Treatment of MDR/RR-TB: Present and Future

5th KATRD TB & NTM International Symposium

Innovations in TB & NTM Treatment

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Summary

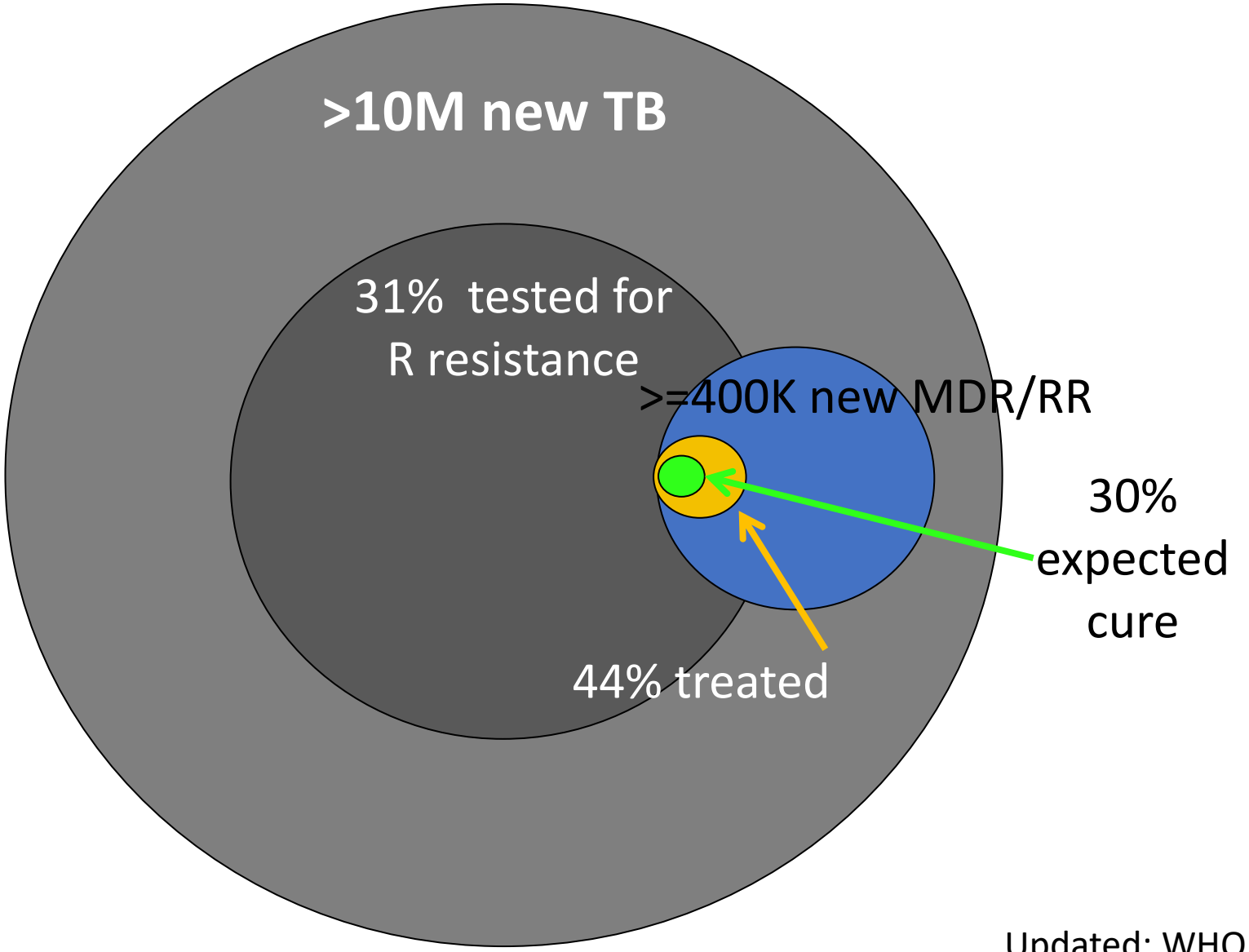
1. Burden/classification
2. Current treatment
   - Recommendations
   - Evidence & gaps
3. Pipeline
4. Future
5. Wrap-up

Burden/classification of DR-TB

WHO classifications of DR-TB [practical]

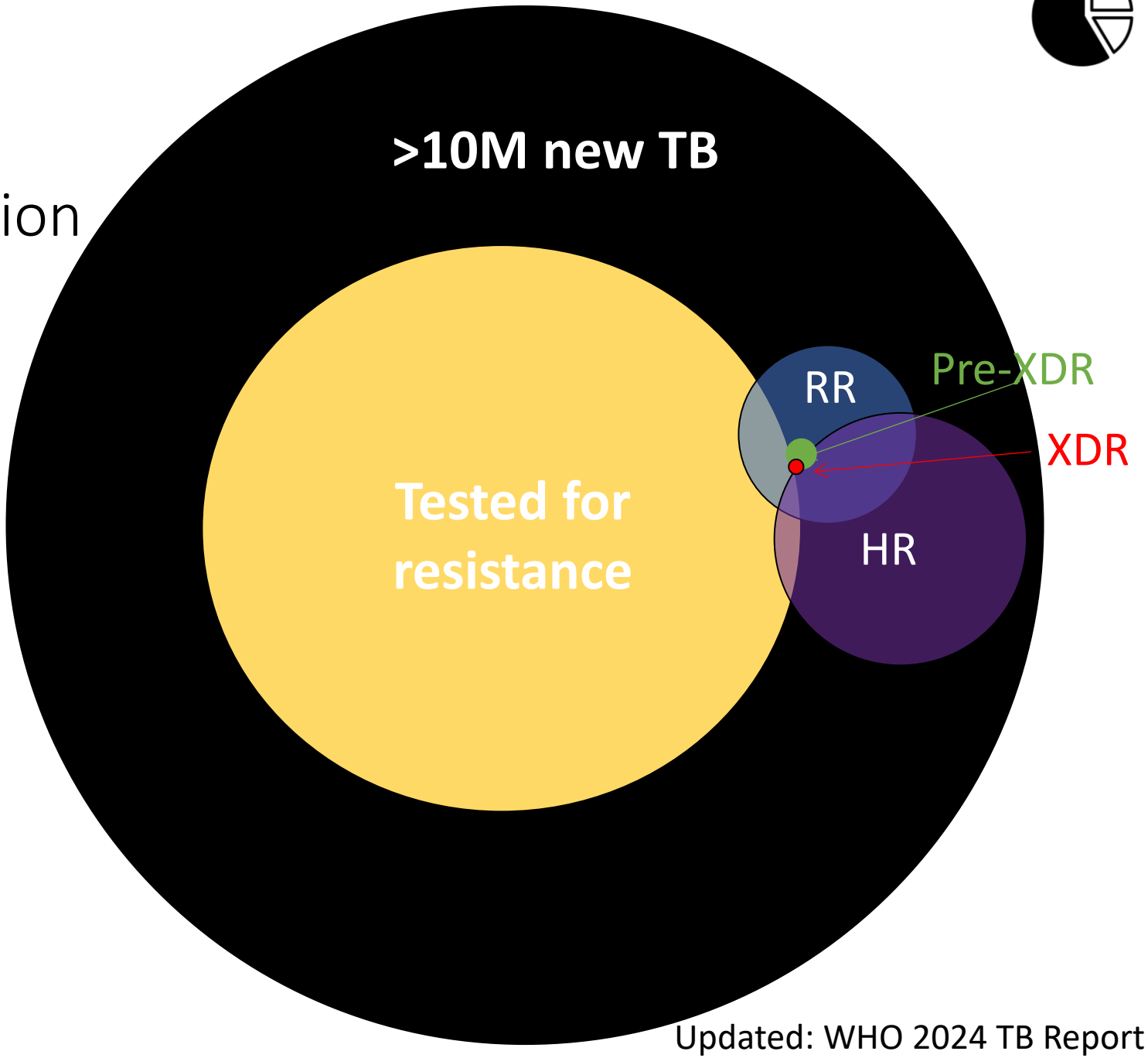
- isoniazid-resistant (HR): resistant to isoniazid [in the absence of resistance to rifampin]
- rifampin-resistant (RR): resistant to rifampin [in the absence of resistance to isoniazid]
- multidrug-resistant (MDR): resistant to rifampin & isoniazid
- MDR/RR-TB: either MDR or RR [excluding pre-XDR and XDR]
- pre-extensively drug-resistant (pre-XDR): resistant to rifampin and any fluoroquinolone
- XDR-TB, resistant to rifampin, any fluoroquinolone, & >=1 of either bedaquiline or linezolid.

Annual, global burden of MDR/RR-TB is large; access to quality care is poor



Updated: WHO 2024 TB Report

Less is known about distribution of (or prognosis of treatment for) other forms of TB



Updated: WHO 2024 TB Report

Current guidelines for treatment of MDR/RR-TB

WHO treatment options[1]				FQ
6BPaL(M)	✓			✓
6BDLC/Lfx	✓	✓	✓	✓
9BLMZ 9BCLLfxZ 9BDLLfxZ	✓	✓	✓	
9-11M Regimens	✓	✓	✓*	
18-24M indiv. regimen	✓	✓	✓	✓

ATS/CDC/ERS treatment options[2]				FQ
6BPaL(M)	✓			✓
>=15M indiv. regimen	✓	✓	✓	✓

9-11M Regimens : BEtoLfx/MCZEHh and BLLfx/MCZEHh*; B=bedaquiline; Pa=pretomanid; L=linezolid; M=moxifloxacin; D=delamanid; Lfx=levofloxacin; C=clofazamine; Z=pyrazinamide; Eto=ethionamide; E=ethambutol; Hh=high-dose isoniazid

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[2]Saukkonen et al, AJRCCM, 2025.

Current guidelines for treatment of MDR/RR-TB: summary dosing & efficacy

WHO treatment Options[1]	B[a]	Nitro	L 600 mg/ day	FQ (Mfx 400, Lfx 750-1000 mg/day)	Other	Other	End of FU efficacy (m/ITT)
6BPaL(M)							88.3%[1]
6BDLC/Lfx							86.1%[2]
9BLMZ							89.0%[3]
9BCLLfxZ							90.4%[3]
9BDLLfxZ							85.2%[3]
9-11M regimens							64%/66%[4]
18M (BLLC)							<=80.7%[3]

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b. 300 mg daily

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c. Lfx retained in case of FQ-S; C retained in case of FQ-R

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b. 300 mg daily
c. Lfx retained in case of FQ-S; C retained in case of FQ-R
d. Randomized 300 mg daily or 600 mg 3x week

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9-11M regimens	label	--	L[e]	Lfx/Mfx	C, Hh, E, Z, Eth[e]		64%/66%[4]
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b. 300 mg daily
c. Lfx retained in case of FQ-S; C retained in case of FQ-R
d. Randomized 300 mg daily or 600 mg 3x week
e. 7-drugs w/ L or ethionamide

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d. Randomized 300 mg daily or 600 mg 3x week
e. 7-drugs w/ L or ethionamide

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d. Randomized 300 mg daily or 600 mg 3x week
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Current guidelines for treatment of pre-XDR-TB

WHO treatment options[1]				FQ
6BPaL(M)	✓			✓
6BDLC	✓	✓	✓	✓
18-24M indiv. regimen	✓	✓	✓	

ATS/CDC/ERS treatment options[2]				FQ
6BPaL	✓			✓
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6BPaL(M)	either	Pa	reduced week 16[b]	Mfx[c]	--	--	87%[1]
6BDLC(Lfx)							74%[2]
18M x 4[e] drugs (e.g., BLCCs or BDLC)[4]							89%[3]

a. B label: 400 mg daily 2 weeks; 200 mg 3xweek; B off-label: 200 mg daily, 8 weeks; 100 mg daily 18 weeks
b. 300 mg daily
c. Drop if FQ-resistance confirmed
d. In FQ-R only
e. 4 likely effective at start, 3 if B is discontinued

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Baseline characteristics of study populations informing WHO Guidelines

Characteristic	BPaL(M) PRACTECAL[1] (n = 138)	9BLMZ endTB[2] (n = 118)	9BCLLfxZ endTB[2] (n = 115)	9BDLLfxZ endTB[2] (n = 122)	6BCDLLfx BEAT[3] (n = 203)
Median age in years, [IQR]	35 [27.0;45.0]	31.0 [25.0;41.0]	38.0 [26.0;50.0]	32.0 [22.0;45.0]	35.0 [28.0;43.0]
Female	61 (44.2%)	41 (34.7%)	37 (32.2%)	55 (45.1%)	85 (42%)
Median BMI (kg/m²) [IQR]	19.7 [17.7;22.7]	19.9 [17.5;22.1]	20.0 [18.4;23.6]	20.9 [18.8;22.8]	19.1 [17.0;22.0]
PZA resistance	--	57 (48.3%)	63 (54.8%)	66 (54.1%)	--
HIV seropositive	34 (24.6%)	15 (12.7%)	14 (12.2%)	17 (13.9%)	105 (52%)
On ART		12/15 (80.0%)	9/14 (64.3%)	10/17 (58.8%)	
Hepatitis B		3 (2.5%)	3 (2.6%)	0 (0.0%)	--
Hepatitis C		5 (4.2%)	5 (4.3%)	3 (2.5%)	--
Diabetes		19 (16.1%)	19 (16.5%)	20 (16.4%)	--
Cavitary disease	62 (45%)	68 (57.6%)	69 (60.0%)	73 (59.8%)	37 (18.2%)*

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[2]Guglielmetti et al. NEJM, 2025;
[3] https://www.medrxiv.org/content/10.1101/2025.05.04.25326549v1.
*Missing in 111 (53%).

Summary of safety data in study populations informing WHO Guidelines

Participants with events	BPaL(M) PRACTECAL[1] (n = 138)	9BLMZ endTB[2] (n = 118)	9BCLLfxZ endTB[2] (n = 115)	9BDLLfxZ endTB[2] (n = 122)	6BCDLLfx BEAT[3] (n = 203)
Deaths	0 (0%)	3 (2.4%)	1 (0.8%)	3 (2.4%)	4 (2.0%)
≥1 SAE	13 (8.6%)	18 (14.3%)	16 (13.1%)	20 (15.8%)	45 (22.3%)
≥1 AE & permanent discontinuation of ≥1 study drug		29 (23.0%)	32 (26.2%)	41 (32.3%)	--
≥1 AE grade ≥3	34 (22.5%)	69 (54.8%)	68 (55.7%)	78 (61.4%)	69 (34.2%)
Hematologic toxicity	10 (6.6%)	11 (8.7%)	9 (7.4%)	10 (7.9%)	33 (16.3%)
Peripheral neuropathy	14 (9.0%)	4 (3.2%)	5 (4.1%)	9 (7.1%)	15 (7.4%)
Optic neuritis	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	5 (2.5%)
QT Interval prolonged	1 (0.7%)	0 (0.0%)	4 (3.3%)	0 (0.0%)	6 (3.0%)
Hepatotoxicity	17 (11.3%)	23 (18.3%)	17 (13.9%)	8 (6.3%)	4 (2.0%)

[1]Nyang'wa et al. NEJM 2022, Nyang'wa et al. Lancet Respir Med 2024;
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Evidence gaps

Evidence gaps & progress/potential

1. Comparative efficacy & safety among recommended regimens
2. Battle of the fluoroquinolones: levofloxacin vs. moxifloxacin
   - Optimal dose of levofloxacin
3. Battle of the nitroimidazoles: pretomanid vs. delamanid
4. Optimal treatment composition & duration for extensive, pre-XDR
   - How to stratify, personalize
5. Role of PZA in presence of resistance
6. Lzd dosing to optimize efficacy/safety balance
7. Improve treatment for Bdq-resistant TB

1. Direct comparisons between recommended regimens are rare

	PRACTECAL	Beat	endTB			STREAM 2*
Comparator	6BPaL(M)	6BCL(LfxC)	9BLMZ	9BCLLfxZ	9BDLLfxZ	9-12BCLfxEZHhPto
6BPaLM						
6BCL(LfxC)						
9BLMZ						
9BCLLfxZ						
9BDLLfxZ						
9-12BCLfxEZHhPto						
9-12BCLfxEZHhL						
18AolTR						

Legend:
- No direct comparison
- Minority pop w/direct comparison
- Majority pop w/direct comparison
- Same regimen

*STREAM 2 data not used by WHO GDG in endorsement of the regimen.

1. Comparative efficacy & safety of recommended regimens

endTB exploratory analysis

endTB arms compared	Composition of compared regimens (differences)	Drugs compared	Provisional findings	
			Efficacy	Safety
One-drug difference between regimens				
2 vs 3	BCLLfxZ vs BDLLfxZ	C vs D	C ≅ D	C>D
2 vs 4	BCLLfxZ vs BCLLfxZ	B vs D	B > D	B>D
3 vs 4	BDLLfxZ vs BCLLfxZ	B vs C	B ≥ C	C>B
Two-drug difference between regimens				
1 vs 2	BLMZ vs BCLLfxZ	M vs Lfx (+C)	M ≅ Lfx+C	M<Lfx+C
1 vs 3	BLMZ vs BDLLfxZ	M vs Lfx (+D)	M ≅ Lfx+D	M>Lfx+D
5 vs 4	DCMZ vs DCLLfxZ	M vs Lfx (+L)	M ≅ Lfx+L	M>Lfx+L

1. Comparative efficacy & safety of recommended regimens between trials

- Explore differences between trial populations
- Apply modern epidemiologic methods to compare regimens tested between trials
  - Emulate a target trial
- Use direct and/or indirect comparisons
  - Latter done in network meta-analyses

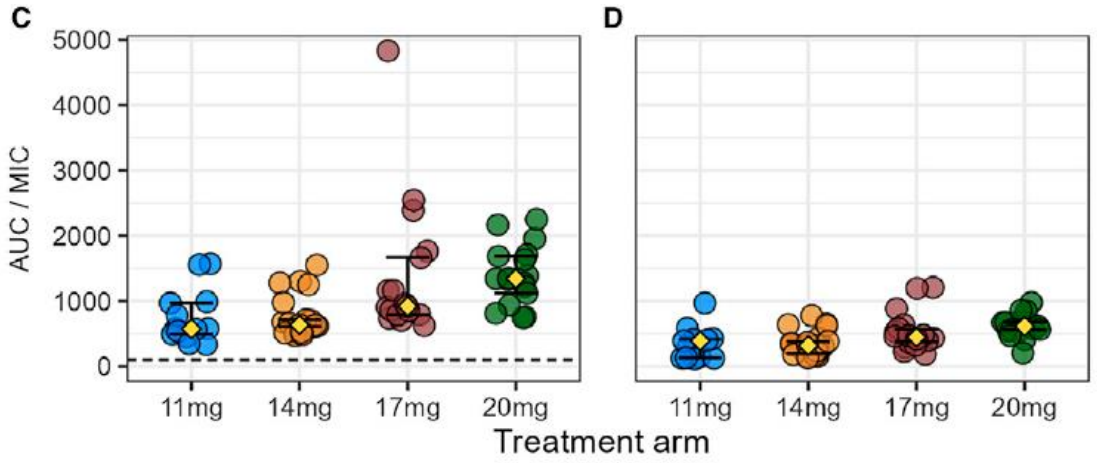
*To compare treatment strategies tested in different RCTs (**e.g. BPaLM vs. endTB**), the Target Trial Framework aids design of an analysis that appropriately accounts for differences in underlying trial populations AND differences in trial protocols and outcome definitions*

	Target trial	**Emulated trial**
Eligibility	**FQ-susceptible MDR/RR-TB patients** ≥ 15 years, with no prior exposure to novel or repurposed study drugs	same
Treatment	**6BPaLM, 9BLMZ**	same
Assignment	**Open-label, fixed randomization (1:1)**	Non-randomized, using IPW to balance per baseline covariates
Follow-up	From assignment until first of: 73 weeks post-randomization, death, or LTFU	
Outcomes	WHO success	same
Follow-up	From assignment until first of: 73 weeks post-randomization, death, or LTFU	same (w/1-week grace period)
Outcomes	WHO success	same

2. Battle of the fluoroquinolones

- endTB: not distinguishable, though levofloxacin always used with an extra drug; moxifloxacin has suggestions of increased cardio/hepatotoxicity
- BPaLL & BPaLM being used operationally, potential for comparison

750-1000 mg levo to optimize efficacy/safety[1]



	Daily Levofloxacin Dose			
	11 mg/kg	14 mg/kg	17 mg/kg	20 mg/kg
Total pts. in safety analysis	25	28	28	27
Any grade 3–5 AE	4 (16.0%)	4 (14.3%)	7 (25.0%)	10 (37.0%)
Any SAE	2 (8.0%)	1 (3.6%)	4 (14.3%)	3 (11.1%)
Death	0	0	1 (3.6%)	0
QTcF >450 ms	0	6 (21.4%)	1 (3.6%)	3 (11.1%)
QTcF >500 ms	0	0	0	1 (3.7%)

[1]Phillips PPJ et al. Am J Respir Crit Care Med. 2025

3. Battle of the nitroimidazoles: pretomanid vs. delamanid

- Early mouse/*in vitro* data suggested activity favored D[1]
- Greater lesion penetration by Pa?
- Preliminary results from PAN-TB do not support a difference[2]

Culture conversion			
Month	DBQS N=18	PBQS N=16	HRZE N=17
2	5 (27.8)	5 (31.3)	6 (35.3)
3	10 (55.6)	8 (50.0)	9 (52.9)

D=delamanid
P=pretomanid
B=bedaquiline
Q=quabodepistat
S=sutezolid

- D dosed BID, PK modeling suggests 300 QD as alternative, decreased exposure[3]
- Pa not recommended < 14 years or in pregnancy, D recommended for both
- NCT07126639: testing 6BPaLM vs 6BDLL (in FQ-S) and 6BDLC (in FQ-R) (N=200)

[1]Tasneen et al., Antimicrob Agents Chemother, 2014; [2]Holtzman et al, presentation Union, 2024.
[3]Lin et al, Clin Pharmacol Ther, 2025

4. Optimal treatment composition & duration for extensive, pre-XDR

Stratified analyses FQ-S RR-TB vs FQ-R RR-TB: Risk difference in unfavorable outcomes				
Overall	**6BPaLM vs. control (N=128)[1]**		**6BDL(CLfx) vs. control (N=402)[2]**	
Risk difference (95% CI)	**-37.2% (-52.8, -21.6)**		**-0.1% (-6.9, 6.6)**	
Subgroup (baseline)	**FQ-S (N=94)**	**FQ-R (N=29)**	**FQ-S (N=246)**	**FQ-R (N=85)**
Risk difference (95% CI)	-45.3% (-63.7, -26.9)	-17.3% (-45.1, -10.5)	-4.9% (-13.3, 3.5)	7.6% (-10.1, 25.3)

Relative benefit of experimental vs. control reduced w/FQ resistance

Stratified analyses disease extent: Risk difference in unfavorable outcomes				
Overall	**6BPaLM vs. control (N=128)[1]**		**9BDCL vs. control (N=247)[3]**	
Risk difference (95% CI)	**-37.2% (-52.8, -21.6)**		**-0.2% (-9.5, 9.1)**	
Subgroup (baseline)	**No cavity (N=48)**	**Cavity (N=80)**	**Limited (N=90)**	**Extensive (N=157)**
Risk difference (95% CI)	-38.8% (-66.7, -11.0)	-37.7% (-56.4, -19.0)	-5.6%(7.6,8.8)	7.5% (-3.2, 18.3)

Relative benefit of BDCL vs. control reduced extensive disease in BDCL

[1]Nyang'wa et al. NEJM 2022, Nyang'wa et al. Lancet Respir Med 2024; [2] https://www.medrxiv.org/content/10.1101/2025.05.04.25326549v1; [3]Guglielmetti et al. NEJM, 2025.

4. Worrying recurrence & acquired drug resistance with (regimens for) FQ-R TB

	endTB-Q[1]		BEAT-Tuberculosis ZA[2]		BPaL				BPaLC
	6/9BDLC	SOC	6BDL(CLfx)	SOC	BPaL[3]	BPaL[4]	mBPaL[5]	PRACTECAL[6,7]	
N (FQ-R)	163	84	202 (42)	200 (43)	109 (71)	181 (160)	403 (378)	60 (25)	64 (22)
Recurrence in (m)ITT (%)	4.9	0.0	5.0	2.0	1.8	6.1	3.5	3.0	2.0
Acquired drug resistance to BCLD* in FQ-R					Not reported				
ADR among tested	14/25 (58.3%)	2/3 (66.7%)	5/9 (55.6%)	3/6 (50.0%)					
ADR among N	14/163 (8.6%)	2/84 (2.4%)	5/42 (11.9%)	3/43 (7.0%)					

Red text=specific to FQ-R

*D not tested in BEAT-Tuberculosis.

[1] Guglielmetti et al, Lancet RM, 2025 ; [2]Conradie et al, https://doi.org/10.1101/2025.05.04.25326549 +supplement; [3]Conradie et al, NEJM. 2020; [4]Conradie et al, NEJM. 2022; [5] Padmapriyadarsini et al., CID, 2024; [6] Nyang'wa et al., Lancet RM, 2023; [7] Nyang'wa et al., NEJM, 2022;

4. Selection of participants for differentiated duration

endTB-Q[1]: Duration assignment
Baseline & on treatment

Cavity	Smear Neg	Smear 1+	Smear 2+	Smear 3+
Absent	Limited	Limited	Extensive	Extensive
Present	Limited	Extensive	Extensive	Extensive

Baseline assignment

- Extensive = **39-week** treatment
- Limited = **24-week** treatment

Treatment Response	Duration
Earlier	24 weeks
Later	39 weeks

PRISM[2]: Duration assignment
Baseline, risk score (from IPD-MA): Cutoff >0.15

Parameters	Estimates
$\theta_{Intercept}$	-2.66
θ_{Age}	If age > 36 years, θ_{Age}= 0.5 If age ≤36 years, θ_{Age}=0
θ_{Sex}	If sex =female , θ_{sex}= 0.17 If sex =male , θ_{sex}=0
θ_{BMI}	If BMI > 20 kg/m^2, θ_{BMI}= 0.67 If BMI ≤20 kg/m^2, θ_{BMI}=0
θ_{HIV}	If living w/HIV+, θ_{HIV}= 0.83 If not living w/HIV, θ_{HIV}=0
θ_{Xpert}	If Xpert>very low, θ_{Xpert}= 0.61 If Xpert≤very low, θ_{Xpert}=0
θ_{Cavity}	If cavity present, θ_{cavity}= 0.5 If cavity not present, θ_{cavity}= 0.0
$\theta_{Age} + \theta_{Sex} + \theta_{BMI} + \theta_{HIV} + \theta_{Xpert} + \theta_{Cavity}$ $Risk\ score = \frac{exp(linpred)}{1 + exp(linpred)}$	

[1] Patil et al., Trials, 2023; Guglielmetti et al., Lancet RM, 2025;
[2]Velasquez G, personal communication, Sep 2025

5. Linezolid dosing to optimize efficacy/safety balance

Regimen	Linezolid duration	AE>= Grade 3	Efficacy W52 (mITT)
6-9BPaL$_{600BID}$[1]	26w	61%	92%
6-9BPaL$_{1200}$[1]	26w	54%	
6-9BPaL$_{1200}$[2]	26w	31%	93%
6-9BPaL$_{1200}$[2]	9w	24%	89%
6-9BPaL$_{600}$[2]	26w	20%	91%
6-9BPaL$_{600}$[2]	9w	24%	84%

Regimen	Linezolid reduction	L-related AE>= Grade 3	Efficacy W72/3 (mITT)
6BPaL$_{600}$M[3]	16w, 300 daily	19%*	89%
endTB[4] + endTB-Q[5]	16w, 300 daily	16.3%	91%
	16w, 600 3xweek	16.6%	89%

*Any AE >=grade 3.

It is similarly safe and effective to reduce linezolid from 600 mg/day to either 300 mg/day or 600 mg 3xweek at 16 weeks.

[1]Conradie et al. NEJM 2020 (Nix); [2]Conradie et al. NEJM 2022 (ZeNix);[3] Nyang'wa et al. NEJM 2022, Nyang'wa et al. Lancet Respir Med 2024; [4]Guglielmetti et al., NEJM, 2025 ; [5]Guglielmetti et al., Lancet RM, 2025; publication in preparation

6. PZA: Uncertainty about efficacy w/resistance, risk/benefit balance of PZA discontinuation

endTB arms	Control	BLMZ	BCLLfxZ	BDLLfxZ
Pyrazinamide resistance	59/119 (49.6%)	61/118 (51.7%)	63/115 (54.8%)	66/122 (54.1%)
Overall efficacy		**Favorable outcome**	**Favorable outcome**	**Favorable outcome**
Frequency (%)	96 (80.7)	105 (89.0%)	104 (90.4%)	104 (85.2%)
Difference from control, 95% CI		8.3% -0.8,17.4	9.8% 0.9,18.7	4.6% 4.9,14.1
Subgroup efficacy		**Favorable outcome Difference from control**	**Favorable outcome Difference from control**	**Favorable outcome Difference from control**
PZA-Sensitive		16.2% 3.7%;28.8%	15.1% 2.0%;28.3%	12.1% -1.5%;25.7%
PZA-Resistant		1.2% -12.4%;14.7%	5.8% -6.5%;18.2%	-1.2% -14.6%;12.2%
Permanent d/c PZA	11/119 (9.2%)	22/118 (28.6%)	22/115 (23.5%)	20/122 (16.4%)
Favorable among d/c	8 (72.7%)	17 (81.0%)	18 (81.8%)	18 (90.0%)

Publications in process on hepatotoxicity and PZA resistance/exposure.

7. Improve treatment for bedaquiline-resistant TB

- Growing resistance to bedaquiline
- B-sparing shortened regimens to date show important drop-off in efficacy (mITT) compared to B-containing (>85% in trials)
  - 9DLLfxZ[1]: 75.0% efficacy
  - 9DCMZ[2]: 83.2% efficacy (7% acquired DR)
  - 9DCLLfxZ[2]: 78.8%
- Possible trials[3]
  - CLOBBER-TB
  - EX-DR
- Expanded Access/Compassionate Use-BETTER Initiative

- Pa=pretomanid
- G= ganfeborole: oxaborole, inhibits protein synthesis
- Q=quabodepistat: carbostyril, cell wall (DprE1) inhibitor
- S=sutezolid: ozazolidinone, inhibits protein synthesis (50S ribosomal subunit)
- TBAJ-587: diarylquinoline, inhibits ATP synthase
- Dzd: delpazolid, ozazolidinone, inhibits protein synthesis (50S ribosomal subunit)
- TBAJ-876 (sorfequiline): diarylquinoline, inhibits ATP synthase & bacterial respiration
- J=TBAJ-876/TBAJ-587

[1]Mok et al., Lancet, 2022; [2]Guglielmetti et al., NEJM, 2025;[3]McKenna L, 2025 TB Treatment Pipeline Report.

Pipeline of new drugs

2024 Global New TB Drug Pipeline[1]

Discovery | Preclinical Development | Clinical Development

Lead Optimization

Indazole sulfonamides

Diarylthiazoles

DprE1 Inhibitors

Direct InhA Inhibitors

Mtb energy metabolism

Gyrase Inhibitors

Arylsulfonamides

Inhibitors of MmpL3, Translocase-1, ClpC1, ClpP1P2, PKS13, F-ATP synthase, RNAP

Oxazolidinones

DnaE1 / Nargenicin analogs

Early Stage Development

TBD10 (MK-3854)

FIM-3002*

CMZ523*

MPL-447*

JSF-3285*

CPZEN-45*

NTB-3119*

MBX-4888A (1810)*

FNDR-20364*

GMP / GLP Tox.

OTB-658

TBD11 (CLB-073)*

GSK-839*

Phase 1

TBD09 (MK-7762)

TBI-223

TBAJ-587

GSK-286*

Macozinone* (PBTZ-169)

Phase 2

Delpazolid

Sutezolid, Tedizolid

TBAJ-876

Sanfetrinem

BTZ-043*

TBA-7371*

Quabodepistat (OPC-167832*)

Alpibectir (BVL-GSK098)*

Ganfeborole (GSK-656*)

Telacebec* (Q203)

Pyrifazimine (TBI-166)

SQ-109*

Phase 3

Sudapyridine (WX-081)

Regulatory Market Approvals

Bedaquiline*

Delamanid*

Pretomanid*

Underline = updates since November 2024

*New chemical class. Known chemical classes for any indication are color coded: rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound identified: http://www.newtbdrugs.org/pipeline/discovery

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: November 2024

Clinical Development

Phase 1	Phase 2	Phase 3	Regulatory Market Approvals
TBD09 (MK-7762)	Delpazolid		
TBI-223	Sutezolid, Tedizolid		
TBAJ-587	TBAJ-876	Sudapyridine (WX-081)	Bedaquiline*
GSK-286*	Sanfetrinem		
Macozinone* (PBTZ-169)	BTZ-043*		Delamanid*
	TBA-7371*		Pretomanid*
	Quabodepistat (OPC-167832*)		
	Alpibectir (BVL-GSK098)*		
	Ganfeborole (GSK-656*		
	Telacebec* (Q203)		
	Pyrifazimine (TBI-166)		
	SQ-109*		

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*New chemical class. Known chemical classes for any indication are color coded: rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

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Ongoing projects without a lead compound identified: http://www.newtbdrugs.org/pipeline/discovery

New Chemical Entities—Phase I (1/2)

TBD09 (MK-7762)

- Oxazolidinone with rRNA/ribosome target
- Discovered by Merck (MSD), agreement w/Gates MRI for development
- 2 studies underway: single- and multiple- ascending dose for safety, tolerability, PK, & food effect
- Main interest is long-acting injectable (LAI)

TBI-223

- Oxazolidinone, with better activity/safety profile[1]
- Developed by TB Alliance (TBA)
- Multiple-ascending dose study for safety, tolerability, PK, & food effect

TBAJ-587

- Diarylquinoline (inhibition of ATP synthase)
- Developed by TBA, ERA4TB, University of Auckland, Merck
- Dropped in favor of TBAJ-786?

WORKING GROUP ON NEW TB DRUGS
www.newtbdrugs.org

[1]Negatu et al., AAC, 2023, doi: 10.1128/aac.01655-22; McKenna L, 2025 TB Treatment Pipeline Report; Treatment Action Group.

New Chemical Entities—Phase I (2/2)

TBD11 (CLB073)

- New class, unknown mechanism, inhibits cholesterol metabolism
- Developed by Gates MRI
- Single- & multiple-ascending dose study for safety, tolerability, PK, & food effect

- Macozinone (PBTZ-169)
  - Developed by iM4TB, BMGF and Nearmedic in Russia
  - DprE1 (cell wall) inhibitor
  - Encouraging safety results from Phase 1; Phase 2a stopped for lack of enrollment
  - Being developed for long-acting use

McKenna L, 2025 TB Treatment Pipeline Report; Treatment Action Group.

Clinical Development

Phase 1	Phase 2	Phase 3	Regulatory Market Approvals
TBD09 (MK-7762)	Delpazolid	Sudapyridine (WX-081)	Bedaquiline*
TBI-223	Sutezolid, Tedizolid		
TBAJ-587	TBAJ-876		Delamanid*
GSK-286*	Sanfetrinem		Pretomanid*
Macozinone* (PBTZ-169)	BTZ-043*		
	TBA-7371*		
	Quabodepistat (OPC-167832*)		
	Alpibectir (BVL-GSK098)*		
	Ganfeborole (GSK-656*)		
	Telacebec* (Q203)		
	Pyrifazimine (TBI-166)		
	SQ-109*		

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*New chemical class. Known chemical classes for any indication are color coded: rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound identified: http://www.newtbdrugs.org/pipeline/discovery

Other (newish) medications in Phase 2

Sanfetrinem-cilextil[1]

- Oral Beta-lactam-carbapenem
- Developed by GSK, BMGF
- Phase 2a (NCT05388448) completed Aug 2024; not yet published

TBAJ-876 (sorfequiline)

- Diarylquinoline
- Less QT-interval prolonging effect than B
- 8-week dose-ranging study with PaL (NC-009)
- LAI?

Telacebec[2,3]

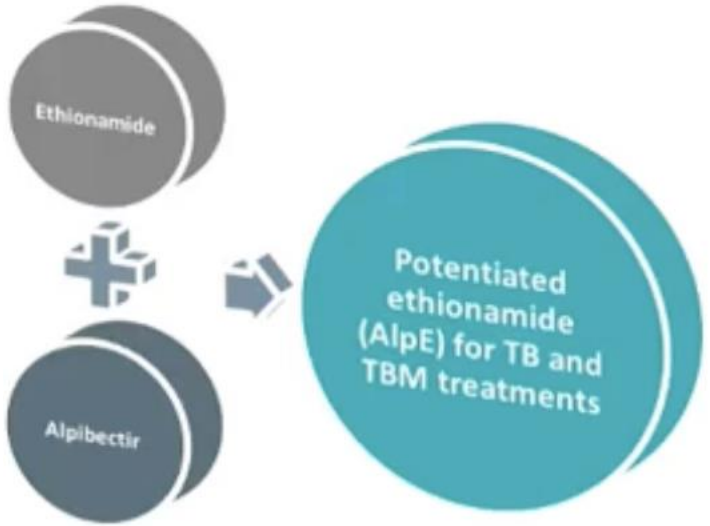
- Imidazopyridine amide (Qurient)-first-in-class
- ATP synthase inhibitor
- Dose-dependent activity against multiple mycobacteria
- Well-tolerated/safe
- Strain-dependent synergy with B, C (HN878, not in H37Rv)

WORKING GROUP ON NEW TB DRUGS
www.newtbdrugs.org

[1]Ramon-García et al., Drug Resist Updat. 2025 ; [2]Janssen et al., Am J Respir Crit Care Med. 2025 ·
[3]Komm et al., AAC, 2025, doi: /10.1128/aac.00962-24; McKenna L, 2025 TB Treatment Pipeline Report; Treatment Action Group.

Alpibectir (Alp): new molecule for use with ethionamide (Eto)

- Objective: Co-formulate Alp+Eto in a fixed dose combination for pulmonary, meningeal TB
- Eto: good activity, poor tolerability, low resistance threshold.
- Alp: transcriptional regulator that stimulates new activation route (?). Could reduce Eto dose, improve tolerability, overcome resistance.
- Phase 1 showed dose-proportional PK, food effect, and decent tolerability[1]



Union, 2024, Bali; [1]Pieren M, et al J Antimicrob Chemother. 2024

Phase 3 MDR FQ-S/FQ-R: QUANTUM for quabodepistat

Can Q (DprE1 inhibitor) shorten treatment for FQ-S TB & provide safe alternative to L in FQ-S/FQ-R TB?

- FQ-S (N=432)
  - 4BPaQM vs. 6BPaLM
- FQ-R (N=100)
  - 6BPaQ vs. 6BPaL

- 40 sites
- 12 countries, including S. Korea
- Started (?) with results anticipated in 2028
- Inclusion/Exclusion
  - RIF-resistant
  - Age >=14 years
  - Prior treatment with study drug (classes) <1 month in last 3
  - HIV viral load <200 copies/mL and CD4>100 cells/mL
  - No PN, optic neuritis, QTcF>450 msec/470 msc (women)

XDR-TB trials in development[1]

CLOBBER-TB

- N=120 XDR-TB
- 6–9PaGQS+TBAJ-587 vs. 18- to 20-month individualized regimen
- US NIH?

EX-DR

- N=400 XDR-TB
- 9PaGTDzd vs. 6PaGTDzdJ vs. SoC
- EDCTP

Both use Pa, G (protein-synthesis inhibitor, first in class), oxazolidinone, & diarylquinoline (TBAJ-587) or DprE1 inhibitor (T)

Pa=pretomanid; G= ganfeborole: oxaborole, inhibits protein synthesis; Q=quabodepistat: carbostyril, cell wall (DprE1) inhibitor; S=sutezolid: ozazolidinone, inhibits protein synthesis (50S ribosomal subunit); TBAJ-587: diarylquinoline, inhibits ATP synthase; Dzd: delpazolid, ozazolidinone, inhibits protein synthesis (50S ribosomal subunit); TBAJ-876 (sorfequiline): diarylquinoline, inhibits ATP synthase & bacterial respiration; J=TBAJ-876/TBAJ-587

McKenna, TB Treatment Pipeline, 2025.

4. Future

Strategy, New Research Design/Objectives

Strategy/Design	Examples[1]
Reduce risk of Phase 3: More PK-PD models, Use Phase 2C design	TB-REFLECT, PARADIGM4TB, SPECTRA-TB, PredictTB
Shortening • Duration-randomized design • Risk Stratification • Avoid overtreatment • One-size-Fits-All	DRAMATIC, SPECTRA endTB-Q, PRISM TRUNCATE, SPECTRA PAN-TB
Inform/individualize treatment by WGS/NGS	InDEX, GRACE, SMARTT, TBTRUSTplus
Test combinations earlier in development	quabodepistat, DECODE
Increased efficiency, adaptive designs (MAMS, RAR)	endTB, TB-PRACTECAL, PARADIGM4TB
Person-centered care	endTB, SMART4TB project, TB-PRACTECAL substudy
Simplified daily dosing (B & D) adults & kids	PARADIGM4TB, IMPACT4TB

[1]https://www.resisttb.org/clinical-trials-progress-report

Long-acting injections/formulations

- Benefits
  - Shorten, simplify treatment schedule
  - Lower pill burden
  - Privacy
  - Improve tolerability
- Properties
  - Safe
  - Low water solubility
  - High potency
  - Long half-life
- Formulations
  - Injections, patches, implants
- Uses
  - Prevention
  - Treatment
- Candidates for MDR in development: diarylquinolines (B, sorfequiline, TBAJ-587), telacebec, Pa, Q, macozinone

McKenna L, 2025 TB Treatment Pipeline Report; Treatment Action Group.

Host-directed therapy

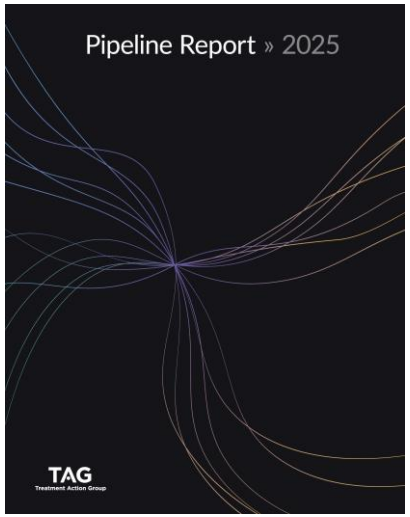
- Hypothesized benefits
  - Accelerate eradication of M.tb/shorten treatment
  - Reduce inflammatory response in lung: preserve post-TB lung function
  - Protect liver: reduce toxicity
- Candidates
  - Corticosteroids
  - Vitamin D
  - N-acetyl cysteine
  - Statins
  - Doxycycline
  - Metformin
  - Etc.
- Recent encouraging trials of, e.g.: N-acetyl cysteine[1], metformin[2], atorvastatin[3]
- Scoping review under review

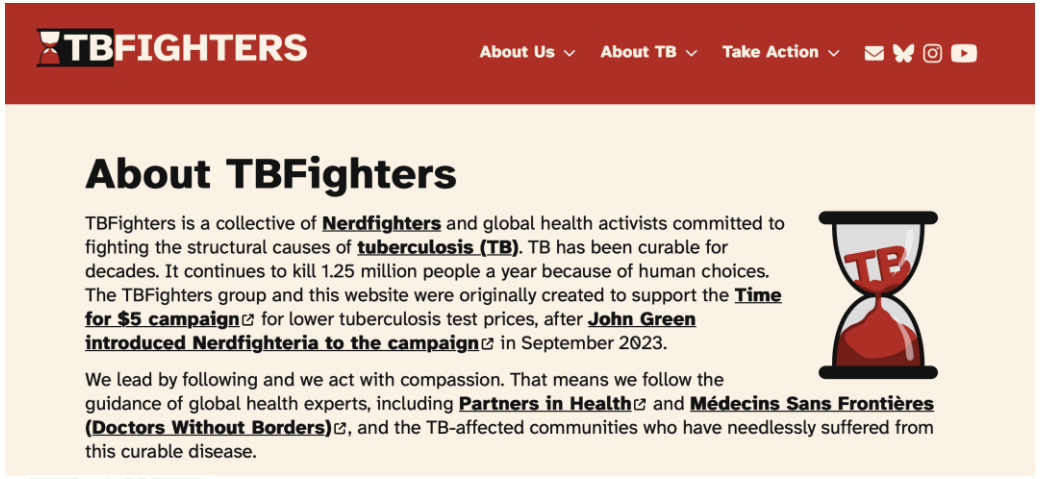
[1]Wallis et al., NEJM Evidence, 2024; [2]Padmapriydarsini et al., CID, 2022; [3]Adewole et al., IJTLD, 2023;

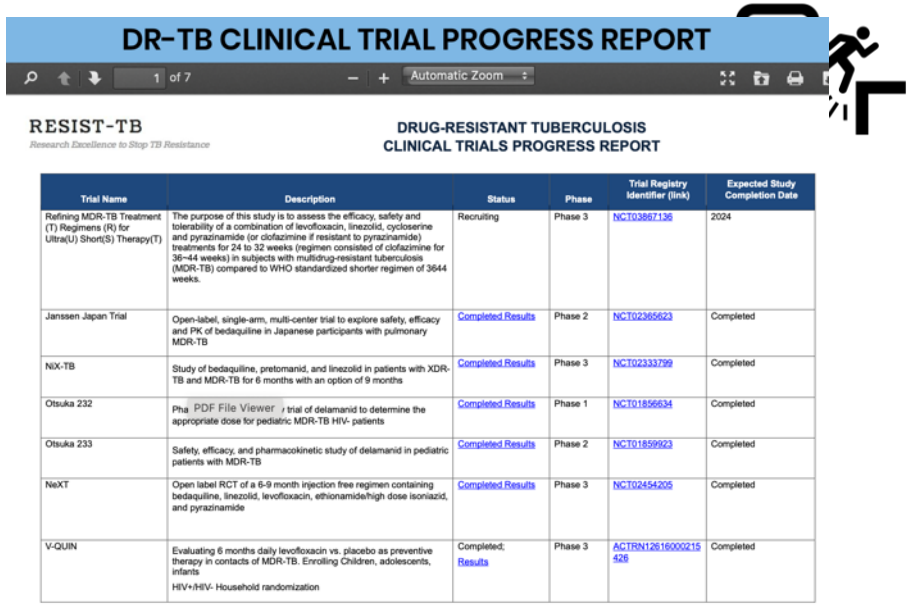
Wrap-up

Conclusions & Final Points

- Revolutionary, recent progress in treatment of MDR/RR-TB
  - Less profound for pre-XDR, extensive disease
  - Uncertainty about choice between single drugs will persist w/combination designs
  - XDR-TB new frontier
- Robust pipeline, mostly being tested in DS-TB
- Innovations in design, delivery, adjunctive therapies exciting
- One-size-fits-all conflicts with person-centered care
- Diagnostics not keeping up w/treatment
- Current US, European abdication of shared responsibility for global health will be devastating







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Acknowledgements and other resources