Treating Patient, Not Disease: People-Centered Approach

7th TB Symposium – Ministry of Health of the Kyrgyz Republic and Médecins Sans Frontières

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Sputum conversion/reversion among patients on new TB drugs: endTB cohort

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What is endTB?
Expand New Drugs for TB

Consortium partners:
- Partners In Health (PIH)
- Médecins Sans Frontiéres (MSF)
- Interactive Research and Development (IRD)

Funding partner: Unitaid

Project duration: 4 years (2015-2019)

Project budget: 60.4 million USD

Goal:
- Expand access to bedaquiline & delamanid
- Produce evidence on new TB drugs: observational study
endTB project implementation

- At least 2600 patients in 17 countries
endTB observational study

- **Objectives:** Assess efficacy and safety of bedaquiline (Bdq) and delamanid (Dlm) in programmatic conditions
- **Design:** Multicentric prospective and retrospective observational cohort study
- **Population:** Patients on Bdq or Dlm who signed informed consent
- **Preliminary cohort analyses:**
  - Culture conversion by 6 months
  - Culture reversion by 12 months
  - Adverse Events of Interest and Serious Adverse Events
  - Expanded indications
Culture conversion

- We report the proportion of patients whose sputum converted to negative during the first 6 months of treatment with Bdq or Dlm

- Cohort: 1\textsuperscript{st} April 2015 – 30\textsuperscript{th} Sep 2016

- Population: positive sputum culture up to 90 days before Bdq or Dlm start

- Conversion date: the date of the first of two negative cultures \( \geq 15 \) days apart
Enrollment by country (N=356)

- Georgia: 37%
- Kazakhstan: 24%
- Armenia: 14%
- Bangladesh: 5%
- Belarus: 8%
- Ethiopia: 0%
- Pakistan: 5%
- Kenya: 1%
- Lesotho: 6%
## Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age [range]</td>
<td>38 [17-82]</td>
</tr>
<tr>
<td>Male</td>
<td>261 (73)</td>
</tr>
<tr>
<td>Body mass index &lt;18.5</td>
<td>127 (37)</td>
</tr>
<tr>
<td>Bilateral disease</td>
<td>221 (68)</td>
</tr>
<tr>
<td>Resistance</td>
<td></td>
</tr>
<tr>
<td>MDR or Xpert RR</td>
<td>51 (15)</td>
</tr>
<tr>
<td>Pre-XDR (Inj)</td>
<td>26 (7)</td>
</tr>
<tr>
<td>Pre-XDR (FQ)</td>
<td>109 (31)</td>
</tr>
<tr>
<td>XDR</td>
<td>161 (46)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>36 (10)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>65 (19)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>42 (13)</td>
</tr>
<tr>
<td>Previously treated w/ SLDs</td>
<td>281 (79)</td>
</tr>
</tbody>
</table>
Culture conversion

356 patients with positive culture at start (April 2015 to Sep 2016)

- 291 converted by 6 months
  - 82% conversion (95%CI: 77-85)

- 65 (18%) no conversion:
  - 17 deaths
  - 16 LTFUs
  - 1 transfer out of country
  - 31 on treatment

Culture conversion: 2 negative cultures with sample collected at least 15 days apart
Time to culture conversion

Median conversion time among converted: 52 days [IQR: 29 – 73 days]
## Conversion in subgroups

<table>
<thead>
<tr>
<th></th>
<th>Conversion %</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (N=36)</td>
<td>67</td>
<td>0.01</td>
</tr>
<tr>
<td>Negative (N=318)</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatitis C</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (N=65)</td>
<td>78</td>
<td>0.42</td>
</tr>
<tr>
<td>Negative (N=284)</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (N=42)</td>
<td>86</td>
<td>0.55</td>
</tr>
<tr>
<td>No (n=294)</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td><strong>XDR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (N=161)</td>
<td>80</td>
<td>0.48</td>
</tr>
<tr>
<td>No (N=189)</td>
<td>83</td>
<td></td>
</tr>
</tbody>
</table>

**HIV patients:**
- 25% recently diagnosed
- 86% on ARVs
- 10/12 not converted died
- Time to death: 64 days
- CD4 cell count: 145
Culture reversion

• We report the proportion of patients whose sputum reverted to positive after culture conversion during the first 12 months of treatment with Bdq or Dlm

• **Cohort**: 1\textsuperscript{st} April 2015 to 28\textsuperscript{th} Feb 2016

• **Reversion**: two consecutive positive cultures after culture conversion

• **Countries**: Armenia, Belarus, Georgia, Kazakhstan, Lesotho
Patients’ characteristics

- **Population:** 98
- **Men:** 78 (79.6%)
- **Age:** 39 years [IQR 31-51]
- **Resistance patterns:**
  - Pre-XDR Fluoroquinolones: 32 (32.6%)
  - Pre-XDR Injectables: 9 (9.2%)
  - XDR: 51 (52.0%)
- **Cultures during follow-up period:** 10 [IQR 7-12] /patient
Culture reversion

• **Reversion rate:** 3.1% (95%CI 0.6-8.7%)

• Time to reversion from conversion:
  - After 1, 5 and 6 months

• Time to reversion from new drug start:
  - After 2, 8 and 9 months

• Deaths during reversion period: 3
Conclusions

• Favorable conversion percentages in a cohort of treatment-experienced patients with high-grade resistance and extensive disease
• Early deaths among patients with advanced HIV drive lower conversion percentages among patients living with HIV
• Low proportion of reversion
• More data needed to identify risk factors for reversion and role of treatment duration >24 weeks and concomitant use of bedaquiline and delamanid.
• Further interim results expected in 2018
Thank you
### Description of the 3 patients who reverted

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Sex</th>
<th>Country</th>
<th>HIV</th>
<th>Hep C</th>
<th>Previous MDRTB failure</th>
<th>Resistant to FQ</th>
<th>Treatment regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>28</td>
<td>M</td>
<td>Belarus</td>
<td>Neg</td>
<td>Neg</td>
<td>Yes</td>
<td>XDR</td>
<td>Lzd+Dlm+ Amx-Clv+ Cfz+Cilastatin/Imipenem</td>
</tr>
<tr>
<td>Patient 2</td>
<td>39</td>
<td>M</td>
<td>Georgia</td>
<td>Neg</td>
<td>Neg</td>
<td>No</td>
<td>Pre-XDR (Fq)</td>
<td>Bdq+Cs+Cm+ Lzd+Pto+ Lfx+Cfz</td>
</tr>
<tr>
<td>Patient 3</td>
<td>69</td>
<td>F</td>
<td>Kazakhstan</td>
<td>Neg</td>
<td>Neg</td>
<td>Yes</td>
<td>XDR</td>
<td>Bdq+Lfx+ Cm+Cs+Cfz+ Lzd</td>
</tr>
</tbody>
</table>