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

Lorenzo Guglielmetti

co-Principal Investigator, endTB-Q Trial

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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)

* 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

endTB-Q | Eligibility (Main)

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%)

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]

endTB-Q | Control arm (at initiation) description (N=84)

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

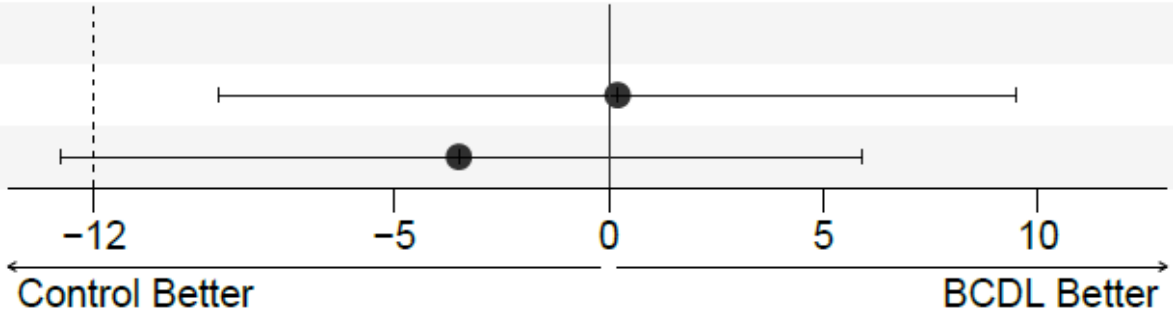
Results: efficacy

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%)

endTB-Q | Adjusted* forest plots: mITT & PP efficacy at Week 73

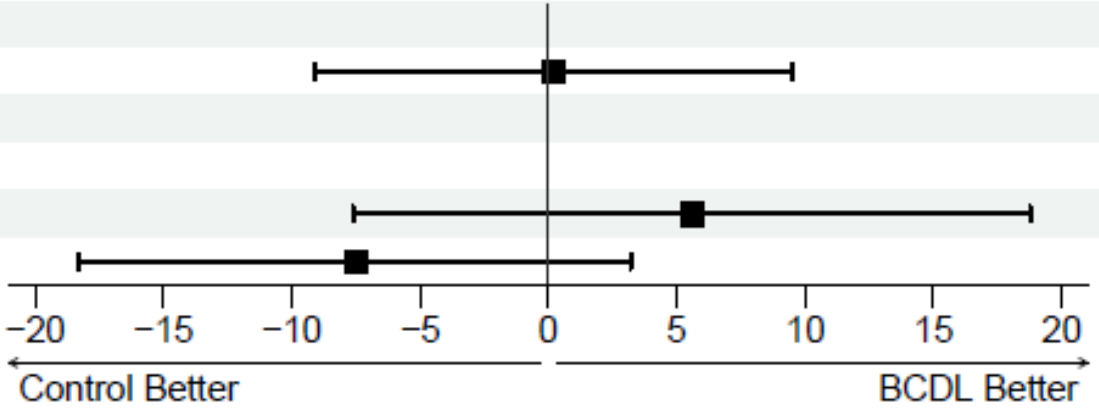
Analysis population	BCDL	Control	Risk Difference with 95% Confidence Interval
	n with favorable outcome/N (%)		
W73			
mITT	141/163 (86.5%)	75/84 (89.3%)	0.2% [−9.1%;9.5%]
PP	138/157 (87.9%)	71/76 (93.4%)	−3.5% [−12.8%;5.9%]



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

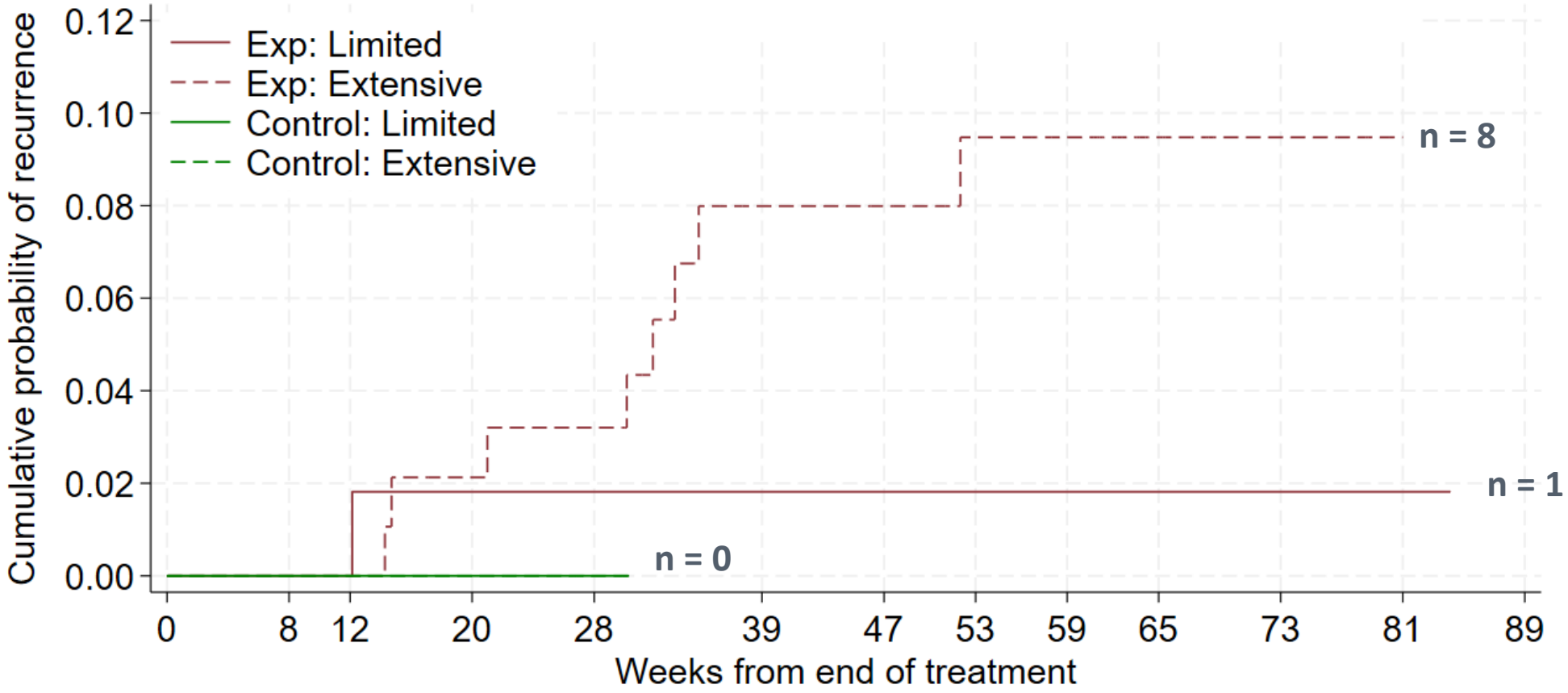
endTB-Q | Adjusted* forest plots: mITT & PP efficacy at Week 73, stratified by baseline disease extent

Analysis population	BCDL	Control	Risk Difference with 95% Confidence Interval
	no. with favorable outcome/total no. (%)		
mITT	**141/163 (86.5%)**	**75/84 (89.3%)**	**0.2% [−9.1%;9.5%]**
Baseline disease extent			
Limited	54/58 (93.1)	28/32 (87.5)	5.6% [−7.6%; 18.8%]
Extensive	87/105 (82.9)	47/52 (90.4)	−7.5% [−18.3%; 3.2%]



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

endTB-Q | Time to recurrence from treatment end, stratified by baseline disease extent (mITT)



Whole genome sequencing available for 8/9 recurrences (1 pending)

- 8/8 confirmed relapses
- 6/8 acquired drug resistance

Results: safety

endTB-Q | Adverse Events: Total, Grade ≥3 & SAE at treatment end + 4 weeks# (Safety population)

	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.

endTB-Q | AESI by category at treatment end + 4 weeks# (Safety population)

	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

Special thanks to the people and organizations who made the endTB-Q clinical trial a reality…

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

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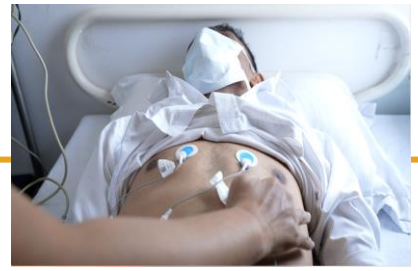
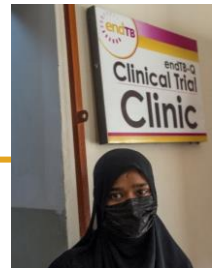
We are grateful to all endTB-Q trial participants and endTB-Q teams!











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.

Scan this QR code to learn more about eDSI

endTB

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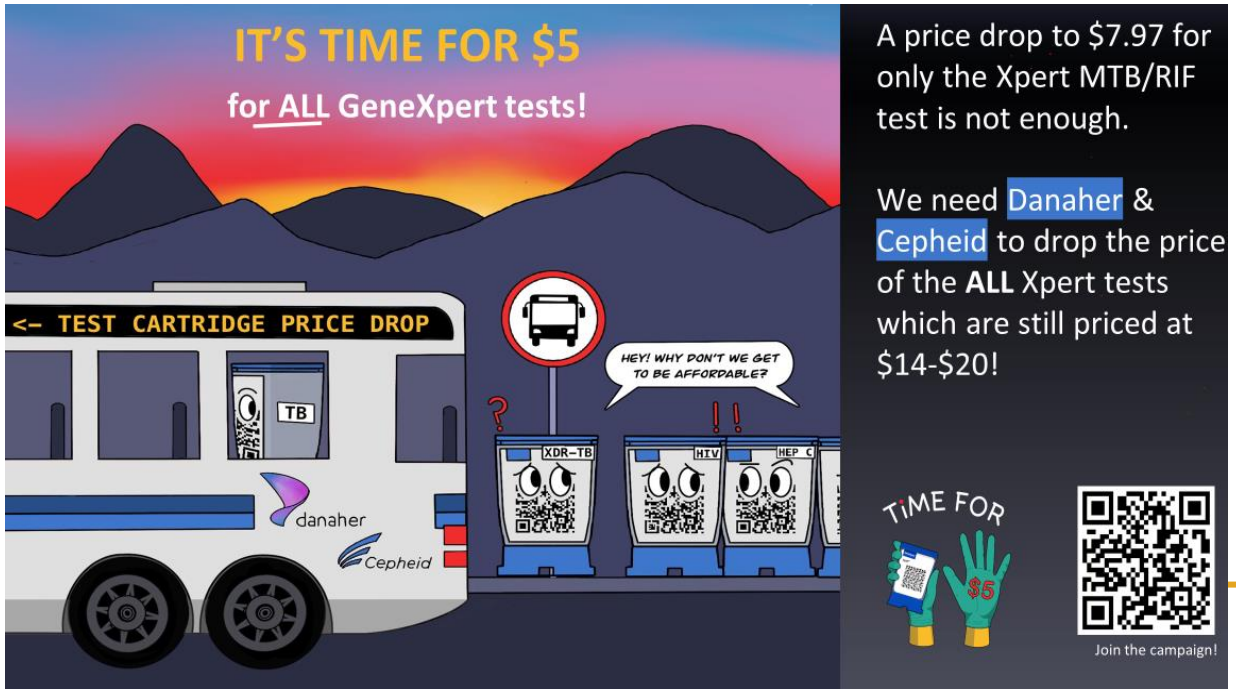
October 2024



Thank you! Questions?