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

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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

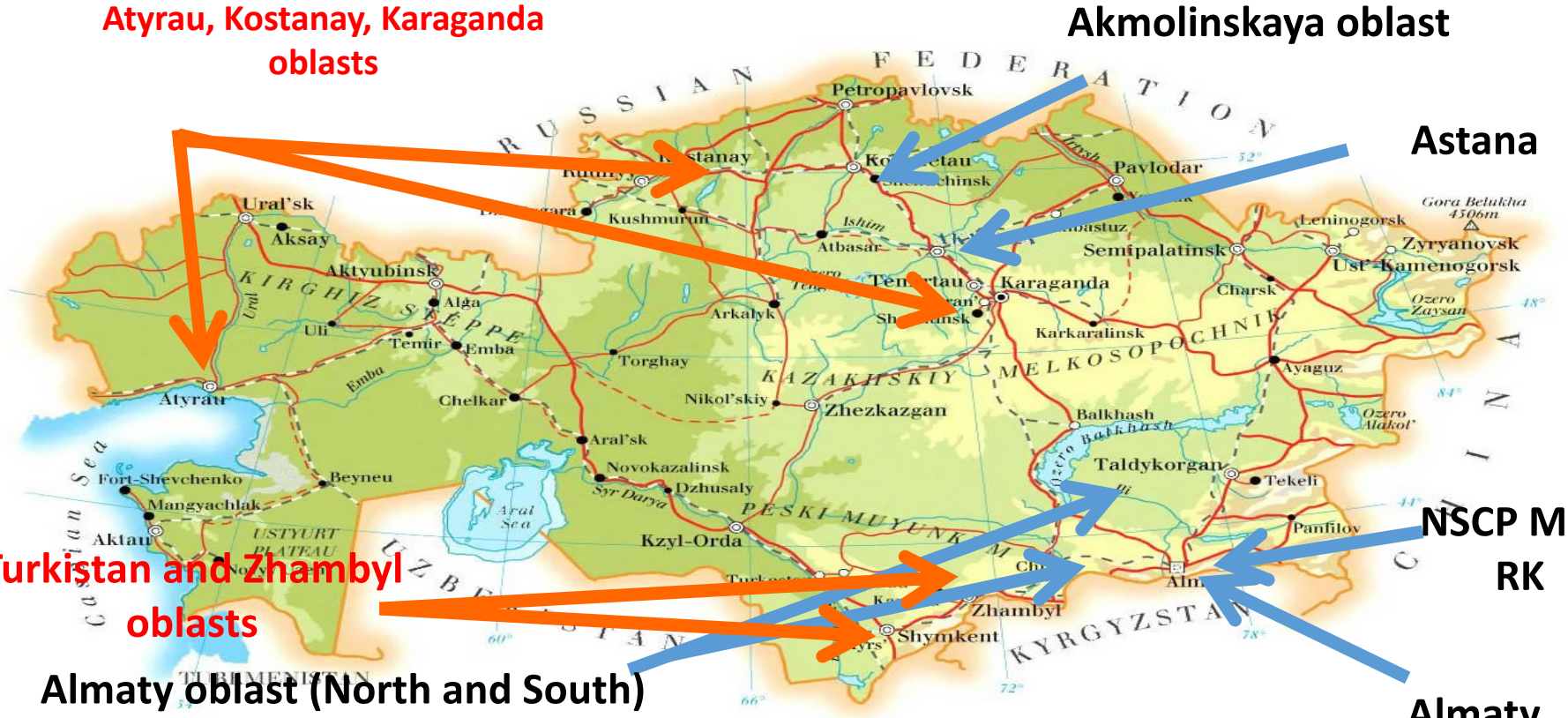
- High-burden country for MDR-TB;
- 2017:
  - 5,893 new RR/MDR-TB cases;
  - 547 diagnosed with XDR-TB;
  - MDR among:
    - new cases 26% (25-28);
    - Previously treated 44% (42-46);
- PIH is supporting NTP/MOH since 2010:
  - 2010-2013: GF R8 – scaling up access to MDR-TB treatment at prison and 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

endTB treatment sites



Baseline cohort characteristics (N=543*)

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

* Patients initiating bedaquiline or delamanid from 1 April 2015 – 31 May 2018

Baseline cohort characteristics (N=543*)

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

* Patients initiating bedaquiline or delamanid from 1 April 2015 – 31 May 2018

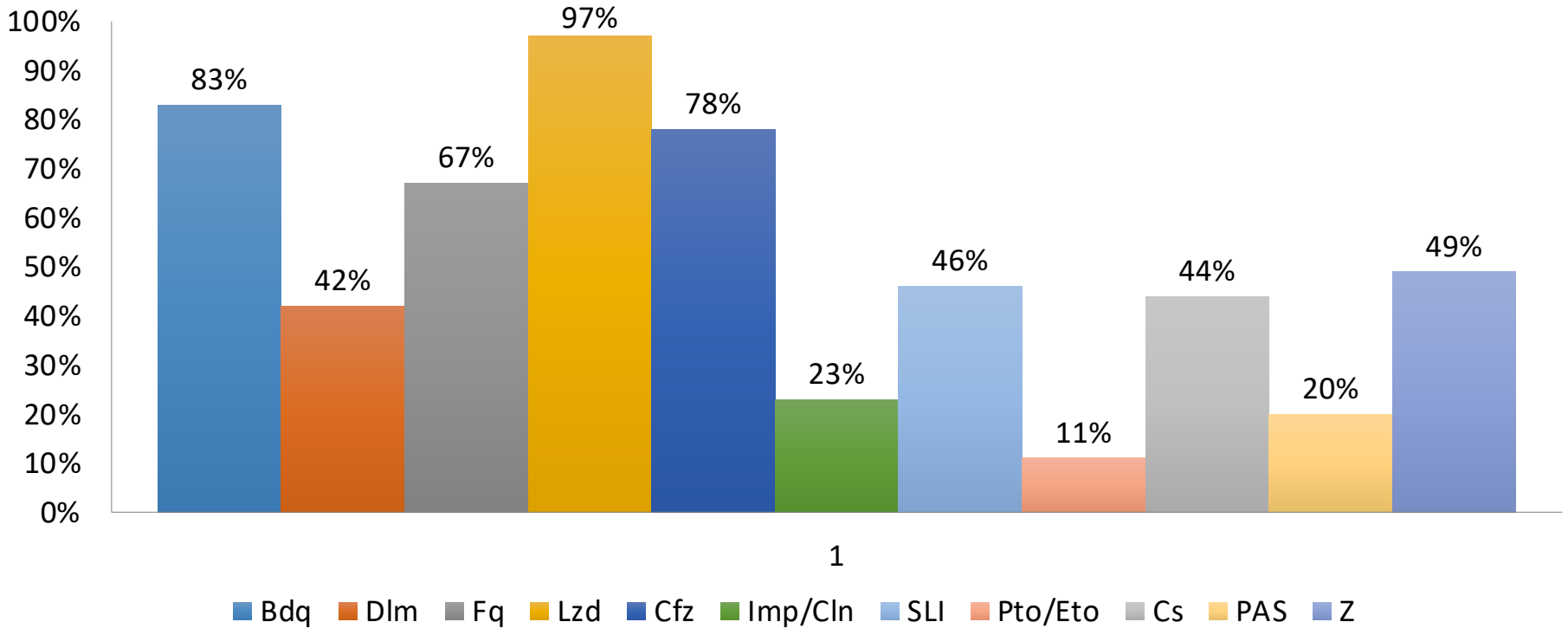
Baseline cohort characteristics (N=543*)

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

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

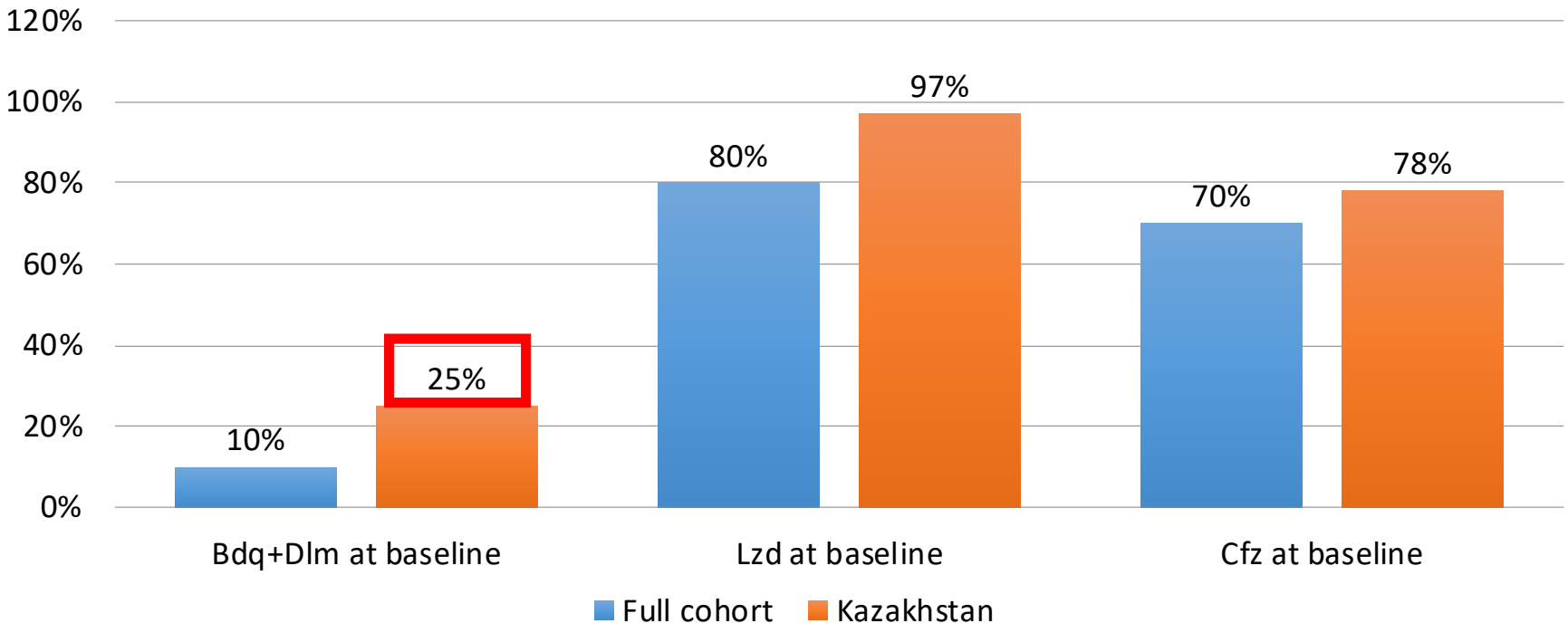
* Patients initiating bedaquiline or delamanid from 1 April 2015 – 31 May 2018

New and repurposed TB drugs in treatment regimens (N=543*)

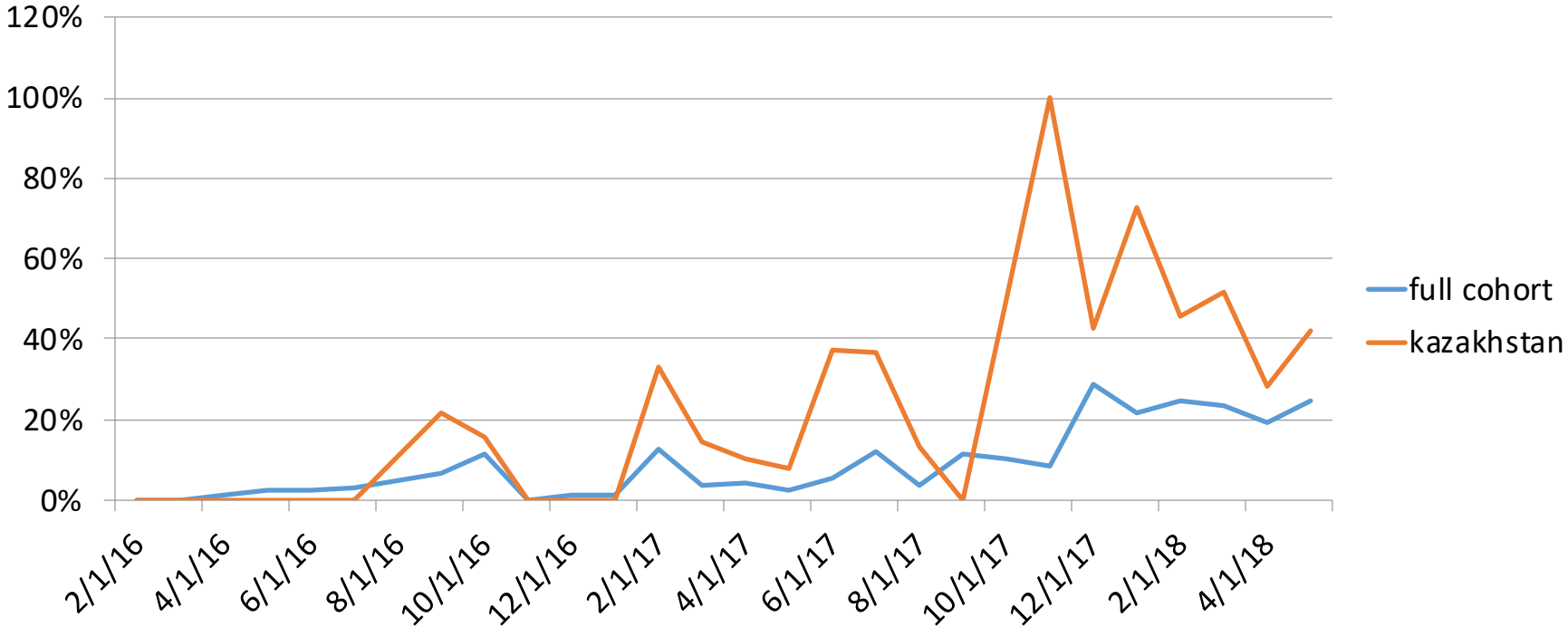


* Patients initiating bedaquiline or delamanid from 1 April 2015 – 31 May 2018

% of endTB patients receiving Bdq+Dlm, Lzd and Cfz at baseline (N=543)



% 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;

Drug	<190 days	>190 days	Total # patients with drug at baseline
Bdq	97 (21%)	370 (79%)	467
Dlm	62 (25%)	191 (75%)	253
Bdq+Dlm	29 (18%)	132 (82%)	161

Extended use of Bdq and Dlm

Duration among all receiving drugs (days)			
	Median	**25%**	**75%**
Bdq	268	204	404
Dlm	278	202	386
Bdq+Dlm	271	225	335
Duration among those receiving drug more than 190 days			
Bdq	313	252	471
Dlm	316	260	456
Bdq+Dlm	299	251	371

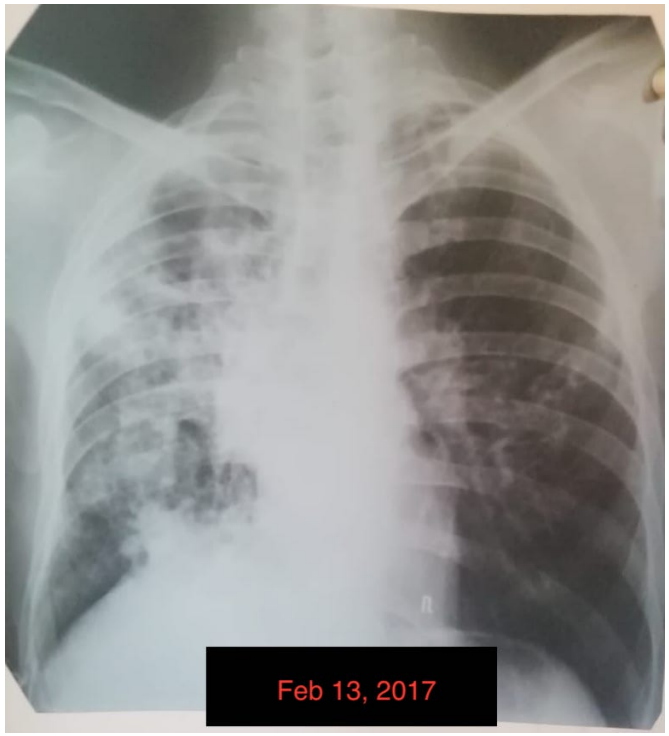
- Priority is to have at least 5 effective drugs throughout first six months of the regimen and at least 4 drugs thereafter;
- Bdq or/and Dlm were extended beyond 24 weeks in majority of patients; often used throughout entire duration of treatment;
- Doctors feel comfortable extending the use of Bdq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

Clinical case 1: extended use of Bdq

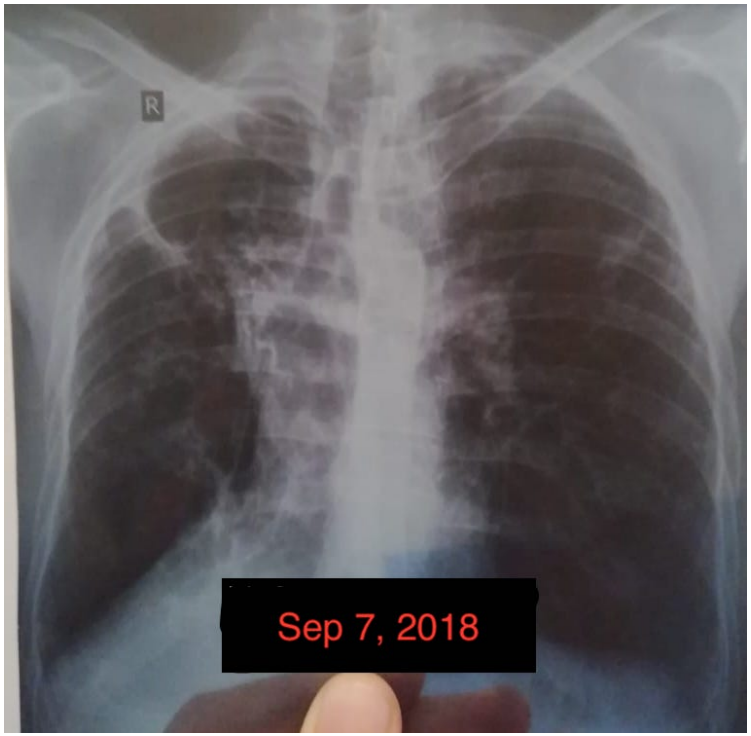
- Male, 45 years old;
- 1997: Diagnosed and treated for the first time;
- 1998: Treated again;
- 2000: Underwent removal of part of his left lung; bought ethionamide and added it to his regimen;
- 2002: Treated agai;
- 2005: Received full 2 year course of treatment; declared "cured";
- 2009: Treated 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 1th month;
- Good level of adherence and tolerance;
- Currently on 6th 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, 3018;
  - 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:

	2016	2017	2018	2019	2020	2021	Total
Actual endTB	215	158	302	0	0	0	675
Actual GF	0	0	674	221	0	0	895
Actual MOH	0	0	0	732	Unknown	Unknown	732 + ?
# RR/MDR pts diagnosed	6314	5893	5500*	5200*	4900*	4600*	
Access to regimens	3%	3%	18%*	18%*	Unknown	Unknown	

* 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
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- Stop TB Partnership
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