New frontiers: Innovation and Access

The role of molecular genetic methods in increasing the efficacy of MDR-TB treatment at CTRI

Prof. L.N. Chernousova
Central Tuberculosis Research Institute (CTRI)

28 February — 1 March, 2019
TB incidence and mortality in Russia, 1970-2017 (per 100K population)

Prof. L.N. Chernousova, Head of Microbiology Department at CTRI
The role of molecular genetic methods in increasing the efficacy of MDR-TB treatment at CTRI

New frontiers: Innovation and Access
8th TB Symposium —
Ministry of Health of the Republic of Uzbekistan
Médecins Sans Frontières
Multi-drug resistant TB (MDR-TB) in Russia in 1999-2017, %

<table>
<thead>
<tr>
<th>Year</th>
<th>Proportion of MDR-TB in new TB cases</th>
<th>Proportion of MDR-TB in all TB patient populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>6.7</td>
<td>10.5</td>
</tr>
<tr>
<td>2000</td>
<td>7.1</td>
<td>11.2</td>
</tr>
<tr>
<td>2001</td>
<td>7.8</td>
<td>14.4</td>
</tr>
<tr>
<td>2002</td>
<td>8.1</td>
<td>14.5</td>
</tr>
<tr>
<td>2003</td>
<td>8.3</td>
<td>16.2</td>
</tr>
<tr>
<td>2004</td>
<td>9.5</td>
<td>16.5</td>
</tr>
<tr>
<td>2005</td>
<td>9.8</td>
<td>18.7</td>
</tr>
<tr>
<td>2006</td>
<td>10.7</td>
<td>20.3</td>
</tr>
<tr>
<td>2007</td>
<td>13</td>
<td>21.4</td>
</tr>
<tr>
<td>2008</td>
<td>13</td>
<td>23.4</td>
</tr>
<tr>
<td>2009</td>
<td>15.5</td>
<td>26.5</td>
</tr>
<tr>
<td>2010</td>
<td>16.2</td>
<td>30.1</td>
</tr>
<tr>
<td>2011</td>
<td>17.4</td>
<td>34.2</td>
</tr>
<tr>
<td>2012</td>
<td>20.4</td>
<td>37.5</td>
</tr>
<tr>
<td>2013</td>
<td>23</td>
<td>40</td>
</tr>
<tr>
<td>2014</td>
<td>25.7</td>
<td>43.9</td>
</tr>
<tr>
<td>2015</td>
<td>27.4</td>
<td>51.2</td>
</tr>
<tr>
<td>2016</td>
<td>54</td>
<td>54</td>
</tr>
</tbody>
</table>

Prof. L.N. Chernousova, Head of Microbiology Department at CTRI
The role of molecular genetic methods in increasing the efficacy of MDR-TB treatment at CTRI

New frontiers: Innovation and Access
8th TB Symposium — Ministry of Health of the Republic of Uzbekistan Médecins Sans Frontières
Stages of microbiological diagnostics of TB used at CTRI, including rapid methods for detecting MTB and drug susceptibility

Stage 1:
Perform primary examination of sputum samples using molecular genetic methods; it takes 1-2 days to detect mutations associated with resistance to Rifampicin, Isoniazid and Fluoroquinolones and therefore detect resistance to major TB drugs

Admit MDR-TB patients to a specialized hospital unit

Stage 2:
Detect phenotypic drug susceptibility using the BACTEC MGIT 960 automated system (the fastest standardized method to detect resistance to a wide range of TB drugs; it takes on average 4-14 days to obtain the results after the inoculation)

Compose an individual treatment regimen containing the maximum number of TB drugs to which MTB is susceptible

Prof. L.N. Chernousova, Head of Microbiology Department at CTRI
The role of molecular genetic methods in increasing the efficacy of MDR-TB treatment at CTRI

New frontiers: Innovation and Access
8th TB Symposium — Ministry of Health of the Republic of Uzbekistan Médecins Sans Frontières
GeneXpert MTB/RIF cartridge technology (Cepheid, Inc.)

- simultaneously detects MTB and Rifampicin resistance;
- results are ready within two hours after sputum is obtained from a patient;
- presents minimal bio-hazard risk and can be used in general laboratories;
- endorsed by WHO

Prof. L.N. Chernousova, Head of Microbiology Department at CTRI

The role of molecular genetic methods in increasing the efficacy of MDR-TB treatment at CTRI
CTRI performed a study to evaluate the role of rapid microbiological diagnostic methods in improving the efficacy of MDR-TB treatment

- We evaluated the treatment efficacy in patients with drug-sensitive pulmonary TB and patients with Rifampicin-resistant pulmonary TB; treatment regimens were composed based on the results of the GeneXpert MTB/RIF cartridge-based assay and subsequently adjusted based on the results of drug susceptibility testing (DST) in liquid media using BACTEC MGIT 960.

- We compared the findings with the treatment outcomes in the control group — MDR-TB patients not tested with rapid molecular tests.

- The study included 185 patients with pulmonary TB, 130 of which were tested using GeneXpert MTB/RIF.
Patient groups:

- **Group 1**: 76 patients with Rifampicin susceptibility detected by GeneXpert MTB/RIF; the patients started a standard first-line regimen, subsequently adjusted based on the results of liquid media DST (BACTEC MGIT 960).

- **Group 2**: 54 patients with Rifampicin resistance detected by GeneXpert MTB/RIF; the patients started an MDR-TB regimen, subsequently adjusted based on the results of liquid media DST (BACTEC MGIT 960).

- **Group 3**: 55 patients not tested on GeneXpert MTB/RIF or other molecular tests to detect Rifampicin resistance; the patients started an empiric first-line regimen, subsequently adjusted based on the results of phenotypic DST.

Prof. L.N. Chernousova, Head of Microbiology Department at CTRI
The role of molecular genetic methods in increasing the efficacy of MDR-TB treatment at CTRI
Frequency of and time to sputum smear conversion in patient groups confirmed by fluorescence microscopy

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>Group 1: GX+, R-susc.</th>
<th>Group 2: GX+, R-res.</th>
<th>Group 3: GX n/e</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 1</td>
<td>49 (n=49)</td>
<td>39 (n=44)</td>
<td>0 (n=47)</td>
</tr>
<tr>
<td>Month 2</td>
<td>80 (n=49)</td>
<td>64 (n=44)</td>
<td>17 (n=47)</td>
</tr>
<tr>
<td>Month 4</td>
<td>96 (n=49)</td>
<td>86.4 (n=44)</td>
<td>27.7 (n=47)</td>
</tr>
<tr>
<td>Month 6</td>
<td>100 (n=49)</td>
<td>100 (n=44)</td>
<td>49 (n=47)</td>
</tr>
</tbody>
</table>

Prof. L.N. Chernousova, Head of Microbiology Department at CTRI
The role of molecular genetic methods in increasing the efficacy of MDR-TB treatment at CTRI

New frontiers: Innovation and Access
8th TB Symposium — Ministry of Health of the Republic of Uzbekistan Médecins Sans Frontières
Frequency of and time to sputum smear conversion in patient groups confirmed by culture

Prof. L.N. Chernousova, Head of Microbiology Department at CTRI
The role of molecular genetic methods in increasing the efficacy of MDR-TB treatment at CTRI
Study findings:

- Group 1 showed the lowest time to sputum smear conversion confirmed by fluorescence microscopy. The smear conversion rates were comparable in Group 1 and Group 2 ($p_{1-2} > 0.05$). Group 3 had the statistically lowest frequency of smear conversion.

- Group 1 also showed the highest results in sputum smear conversion confirmed by culture: all patients in the group were smear-negative after six months of treatment. Group 2 showed relatively lower sputum conversion rates; however, all patients in the group also achieved sputum smear conversion after six months of treatment ($p_{1-2} > 0.05$). The highest time to sputum smear conversion was in Group 3.
Study findings:

Therefore, Group 2 (MDR-TB patients who were tested by GeneXpert MTB/RIF and started an MDR-TB regimen without delay) showed the higher frequency of and lower time to sputum smear conversion than Group 3 (MDR-TB patients who started an adequate regimen with delay after obtaining the results of phenotypic DST). In Group 2 and Group 3, the proportions of patients who achieved sputum smear conversion after six months of treatment were 100% and 49% ($p < 0.05$) as confirmed by microscopy and 100% and 36.4% ($p < 0.05$) as confirmed by culture, respectively.

Prof. L.N. Chernousova, Head of Microbiology Department at CTRI
The role of molecular genetic methods in increasing the efficacy of MDR-TB treatment at CTRI
Study findings:

- Regeneration of destructive lung lesions was more frequent in Group 2 (MDR-TB patients who started an effective treatment regimen after rapid Rifampicin resistance detection using GeneXpert MTB/RIF) than in Group 3 (MDR-TB who started an empiric first-line regimen). Lung lesions regenerated in 92% and 63% patients of Group 2 and Group 3 ($p < 0.05$) after six months of treatment, respectively.
Conclusion

- MDR-TB treatment is more effective with the use of rapid molecular genetic tests to detect Rifampicin resistance directly from sputum samples, as well as the immediate initiation of a personalized treatment regimen and its subsequent adjustment based on the results of phenotypic DST in liquid media.
THANK YOU FOR YOUR ATTENTION!

Co-authors:
E.V. Sevastyanova
E.E. Larionova
T.G. Smirnova
S.N. Andreevskaya
M.V. Burakova

Prof. L.N. Chernousova, Head of Microbiology department at CTRI
The role of molecular genetic methods in increasing the efficacy of MDR-TB treatment at CTRI