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Treatment Action Group

TB Treatment Trials Results in Context for Communities

Getting the Balance Right: A TB Update from CROI, 2023

March 14, 2023

Dr. Jennifer Furin
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Featured Speaker

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Cheat Sheet: TB Drug & Regimen Abbreviations

- Numbers at the beginning of each regimen or after the forward slash (for regimens with intensive and continuation phases) represent the duration of treatment in months
- Letters represent the individual drugs comprising each regimen
- Subscripts indicate dosing in mg; Hd = high dose

H = isoniazid
R = rifampicin
P = rifapentine
Z = pyrazinamide
E = ethambutol
Lx, Lfx = levofloxacin
M, Mx, Mfx = moxifloxacin

Bdq, B = bedaquiline
Ptd, Pa = pretomanid
Dlm, D = delamanid
L, Lz, Lzd = linezolid
Cfz, C = clofazimine
Cs = cycloserine
K = kanamycin

H_{Hd} = high dose isoniazid
R_{Hd} = high dose rifampicin

SOC = standard of care
IA = injectable agent

2 H R Z E / 4 H R

Two months of daily treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol followed by two months of daily treatment with isoniazid and rifampicin.

2 H P M Z / 2 H P M

Two months of daily treatment with isoniazid, rifapentine, moxifloxacin and pyrazinamide, followed by two months of daily treatment with isoniazid, rifapentine, moxifloxacin

6 B Pa L M

Six months of daily treatment with bedaquiline, pretomanid, linezolid, and moxifloxacin.

DS-TB = drug-sensitive TB; no resistance
RR-/MDR-TB = rifampicin-/multidrug-resistant TB; resistance to rifampicin and isoniazid
pre-XDR-TB = pre-extensively drug-resistant TB; MDR-TB with additional resistance to the fluoroquinolones
XDR-TB = pre-extensively drug-resistant TB with additional resistance to other group A drugs (Bdq or Lzd)

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2010–2020+ TB TX RESEARCH AGENDA: DS-TB, DR-TB

- **Drug-sensitive TB (DS-TB)**
- Focused on shortening treatment to 2–4 months by optimizing rifamycin selection (i.e., rifampicin vs. rifapentine) and dosing, and/or by introducing new and repurposed medicines to first-line regimens (e.g., bedaquiline, pretomanid, linezolid, clofazimine, moxifloxacin/ levofloxacin)
- E.g., TBTC Study 31 (4HPZM); RIFASHORT (4HR_{Hd}ZE); TRUNCATE-TB (hdRif + second-line drugs); SimpliciTB (4BPaMZ)
- **Drug-resistant TB (DR-TB)**
- Focused on shortening treatment to 6–12 months and improving outcomes and tolerability by replacing injectables, optimizing linezolid dose and duration, and/or by evaluating different combinations of new and repurposed medicines (e.g., bedaquiline, delamanid, pretomanid, clofazimine, moxifloxacin/ levofloxacin)
- E.g., STREAM 2 (9-12 months, all-oral, BDQ), MDR-END, ZeNix (6-9BPaL), TB-PRACTECAL (6-9BPaLM), BEAT-Tuberculosis (6BDLz + Lx, C or both), BEAT TB (6-9BDLzC), endTB/endTB-Q

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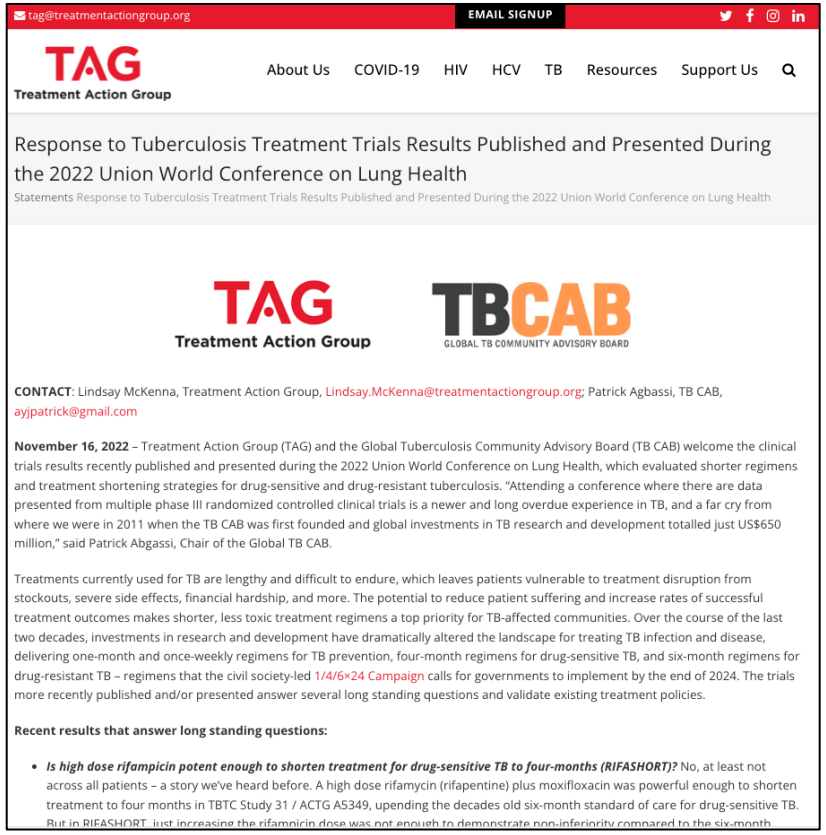
Table 1. Key Findings from Recently Completed Treatment-Shortening Trials

Study Name (Type of TB; Sample Size)	**Study Arms** Experimental Regimens [Control Regimen]	**Key Findings**
RIFASHORT NCT02581527 (DS-TB; 672)	$2HR_{1200}ZE/2HR_{1200}$ $2HR_{1800}ZE/2HR_{1800}$ [2HRZE/4HR]	The four-month high-dose rifampicin regimens were safe but failed to demonstrate non-inferiority to the standard of care
TRUNCATE-TB NCT03474198 (DS-TB; 675; PLHIV not included)	$2HR_{Hd}ZELz_{600}$ $2HZELz_{600}B$ [2HRZE/4HR]	The two-month bedaquiline- and linezolid-containing regimen demonstrated non-inferiority to the standard of care. No statistically significant differences in safety were detected between arms.
SimpliciTB NCT03338621 (DS-TB, RR-/MDR-TB; 455)	4BPaMZ [2HRZE/4HR] 6BPaMZ	The four-month BPaMZ regimen converted TB cultures to negative more quickly but there were more unfavorable outcomes driven by withdrawals from treatment due to adverse events (predominantly hepatotoxicity).
STREAM II NCT02409290 (RR-/MDR-TB; 588)	$4BCLxEZH_{Hd}Pto/5BCLxEZ$ $2BCLxZH_{Hd}K/4BCLxZ$ [4CLxEZHHdKPto/5CLxZE]	Both bedaquiline-containing regimens demonstrated non-inferiority and superior efficacy to the nine-month injectable-containing regimen. No significant differences in safety were detected between arms, except hearing loss observed at significantly higher rates in the nine-month injectable-containing control compared to the nine-month all-oral regimen.
TB-PRACTECAL NCT02589782 (RR-/MDR-TB Pre-XDR-TB; 552)	6BPaLzM 6BPaLzC 6BPaLz [9–20mo local SOC]	All three bedaquiline- and pretomanid-based regimens demonstrated non-inferiority and an improved safety profile compared with the standard-of-care group. The incidence of adverse events was lower in the groups receiving bedaquiline- and pretomanid-based regimens.
BEAT-TB India CTRI/2019/01/017310 (Pre-XDR-TB; 165; PLHIV not included)	6BDLzC [none]	The six-month bedaquiline- and delamanid-containing regimen was efficacious, producing a favorable outcome among 91% of participants at treatment completion and 86% of participants six months later. The six-month bedaquiline- and delamanid-containing regimen was generally safe with most AEs easily identified and managed (e.g., anemia, neuropathy, skin hyperpigmentation).
BEAT Tuberculosis South Africa NCT04062201 (RR-/MDR-TB, Pre-XDR; 374 enrolled, 199 included in interim analysis)	6BDLz (Lx, C, or both) [9–12mo SOC]	The six-month bedaquiline- and delamanid-based regimen had similar efficacy and safety to the standard-of-care regimen.
MDR-END NCT02619994 (MDR-TB; 214; PLHIV not included)	9DLzLxZ [20mo IA-containing regimen]	The nine-month delamanid-based regimen demonstrated non-inferiority to a 20-month injectable-containing regimen – the standard of care in 2014. No statistically significant differences in safety were detected between arms.

RESOURCES

https://www.treatmentactiongroup.org/resources/pipeline-report/2022-pipeline-report/



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Response to Tuberculosis Treatment Trials Results Published and Presented During the 2022 Union World Conference on Lung Health

Statements Response to Tuberculosis Treatment Trials Results Published and Presented During the 2022 Union World Conference on Lung Health

TAG Treatment Action Group TBCAB GLOBAL TB COMMUNITY ADVISORY BOARD

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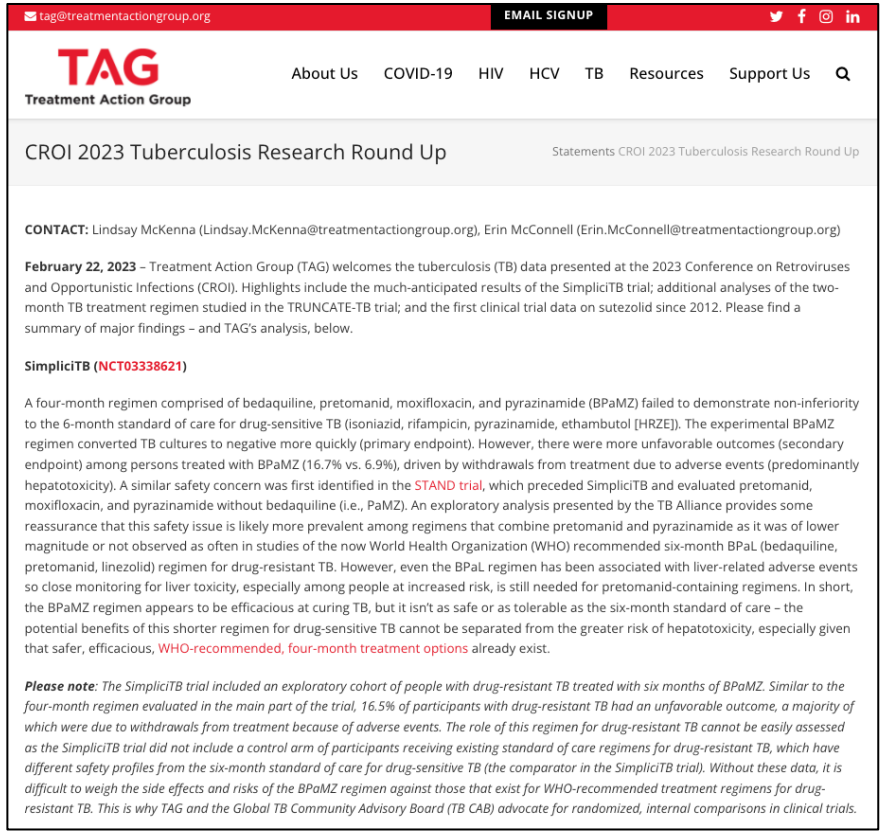
November 16, 2022 – Treatment Action Group (TAG) and the Global Tuberculosis Community Advisory Board (TB CAB) welcome the clinical trials results recently published and presented during the 2022 Union World Conference on Lung Health, which evaluated shorter regimens and treatment shortening strategies for drug-sensitive and drug-resistant tuberculosis. "Attending a conference where there are data presented from multiple phase III randomized controlled clinical trials is a newer and long overdue experience in TB, and a far cry from where we were in 2011 when the TB CAB was first founded and global investments in TB research and development totalled just US$650 million," said Patrick Abgassi, Chair of the Global TB CAB.

Treatments currently used for TB are lengthy and difficult to endure, which leaves patients vulnerable to treatment disruption from stockouts, severe side effects, financial hardship, and more. The potential to reduce patient suffering and increase rates of successful treatment outcomes makes shorter, less toxic treatment regimens a top priority for TB-affected communities. Over the course of the last two decades, investments in research and development have dramatically altered the landscape for treating TB infection and disease, delivering one-month and once-weekly regimens for TB prevention, four-month regimens for drug-sensitive TB, and six-month regimens for drug-resistant TB – regimens that the civil society-led 1/4/6×24 Campaign calls for governments to implement by the end of 2024. The trials more recently published and/or presented answer several long standing questions and validate existing treatment policies.

Recent results that answer long standing questions:

- ***Is high dose rifampicin potent enough to shorten treatment for drug-sensitive TB to four-months (RIFASHORT)?*** No, at least not across all patients – a story we've heard before. A high dose rifamycin (rifapentine) plus moxifloxacin was powerful enough to shorten treatment to four months in TBTC Study 31 / ACTG A5349, upending the decades old six-month standard of care for drug-sensitive TB. But in RIFASHORT, just increasing the rifampicin dose was not enough to demonstrate non-inferiority compared to the six-month

https://www.treatmentactiongroup.org/statement/response-to-tuberculosis-treatment-trials-results-published-and-presented-during-the-2022-union-world-conference-on-lung-health/



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CROI 2023 Tuberculosis Research Round Up

Statements CROI 2023 Tuberculosis Research Round Up

CONTACT: Lindsay McKenna (Lindsay.McKenna@treatmentactiongroup.org), Erin McConnell (Erin.McConnell@treatmentactiongroup.org)

February 22, 2023 – Treatment Action Group (TAG) welcomes the tuberculosis (TB) data presented at the 2023 Conference on Retroviruses and Opportunistic Infections (CROI). Highlights include the much-anticipated results of the SimpliciTB trial; additional analyses of the two-month TB treatment regimen studied in the TRUNCATE-TB trial; and the first clinical trial data on sutezolid since 2012. Please find a summary of major findings – and TAG's analysis, below.

SimpliciTB (NCT03338621)

A four-month regimen comprised of bedaquiline, pretomanid, moxifloxacin, and pyrazinamide (BPaMZ) failed to demonstrate non-inferiority to the 6-month standard of care for drug-sensitive TB (isoniazid, rifampicin, pyrazinamide, ethambutol [HRZE]). The experimental BPaMZ regimen converted TB cultures to negative more quickly (primary endpoint). However, there were more unfavorable outcomes (secondary endpoint) among persons treated with BPaMZ (16.7% vs. 6.9%), driven by withdrawals from treatment due to adverse events (predominantly hepatotoxicity). A similar safety concern was first identified in the STAND trial, which preceded SimpliciTB and evaluated pretomanid, moxifloxacin, and pyrazinamide without bedaquiline (i.e., PaMZ). An exploratory analysis presented by the TB Alliance provides some reassurance that this safety issue is likely more prevalent among regimens that combine pretomanid and pyrazinamide as it was of lower magnitude or not observed as often in studies of the now World Health Organization (WHO) recommended six-month BPaL (bedaquiline, pretomanid, linezolid) regimen for drug-resistant TB. However, even the BPaL regimen has been associated with liver-related adverse events so close monitoring for liver toxicity, especially among people at increased risk, is still needed for pretomanid-containing regimens. In short, the BPaMZ regimen appears to be efficacious at curing TB, but it isn't as safe or as tolerable as the six-month standard of care – the potential benefits of this shorter regimen for drug-sensitive TB cannot be separated from the greater risk of hepatotoxicity, especially given that safer, efficacious, WHO-recommended, four-month treatment options already exist.

***Please note**: The SimpliciTB trial included an exploratory cohort of people with drug-resistant TB treated with six months of BPaMZ. Similar to the four-month regimen evaluated in the main part of the trial, 16.5% of participants with drug-resistant TB had an unfavorable outcome, a majority of which were due to withdrawals from treatment because of adverse events. The role of this regimen for drug-resistant TB cannot be easily assessed as the SimpliciTB trial did not include a control arm of participants receiving existing standard of care regimens for drug-resistant TB, which have different safety profiles from the six-month standard of care for drug-sensitive TB (the comparator in the SimpliciTB trial). Without these data, it is difficult to weigh the side effects and risks of the BPaMZ regimen against those that exist for WHO-recommended treatment regimens for drug-resistant TB. This is why TAG and the Global TB Community Advisory Board (TB CAB) advocate for randomized, internal comparisons in clinical trials.*

https://www.treatmentactiongroup.org/statement/croi-2023-tuberculosis-research-round-up/

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Getting the Balance Right: A TB Update from CROI, 2023

Discussion of Findings from SmplciTB, TRUNCATE TB, and SUDOCU r

Jennifer Furin, MD., PhD

Harvard Medical School

March 2023

Conflicts of Interest

- I receive grant funding from the Stop TB Partnership's Global Drug Facility to support the roll out of child-friendly formulations of second-line TB drugs

Exciting Times in TB

- More high-quality science means better data to drive treatment decision making;
- TRUNCATE TB and SimpliciTB are important randomized controlled trials for understanding treatment approaches;
- Both have important ramifications impacted communities and the future direction on TB research;
- Discussion here based review of materials from CROI (Seattle, Feb 19-22, 2023) and conversations with CROI attendees and presenters.

TRUNCATE TB

- Proof of concept study looking at greatly shortening treatment duration for drug-susceptible TB;
- Underlying principle that most people living with TB are OVERTREATED in order to “prevent relapse” in a smaller percentage;
- Study used a novel trial design (MAMS), was largely concentrated in Southeast Asia, and did not enroll a single person with HIV;
- Logistical challenges drove the study progress/decision making—nobody with HIV in study population;
- Results will not have any treatment implications for the next few years but may drive the research agenda;
- Included a (very basic) study of acceptability;
- Updated presentation with relapse now considered as an UNFAVORABLE outcome

Trial Regimens

Standard Treatment	24w	Rifampicin 10mg/kg	Isoniazid	Pyrazinamide (first 8w)	Ethambutol (first 8w)	
hRIF-LZD	8w	↑ Rifampicin 20-35 mg/kg	Isoniazid	Pyrazinamide	Ethambutol	Linezolid 600mg
hRIF-CFZ	8w	↑ Rifampicin 35 mg/kg	Isoniazid	Pyrazinamide	Ethambutol	Clofazimine 200mg
RPT-LZD	8w	Rifapentine 1200mg	Isoniazid	Pyrazinamide	Levofloxacin 1000mg	Linezolid 600mg
BDQ-LZD	8w	Bedaquiline 400/200mg	Isoniazid	Pyrazinamide	Ethambutol	Linezolid 600mg

Enrollment and retention

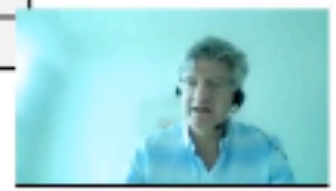
- Randomised in trial: 675
  - Randomised in error, immediately withdrawn: 1 (0.2%)
  - Lost to follow-up or withdrawal: 4 (0.6%)
  - Died before week 96: 10 (1.5%)

- Alive and under follow-up at W96: 660
  - Evaluated at W96: 660
  - 643 (97%) in person
  - 17 (3%) by telephone

18 sites
Indonesia, Philippines, Thailand, India, Uganda

Primary efficacy outcome, ITT population: TRUNCATE strategy (BDQ/LZD) arm

Outcome	Standard treatment (N= 181)	TRUNCATE strategy (BDQ/LZD) (N=189)	Adjusted difference (97.5% CI)
Unsatisfactory outcome – no. (%)	**7 (3.9)**	**11 (5.8)**	**0.8 (-3.4 to 5.0)**
On tuberculosis treatment at W96	2 (1.1)	5 (2.6)	-
Tuberculosis disease activity at W96	1 (0.6)	3 (1.6)	-
Death before W96	2 (1.1)	1 (0.5)	-
Telephone evaluation W96 – insufficient evidence of disease clearance when last seen	2 (1.1)	1 (0.5)	-
No evaluation W96 - insufficient evidence of disease clearance when last seen	0	1 (0.5)	-
Participants with unassessable outcome – no. (%)	**1 (0.6)**	**2 (1.1)**	-
Single positive culture at W96	0	0	-
Death (not related to tuberculosis)	1 (0.6)	0	-
No evaluation W96 – evidence of disease clearance when last seen	0	2 (0.9)	-
Participants with satisfactory outcome – no. (%)	**173 (95.6)**	**176 (93.1)**	-



Regimen analysis: unfavourable outcome

	24 weeks Standard Rx (N=181)	8 weeks hRIF/LZD (N=184)	8 weeks BDQ/LZD (N=189)
Unfavourable outcome – no (%)	7 (3.9%)	46 (25.0%)	26 (13.8%)
Treatment failure at switch to standard Rx	0 (0.0)	0 (0.0)	1 (0.5)
Treatment failure at end of treatment	0 (0.0)	0 (0.0)	1 (0.5)
Confirmed relapse	4 (2.2)	39 (21.2)	20 (10.6)
Un-confirmed relapse	0 (0.0)	0 (0.0)	3 (1.6)
Death by W96, possible TB-related cause	2 (1.1)	5 (2.7)	0 (0.0)
Did not attend W96, lacks evidence of cure at last attended visit	1 (0.6)	2 (1.1)	1 (0.5)
Unassessable outcome	6 (3.3)	29 (15.8)	16 (8.5)

Unfavourable outcome

	24 weeks Standard Rx (N=181)	8 weeks hRIF/LZD (N=184)	8 weeks BDQ/LZD (N=189)
Unfavourable outcome – no (%)	7 (3.9%)	46 (25.0%)	26 (13.8%)
Treatment failure at switch to standard Rx	0 (0.0)	0 (0.0)	1 (0.5)
Treatment failure at end of treatment	0 (0.0)	0 (0.0)	1 (0.5)
Confirmed relapse	4 (2.2)	39 (21.2)	20 (10.6)
Un-confirmed relapse	0 (0.0)	0 (0.0)	3 (1.6)
Death by W96, possible TB-related cause	2 (1.1)	5 (2.7)	0 (0.0)
Did not attend W96, lacks evidence of cure at last attended visit	1 (0.6)	2 (1.1)	1 (0.5)
Unassessable outcome	6 (3.3)	29 (15.8)	16 (8.5)

Unfavourable outcome: Bayesian analysis

	24 weeks Standard Rx (N=181)	8 weeks hRIF/LZD (N=184)	8 weeks BDQ/LZD (N=189)
Adjusted proportion (95% BCI)*	3.4% (1.3 to 6.3%)	23.7% (17.2 to 30.9%)	12.5% (7.9 to 18.1%)
Probability that proportion difference <12%*	-	0.01	0.85

Estimate using Bayesian model with flat (uninformative") prior; adjusted for country and baseline relapse risk
Following approach described by Laptook et al, JAMA 2017; DOI: 10.1001/jama.2017.14972

Probability of achieving absolute relapse rate < 20% by regimen and subgroup

	Probability of unfavourable outcome < 20%		
	24 wk Standard treatment (N=181)	**8wk hRIF/LZD (N=184)**	**8wk BDQ/LZD (N=189)**
All participants	1	0.052	0.989
Smear grade			
Negative	1	0.819	0.994
Scanty/1+	1	0.433	0.956
2+	0.994	0	0.779
3+	0.964	0.265	0.31
Xpert MTB/RIF burden			
Very low/low	1	0.913	0.996
Medium	1	0.019	0.994
High	0.94	0.001	0.062
CXR % lung affected			
< 25%	1	0.808	0.987
25-50%	1	0.015	0.897
> 50%	0.99	0.13	0.785

>0.8

0.5 to 0.8

<0.5

Safety outcomes

	Standard treatment (N= 181)	TRUNCATE strategy (hRIF/LZD) (N=184)	P value	TRUNCATE strategy (BDQ/LZD) (N=189)	P value
Any grade 3 or 4 adverse event – no. (%)	27 (14.9)	30 (16.3)	0.664	30 (16.2)	0.666
Any serious adverse event – no. (%)	11 (6.1)	18 (9.8)	0.168	14 (7.4)	0.530
Death no. (%)	3 (1.7)	5 (2.7)	0.724	1 (0.5)	0.362
Respiratory disability at W96					
MRC breathlessness scale ≥ 3 – no. (%)	0	3 (1.6)	0.122	2 (1.1)	0.499
FEV1% < 50% – no. (%)	18.9 (9.9)	14 (7.6)	0.597	14 (7.4)	0.378

Acquired drug resistance

Participant 1

- Baseline INH resistance
- Missed 14 days (12 consecutive) of all drugs during the first 4 weeks
- Relapsed at W52 with new phenotypic resistance to BDQ (and CFZ) [with compatible mutations]
- Retreatment with standard treatment (with quinolone added) was successful.

Participant 2

- No baseline drug resistance
- Adherent to initial 8-week treatment
- Relapsed at W36 with new phenotypic resistance to BDQ (and CFZ) [with compatible mutations]
- Retreatment with standard treatment was successful.

No acquired drug resistance in the other TRUNCATE strategy or standard treatment arm

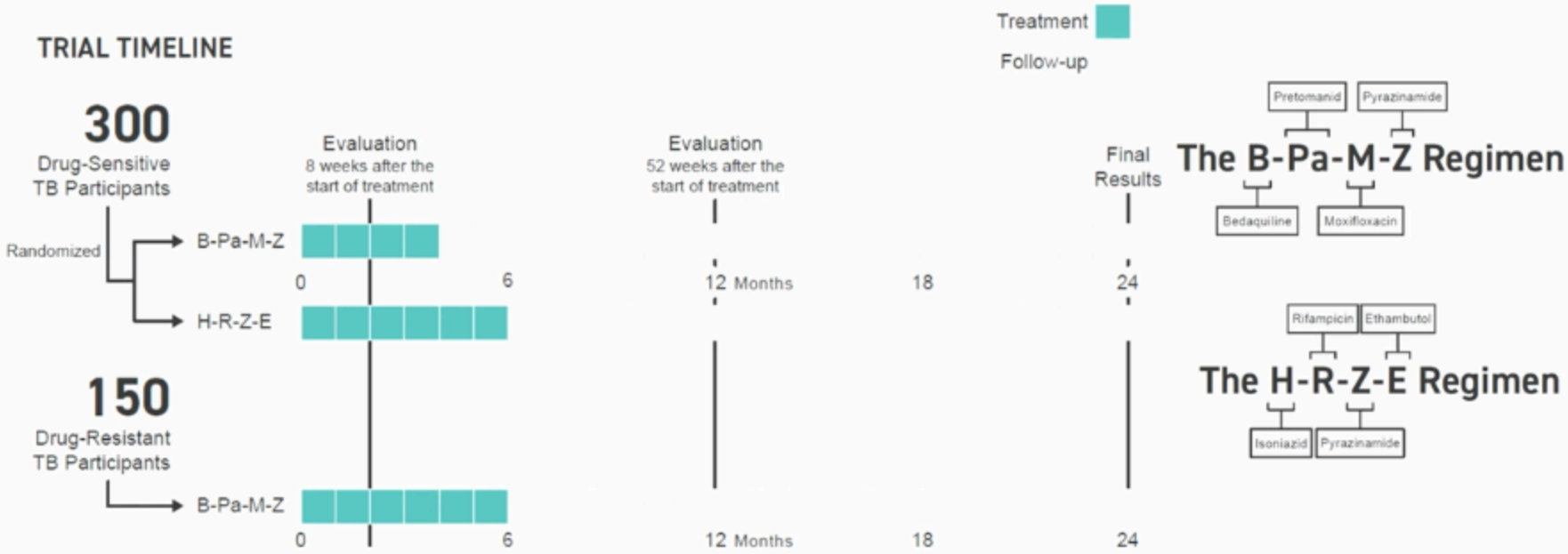
SimpliciTB

- Universal regimen approach looking at a four-month regimen of BPaMZ for DS-TB and DR-TB (although both populations compared to HREZ);
- Added bedaquiline to the regimen used in the STAND trial (a study that was halted due to hepatotoxicity, supposedly from a combination of PZA and pretomanid);
- Assessed efficacy as “time to culture negative status” in liquid media by 8 weeks;
- Also looked at secondary endpoint of percentage of participants with composite of unfavorable outcome at week 52 after treatment initiation ;
- No assessment of patient acceptability or preferences

SimpliciTB Study Design

SIMPLICITB

TRIAL TIMELINE



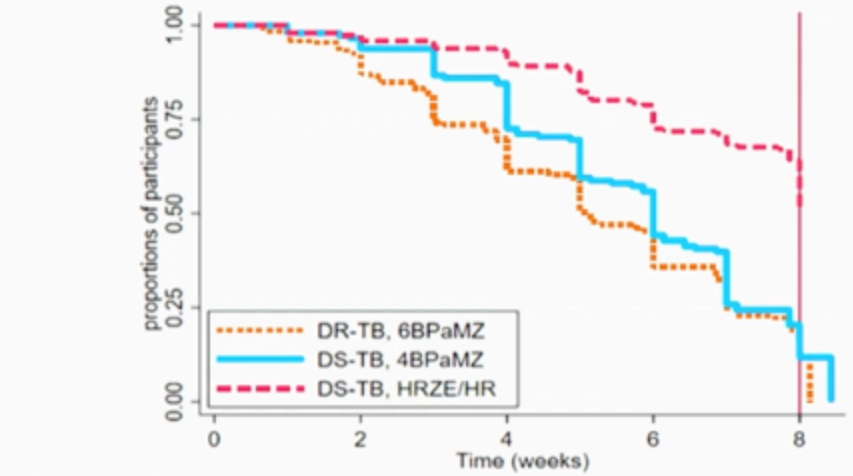
BPaMZ Dosing: Bedaquiline (B) at a dose of 200 mg daily for eight weeks followed by 100 mg daily to end of treatment, together with daily pretomanid (Pa) 200mg, moxifloxacin (M) 400mg and pyrazinamide (Z) 1500mg

SimpliciTB Participant Baseline Characteristics

Parameter		2HRZE/4HR (N=153) n (%)	4BPaMZ (N=150) n (%)	6BPaMZ (N=152) n (%)
Median Age (years) - IQR		34.0 (26.0, 46.0)	35.0 (25.0, 45.0)	35.0 (26.0, 47.0)
Male sex – n (%)		118 (77.1%)	112 (74.7%)	94 (61.8%)
Race	White	25 (16.3%)	29 (19.3%)	31 (20.4%)
	Black	119 (77.8%)	108 (72.0%)	82 (54.0%)
	Mixed	6 (3.9%)	5 (3.3%)	26 (17.1%)
	Asian	3 (2.0%)	8 (5.3%)	13 (8.6%)
HIV positive – n (%)		27 (17.6%)	25 (16.7%)	35 (23.0%)
Median BMI - (kg/m^2)		18.7 (17.2, 20.4)	19.3 (17.6, 21.4)	19.3 (17.1, 22.2)
WHO Smear grade				
	1+	28 (18.3%)	20 (13.3%)	37 (24.3%)
	2+	53 (34.6%)	49 (32.7%)	47 (30.9%)
	3+	72 (47.1%)	81 (54.0%)	67 (44.1%)
Median time to positive sputum culture at baseline (IQR)		5.0 (4.2, 6.5)	4.6 (3.9, 6.2)	6.2 (4.7, 8.9)
Cavities in chest XR				
	Absent	37 (24.2%)	31 (20.7%)	31 (20.4%)
	Unilateral	76 (49.7%)	75 (50.0%)	70 (46.0%)
	Bilateral	40 (26.1%)	44 (29.3%)	50 (32.9%)

Primary Efficacy Endpoint
Time To Culture Negative Status By 8 Weeks (MITT)

SIMPLICITB



Number at risk

DR-TB, 6BPaMZ	133	122	90	57	24
DS-TB, 4BPaMZ	145	139	119	77	26
DS-TB, HRZE/HR	148	143	136	114	93

HAZARD RATIO

4BPaMZ is superior
Culture negative by 8 weeks is more likely with BPAMZ

*2.17-3.96 (95%CI)

PROPORTION OF PTS CULTURE NEGATIVE AT WEEK 8

Drug-Sensitive TB

HRZE 47.3%

4BPaMZ 84.1%

Drug-Resistant TB

6BPaMZ 85.7%

Key Secondary Efficacy Endpoint (52 Weeks): % Unfavorable Outcome TB-MITT

SIMPLICITB

	DS-TB		DR-TB
	2HRZE/4HR (N=153) n (%)	4BPaMZ (N=150) n (%)	6BPaMZ (N=152) n (%)
Unassessable	9	6	19
Total assessable	144	144	133
Favorable	134 (93.1%)	120 (83.3%)	111 (83.5%)
Unfavorable	10 (6.9%)	24 (16.7%)	22 (16.5%)
95% CI for Favorable	87.6% to 96.6%	76.2% to 89.0%	83.1% to 89.8%
(Risk difference) unadjusted	9.72%		
Two-sided 95% CI (unadjusted)	(2.35% to **17.09%**)		

Key Secondary Efficacy Endpoint (52 Weeks): % Unfavorable Outcome TB-MITT

SIMPLICITB

Status	Outcome		DS-TB 2HRZE/4HR (N=153) n (%)	DS-TB 4BPaMZ (N=150) n (%)	DR-TB 6BPaMZ (N=152) n (%)
	Total Assessable (%)		144 (94.1%)	144 (96.0%)	133 (87.5%)
Favorable	Culture negative status at 52 weeks post randomisation		134	120	111
	Total Favorable (% of assessable)		134 (93.1%)	120 (83.3%)	111 (83.5%)
Unfavorable	During treatment	Death (Non-violent)	1	2	2
		Withdrawn (AE)	1	14	14
		Withdrawn (Investigator/Sponsor decision)	2	1	5
		Withdrawn (Participant decision)	2	3	0
		Withdrawn (Treatment failure)	2	0	0
	Post treatment	Confirmed relapse at 52 weeks post randomisation	1	2	1
		Re-treatment	1	2	0
	Total Unfavorable (% of assessable)		10 (6.9%)	24 (16.7%)	22 (16.5%)

Safety Summary
SimpliciTB – Safety Population

SIMPLICITB

	DS-TB		DR-TB
	2HRZE/4HR (N=153) n (%)	4BPaMZ (N=150) n (%)	6BPaMZ (N=149) n (%)
Any TEAE	144 (94.1%)	139 (92.7%)	142 (95.3%)
Any grade ≥ 3 TEAE	61 (39.9%)	68 (45.3%)	47 (31.5%)
Any study drug-related TEAE	99 (64.7%)	119 (79.3%)	123 (82.6%)
Any serious TEAE	7 (4.6%)	17 (11.3%)	16 (10.7%)
Any TEAE leading to study drug discontinuation	3 (2.0%)	17 (11.3%)	16 (10.7%)
Any TEAE leading to study drug interruption	14 (9.2%)	15 (10.0%)	23 (15.4%)
Any TEAE leading to death	1 (0.6%)	3 (2.0%)	2 (1.3%)

SUDOCU Study of Sutezolid

- Seeking a “less toxic” alternative to linezolid in the oxazolidinone family;
- Drug has been around for more than a decade;
- Dose-ranging study over 12 weeks given in combination with BDQ-DLM-MFX followed by total treatment of 6 months;
- 75 participants enrolled and randomized to one of five arms (placebo plus four doses of sutezolid)

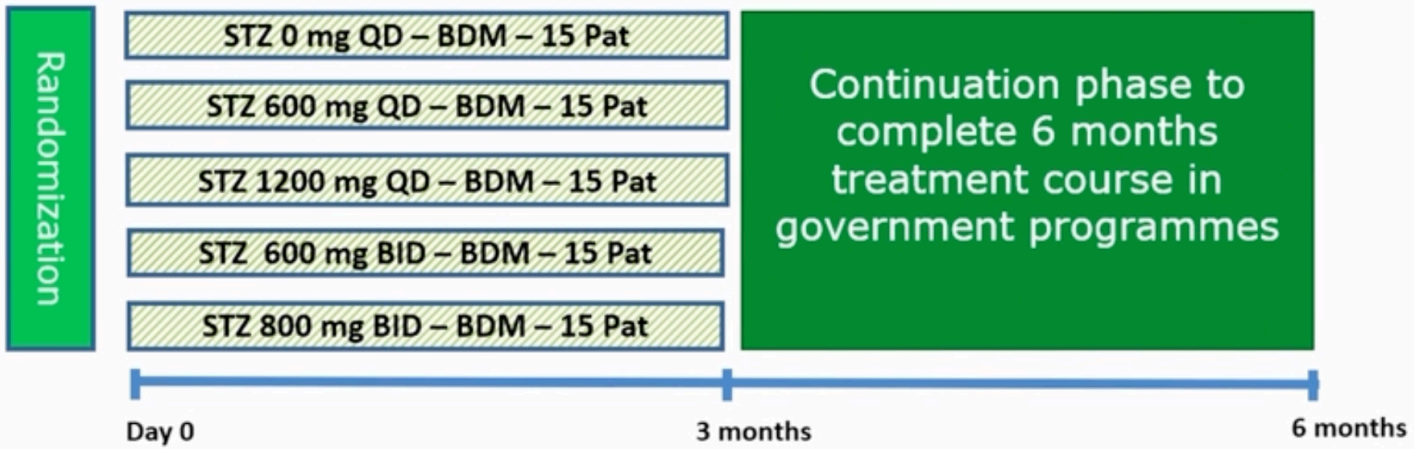
SUDOCU – sutezolid dose-finding and combination development

Objectives:

- Exposure – response modelling
- Exposure - toxicity modelling
- Select sutezolid dose with good safety and efficacy
- Assess CYP 3A4 enzyme induction potential

Primary Endpoint:

- Change in bacterial load as measured by MGIT TTP, over 12 weeks



STZ – sutezolid. BDM – bedaquiline, delamanid, moxifloxacin at standard doses.

PanACEA

EDCTP

This project is part of the EDCTP2 programme supported by the European Union

LMU KLINIKUM

Safety

	Arm 1: U0	Arm 2: U600	Arm 3: U1200	Arm 4: U600 BD	Arm 5: U800 BD	Total
Total randomized	16	15	14	15	15	75
Number of AEs reported	10	12	12	22	8	64
Number of Participants with AEs	6 (37.5%)	5 (33.3%)	7 (50%)	7 (46.7%)	4 (26.7%)	29 (38.67%)
Number of SAEs reported	0	1	2	5	1	9
Number of Participants with SAEs	0	1 (6.67%)	1 (7.1%)	4 (26.7%)	1 (6.67%)	7 (9.3%)
Number of AEs by Severity	**Arm 1: U0**	**Arm 2: U600**	**Arm 3: U1200**	**Arm 4: U600 BD**	**Arm 5: U800 BD**	**Total**
Grade 1: Mild	5	2	2	4	1	14
Grade 2: Moderate	3	7	5	9	3	27
Grade 3: Severe	1	2	5	5	4	17
Grade 4: Life Threatening	1	1	0	3	0	5
Grade 5: Death	0	0	0	1	0	1

- NO neuropathy
- 1 grade 4 neutropenia - 600BD (possible „benign ethnic neutropenia")
- 1 grade 4 DILI - 600 BD
- 1 COVID-19 related death - 600 BD
- 4 events of QT prolongation >60ms (no prolongation >500ms absolute)

Summary

Safety:

- Good safety of the combination +/- sutezolid
- 4 SAEs QTcF prolongation: due to 60ms cutoff; no measurements beyond 470 ms
- 1 case of grade 4 liver toxicity, 1 case of neutropenia

Efficacy:

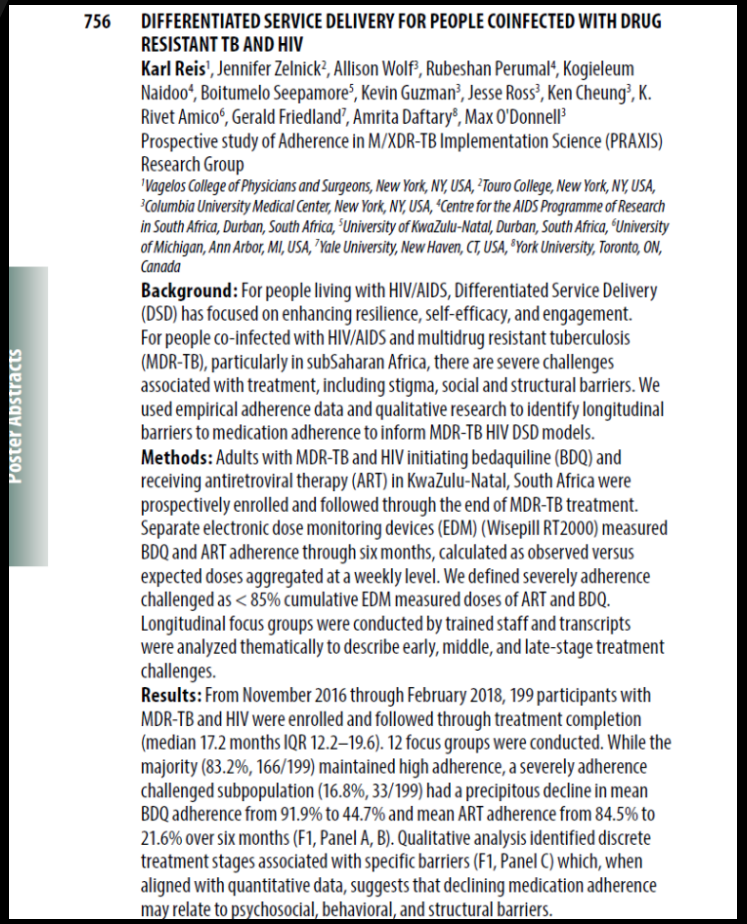
- BDM backbone similar to HRZE in historical comparison;
- PK-PD: 40% steeper slope for highest observed sutezolid exposures
- Sutezolid added efficacy to BDM
- No plateau in exposure or efficacy seen in SUDOCU

Discussion Points from the Meeting

- “Pan-TB” regimen—will donors and programs keep pursuing this?
- Options should exist (but will the move be toward sacrificing the vulnerable “few” in service of the many?);
- Trials are being driven by “proof of concept” studies that may be most exciting to donors or researchers;
- People are very excited to over-interpret the study findings (see STREAM-2 from Union as an example of this!)…
- …and to always suggest more studies of similar things—for example the safety issue with PaMZ was well known so why did BPaMZ go forward?

Issues to Consider for Communities

- Bedaquiline-oxazolidinone combination seems potent and sutezolid may be a less toxic alternative ;
- Beware vulnerable sub-populations being left out of advances (i.e. “overtreating the many in deference to the few”);
- TB studies always outperform what is seen in real-life (this is why we need controlled trials);
- Best ways to balance toxicity, duration, and relapse issues;
- Advocacy for access but also for including studies of preferences and needs of impacted populations as a key part of future TB trials;
- Differentiated models of service delivery;
- Donors, programs and scientists driving the research agenda (and funding) may not always share views with communities about what is important—so ongoing advocacy needed



Poster Abstracts

756 **DIFFERENTIATED SERVICE DELIVERY FOR PEOPLE COINFECTED WITH DRUG RESISTANT TB AND HIV**

Karl Reis[1], Jennifer Zelnick[2], Allison Wolf[3], Rubeshan Perumal[4], Kogieleum Naidoo[4], Boitumelo Seepamore[5], Kevin Guzman[3], Jesse Ross[3], Ken Cheung[3], K. Rivet Amico[6], Gerald Friedland[7], Amrita Daftary[8], Max O'Donnell[3]
Prospective study of Adherence in M/XDR-TB Implementation Science (PRAXIS) Research Group
[1]Vagelos College of Physicians and Surgeons, New York, NY, USA, [2]Touro College, New York, NY, USA, [3]Columbia University Medical Center, New York, NY, USA, [4]Centre for the AIDS Programme of Research in South Africa, Durban, South Africa, [5]University of KwaZulu-Natal, Durban, South Africa, [6]University of Michigan, Ann Arbor, MI, USA, [7]Yale University, New Haven, CT, USA, [8]York University, Toronto, ON, Canada

Background: For people living with HIV/AIDS, Differentiated Service Delivery (DSD) has focused on enhancing resilience, self-efficacy, and engagement. For people co-infected with HIV/AIDS and multidrug resistant tuberculosis (MDR-TB), particularly in subSaharan Africa, there are severe challenges associated with treatment, including stigma, social and structural barriers. We used empirical adherence data and qualitative research to identify longitudinal barriers to medication adherence to inform MDR-TB HIV DSD models.

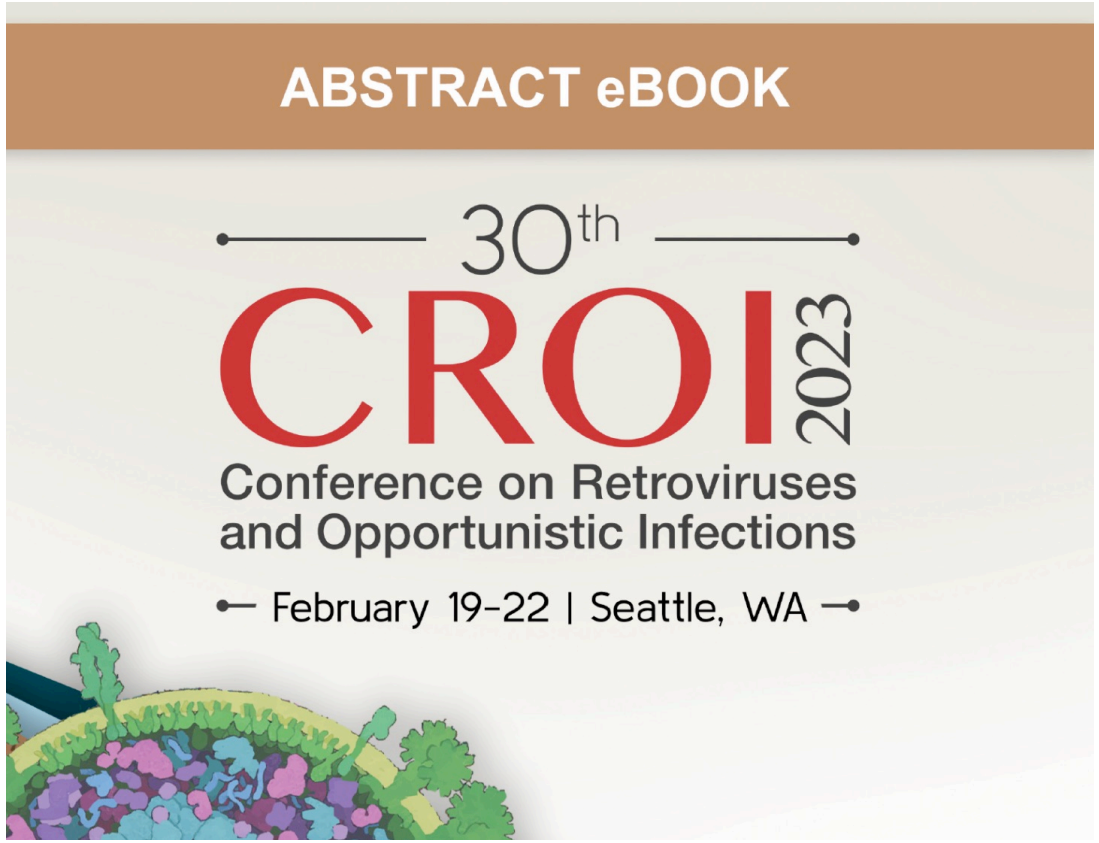
Methods: Adults with MDR-TB and HIV initiating bedaquiline (BDQ) and receiving antiretroviral therapy (ART) in KwaZulu-Natal, South Africa were prospectively enrolled and followed through the end of MDR-TB treatment. Separate electronic dose monitoring devices (EDM) (Wisepill RT2000) measured BDQ and ART adherence through six months, calculated as observed versus expected doses aggregated at a weekly level. We defined severely adherence challenged as < 85% cumulative EDM measured doses of ART and BDQ. Longitudinal focus groups were conducted by trained staff and transcripts were analyzed thematically to describe early, middle, and late-stage treatment challenges.

Results: From November 2016 through February 2018, 199 participants with MDR-TB and HIV were enrolled and followed through treatment completion (median 17.2 months IQR 12.2–19.6). 12 focus groups were conducted. While the majority (83.2%, 166/199) maintained high adherence, a severely adherence challenged subpopulation (16.8%, 33/199) had a precipitous decline in mean BDQ adherence from 91.9% to 44.7% and mean ART adherence from 84.5% to 21.6% over six months (F1, Panel A, B). Qualitative analysis identified discrete treatment stages associated with specific barriers (F1, Panel C) which, when aligned with quantitative data, suggests that declining medication adherence may relate to psychosocial, behavioral, and structural barriers.

Thank you!

jenniferfurin@gmail.com

Great gratitude to the TAG team members who supported this work on many levels



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Questions?

Want to stay in touch?

Sign up for TAG's email list to recieve updates on TB science, advocacy opportunities, and webinars.

Figure 1. 2022 Pipeline of New TB Drugs in Clinical Development

Phase 1	Phase 2	Phase 3 Results expected in 2023	Regulatory Market Approvals
TBAJ-587 TBAJ-876 TBI-223 GSK.286 SPR720	Sudapyridine (WX-081) Delpazolid Sutezolid Tedizolid BTZ-043 Macozinone (PBTZ-169) TBA-7371 OPC-167832 Pyrifazimine (TBI-166) GSK-656 Telacebec BVL-GSK098 Sanfetrinem SQ-109	Simplici TB (4-month regimen, DS-TB) endTB (9-month regimen, DR-TB) BEAT-Tuberculosis (6-month regimen, DR-TB)	Bedaquiline Delamanid Pretomanid Linezolid* Clofazimine* Moxifloxacin* Levofloxacin*

Figure adapted from Stop TB Partnership Working Group on New Drugs. * Approved by Stringent Regulatory Authority and used to treat TB, but label does not include TB among approved indications. Diarylquinoline; Oxazolidinone; DprE1 inhibitor; Riminophenazine; Nitroimidazole; Fluroquinolone. DS-TB = drug-sensitive TB; DR-TB = drug-resistant TB.

2023 & BEYOND TB TX RESEARCH AGENDA:
DS-TB, DR-TB, Pan-TB

- **Drug-sensitive TB (DS-TB)**
- Focused on iterating on 2–4-month regimens by using a stratified medicine approach to go shorter for certain low risk groups, swapping in high dose rifampicin for rifapentine, or by introducing new and repurposed medicines to first-line regimens (e.g., clofazimine, bedaquiline, delamanid).
- E.g., SPECTRA (stratified medicine approach to HPMZ), STEP2C ($3R_{Hd}HZM_{Hd}$), OptiRiMoxTB ($4HR_{Hd}MZ$), CLO-FAST (2CHPZE/1CHPZ), CRUSH-TB (4BMZ + D or Rb)
- **Drug-resistant TB (DR-TB)**
- Focused on shortening treatment by combining bedaquiline and delamanid and repurposed medicines (pretomanid-sparing regimens), and introducing stratified medicine approaches
- E.g., endTB-Q (6-9BDLzC), DRAMATIC (4-9BDCLxLz)
- **Pan-TB**
- Focused on advancing novel drugs in the context of new 2–4-month regimens, mostly using a bedaquiline and delamanid or pretomanid backbone, and swapping in new drugs with new mechanisms of action (e.g., DprE1 inhibitors) or advantaged alternatives to existing drugs (e.g., next generation oxazolidinones or diarylquinolines)
- E.g., PAN-TB, UNITE4TB, Otsuka Trial 323

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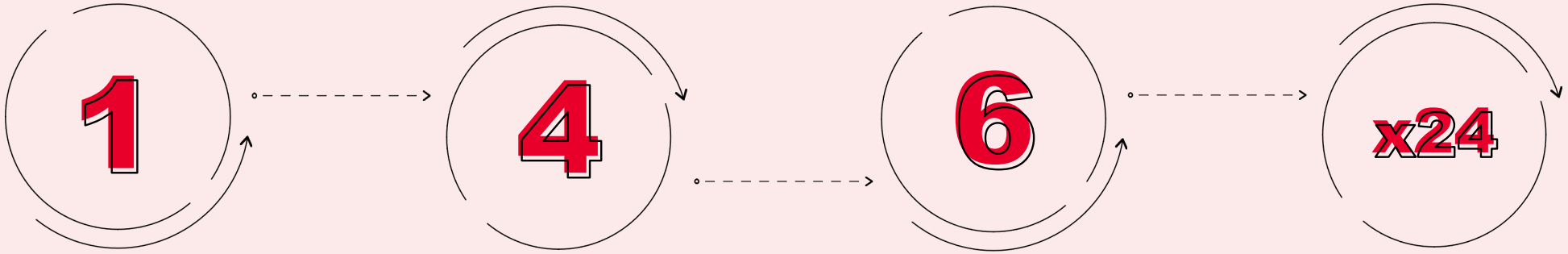
1/4/6x24

A Campaign to Rally Energy, Political Will & Funding to End TB

WHAT DOES IT MEAN?



one-month or once weekly treatment regimens for <u>TB prevention</u>.

1HP, 3HP, 3HR from ACTG A5279 and TBTC Study 26 / ACTG A5259

four-month treatment regimens for drug-sensitive TB.

4HPMZ, 4HRZ[E] from TBTC Study 31 / ACTG A5349 and the SHINE trial

six-month treatment regimens for drug-resistant TB.

6BPaL[M] from TB-PRACTECAL and ZeNix trials

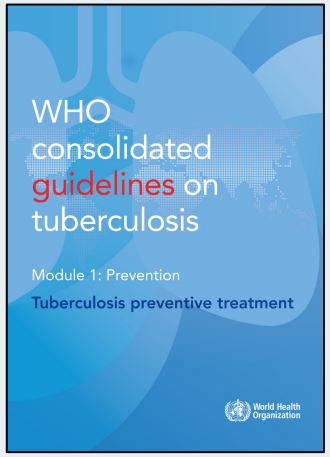
by the end of 2024.

A deadline for having in place the "staff, stuff, space, systems, and support" needed for shorter TB regimens to be made accessible to everyone, everywhere as a human right.

& priority research to extend the benefits of short treatment and prevention regimens to any groups who cannot currently use them due to data gaps or research exclusions.

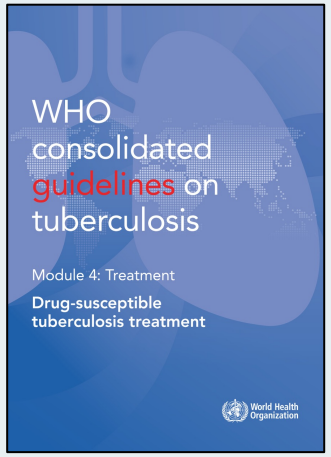
CAMPAIGN RESOURCES (3/3)

WORLD HEALTH ORGANIZATION GUIDELINES+



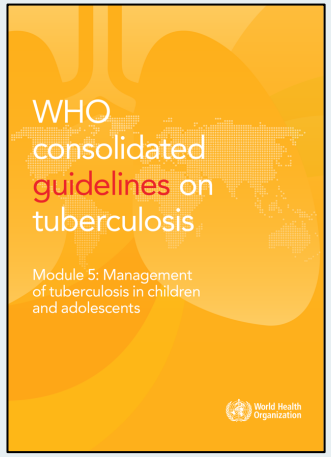
WHO consolidated guidelines on tuberculosis, Module 1: Prevention: Tuberculosis preventive treatment:

https://www.who.int/publications/i/item/9789240001503



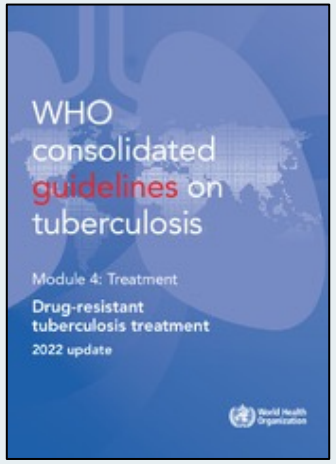
WHO consolidated guidelines on tuberculosis, Module 4: Treatment: Drug-susceptible tuberculosis treatment:

https://www.who.int/publications/i/item/9789240048126



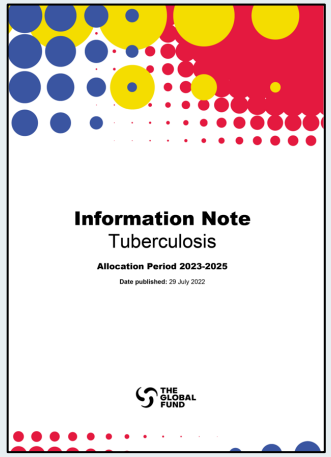
WHO consolidated guidelines on tuberculosis, Module 5: Management of tuberculosis in children and adolescents:

https://www.who.int/publications/i/item/9789240046764



WHO consolidated guidelines on tuberculosis, Module 4: Treatment of drug-resistant tuberculosis:

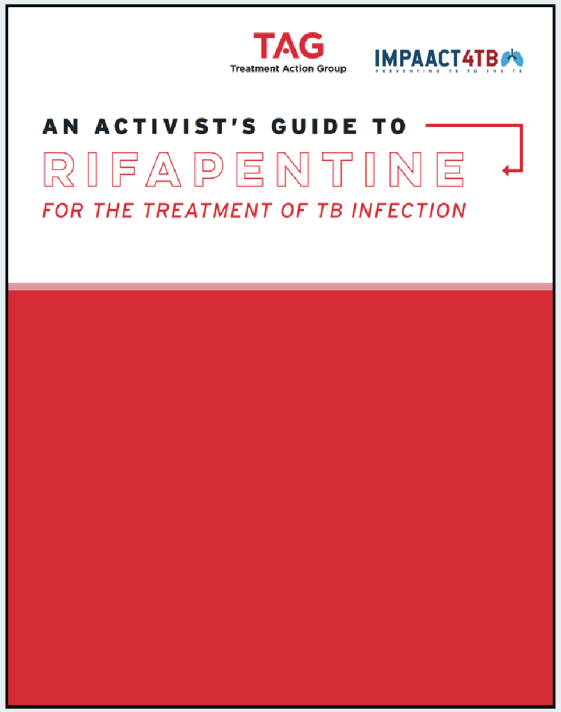
https://www.who.int/publications/i/item/9789240063129



Global Fund Tuberculosis Information Note, Allocation Period 2023–2025:

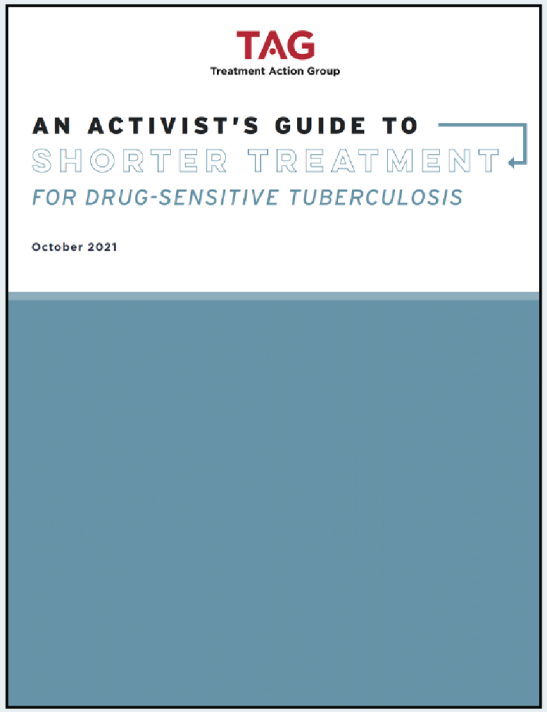
https://www.theglobalfund.org/media/4762/core_tuberculosis_infonote_en.pdf

CAMPAIGN RESOURCES (1/3)
ACTIVIST GUIDES



An Activist's Guide to Rifapentine for TB Infection:

https://www.treatmentactiongroup.org/publication/an-activists-guide-to-rifapentine-for-the-treatment-of-tb-infection/



An Activist's Guide to Shorter Treatment for Drug-Sensitive Tuberculosis:

https://www.treatmentactiongroup.org/publication/an-activists-guide-to-shorter-treatment-for-drug-sensitive-tuberculosis/

GFAN Advocacy Briefs:

https://www.globalfundadvocatesnetwork.org/resource/advocacy-guides-to-1-4-6x24-shorter-regimens-for-tb/

1/4/6x24 Community Campaign Training Materials

https://www.treatmentactiongroup.org/publication/1-4-6x24-community-campaign-training-materials/

www.treatmentactiongroup.org

FOR MORE INFORMATION, AND TO FIND COMMITMENTS AND OTHER CAMPAIGN RESOURCES