endTB-Q trial: a caveat on confounding by baseline drug resistance

Authors' reply

We read with interest the letter by Kwok Chiu Chang and appreciate the potential implications they raise for individuals in settings in which rapid, reliable, and complete drug susceptibility testing for bedaquiline, delamanid, linezolid, and clofazimine (BDLC) is available at treatment initiation. The unfortunate, present reality is that these circumstances are exceptional. There are no WHO-endorsed rapid molecular tests available for these four drugs. Existing sequencing strategies lack comprehensiveness, speed, or interpretability.[1] Phenotypic drug susceptibility testing remains the reference standard, with results reported months after sample collection. Until drug susceptibility testing tools become rapid, reliable, and widely available, most decisions about the use of the endTB-Q strategy will occur in circumstances like those in the endTB-Q trial.[2]

In the trial, phenotypic drug susceptibility testing for one or more study drugs was done at local laboratories in only 150 (46%) of 323 participants. Exclusion from the primary analysis populations (modified intent to treat [mITT] and per protocol) was based solely on these local laboratory results. In addition, the Institute of Tropical Medicine (ITM; Antwerp, Belgium) performed phenotypic drug susceptibility testing to all study drugs, and whole genome sequencing on samples shipped in batches from study sites.[2] These results informed neither clinical management nor exclusion from analysis populations because they were not available in real time. Previously reported baseline resistance results from ITM were only among the subgroup (n=27) who also had a positive *Mycobacterium tuberculosis* culture at 16 weeks or later after randomisation; those at risk for acquired resistance. In response to the Correspondence, we present a post-hoc sensitivity analysis of efficacy in the endTB-Q participants, excluding individuals with baseline resistance to any study drug as per ITM testing.

The post-hoc mITT population included 228 participants and the per-protocol population included 215 participants (table). For mITT, favourable outcomes occurred in 130 of 147 (88%; 95% CI 82–93) in the BDLC group and among 73 of 81 (90%; 81·5–96) in the control group, with an adjusted risk difference of 1·2% (95% CI –9·0 to 11·5). For per protocol, favourable outcomes occurred in 127 of 141 (90%; 95% CI 84–94·5) in the BDLC group and among 69 of 74 (93%; 85–98) in the control group, with an adjusted risk difference of –1·2% (95% CI –11·0 to 8·7). This post-hoc analysis supports the overall non-inferiority of the BDLC strategy (with a –12% non-inferiority margin) among individuals without baseline resistance to any of the four study drugs.

Based on the primary analysis, we had concluded that the BDLC strategy was not non-inferior to the control regimen, which was longer and often reinforced with one or two additional drugs. The advantage in the control group was most pronounced in people with extensive disease. The present analysis suggests that, if resistance to all study drugs could be ruled out, then the BDLC strategy might be a viable

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	mITT population		Per-protocol population	
	BDLC group (n=147)	Control group (n=81)	BDLC group (n=141)	Control group (n=74)
Favourable outcome				
Number of participants	130 (88%)	73 (90%)	127 (90%)	69 (93%)
Adjusted absolute difference from the control, % (95% CI)*	1·2% (–9·0 to 11·5)	..	–1·2% (–11·0 to 8·7)	..
Participants with negative culture results, weeks 65 and 73	129 (88%)	72 (89%)	126 (89%)	68 (92%)
Participants with favourable bacteriological, clinical and radiological evolution†	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Unfavourable outcomes				
Number of participants	17 (12%)	8 (10%)	14 (10%)	5 (7%)
All-cause mortality‡	4 (3%)	2 (2%)	4 (3%)	2 (3%)
Participants with treatment failure§	4 (3%)	3 (4%)	4 (3%)	3 (4%)
Participants with relapse¶	6 (4%)	0	6 (4%)	0
Participants with permanent treatment discontinuation due to adverse event	1 (1%)	0	0	0
Participants with poor treatment adherence or lost to follow-up	1 (1%)	0	0	0
Participants who withdrew consent	1 (1%)	3 (4%)	0	0

Data are n (%) or % (95% CI). Deferred, batched testing was done at the Institute of Tropical Medicine (ITM; Antwerp, Belgium) and was not available to inform treatment. The post-hoc mITT population included participants who were randomly assigned, received at least one dose of trial treatment, and had a culture positive for *Mycobacterium tuberculosis* before random assignment. It excluded participants whose baseline isolates were tested at ITM and found to have phenotypic resistance to bedaquiline, delamanid, linezolid, or clofazimine. The post-hoc per-protocol population included participants from the post-hoc mITT population who did not receive more than 7 days of either a prohibited concomitant medication or a trial drug that was not prescribed according to the protocol and completed a protocol consistent course of treatment (at least 80% of expected doses taken within 120% of the regimen duration and no more than 120% of the expected doses in participants who were to receive 24 weeks of treatment duration) or who did not do so because of treatment failure or death. BDLC=bedaquiline, delamanid, linezolid, and clofazimine. mITT=modified intention-to-treat. *Analyses adjusted for country and baseline extent of tuberculosis disease (mITT n=210, with 18 observations dropped because of perfect separation; per protocol n=198, with 17 observations dropped because of perfect separation). †Participants without culture results between weeks 65 and 73. ‡Six mITT participants died (part of the treatment outcome) and three died in the safety population (excluded from the mITT population). §Participants who permanently discontinued treatment because of a positive sputum culture at week 16 or later; or who had a positive sputum culture between weeks 65 and 73; or who had a combination of culture results insufficient to establish favourable outcome and unfavourable bacteriological, radiological, or clinical evolution. ¶Participants who, after treatment completion, started a new treatment regimen and had a confirmed relapse (same strain on baseline and post-treatment sample).

Table: **Post-hoc sensitivity analysis for week 73 treatment outcomes among individuals without baseline resistance to BDLC per deferred, batched testing**

alternative for all patients. However, the risk of using the BDLC strategy is growing with the emergence of background resistance to the drugs used in the regimen.[3] This risk will recur with new drugs without a commitment from drug developers to support efforts to shorten the time to drug susceptibility testing for novel compounds.[4]

Although the present sensitivity analysis offers support for the non-inferiority of the BDLC strategy in pre-extensively-drug-resistant tuberculosis, the risks of unfavourable outcomes, including acquired drug resistance, are high enough to warrant caution about its use among individuals with extensive disease until, and unless, rapid, reliable drug susceptibility testing supports decision making.

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