Putting Drug-Resistant TB Treatment Guidelines Updates in Context for Communities and Civil Society

November 21, 2024

Agenda

1. Welcome (Joelle) – 5 mins
2. Framing (Lindsay) – 10 mins
3. Putting DR-TB Treatment Guidelines Updates in Context for Communities and Civil Society (Dr Jennifer Furin, Harvard Medical School & Sentinel Project on Pediatric Drug-Resistant TB) – 40 mins
4. Q&A – 35 mins

WORLD HEALTH ORGANIZATION DR-TB TREATMENT GUIDELINES, 2022

The WHO recommends three regimens for the treatment of rifampicin-/multidrug-resistant TB (RR-/MDR-TB), each with slightly different eligibility criteria based on the available data (or lack thereof).

The shorter standardized regimens are prioritized, with the longer individualized regimen recommended for use in populations and individuals otherwise not eligible or able to take the shorter regimens.

1. **Six-month BPaL/M regimen:** six months of bedaquiline, pretomanid, and linezolid given with moxifloxacin for RR-/MDR-TB and without moxifloxacin for pre-XDR-TB.

2. **Nine month standardized, all-oral regimen:** nine months of levofloxacin, clofazimine, pyrazinamide, and ethambutol; supplemented by bedaquiline for the first six months, linezolid for the first two months, and high-dose isoniazid for the first four to six months for RR-/MDR-TB.

3. **18-to-20-month individualized regimen:** 18-to-20-months of a regimen composed of at least four medicines selected from the list of WHO Group A, B, and C medicines according to an individual's drug-susceptibility profile.

WORLD HEALTH ORGANIZATION RAPID COMMUNICATION, AUGUST 2024

1. **6-month BEAT-TB regimen:**

   6BDLz + Lx or C
   bedaquiline, delamanid, linezolid, levofloxacin, clofazimine

   Depending on FQ results, either drop clofazimine or levofloxacin or if don't have DST results continue with both drugs

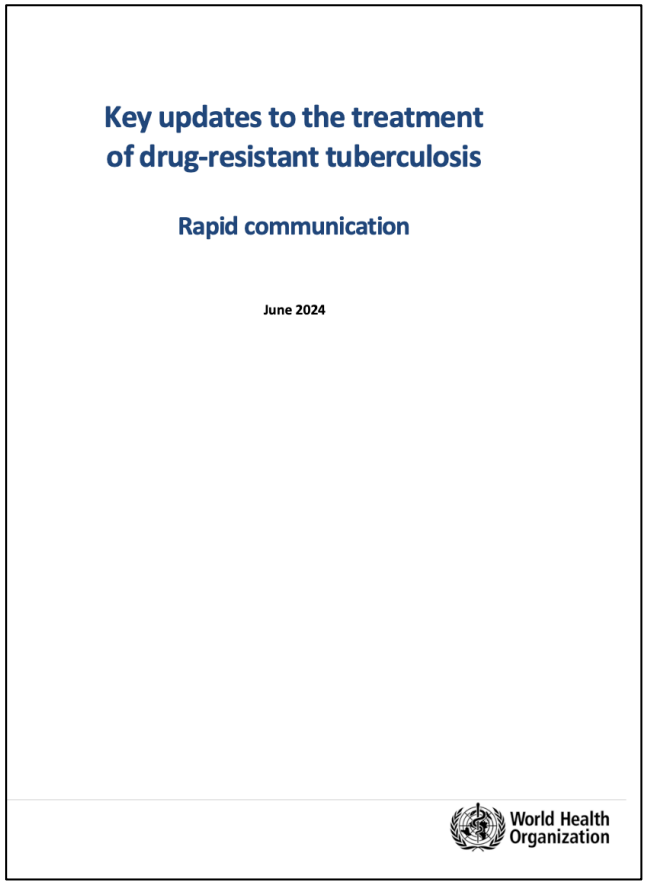
2. **9-month endTB regimens**:

   9BLzMZ
   9BLzLxCZ
   9BLzLxDZ

   bedaquiline linezolid and pyrazinamide given with moxifloxacin; or with levofloxacin and clofazimine; or with levofloxacin and delamanid

   Recommendations against the use of the other two endTB regimens that were bedaquiline-sparing

Read the rapid communication here.



WORLD HEALTH ORGANIZATION DR-TB TREATMENT GUIDELINES, 2024

1. **Six-month regimens**

    a) **BPaL/M regimen:** six months of bedaquiline, pretomanid, and linezolid given with moxifloxacin for RR-/MDR-TB and without moxifloxacin for pre-XDR-TB.

    b) **BEAT-TB regimen:** six months of bedaquiline, delamanid, linezolid, levofloxacin or clofazimine

2. **Nine-month regimens**

    a) **endTB regimen:** nine months of bedaquiline linezolid and pyrazinamide given with moxifloxacin; or with levofloxacin and clofazimine; or with levofloxacin and delamanid

    b) **Nine month standardized, all-oral regimen:** nine months of levofloxacin, clofazimine, pyrazinamide, and ethambutol; supplemented by bedaquiline for the first six months, linezolid for the first two months, and high-dose isoniazid for the first four to six months for RR-/MDR-TB

3. **18-to-20-month individualized regimen:** 18-to-20-months of a regimen composed of at least four medicines selected from the list of WHO Group A, B, and C medicines according to an individual's drug-susceptibility profile.

Putting Drug-Resistant TB Treatment Guidelines Updates in Context for Communities and Civil Society

1. Walk through rapid communication from August 2024
2. Breakdown BEAT-TB and endTB regimens and evidence base behind latest WHO recommendations
3. Explain extrapolation to children and pregnant women
4. Point out differences / similarities between BEAT, endTB. and other WHO-recommended regimens for DR-TB
5. Provide context for where BEAT and endTB regimens fit in, e.g., how they are likely to be incorporated into national guidelines and TB programs in practice

Dr. Jennifer Furin is an infectious diseases physician and medical anthropologist with more than 30 years of experience working for people with drug-resistant TB all over the world.

Understanding Updates to the WHO Guidelines for RR/MDR-TB, 2024

Jennifer Furin, MD., PhD.

Presentation for Treatment Action Group

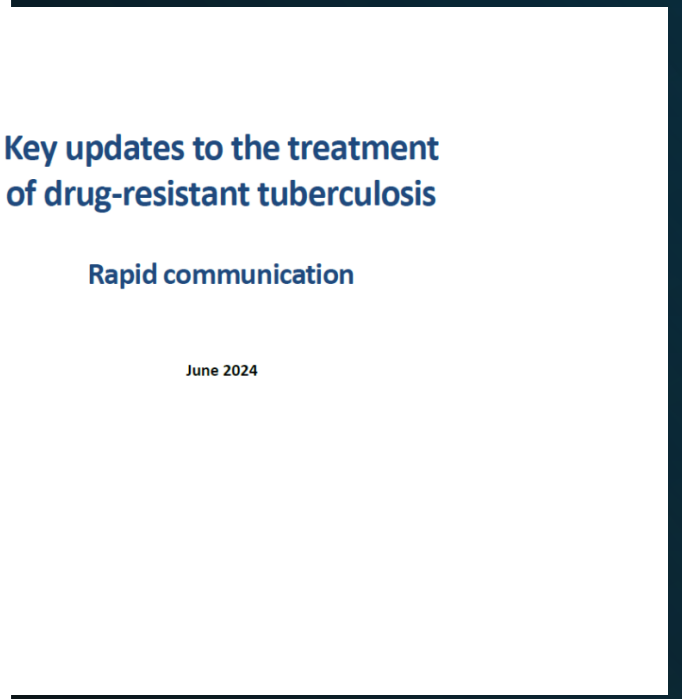
October, 2024

Objectives

- To review the recent updates to RR/MDR-TB treatment issued by WHO in August, 2024;
- To briefly present the evidence supporting these recommendations;
- To discuss possible approaches for countries given multiple options now available for treating RR/MDR-TB

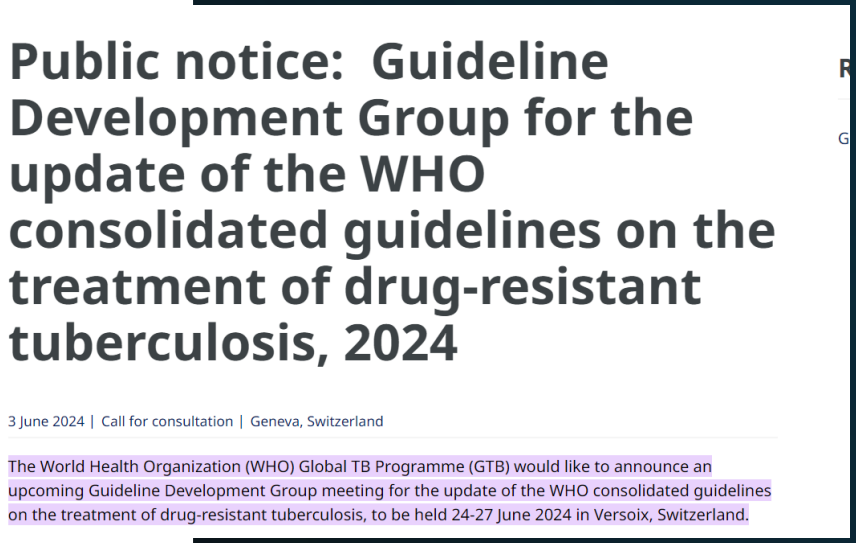
WHO Rapid Communication, August 2024

- Reviewed data from the BEAT Tuberculosis trial and from the endTB trial;
- Did not compare these regimens to one another or to BPaLM in terms of efficacy or safety;
- Did not review the WHO drug groups/classifications



WHO Recommendations

- WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine (BDLLfxC) in MDR/RR-TB patients with or without fluoroquinolone resistance(conditional recommendation, very low certainty of evidence). The available evidence included children, adolescents, pregnant and breastfeeding women, flagging the possible use of the regimen in these population groups.
- WHO suggests using the 9-month all-oral regimens (BLMZ, BLLfxCZ and BDLLfxZ) over currently recommended longer (>18 months) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. Amongst these regimens, using BLMZ is suggested over using BLLfxCZ, and BLLfxCZ is suggested over BDLLfxZ (conditional recommendation, very low certainty of evidence).



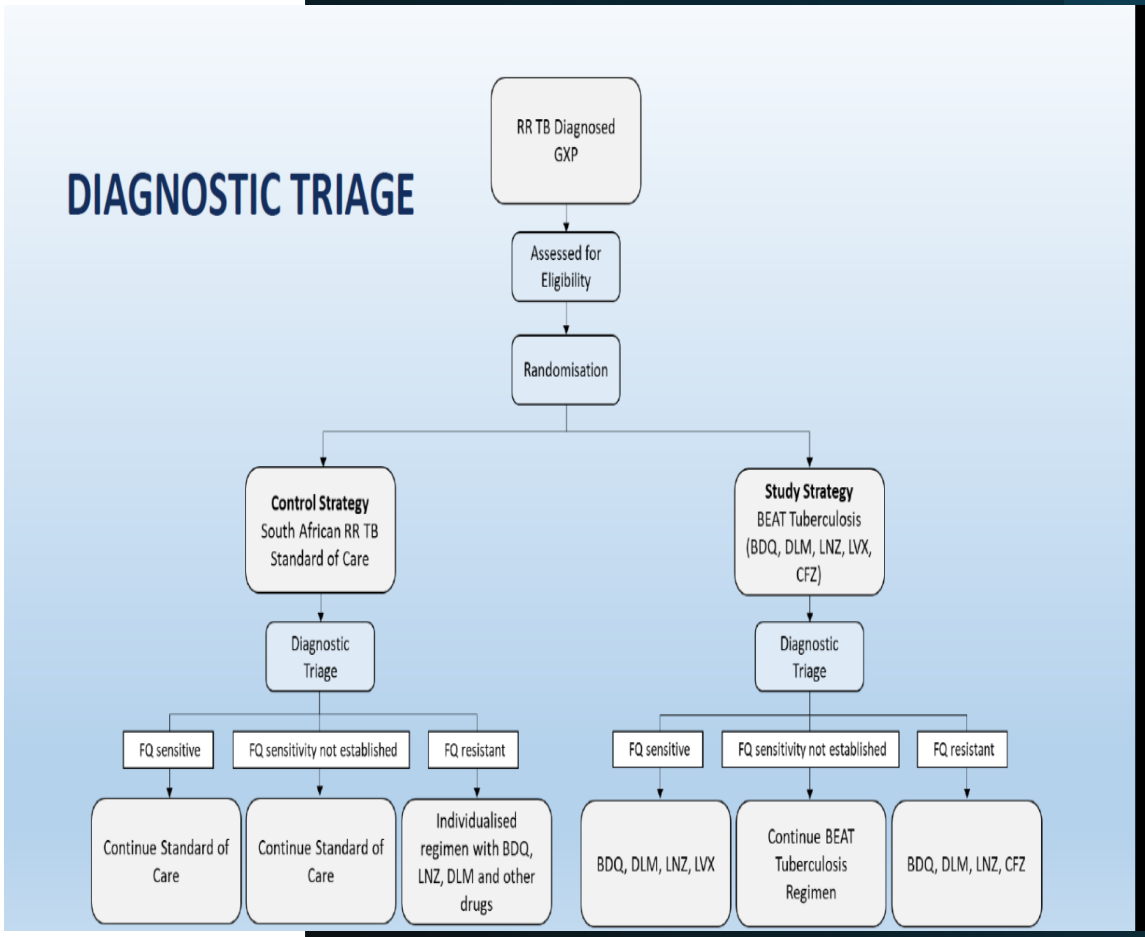
Public notice: Guideline Development Group for the update of the WHO consolidated guidelines on the treatment of drug-resistant tuberculosis, 2024

3 June 2024 | Call for consultation | Geneva, Switzerland

The World Health Organization (WHO) Global TB Programme (GTB) would like to announce an upcoming Guideline Development Group meeting for the update of the WHO consolidated guidelines on the treatment of drug-resistant tuberculosis, to be held 24-27 June 2024 in Versoix, Switzerland.

BEAT Tuberculosis Trial

- Randomized, controlled, non-inferiority trial done only in South Africa;
- Compared the 9-month, all-oral SOC regimen in SA with a 6-month, 4/5 drug regimen consisting of BDQ, DLM, CFZ, LFX, and LZD;
- Regimen could be refined if DST to the FLQ established.



PRIMARY OBJECTIVES

Non-inferiority design

EFFICACY

Successful treatment is assessed at the end of treatment
and
the end of follow-up (76 weeks post randomisation)

SAFETY

Grade 3 or greater adverse events during treatment

EFFICACY ENDPOINT: END OF TREATMENT OUTCOME

Successful	Unsuccessful
Cured	**Treatment failed** ○ lack of sputum culture conversion by the end of treatment OR ○ bacteriological reversion after sputum culture conversion to negative OR ○ if two or more anti-TB drugs are substituted due to Adverse Drug Reactions (ADRs)
Treatment completed	**Death during the treatment from any cause**
	Lost to follow-up
	Not evaluated

EFFICACY ENDPOINT: END OF FOLLOW-UP OUTCOME (76 weeks post randomization)

Successful	Unsuccessful
Cured	**Relapse** ○ Two consecutive positive cultures separated by at least 14 days OR ○ One positive after confirmed culture conversion culture with clinical signs & symptoms of TB or no improvement or worsening of radiological changes since baseline
Culture negative when last seen	**Death in follow up from any cause**
	Lost to follow-up with clinical signs and/or symptoms of TB when last seen OR sputum culture positive when last seen OR not sputum culture negative and with clinical signs & symptoms of TB when last seen

INCLUSION CRITERIA (MAJOR)

- Male or female, aged 6 years or older
- Pregnant and breastfeeding women may be included.
- Weigh more than or equal to 30kg
- Pulmonary RR TB
- Willing to have an HIV test and if positive, is willing to be treated with appropriate antiretroviral therapy

EXCLUSION CRITERIA (MAJOR)

- Taken more than 28 days but less than 24 weeks of second line TB drugs including BDQ, LNZ, CLZ, fluoroquinolones or DLM
- Pregnant or breastfeeding
- Complicated or severe extra-pulmonary manifestations of TB, including osteo-articular, pericardial and central nervous system infection
- QTcF interval of > 450 ms

EXCLUSION CRITERIA (MAJOR)

- Following laboratory abnormality at screening
  - Hemoglobin level of < 8.0 g/dL
  - Platelet count < 75,000/mm^3
  - Absolute neutrophil count (ANC) < 1000/ mm^3
  - An estimated creatinine clearance (CrCl) less than 30 mL/min
  - Alanine aminotransferase (ALT) ≥3 x ULN
  - Total bilirubin grade 3 or greater (>2.0 x ULN, or >1.50 x ULN when accompanied by any increase in other liver function test)
  - Serum potassium less than 3.2 mmol/l
- Peripheral neuropathy of grade 3 or 4 using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

BEAT Tuberculosis: Results

- 374 participants enrolled;
- Interim analysis of 199 showed the experimental regimen was non-inferior to the 9-month SOC regimen in terms of efficacy and safety;
- Most of the endpoints were due to regimen changes;
- Awaiting more details in the publication.

Key Findings

Primary Efficacy Outcome:
The six-month bedaquiline- and delamanid-based regimen had similar efficacy to the standard-of-care regimen (ITT).
The NI margin was 10%.

Unfavorable outcomes:		**Risk difference, experimental-control (95% confidence interval)**
(a)	13 (13%)	-1.4 (-10.9 to 8.1)
(b)	14 (14%)	NA

Primary Safety Outcome:
The six-month bedaquiline- and delamanid-based regimen had similar safety to the standard-of-care regimen.

	Any grade 3 or 4 AEs	Any serious AEs	Deaths
(a)	49 (25.7%)	33 (17.3%)	7 (3.7%)
(b)	51 (27.9%)	31 (16.9%)	6 (3.3%)

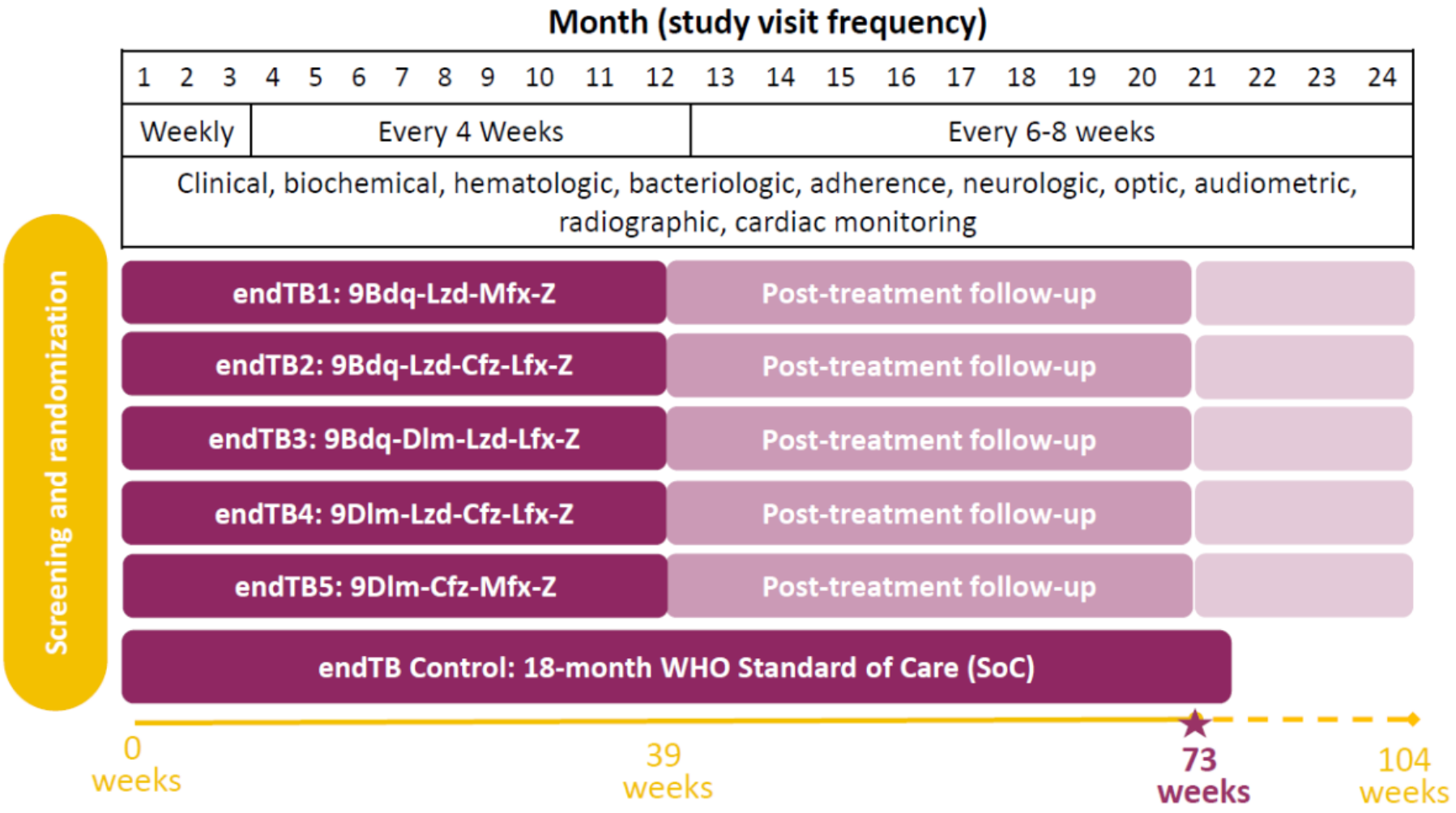
endTB trial

- Multi-country, non-inferiority trials using adaptive randomization to assess multiple 9-month regimens for RR/MDR-TB without fluoroquinolone resistance;
- Aim was to detect as many non-inferior regimens as possible;
- All regimens contained PZA: other combinations of BDQ, DLM, LZD, LFX/MFX, CFZ

endTB Trial Design[1]

- Randomized, controlled, open-label, non-inferiority, Phase III trial
- Compares each of 5 experimental regimens to control
  - Efficacy
  - Safety
- Bayesian adaptive randomization[2,3]:
  - Fixed 1:1:1:1:1:1 for first 180 patients, then
  - Adjusted randomization probabilities according to non-inferior performance of experimental vs control on week 8 culture negativity and week 39 favorable outcome
- Detect as many non-inferior regimens as possible

endTB Trial Design: Study Schema



endTB Trial Design: Main Inclusion & Exclusion Criteria

Inclusion

- Pulmonary TB, RIF-resistant, FQ-susceptible
- ≥ 15 years of age
- Negative pregnancy test
- Informed consent

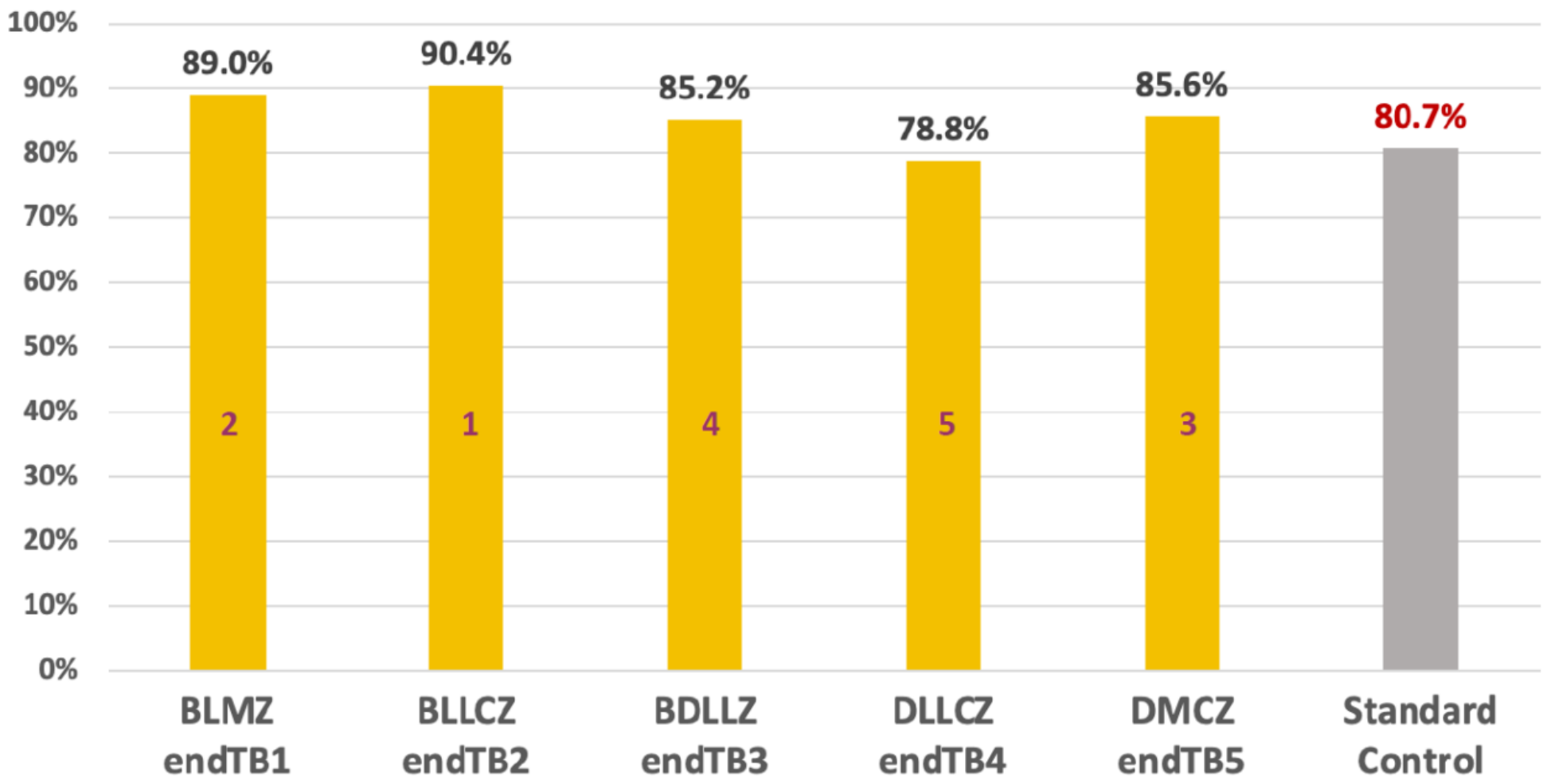
Exclusion

- Allergy or hypersensitivity to study drugs
- Exposure, resistance: Bdq, Dlm, Lzd, Cfz
- Pregnancy, breastfeeding
- Severe lab abnormalities
  - K+ disorders Grade 2 or higher*
  - Other electrolytes disorders*, hemoglobin, creatinine, liver enzymes Grade 3 or higher
  - Other tests Grade 4 or higher
- Cardiac risk factors
  - QTcF≥ 450 ms
  - Other factors predisposing to cardiac arrhythmia

Randomized patients by country

Country	endTB1 (BLMZ) (n = 127)	endTB2 (BLLCZ) (n = 124)	endTB3 (BDLLZ) (n = 128)	endTB4 (DLLCZ) (n = 125)	endTB5 (DMCZ) (n = 120)	endTB6 (Control) (n = 130)	Total (N = 754)
Georgia	2 (1.6%)	3 (2.4%)	1 (0.8%)	3 (2.40%)	1 (0.8%)	3 (2.3%)	13 (1.7%)
India	10 (7.9%)	4 (3.2%)	4 (3.1%)	5 (4.0%)	3 (2.5%)	5 (3.9%)	31 (4.11%)
Kazakhstan	31 (24.4%)	37 (29.8%)	34 (26.6%)	23 (18.4%)	30 (25.0%)	29 (22.3%)	184 (24.4%)
Lesotho	14 (11.0%)	13 (10.5%)	16 (12.5%)	11 (8.8%)	14 (11.7%)	13 (10.0%)	81 (10.7%)
Peru	40 (31.5%)	41 (33.1%)	51 (39.8%)	55 (44.0%)	47 (39.2%)	53 (40.8%)	287 (38.1%)
Pakistan	20 (15.7%)	17 (13.7%)	14 (10.9%)	14 (11.2%)	19 (15.8%)	18 (13.8%)	102 (13.5%)
South-Africa	10 (7.9%)	9 (7.3%)	8 (6.3%)	14 (11.2%)	6 (5.0%)	9 (6.9%)	56 (7.4%)

endTB Regimens | Primary Efficacy Endpoint, mITT (W73)



Efficacy Conclusions

- Provides robust evidence for 3 regimens that are NI to a contemporaneous, modern, control regimen (endTB1=BLMZ, endTB2=BLLCZ, endTB3=BDLLZ)
  - Offers **patient-centered treatment options** for all age groups: adults, adolescents, children (all drugs in the regimens have pediatric formulations, endorsements for use in kids), and pregnant people
  - **3 distinct, non-inferior (including one superior) regimens** can be composed with 7 different drugs that are already available for routine treatment of MDR-TB
  - Excellent results in population with **severe disease, comorbidities** (HIV, DM, Hepatitis B/C)
- In addition, endTB5 (DMCZ) offers possible, shortened, all-oral alternative for patients unable to take linezolid or bedaquiline
- Importance of well-performing control arm
  - Sets a **high bar for non-inferiority** (compared to other trials)
  - Could result in **higher certainty of evidence**, strong recommendation

endTB trial – Safety Conclusions

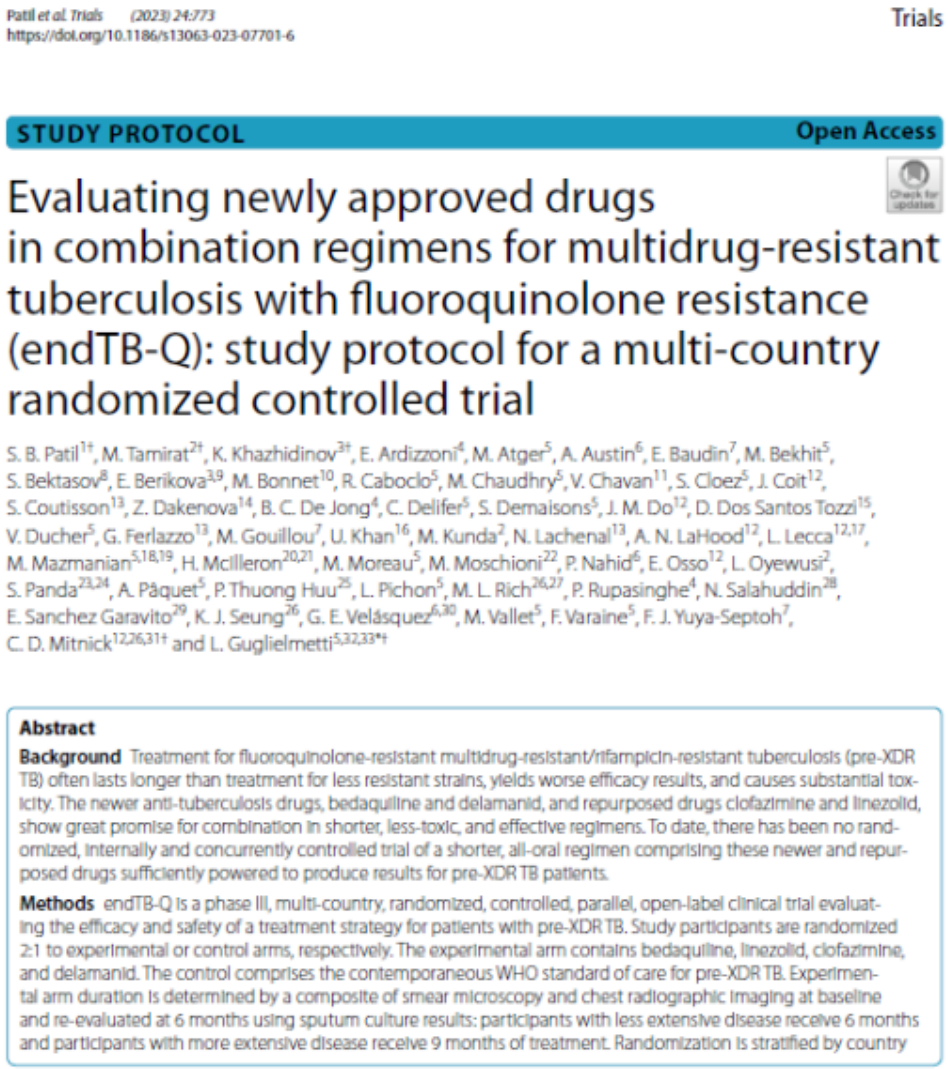
- Low mortality (experimental and control)
- Permanent drug stoppage due to AEs more frequent in the control arm
  - Z the most commonly stopped drug, treatment efficacy still satisfactory
- Comparable frequency of important AEs in experimental and control arms
  - Higher than expected in all arms: reflects comprehensive pharmacovigilance in the trial, includes many unrelated events
  - Linezolid-related toxicity common in control & experimental, QT prolongation not a major issue, more hepatic toxicity in experimental arms (none fatal)
- Confirms importance of appropriate, risk-based AE monitoring and prompt management
  - Regular monitoring permitted early detection and frequent resolution, e.g., linezolid-related toxicities, hepatotoxicity
  - ECG monitoring may be reduced and adapted according to individual risk level

Conclusions

- Two linezolid dose reduction strategies (300 mg daily or 600 mg thrice weekly) implemented at Week 16 or earlier due to AEs were similar with respect to severe linezolid-associated toxicity.
- The two strategies were also similar with respect to treatment efficacy.
- A limitation of this analysis was limited power due to delayed accrual (protocol amendment) and overestimation of events.
- Linezolid 300 mg daily is the most common dose reduction strategy in use — our findings support linezolid 600 mg thrice weekly as an alternative.

endTB-Q…hot off the presses

- RCT among people whose strains of RR/MDR-TB have additional resistance to the FLQs;
- Only trial done specifically in this population;
- Compared 6-9 month regimen of BDQ-LZD-DLM-CFZ with longer, individualized treatment;
- Excellent outcomes but did NOT meet non-inferiority criteria;
- People with non-severe disease had 93% success rate;
- Severe disease did not do as well—has ramifications for BEAT Tuberculosis and for BPaL regimens as well.



Patil et al. Trials (2023) 24:773
https://doi.org/10.1186/s13063-023-07701-6

STUDY PROTOCOL Open Access

Evaluating newly approved drugs in combination regimens for multidrug-resistant tuberculosis with fluoroquinolone resistance (endTB-Q): study protocol for a multi-country randomized controlled trial

S. B. Patil[1†], M. Tamirat[2†], K. Khazhidinov[3†], E. Ardizzoni[4], M. Atger[5], A. Austin[6], E. Baudin[7], M. Bekhit[5], S. Bektasov[8], E. Berikova[3,9], M. Bonnet[10], R. Caboclo[5], M. Chaudhry[5], V. Chavan[11], S. Cloez[5], J. Coit[12], S. Coutisson[13], Z. Dakenova[14], B. C. De Jong[4], C. Delifer[5], S. Demaisons[5], J. M. Do[12], D. Dos Santos Tozzi[15], V. Ducher[5], G. Ferlazzo[13], M. Gouillou[7], U. Khan[16], M. Kunda[2], N. Lachenal[13], A. N. LaHood[12], L. Lecca[12,17], M. Mazmanian[5,18,19], H. McIlleron[20,21], M. Moreau[5], M. Moschioni[22], P. Nahid[6], E. Osso[12], L. Oyewusi[2], S. Panda[23,24], A. Pâquet[5], P. Thuong Huu[25], L. Pichon[5], M. L. Rich[26,27], P. Rupasinghe[4], N. Salahuddin[28], E. Sanchez Garavito[29], K. J. Seung[26], G. E. Velásquez[6,30], M. Vallet[5], F. Varaine[5], F. J. Yuya-Septoh[7], C. D. Mitnick[12,26,31†] and L. Guglielmetti[5,32,33*†]

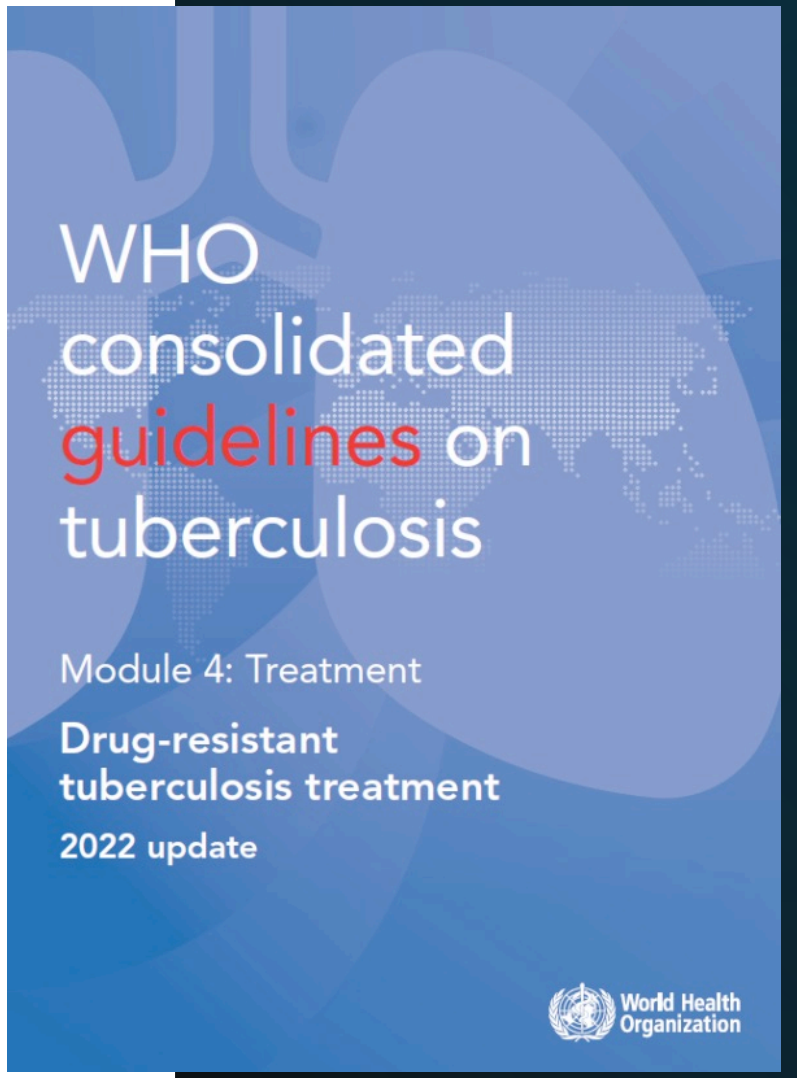
Abstract

Background Treatment for fluoroquinolone-resistant multidrug-resistant/rifampicin-resistant tuberculosis (pre-XDR TB) often lasts longer than treatment for less resistant strains, yields worse efficacy results, and causes substantial toxicity. The newer anti-tuberculosis drugs, bedaquiline and delamanid, and repurposed drugs clofazimine and linezolid, show great promise for combination in shorter, less-toxic, and effective regimens. To date, there has been no randomized, internally and concurrently controlled trial of a shorter, all-oral regimen comprising these newer and repurposed drugs sufficiently powered to produce results for pre-XDR TB patients.

Methods endTB-Q is a phase III, multi-country, randomized, controlled, parallel, open-label clinical trial evaluating the efficacy and safety of a treatment strategy for patients with pre-XDR TB. Study participants are randomized 2:1 to experimental or control arms, respectively. The experimental arm contains bedaquiline, linezolid, clofazimine, and delamanid. The control comprises the contemporaneous WHO standard of care for pre-XDR TB. Experimental arm duration is determined by a composite of smear microscopy and chest radiographic imaging at baseline and re-evaluated at 6 months using sputum culture results: participants with less extensive disease receive 6 months and participants with more extensive disease receive 9 months of treatment. Randomization is stratified by country

Current Options for RR/MDR-TB

- 6 months BPaLM
- 6 months BDQ-DLM-CFZ-LFX-LZD
- endTB 1, 2, or 3 (9 months, 4-5 drugs);
- All-oral 9-month regimen based on STREAM study;
- None compared to each other.



Extrapolation to Children and Pregnant Women/People

- BEAT Tuberculosis included children (down to age 6 years enrolled) and pregnant women/people;
- endTB let pregnant women/people stay in the study if they became pregnant during the trial;
- All drugs in both these regimens have been used in children and pregnant women/people;
- Dosing in children established and child-friendly formulations exist.

Multiple Options: How to Choose?

- Decisions on appropriate regimens should be made according to clinical judgement and patient preference, considering DST results, treatment history, risk of adverse events, and severity and site of the disease.
- Duration, pill burden, side effects, access/drug supply, FLQ resistance testing;
- Persons with meningitis, OA disease cannot get these regimens;
- Persons with previous treatment using drugs in the regimens cannot receive them unless susceptibility confirmed;
- Children and pregnant women/people cannot get pretomanid;
- Robustness of the study?
- Drug availability and pricing will likely drive these decisions.

Regimen	Duration	Pill Burden (for 65kg person)	Side Effects	Resistance testing	Monitoring	Special populations	Evidence base	Other
BPaLzM	6 mos	5-7 tablets Planned LZD dose reduction at week 16	QTcF prolongation, bone marrow suppression, optic neuritis, peripheral neuropathy, ? liver toxicity	FLQ	Monthly clinical, ECG, vision testing, peripheral neuropathy screen	Not for pregnancy or pediatrics	Multi-country RCT, stopped early, composite endpoint, compared with local SOCs	Baseline anemia management
BDLzL(C)	6mos	8-12 tablets LZD dose reductions allowed but not systematically assessed	QTcF prolongation, bone marrow suppression, optic neuritis, peripheral neuropathy, skin hyperpigmentation	FLQ	Monthly clinical, ECG, vision testing, peripheral neuropathy screen	Small number of children and pregnant people in the trial	Single country, RCT, compared with shorter, all-oral regimen	Baseline anemia management Counseling about hyperpigmentation
endTB 1 (BLzMZ)	9mos	7-9 tablets Planned LZD dose reduction at week 16	QTcF prolongation, bone marrow suppression, optic neuritis, peripheral neuropathy, liver toxicity	FLQ (?PZA)	Monthly clinical, ECG, vision testing, peripheral neuropathy screen, LFTs	Pregnant people allowed to stay in study, all drugs have been used in children and pregnant people	Multi-country, RCT, composite endpoint, compared with local SOCs	Baseline anemia management

endTB 2 (BLzLCZ)	9mos	11-13 tablets Planned LZD dose reduction at week 16	QTcF prolongation, bone marrow suppression, optic neuritis, peripheral neuropathy, skin hyperpigmentation, liver toxicity	FLQ (?PZA)	Monthly clinical, ECG, vision testing, peripheral neuropathy screen, LFTs	Pregnant people allowed to stay in study, all drugs have been used in children and pregnant people	Multi-country, RCT, composite endpoint, compared with local SOCs	Baseline anemia management Counseling about hyperpigmentation
endTB 3 (BDLzLZ)	9mos	14-16 tablets Planned LZD dose reduction at week 16	QTcF prolongation, bone marrow suppression, optic neuritis, peripheral neuropathy, liver toxicity	FLQ (?PZA)	Monthly clinical, ECG, vision testing, peripheral neuropathy screen, LFTs	Pregnant people allowed to stay in study, all drugs have been used in children and pregnant people	Multi-country, RCT, composite endpoint, compared with local SOCs	Baseline anemia management
All-oral 9-month (BLzLCHEZ)	9mos	16-18 tablets LZD for 2 months	QTcF prolongation, bone marrow suppression, optic neuritis, optic neuropathy, peripheral neuropathy*, liver toxicity	FLQ	Monthly clinical, ECG, vision testing, peripheral neuropathy	All drugs have been used in children and pregnant people	Program data, control arm in BEAT Tuberculosis	Baseline anemia management Counseling about hyperpigmentation

					screen, LFTs			
Individual 18 month	18 mos	Dependent on the drugs used	Dependent on the drugs used	Should be designed based on DST	Dependent on drugs used	Dependent on drugs used	No RCT	"

Multiple Options: Switching between Regimens?

- Studies did not assess this, and if the regimen was changed, an endpoint was met;
- If toxicity to a single agent develops and patient is doing well, could consider switching (?);
- Should doses received count?

Options for people with FLQ resistant strains

- BEAT Tuberculosis regimen with BDQ-DLM-CFZ-LZD;
- BPaL (?);
- endTB-Q study results;
- People with FLQ-resistant strains may be at increased risk for amplification of resistance;
- Backbone of BDQ, LZD, FLQ common in most of these regimens: resistance to any of these likely compromises ability to use shorter regimens.

Future Directions

- Patient preference studies (including asking those receiving care to actually choose their regimens);
- Compare these regimens to one another?

Thank you!

- endTB team for their slides;
- Francesca Conradie for the BEAT Tuberculosis slides

- jenniferfurin@gmail.com