Efficacy and Safety of endTB Regimens for Fluoroquinolone-Susceptible RR-TB in People With HIV

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BACKGROUND

- endTB (ClinicalTrials.gov NCT02754765) was an open-label Phase 3 randomized, controlled clinical trial that evaluated the efficacy and safety of five 9-month, all-oral regimens for fluoroquinolone-susceptible rifampin-resistant TB (RR-TB), compared to the 18-24 month WHO-recommended standard of care, in people 15 years of age or older.
- In the primary analysis, three experimental regimens (9BLMZ, 9BCLLfxZ, and 9BDLLfxZ) had noninferior efficacy compared to the control and were safe **(Table 1)**. Here, we present efficacy and safety results among people with HIV (PWH).

Table 1. Primary efficacy outcomes in the endTB trial.

Regimens	Bdq	Dlm	Cfz	Lzd	FQ	Z	Non-inferiority established	Efficacy at W73
9BLMZ	Bdq			Lzd	Mfx	Z	Yes	89.0% mITT, 95.9% PP
9BCLLfxZ	Bdq		Cfz	Lzd	Lfx	Z	Yes*	90.4% mITT, 95.8% PP
9BDLLfxZ	Bdq	Dlm		Lzd	Lfx	Z	Yes	85.2% mITT, 94.2% PP
9DCLLfxZ		Dlm	Cfz	Lzd	Lfx	Z	No	78.8% mITT, 85.4% PP
9DCMZ		Dlm	Cfz		Mfx	Z	Inconclusive**	85.6% mITT, 88.2% PP
Control	18-24 month standard of care, according to WHO guidelines							80.7% mITT, 95.9% PP

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METHODS

- endTB inclusion was irrespective of HIV status or CD4 count. The safety population included all randomized participants who started study treatment, and the modified intention-to-treat (mITT) population included those in the safety population who had a positive pre-randomization TB culture and no resistance to study drugs.
- The primary efficacy endpoint was favorable outcome at Week 73 post-randomization, defined as either [1] two consecutive, negative cultures (one between Weeks 65 and 73); or [2] favorable evolution. Unfavorable outcomes included death, treatment failure, drug addition or replacement, and retreatment.
- Safety outcomes were Grade 3-4 adverse events (AEs); serious AEs (SAEs); deaths; AEs of special interest (AESIs) defined as Grade 3-4 hepatotoxicity, myelosuppression, optic neuritis, peripheral neuropathy, or prolonged QTcF; and AEs leading to permanent discontinuation of at least one drug.

Three 9-month oral regimens for FQ-S MDR/RR-TB were noninferior to the WHO standard-of-care control. Two (9BLMZ, 9BCLLfxZ) were efficacious in people living with HIV.

Table 2. Participant characteristics among people with HIV, mITT population.

Characteristic	Total (N = 98)
Country	
Kazakhstan	8 (8.2%)
Lesotho	55 (56.1%)
Pakistan	1 (1.0%)
Peru	4 (4.1%)
South Africa	30 (30.6%)
Age, years, median (IQR)	39 (32-45)
Sex	
Female	46 (46.9%)
Male	52 (53.1%)
CD4, cells/mm^3, median (IQR)	296 (118-497)
Receiving ART at baseline	61 (62.2%)
Timing of start of ART	
Before enrollment	61 (62.2%)
Within 8 weeks after enrollment	33 (33.7%)
Not during study follow-up	4 (4.1%)

Table 3. Efficacy and safety of endTB regimens at Week 73 in people with HIV.
B, bedaquiline; C, clofazimine; D, delamanid; L, linezolid; Lfx, levofloxacin; M, moxifloxacin; Z, pyrazinamide.

RESULTS

- From 2017-2021, we randomized 754 participants in 7 countries; 104 (13.8%) were PWH. The safety population included 103 (99.0%) and the mITT 98 (94.2%). 85 (86.7%) were from Lesotho or South Africa; median age was 39 years (range 19-70 years); 46 (46.9%) were female; median CD4 count was 296 (range 5-1294); and 61 (62.2%) were already on antiretrovirals **(Table 2)**.
- Two of the noninferior experimental arms from the endTB trial demonstrated high efficacy in PWH, with favorable outcomes in 93.3% (9BLMZ) and 100.0% (9BCLLfxZ). The remaining three experimental arms and the control also performed well but showed relatively lower efficacy: 70.6% (9BDLLfxZ), 83.3% (9DCLLfxZ), 73.3% (9DCMZ), and 89.5% (control) **(Table 3, Figure 1)**. Grade 3+ AEs or SAEs, AESIs, and AEs leading to drug discontinuation were more common in the control than in experimental arms **(Table 3)**.

Efficacy outcome (mITT population)	endTB1 (9BLMZ) (n = 15)	endTB2 (9BCLLfxZ) (n = 14)	endTB3 (9BDLLfxZ) (n = 17)	endTB4 (9DCLLfxZ) (n = 18)	endTB5 (9DCMZ) (n = 15)	endTB6 (Control) (n = 19)	Total (N = 98)
Favorable outcome at Week 73, 95% CI	14 (93.3%) [68.1%;99.8%]	14 (100.0%) [76.8%;100.0%]	12 (70.6%) [44.0%;89.7%]	15 (83.3%) [58.6%;96.4%]	11 (73.3%) [44.9%;92.2%]	17 (89.5%) [66.9%;98.7%]	83 (84.7%) [76.0%;91.2%]
Safety outcome (safety population)	**(n = 17)**	**(n = 15)**	**(n = 18)**	**(n = 18)**	**(n = 16)**	**(n = 19)**	**(N = 103)**
At least one grade 3 or higher AE or SAE of any grade	11 (64.7%)	8 (53.3%)	12 (66.7%)	12 (66.7%)	8 (50.0%)	16 (84.2%)	67 (65.1%)
At least one SAE	7 (41.2%)	4 (26.7%)	6 (33.3%)	7 (38.9%)	3 (18.8%)	9 (47.4%)	36 (35.0%)
Death	1 (5.9%)	0 (0%)	2 (11.1%)	1 (5.6%)	0 (0%)	0 (0%)	4 (3.9%)
At least one AESI	9 (52.9%)	6 (40.0%)	4 (22.2%)	7 (38.9%)	4 (25.0%)	11 (57.9%)	41 (39.8%)
At least one AE leading to permanent discontinuation of ≥1 drug	6 (35.3%)	4 (26.7%)	8 (44.4%)	3 (16.7%)	1 (6.3%)	13 (68.4%)	35 (34.0%)

CONCLUSIONS

- Among regimens that were noninferior to the WHO control in the primary analysis, 9BLMZ and 9BCLLfxZ appeared to be particularly efficacious for PWH.

ADDITIONAL KEY INFORMATION

- Funding: The endTB clinical trial was funded by Unitaid. GEV received funding from NIH/NIAID (K08 AI141740).

Figure 1. Efficacy outcomes at Week 73, by HIV status.