endTB in Kazakhstan: progress and transition from project to routine implementation

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Askar Yedilbayev, Partners In Health
Outline

• Context for endTB implementation;
• endTB population characteristics;
• Treatment decisions for regimen design and lessons learned from routine care;
• Regulatory status of new and repurposed drugs;
• National plans to expand access to new and repurposed drugs
MDR-TB in Kazakhstan

- High-burden country for MDR-TB;
- 2017:
  - 5,893 new RR/MDR-TB cases;
  - 547 diagnosed with XDR-TB;
  - MDR among:
    - new cases 26% (25-28);
    - Previously treated 44% (42-46);
- PIH is supporting NTP/MOH since 2010:
  - 2010-2013: GF R8 – scaling up access to MDR-TB treatment at prison and civilian sectors and building community-based models of care;
  - 2016-2017: USAID TB CARE II Project;
  - 2015 – present: Unitaid-funded endTB project – introduction of new TB drugs for DR-TB and clinical trial

Population: 18.3 million people
endTB Project in Kazakhstan

• In accordance with the National Complex Plan to Fight TB in Kazakhstan for 2014-2020, which was endorsed by Government Decree 597 of May 31, 2014. Articles 20 и 21:
  ▪ Phased introduction of individualized treatment regimens for M/XDR-TB based on results of DST;

• Memorandum of Collaboration between MOH and Partners In Health of October 27, 2015;

• Approval of Observational study protocols by local IRB;

• Initial projection for enrollment: 593 patients;

• Started in 5 regions and further expanded to another 5 in July 2017 – upon request from the MOH – 65% of territory of Kazakhstan
Baseline cohort characteristics (N=543*)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
</tr>
<tr>
<td>Median age at treatment initiation, years</td>
<td>36 (16-71)</td>
</tr>
<tr>
<td>Female</td>
<td>213 (39%)</td>
</tr>
<tr>
<td>History of incarceration (N=538)</td>
<td>62 (12%)</td>
</tr>
<tr>
<td><strong>Co-morbidities</strong></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (N=541)</td>
<td>55 (10%)</td>
</tr>
<tr>
<td>HIV infection</td>
<td>7 (1%)</td>
</tr>
<tr>
<td>Hepatitis B serology positive (N=541)</td>
<td>29 (5%)</td>
</tr>
<tr>
<td>Hepatitis C serology positive (N=540)</td>
<td>81 (15%)</td>
</tr>
<tr>
<td>At least one other co-morbidity</td>
<td>56 (10%)</td>
</tr>
</tbody>
</table>

* Patients initiating bedaquiline or delamanid from 1 April 2015 – 31 May 2018
Baseline cohort characteristics (N=543*)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TB-related</strong></td>
<td></td>
</tr>
<tr>
<td>No prior TB treatment</td>
<td>14 (3%)</td>
</tr>
<tr>
<td>Prior TB treatment only with FLD</td>
<td>27 (5%)</td>
</tr>
<tr>
<td>Prior TB treatment with SLD</td>
<td>502 (92%)</td>
</tr>
<tr>
<td>Extrapulmonary TB</td>
<td>11 (2%)</td>
</tr>
<tr>
<td><strong>Bilateral disease (N=532)</strong></td>
<td></td>
</tr>
<tr>
<td>Bilateral disease</td>
<td>326 (61%)</td>
</tr>
<tr>
<td><strong>Cavitary disease (N=524)</strong></td>
<td></td>
</tr>
<tr>
<td>Cavitary disease</td>
<td>439 (84%)</td>
</tr>
<tr>
<td><strong>Body mass index &lt;18.5 (N=541)</strong></td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>170 (31%)</td>
</tr>
<tr>
<td><strong>Bacteriologically confirmed TB (N=542)</strong></td>
<td></td>
</tr>
<tr>
<td>Bacteriologically confirmed TB</td>
<td>540 (100%)</td>
</tr>
</tbody>
</table>

* Patients initiating bedaquiline or delamanid from 1 April 2015 – 31 May 2018
Baseline cohort characteristics (N=543*)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
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</thead>
<tbody>
<tr>
<td>Resistance profile</td>
<td></td>
</tr>
<tr>
<td>RR/MDR-TB without any injectable or FQ resistance</td>
<td>118 (22%)</td>
</tr>
<tr>
<td>RR/MDR-TB with any injectable resistance</td>
<td>92 (17%)</td>
</tr>
<tr>
<td>RR/MDR-TB with any FQ resistance</td>
<td>64 (12%)</td>
</tr>
<tr>
<td>XDR-TB</td>
<td>241 (44%)</td>
</tr>
<tr>
<td>No result for RR/MDR-TB resistance</td>
<td>28 (5%)</td>
</tr>
</tbody>
</table>

- More chronic TB patients means more highly resistant TB;
- More highly resistant patients means more need for Cfz and Bdq-Dlm concomitant use

* Patients initiating bedaquiline or delamanid from 1 April 2015 – 31 May 2018
New and repurposed TB drugs in treatment regimens (N=543*)

* Patients initiating bedaquiline or delamanid from 1 April 2015 – 31 May 2018
% of endTB patients receiving Bdq+Dlm, Lzd and Cfz at baseline (N=543)

- Bdq+Dlm at baseline: 10% (Full cohort), 25% (Kazakhstan)
- Lzd at baseline: 80% (Full cohort), 97% (Kazakhstan)
- Cfz at baseline: 70% (Full cohort), 78% (Kazakhstan)
% of endTB patients receiving concomitant Bdq & Dlm at baseline by month 1 Feb 2016 – 31 May 2018 (N=543*)

* Patients initiating bedaquiline or delamanid from 1 April 2015 – 31 May 2018
Extended use of Bdq and Dlm

• Bdq and Dlm are often extended beyond 24 weeks if:
  ▪ Patient cannot tolerate other drugs in the regimen;
  ▪ If extensive disease is present;
  ▪ If there is a high risk of relapse if stopping Bdq and/or Dlm early;

<table>
<thead>
<tr>
<th>Drug</th>
<th>&lt;190 days</th>
<th>&gt;190 days</th>
<th>Total # patients with drug at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bdq</td>
<td>97 (21%)</td>
<td>370 (79%)</td>
<td>467</td>
</tr>
<tr>
<td>Dlm</td>
<td>62 (25%)</td>
<td>191 (75%)</td>
<td>253</td>
</tr>
<tr>
<td>Bdq+Dlm</td>
<td>29 (18%)</td>
<td>132 (82%)</td>
<td>161</td>
</tr>
</tbody>
</table>
Extended use of Bdq and Dlm

<table>
<thead>
<tr>
<th></th>
<th>Duration among all receiving drugs (days)</th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>25%</td>
<td>75%</td>
</tr>
<tr>
<td>Bdq</td>
<td>268</td>
<td>204</td>
<td>404</td>
</tr>
<tr>
<td>Dlm</td>
<td>278</td>
<td>202</td>
<td>386</td>
</tr>
<tr>
<td>Bdq+Dlm</td>
<td>271</td>
<td>225</td>
<td>335</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Duration among those receiving drug more than 190 days</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>25%</td>
<td>75%</td>
</tr>
<tr>
<td>Bdq</td>
<td>313</td>
<td>252</td>
<td>471</td>
</tr>
<tr>
<td>Dlm</td>
<td>316</td>
<td>260</td>
<td>456</td>
</tr>
<tr>
<td>Bdq+Dlm</td>
<td>299</td>
<td>251</td>
<td>371</td>
</tr>
</tbody>
</table>

- Priority is to have at least 5 effective drugs throughout first six months of the regimen and at least 4 drugs thereafter;
- Bdq or and Dlm were extended beyond 24 weeks in majority of patients; often used throughout entire duration of treatment;
- Doctors feel comfortable extending the use of Bdq or and Dlm and recognize importance and need
Clinical case 1: extended use of Bdq

- Male, 45 years old;
- 1997: Diagnosed and treated for the first time;
- 1998: Treated again;
- 2000: Underwent removal of part of his left lung; bought ethionamide and added it to his regimen;
- 2002: Treated again;
- 2005: Received full 2 year course of treatment; declared "cured";
- 2009: Treated again with second-line TB drugs;
- 2013: Treated again with second-line TB drugs for XDR-TB, including Mfx, Amx/Clv, Clr;
- 2016: enrolled in endTB program and started treatment with Bdq, Lzd, Cfz and other SLD;
- Bdq was extended for 24 weeks (48 in total);
- Culture conversion after 1 month, pneumonectomy at 4 month. Finished treatment as cured after 20 months of therapy.
Clinical case 2: concomitant use of Bdq and Dlm

- Male, 46 years old;
- TB since 2014;
- Previously treated with H,R,E,Z and Cm, Am, Lfx, Mfx, Eto, Cs, PAS, Amx/Clv, Clr (treatment failure);
- Baseline DST: HRSE Lfx Mfx Km Eto Cs;
- Enrolled in endTB on February 2017 with Bdq-Dlm-Lzd-Cfz-Z;
- Culture conversion at 5th month;
- Good level of adherence and tolerance;
- Declared cured in October 2018;
- Total duration of regimen 20 months.
Clinical case 2: concomitant use of Bdq and Dlm
Clinical case 3: extended use of Bdq and Dlm

- Female, 26 years old;
- TB since 2013;
- Previously treated with H,R,E,Z and Cm, Am, Lfx, Mfx, Eto, Cs, PAS, Amx/Clv, Clr (treatment completed, treatment failure);
- Baseline DST: HRS Ofx Mfx Am Cm Eto;
- Enrolled in endTB on May 2018 with Bdq-Dlm-Lzd-Cfz-Z;
- Culture conversion at 1\textsuperscript{st} month;
- Good level of adherence and tolerance;
- Currently on 6\textsuperscript{th} month of treatment and decision at 22 weeks was done to extend Bdq and Dlm for another 24 weeks.
Modified shorter regimens for MDR-TB

- Modified shorter regimen for RR/Fq-susceptible patients;
- Bdq-Dlm-Lzd-Lfx-Z for 39 weeks (endTB clinical trial, arm 3);
- Using under operational research conditions;
- Using GDI protocol and operational research conditions;
- Under local ethical approval;
- Limited number of patients (9) enrolled in 2018;
- Interested in enrolling more patients with new funding
Expanding access to Bdq and Dlm in Kazakhstan

- endTB Project served as catalyst to national adoption of Bdq and Dlm in Kazakhstan:
  - Global Fund Project is using the endTB Clinical Guide for regimen design and patient management;
  - October 2017: MOH approval of clinical protocol for treatment of M/XDR TB with new TB drugs;
  - January 2018: MOH approval of National Decree N994 passed for TB, it includes new TB drugs and use of individualized regimens (2018);
  - 2018: Inclusion of Bdq, Dlm, Lzd and Cfz into National Drug Formulary;
  - 2019: Government procurement of Bdq, Dlm, Lzd and Cfz through GDF;

- Registration:
  - Bdq – dossier under review at National Drug Regulatory Authority;
  - Lzd - registered;
  - Dlm and Cfz – an official invitation for registration has been sent to the manufacturers
Expanding access to Bdq and Dlm in Kazakhstan

- Access to individualized regimens with Bdq and Dlm mostly to patients with FQ-resistance in all regions:
  - 2018 – only through external sources:
    - endTB – 675, enrollment stopped on September 30, 2018;
    - Global Fund – 674 (MDR-TB: 383 in civilian and 50 in prison sectors; XDR-TB: 241);
  - 2019 – through external and government sources:
    - Global Fund – 221;
    - MOH – 732;
- Government procurement:
  - Bdq and Dlm through GDF;
  - Lzd and Cfz through national tender
Challenges

• Demand for Bdq and Dlm is extremely high taking into account annual incidence of around 5000-6000 RR/MDR-TB cases and recent release of WHO Rapid Communication (August 2018);
  ▪ Prior August 2018: estimation provided by PIH to NTP/MOH: more than 50% RR/MDR, all pre-XDR and XDR patients (about 3000-3500 patients annually);
  ▪ Expected release of new WHO guidelines will increase the need up to 5000-6000 patients per year;
  ▪ Current gap in covering patients is high:

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<tbody>
<tr>
<td>Actual endTB</td>
<td>215</td>
<td>158</td>
<td>302</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>675</td>
</tr>
<tr>
<td>Actual GF</td>
<td>0</td>
<td>0</td>
<td>674</td>
<td>221</td>
<td>0</td>
<td>0</td>
<td>895</td>
</tr>
<tr>
<td>Actual MOH</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>732</td>
<td>Unknown</td>
<td>Unknown</td>
<td>732 + ?</td>
</tr>
<tr>
<td># RR/MDR pts diagnosed</td>
<td>6314</td>
<td>5893</td>
<td>5500*</td>
<td>5200*</td>
<td>4900*</td>
<td>4600*</td>
<td></td>
</tr>
<tr>
<td>Access to regimens</td>
<td>3%</td>
<td>3%</td>
<td>18%*</td>
<td>18%*</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
</tr>
</tbody>
</table>

* estimated number/percentage
Challenges (continued)

• Severe disease profile of patients, including co-morbidities like viral hepatitis C:
  ▪ Data from endTB Project – > 15% co-infected with HCV;
  ▪ Viral and genotype confirmation is not always available;
  ▪ Despite registration and increasing access to new anti-HCV drugs, therapy for patients with active TB is not yet possible;

• Social status of patients and substance addiction;

• Need for continuous program accompaniment to the NTP on scaling up access to individualized regimens with Bdq and Dlm for DR-TB including introduction of novel shorter regimens under operational research conditions
Acknowledgement

• Patients
• Doctors, nurses and DOT providers
• Ministry of Health of Kazakhstan
• National TB Program of Kazakhstan
• Unitaid
• endTB Project partners: MSF, IRD, HMS, PV Unit, Epicentre
• World Health Organization
• Stop TB Partnership
• USAID-Janssen Donation Program