<td>23.5</td>
<td>26.6</td>
<td>28.6</td>
<td>30.0</td>
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<tr>
<td>Hepatitis</td>
<td>2.9</td>
<td><strong>17.2</strong></td>
<td>3.6</td>
<td>5.0</td>
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<tr>
<td>Headache/vertigo</td>
<td>5.9</td>
<td>9.4</td>
<td>10.7</td>
<td>10.0</td>
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<tr>
<td>Sleep disturbance</td>
<td>5.9</td>
<td>9.4</td>
<td>14.3</td>
<td>15.0</td>
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<tr>
<td>Peripheral neuropathy</td>
<td>5.9</td>
<td>9.4</td>
<td><strong>21.4</strong></td>
<td><strong>20.0</strong></td>
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<tr>
<td>Convulsions</td>
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<td>0.0</td>
<td>0.0</td>
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<tr>
<td>Mental disease</td>
<td>5.9</td>
<td>7.8</td>
<td>12.5</td>
<td>10.0</td>
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<tr>
<td>Hearing disorder/tinnitus</td>
<td>5.9</td>
<td>7.8</td>
<td>8.9</td>
<td>10.0</td>
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<td>Vision disorder</td>
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<td>0.0</td>
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<tr>
<td>Electrolyte imbalance</td>
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<td>21.9</td>
<td>23.2</td>
<td>25.0</td>
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<tr>
<td>Allergy</td>
<td>32.4</td>
<td>37.5</td>
<td>30.4</td>
<td>30.0</td>
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<tr>
<td>Renal impairment</td>
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<td>0.0</td>
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<tr>
<td>Prolongation of interval QT</td>
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<td><strong>7.8</strong></td>
<td><strong>8.9</strong></td>
<td><strong>10.0</strong></td>
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<tr>
<td>Arrhythmia</td>
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<td>7.8</td>
<td>8.9</td>
<td>10.0</td>
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<tr>
<td>Arthralgia</td>
<td>29.4</td>
<td>32.8</td>
<td>37.5</td>
<td>40.0</td>
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</tbody>
</table>
Thank you for your attention!