endTB-Q: Interim results of a randomized controlled trial testing a shorter treatment strategy for pre-XDR-TB

13 November 2024

Design

endTB-Q | Design & Objectives (selected)

- Randomized, controlled, open-label, non-inferiority, Phase III trial for pre-extensively drug-resistant tuberculosis (pre-XDR-TB)*

- Fixed randomization 2:1 (experimental to control), stratified by country, baseline disease extent

- Compares a stratified duration strategy using a regimen containing bedaquiline (B), clofazimine (C), delamanid (D), and linezolid (L)** vs. standard-of-care-control (long conventional regimen)

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* pre-XDR-TB = TB with resistance to rifampicin (R) plus any fluoroquinolone (FQ); ** L dose reduced at Week 16 according to a secondary randomization to 300 mg daily or 600 mg thrice a week.

endTB-Q | Duration assignment (experimental arm)

Baseline characteristics of participants

	Smear Neg	Smear 1+	Smear 2+	Smear 3+
Cavity absent	Limited	Limited	Extensive	Extensive
Cavity present	Limited	Extensive	Extensive	Extensive

Limited = **24-week** treatment duration; if **delayed treatment response*** = **39-week** duration

Extensive = **39-week** treatment duration

*delayed treatment response: positive or unassessable sputum culture at W8; *OR* any positive culture after W8

Inclusion

- **Pulmonary TB, R-resistant, FQ-resistant** (or inconclusive in India/Pakistan)

- **≥ 15 years of age**

- Negative pregnancy test

- Informed consent

Exclusion

- Allergy or hypersensitivity to study drugs

- Exposure, resistance: B, C, D, L

- Pregnancy, breastfeeding

- Severe lab abnormalities
  - K+ disorders Grade 2 or higher*
  - Other electrolyte disorders*, hemoglobin, creatinine, liver enzymes Grade 3 or higher
  - Other tests Grade 4 or higher

- Cardiac risk factors for arrhythmia, including QTcF≥ 450 ms

* Uncorrectable

Results

endTB-Q | Timeline and enrollment

Patients screened: 1030 -> **Randomized: 324 (31.5%)** + 138 (19.5%) randomized in endTB trial

Main reasons for screen failure:

- MTB detection, RIF resistance, FQ resistance not established (88.1%)
- Laboratory values outside acceptable range (4.2%)
- Investigator discretion (4.0%)

Vietnam 23 (7%)
Peru 19 (6%)
Lesotho 2 (1%)
Kazakhstan 21 (6%)
Pakistan 122 (38%)
India 137 (42%)

endTB-Q | Analysis populations

	Experimental	Control	Total
Randomized	218 (100.0%)	105 (100.0%)	323[*] (100.0%)
- Treatment not started	5 (2.3%)	0 (0.0%)	5 (1.5%)
Safety	213 (97.7%)	105 (100.0%)	318 (98.5%)
- No FQ-R	18 (8.3%)	12 (11.4%)	30 (9.3%)
- No positive culture	21 (9.6%)	6 (5.7%)	27 (8.4%)
- Resistance to B, C, D or L	7 (3.2%)	3 (2.9%)	10 (3.1%)
- Other	3 (1.4%)	0 (0.0%)	3 (0.9%)
mITT	163 (74.8%)	84 (80.0%)	247 (76.5%)
- Not protocol-adherent**	6 (2.7%)	8 (7.6%)	14 (4.4%)
Per protocol (PP)	157 (72.0%)	76 (72.4%)	**233 (72.1%)**

* 1 participant withdrew consent for study & use of study data after randomization; ** >=80% of expected doses within 120% of the regimen duration, and for those in 24-week treatment, <=120% of expected doses; no exclusion for treatment failure or death)

endTB-Q | Select Baseline Characteristics (mITT)

	Experimental	Control	Total
N (%)	**163 (66.0%)**	**84 (33.9%)**	**247 (100.0%)**
Female	71 (43.6%)	43 (51.2%)	114 (46.2%)
Age*	31 [21.0; 42.0]	28.5[20.0; 44.0]	30 [21.0; 42.5]
<18	11 (6.7%)	7 (8.3%)	18 (7.3%)
BMI*	17.5 [15.6; 20.0]	17.9 [15.3; 20.1]	17.6 [15.4; 20.1]
HIV+	1 (0.6%)	3 (3.6%)	4 (1.6%)
Hepatitis C+	7 (4.3%)	5 (6.0%)	12 (4.9%)
Diabetes	37 (22.7%)	18 (21.4%)	55 (22.3%)
Cavitation	108 (66.3%)	57 (67.9%)	165 (66.8%)
Smear result			
Negative/Scanty	45 (27.6%)	23 (27.4%)	68 (27.6%)
1-2+	80 (49.0%)	39 (46.5%)	119 (48.1%)
3+	38 (23.3%)	22 (26.2%)	60 (24.3%)

* Median [IQR]

Regimens	n (%)
BCDL+Cs	59 (70.2%)
BCDL+Cs+E	5 (6.0%)
BCDL+Z	5 (6.0%)
BCDL other	7 (8.4%)
BCL+Cs+Z	8 (9.5%)

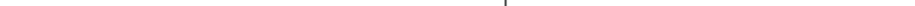| Treatment duration (weeks)*	N = 74
Mean (SD)	77.6 (1.24)
Median [IQR]	78.0 [77.1; 78.0]
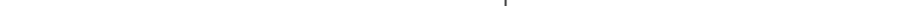
≈90% received BCDL + 1 or more drugs

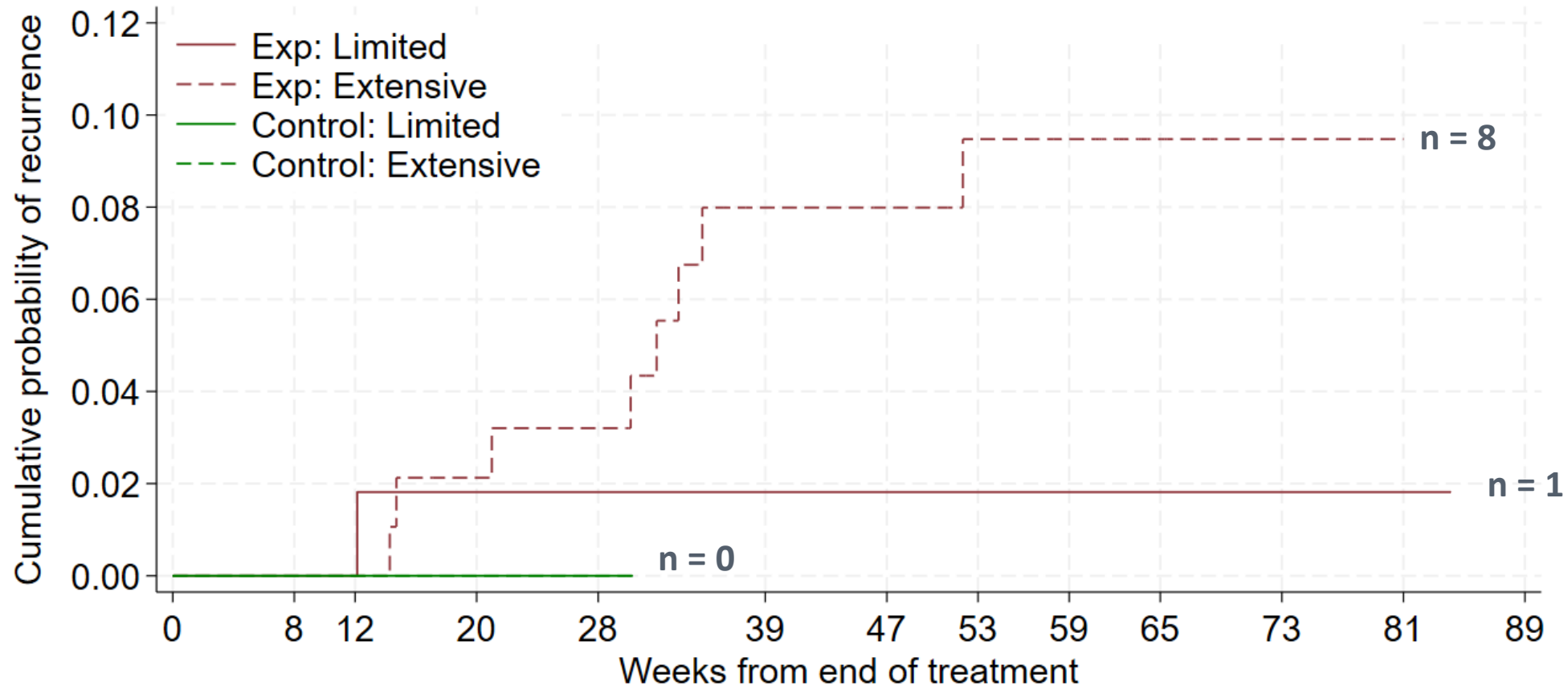* excluding early treatment discontinuations

Results: efficacy

endTB-Q | Efficacy Week 73 (mITT), experimental & control

endTB-Q W73 outcomes, N (%)	Experimental (n = 163)	Control (n = 84)
Favorable	141 (86.5%)	75 (89.3%)
95% CI	[80.2%;91.3%]	[80.6%;95.0%]
Unfavorable	22 (13.5%)	9 (10.7%)
Death	4 (2.4%)	2 (2.4%)
Poor treatment response	7 (4.3%)	3 (3.6%)
Recurrence	8 (4.9%)	0 (0.0%)
Perm Discontinuation AE	1 (0.6%)	0 (0.0%)
Poor Adherence/LTFU	1 (0.6%)	0 (0.0%)
Consent withdrawal	1 (0.6%)	4 (4.8%)

Analysis population	BCDL	Control	Risk Difference with 95% Confidence Interval
	n with favorable outcome/N (%)		
W73			
mITT	141/163 (86.5%)	75/84 (89.3%)	0.2% [−9.1%;9.5%]
PP	138/157 (87.9%)	71/76 (93.4%)	−3.5% [−12.8%;5.9%]

Control Better — BCDL Better

Scale: −12, −5, 0, 5, 10

*adjusted for randomization stratification variables: country & baseline extent of disease

Analysis population	BCDL	Control	Risk Difference with 95% Confidence Interval
mITT	75/84 (89.3%)	141/163 (86.5%)	0.2% [-9.1%;9.5%]
Baseline disease extent			
Limited	28/32 (87.5)	54/58 (93.1)	5.6% [-7.6%; 18.8%]
Extensive	47/52 (90.4)	87/105 (82.9)	-7.5% [-18.3%; 3.2%]

Control Better — BCDL Better

*adjusted for randomization stratification variables: country & baseline extent of disease
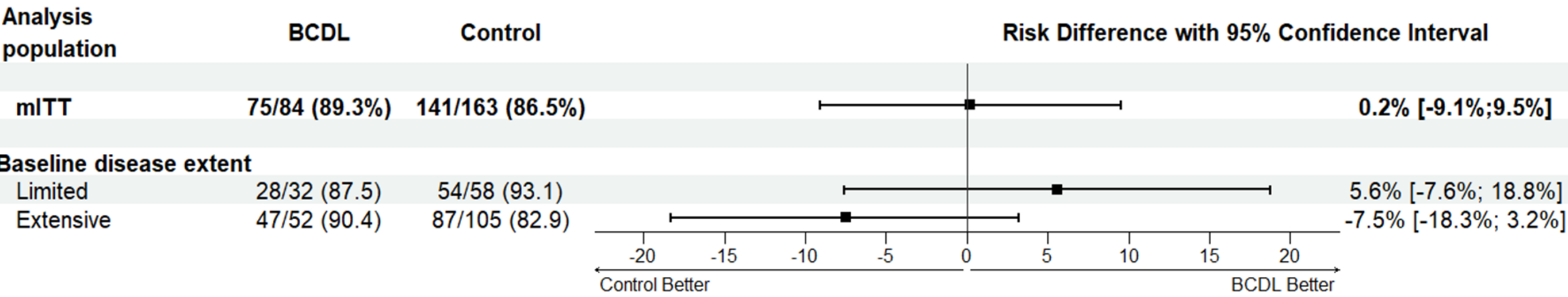
Whole genome sequencing available for 8/9 recurrences (1 pending)
- 8/8 confirmed relapses
- 6/8 acquired drug resistance

Results: safety

	Experimental N=213	Control N=105	Total N=318
Participants with **any Grade ≥3 AE**[*]	136 (63.8%)	80 (76.2%)	216 (67.9%)
Participants with **any SAE**[**]	31 (14.5%)	23 (21.9%)	54 (17.0%)
Permanent discontinuation of ≥1 drug(s) for AEs	30 (14.1%)	57 (54.3%)	87 (27.4%)
Death[#]	9 (4.2%)	2 (1.9%)	11 (3.5%)

Includes all follow-up period; 5 deaths were not included in the efficacy analyses: 3 in people excluded from mITT and 2 that occurred after end of study participation; 2 were TB-related; 2 were TB-drug related

Post hoc analysis; primary safety analysis is at Week 73; * Graded according to MSF Severity Scale; ** Serious adverse event = leading to death or life threatening; or leading to hospitalization, permanent disability or congenital defect; or medically important.

	Experimental N=213	Control N=105	Total N=318
Grade ≥3 **hematologic toxicity***	26 (12.2%)	22 (21.0%)	48 (15.1%)
Grade ≥3 **peripheral neuropathy**	41 (19.2%)	27 (25.7%)	68 (21.4%)
Grade ≥3 **hepatotoxicity**	10 (4.7%)	4 (3.8%)	14 (4.4%)
Grade ≥3 **optic neuropathy**	2 (0.9%)	2 (1.9%)	4 (1.3%)
Grade ≥3 **QT prolongation**	3 (1.4%)	4 (3.8%)	7 (2.2%)

Post hoc analysis; primary safety analysis is at Week 73; * Includes Grade 3 leukemia, anemia or thrombocytopenia

Conclusions

endTB-Q | Conclusions

- The endTB-Q strategy is an excellent option for patients with limited pre-XDR-TB disease. In extensive disease, the conventional regimen may be required to prevent relapse.

- **endTB-Q reinforces the importance of FQ** in RR/MDR-TB treatment:
  - Relapse may be more likely when treating pre-XDR-TB with the current, recommended short regimens (6BCDL, 2.0-5.0% & 6/9 BPaL, 2.7-4.4%)
  - FQ resistance testing is critical in patients with RR-TB

- **Future research** is required to optimize regimen composition, duration:
  - Trials should be designed specifically for pre-XDR-TB population to glean effects in that population
  - Trials require an internal control to correctly interpret well-performing experimental arm

The 323 trial participants and the other patients screened

All the team members, investigators and sites which implemented the trial over 4 years.
The National TB Programs and all local partners in India, Kazakhstan, Lesotho, Pakistan, Peru and Vietnam

The Sponsor and research partners:

The PIs, the central endTB team, all contributing expert teams (Protocol Writing Committee, Scientific Advisory Committee, MSF Logistique, unblinded statisticians, the Clinical Advisory Committee, the Pharmacovigilance unit, Data and Safety Monitoring Board, MSF Access Campaign, Global Tuberculosis Community Advisory Board, WHO) and all other support teams

Our co-funders: MSF, PIH, the Ramón Areces Foundation, the Jung Foundation for Science and Research as well as our long-term partner:

We are grateful to all endTB-Q trial participants and endTB-Q teams!

Are you interested in learning more from the endTB project data?

The **endTB Data Sharing Initiative (eDSI)** aims to give ethical, equitable and transparent access to endTB data for a range of users who share the common goal of increasing information to improve care for MDR-TB patients. It is a unique set of data on more than 3,700 participants spread across 4 continents.

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October 2024

Thank you! Questions?