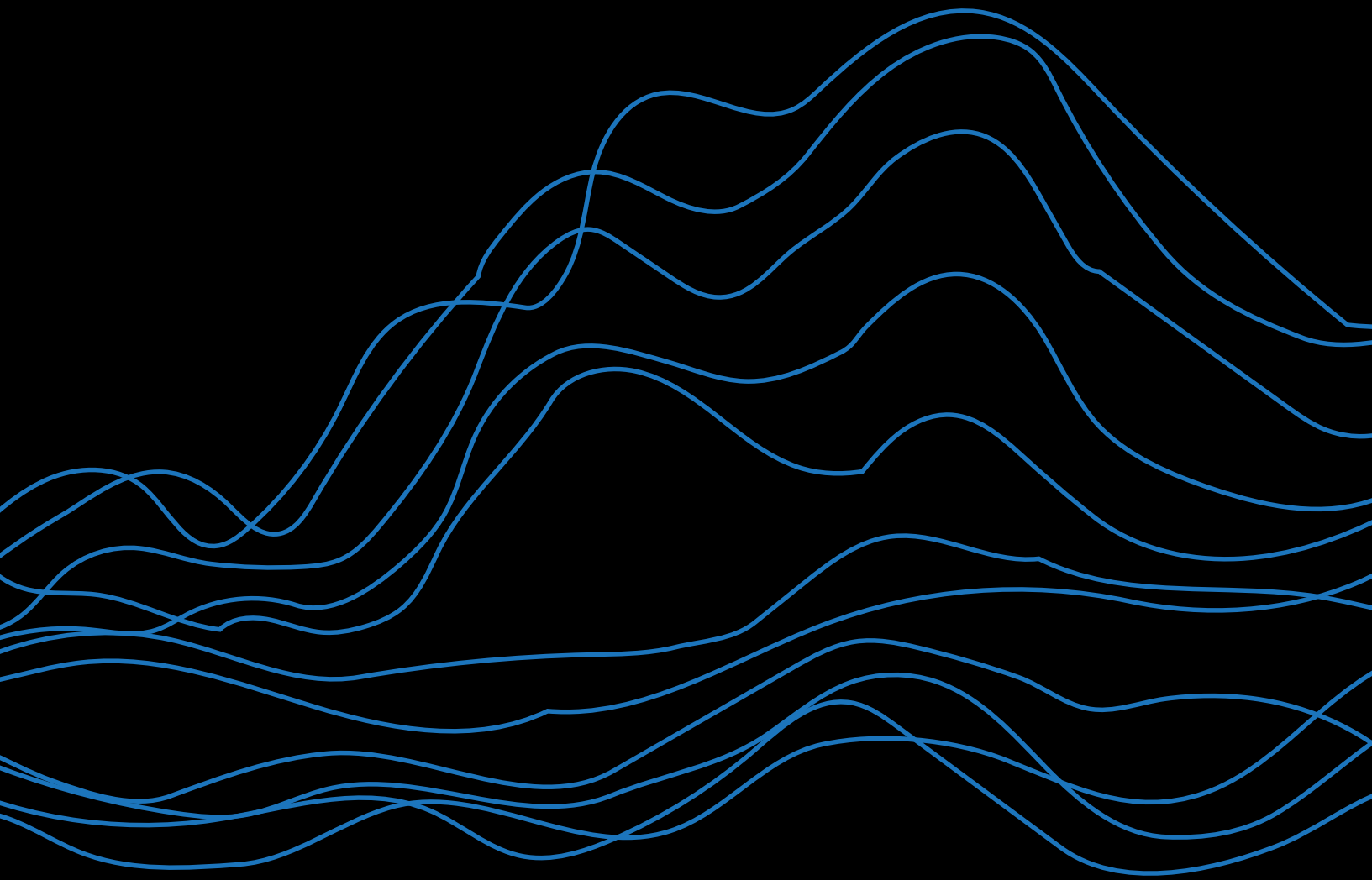
Pipeline Report » 2023

Tuberculosis Treatment



TAG
Treatment Action Group

Tuberculosis Treatment Pipeline Report

By Lindsay McKenna

Introduction

In 2023, trials that opened between 2015 and 2020 continued to produce results and delivered additional shorter treatment regimens for drug-resistant tuberculosis (TB). Ongoing work will expand on these and recent drug-sensitive TB treatment-shortening successes by introducing stratified medicine approaches and, for drug-sensitive TB, attempting to further optimize rifamycin selection and dosing. The research agenda emerging to advance new drugs (e.g., DprE1 inhibitors) and swap in next-generation versions of existing drugs (e.g., diarylquinolines, oxazolidinones) is dominated by a "pan-TB" approach — regimens intended to address both drug-sensitive and drug-resistant TB as they are defined today based on rifampicin and isoniazid susceptibility.

The 2023 Tuberculosis Treatment Pipeline Report reviews recent results and provides an overview of the state of the clinical TB treatment research pipeline in five tables. Table 1 reviews two recently completed trials: endTB and SimpliciTB. Table 2 covers trials of regimens composed of existing drugs, and Table 3 looks at trials attempting to breathe new life into drugs that are older and/or trials that will produce knowledge of limited relevance. New drugs in clinical development for TB are listed in Table 4, and Table 5 covers trials of investigational regimens that advance these new drugs. The TB treatment pipeline is fuller than it's ever been. It's also in a state of dynamic transition — the field is squeezing every last drop out of existing drugs through a variety of approaches to optimization, while simultaneously advancing a new generation of TB drugs using both novel development pathways and collaborations to do so.

Results from Recently Completed Treatment Trials

Results from two phase III trials were presented in 2023 (see Table 1). The endTB trial evaluated nine-month bedaquiline- and/or delamanid-containing regimens for drug-resistant TB and SimpliciTB evaluated a four-month bedaquiline- and pretomanid-containing regimen for drug-sensitive TB. Included in this section is also an update on a phase IIc trial to evaluate a three-month rifapentine- and clofazimine-containing regimen for drug-sensitive TB (A5362/CLO-FAST) sponsored by the U.S. National Institutes of Health (NIH)-funded Advancing Clinical Therapeutics Globally (ACTG) Network (formerly called the AIDS Clinical Trials Group).

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

<table>
<tr><th>Study Name
(Type of TB; Sample Size)</th><th>Study Arms
Experimental Regimens
[Control Regimen]</th><th colspan="4">Key Findings</th></tr>
<tr><td rowspan="15">endTB
NCT02754765
(MDR-TB, N=754)</td><td rowspan="15">(a) 9BLzMZ
(b) 9BLzLxCZ
(c) 9BDLzLxZ
(d) 9DLzLxCZ
(e) 9DMCZ
(f) [9–20mo local SOC]</td><td colspan="4">Primary Efficacy Outcome:
Three of the five nine-month endTB regimens (a, b, c) demonstrated noninferiority to the SOC (mITT and PP analyses). Regimen b also demonstrated superiority. The NI margin was 12%.</td></tr>
<tr><td colspan="2">Favorable outcomes (mITT):</td><td colspan="2">Risk difference, experimental - control (95% confidence interval)</td></tr>
<tr><td>(a)</td><td>105/118 (89.0%)</td><td colspan="2">8.3 (-0.8 to 17.4)</td></tr>
<tr><td>(b)</td><td>104/115 (90.4%)</td><td colspan="2">9.8 (0.9 to 18.7)</td></tr>
<tr><td>(c)</td><td>104/122 (85.2%)</td><td colspan="2">4.6 (-4.9 to 14.1)</td></tr>
<tr><td>(d)</td><td>93/118 (78.8%)</td><td colspan="2">-1.9 (-12.1 to 8.4)</td></tr>
<tr><td>(e)</td><td>89/104 (85.6%)</td><td colspan="2">4.9 (-4.9 to 14.7)</td></tr>
<tr><td>(f)</td><td>96/119 (80.7%)</td><td colspan="2">NA</td></tr>
<tr><td colspan="4">Primary Safety Outcome:
The nine-month regimens had similar safety to the SOC regimen.</td></tr>
<tr><td></td><td>Any grade 3 or 4 AEs</td><td>Any serious AEs</td><td>Deaths</td></tr>
<tr><td>(a)</td><td>69 (54.8%)</td><td>18 (14.3%)</td><td>3 (2.4%)</td></tr>
<tr><td>(b)</td><td>68 (55.7%)</td><td>16 (13.1%)</td><td>1 (0.8%)</td></tr>
<tr><td>(c)</td><td>78 (61.4%)</td><td>20 (15.8%)</td><td>3 (2.4%)</td></tr>
<tr><td>(d)</td><td>75 (60.5%)</td><td>18 (14.5%)</td><td>4 (3.2%)</td></tr>
<tr><td>(e)</td><td>72 (60.0%)</td><td>20 (16.7%)</td><td>2 (1.7%)</td></tr>
<tr><td>(f)</td><td>79 (62.7%)</td><td>21 (16.7%)</td><td>2 (1.6%)</td></tr>
<tr><td colspan="6">Mitnick C, Khan U, Guglielmetti L, et al. SP01 Innovation to guide practice in MDR/RR-TB treatment: efficacy and safety results of the endTB trial. Presented at: Union World Conference on Lung Health. 2023 November 15. https://theunion.floq.live/event/worldconf2023/symposia?objectClass=timeslot&objectId=64ef5819e0400915b209e22f&type=detail.</td></tr>
</table>

<table>
<tr><th>Study Name
(Type of TB; Sample Size)</th><th>Study Arms
Experimental Regimens
[Control Regimen]</th><th colspan="4">Key Findings</th></tr>
<tr><td rowspan="11">SimpliciTB
NCT03338621
(DS-TB; N=303)
*Arm c was enrolled as an exploratory cohort (MDR-TB; N=152)</td><td rowspan="11">(a) 4BPaMZ
(b) [2HRZE/4HR]
(c) 6BPaMZ*</td><td colspan="4">Efficacy Outcomes:
The four-month BPaMZ regimen failed to demonstrate noninferiority to the six-month SOC for DS-TB (mITT). The NI margin was 12%.</td></tr>
<tr><td colspan="2">Favorable outcomes:</td><td colspan="2">Risk difference, experimental - control (95% confidence interval)</td></tr>
<tr><td>(a)</td><td>118/144 (81.9%)</td><td colspan="2">10.27 (3.06 to 17.48)</td></tr>
<tr><td>(b)</td><td>134/144 (93.1%)</td><td colspan="2">NA</td></tr>
<tr><td>(c)</td><td>111/133 (83.5%)</td><td colspan="2">NA</td></tr>
<tr><td colspan="4">Primary Safety Outcome:
The incidence of AEs was higher with 4BPaMZ compared to the 6-month standard of care regimen for DS-TB. A higher proportion of participants withdrew from treatment due to AEs (predominantly hepatotoxicity) in the 4BPaMZ arm.</td></tr>
<tr><td></td><td>Any grade 3 or 4 AEs</td><td>Any serious AEs</td><td>Deaths</td></tr>
<tr><td>(a)</td><td>68 (45.3%)</td><td>17 (11.3%)</td><td>3 (2.0%)</td></tr>
<tr><td>(b)</td><td>61 (39.9%)</td><td>7 (4.6%)</td><td>1 (0.6%)</td></tr>
<tr><td>(c)</td><td>47 (31.5%)</td><td>16 (10.7%)</td><td>2 (1.3%)</td></tr>
<tr><td colspan="5">Eristavi M, Variava E, Haraka F, et al. SimpliciTB Results and Hepatic Safety of Pretomanid Regimens +/1 Pyrazinamide [OA-109]. Presented at: 2023 Conference on Retroviruses and Opportunistic Infections during Oral Abstracts Session-02 TB and Hepatitis. 2023 February 20; Seattle, Washington.</td></tr>
</table>

- AE = adverse event; DS-TB = drug-sensitive TB; mITT = modified intention to treat; MDR-TB = multidrug-resistant TB; N = sample size; NA = not applicable; NI = noninferiority; PP = per protocol; RR-TB = rifampicin-resistant TB; SOC = standard of care
- 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, unless otherwise specified
- Letters represent the individual drugs comprising each regimen: B = bedaquiline, C = clofazimine, D = delamanid, E = ethambutol, H = isoniazid, Lx = levofloxacin, Lz = linezolid, M = moxifloxacin, Pa = pretomanid, R = rifampicin, Z = pyrazinamide

In the endTB trial, three of the five investigational regimens demonstrated noninferiority to the standard of care in both the modified intention to treat (mITT) and per-protocol (PP) analyses – 9BLzMZ, 9BLzLxCZ, and 9BDLzLxZ (nine-month regimens composed of bedaquiline [B], linezolid [Lz], pyrazinamide [Z], plus moxifloxacin [M] or levofloxacin [Lx], with or without delamanid [D] or clofazimine [C]).[1,2] The 9BLzLxCZ regimen also demonstrated superiority. A fourth investigational regimen — 9DMCZ — only demonstrated noninferiority in one of the analyses but is noteworthy because it doesn't contain bedaquiline or linezolid and still performed relatively well, with a treatment success rate of 85.6%. The endTB data are generalizable given the trial's relatively broad inclusion criteria with respect to disease severity, comorbidities (e.g., HIV, HCV, diabetes), prior exposure to second-line medicines, and recruitment of participants across seven countries (Georgia, India, Kazakhstan, Lesotho, Pakistan, Peru, and South Africa). Of note, the trial allowed women who became pregnant to remain in the study.

The World Health Organization (WHO) will convene a Guideline Development Group (GDG)

meeting in 2024 to review endTB alongside data from the BEAT Tuberculosis trial, which evaluated a six-month bedaquiline- and delamanid-containing regimen (6BDLz + Lx or C) in South Africa. Interim results from the BEAT Tuberculosis trial were presented at the Union Conference in 2022 and were covered in the 2022 TB Treatment Pipeline Report.[3,4] The GDG will determine how the nine-month endTB and six-month BEAT Tuberculosis regimens will be situated alongside the prevailing standard-of-care regimen for drug-resistant TB, the six-month BPaL/M regimen. This will be a challenging task given that these regimens have never been directly compared and there are differences across studies in design and implementation. Two areas of difference are worth exploring: control arm composition and changes to treatment.

The endTB regimens and 6BPaLM in TB-PRACTECAL were compared with control arms consisting of the same regimens (9- to 11-month and 18- to 20-month regimens) but in different proportions. In endTB, 125/130 (96%) participants in the control arm received 18- to 20-month regimens versus 96/150 (64%) participants in the control arm in TB-PRACTECAL.[5,6] In both studies, the 9- to 11-month and 18- to 20-month regimens in the control arm contained at least two WHO group A drugs — fluoroquinolones (in 95%), linezolid (in 72%), and bedaquiline (in 80%) in endTB and fluoroquinolones (in 95%), linezolid (in 77%), and bedaquiline (in 76%) in TB-PRACTECAL.[7,8] In BEAT Tuberculosis, participants with fluoroquinolone resistance enrolled in the control arm received 18- to 20-month regimens while participants with fluoroquinolone-susceptible TB enrolled to the control arm received the nine-month South African standard-of-care regimen (with linezolid given in place of ethionamide and for the first two months of treatment). The trials also had different thresholds for allowing changes to treatment. The endTB trial allowed stopping one drug in the experimental arms and any number of drugs in the control arm.[9] TB-PRACTECAL did not allow stopping any drugs in the experimental arms or more than one drug in the control arm except when adjusting for baseline resistance.[10] These nuances matter when you consider that discontinuation of treatment owing to adverse events drove the difference in performance between 6BPaLM and the control arm in TB-PRACTECAL. As such, the WHO GDG and other normative bodies will need to compare the composition and performance of the control arms, how treatment changes were handled and unfavorable outcomes were defined, study populations, and other study design and implementation details.

For the first time ever, data are available from multiple phase III randomized, controlled trials. This novelty presents the need for carefully performed indirect comparisons to help establish whether the regimens that were noninferior to their internal controls in endTB, BEAT Tuberculosis, and TB-PRACTECAL should be considered as equal alternatives or whether priority rankings should be established. The WHO GDG will need to consider more than just the duration and face value efficacy and safety of these regimens. They will also need to consider data to support the use of these regimens and their components in children, pregnant women, and people with co-morbidities; drug availability; and drug and other costs. Additionally, as the Global TB Community Advisory Board (TB CAB) pointed out in a commentary published in 2023, multiple aspects of treatment affect adherence and outcomes — safety, tolerability, pill burden, monitoring requirements, and time spent interacting with the health system — matter to patients (and programs) and should be taken into consideration.[11] The WHO GDG should also evaluate whether the available data warrant a revision to the categorization and role of delamanid in the treatment of drug-resistant TB more generally. Delamanid is currently categorized by the WHO

as a group C medicine and is only recommended for inclusion in 18- to 20-month individualized regimens when a four- to five-drug regimen cannot otherwise be composed using medicines from groups A and B.[12]

In the SimpliciTB trial, a four-month regimen composed of bedaquiline, pretomanid, moxifloxacin, and pyrazinamide (4BPaMZ) failed to demonstrate noninferiority to the six-month standard of care for drug-sensitive TB (isoniazid, rifampicin, pyrazinamide, and ethambutol [6HRZE]).[13] While 4BPaMZ initially looked promising, converting TB cultures to negative more quickly, there were more unfavorable outcomes among persons treated with 4BPaMZ vs. 6HRZE (16.7% vs. 6.9%). Unfavorable outcomes were driven by withdrawals from treatment due to adverse events, predominantly hepatotoxicity. Findings were similar in the exploratory cohort of people with drug-resistant TB enrolled in SimpliciTB and treated with six months of BPaMZ. Among participants with drug-resistant TB, 16.5% had an unfavorable outcome, a majority of which were due to withdrawals from treatment because of adverse events. An exploratory analysis presented by the TB Alliance at the Conference on Retroviruses and Opportunistic Infections (CROI) in 2023 suggested that hepatotoxicity 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 BPaL (e.g., Nix-TB and ZeNix-TB).[14] A similar hypothesis was formed previously and separately based on data published from a phase II study to evaluate pretomanid given in combination with isoniazid, pyrazinamide, and rifampicin or rifabutin for drug-sensitive TB (APT; NCT02256696).[15,16] In APT, pretomanid given in place of ethambutol and in combination with isoniazid, pyrazinamide, and rifabutin improved time to culture conversion, but there was also "a trend toward increased risk of grade three or higher adverse events, more asymptomatic transaminitis, and more protocol-defined withdrawals because of hepatotoxicity."[17] The STAND Trial/NC-006 (NCT02342886) points to a similar effect — hepatotoxicity and serious adverse events were more common in the experimental arms, which combined pretomanid with pyrazinamide (and moxifloxacin).[18]

A phase IIc trial to evaluate a three-month rifapentine- and clofazimine-containing regimen for drug-sensitive TB (A5362/CLO-FAST) was closed early by the study's independent data safety and monitoring board after "an interim analysis showed that participants taking the investigational regimen experienced ongoing or recurring TB at rates above thresholds set in the study protocol."[19] The TRUNCATE-TB trial covered in the 2022 TB Treatment Pipeline Report included a high-dose rifampicin- and clofazimine-containing arm, but it was discontinued early for practical reasons.[20] Available data from A5362 and the clofazimine-containing arm of TRUNCATE-TB should inform other ongoing or planned drug-sensitive treatment-shortening trials that already include or are considering the inclusion of clofazimine. The views of people with lived experience with TB should also be considered. Community advisory boards have previously challenged the role of clofazimine in treatment regimens for drug-sensitive TB because of the drug's common side effect of skin discoloration and concerns about its acceptability to patients, inadvertent disclosure of TB, and stigma. A5362 measured skin discoloration and collected acceptability data that can help quantify and qualify these concerns and anticipate how they might affect adoption of any future clofazimine-containing regimens for drug-sensitive TB, should they prove efficacious and safe.

Negative results from SimpliciTB and A5362 leave the four-month rifapentine- and moxifloxacin-

containing regimen (2HPMZ/2HPM) as the only validated shorter regimen recommended by the WHO for the treatment of adults and adolescents with drug-sensitive TB.* Several national TB programs (i.e., Azerbaijan, Bangladesh, Liberia, Thailand, Vietnam) have incorporated plans to introduce the four-month regimen into their Global Fund funding requests for 2023–2025, albeit initially through smaller pilots or phased approaches.[21] Other countries are planning operational research to inform future introduction of the regimen (e.g., South Africa, Uganda, Tanzania). Fixed-dose combinations that will dramatically reduce the pill burden of the four-month regimen are expected to be quality assured and available globally by the end of 2024; these formulations will hopefully stimulate wider adoption.

Ongoing and planned trials designed to iterate on progress made in shortening TB treatment over the course of the last decade are covered in Table 2. Approaches include altering the dose of rifapentine and/or moxifloxacin, swapping in high-dose rifampicin for rifapentine, and deploying a stratified medicine approach to determine treatment duration.

Table 2. Trials of Treatment-Shortening Regimens Composed of Existing Drugs

Study Name	Experimental Arms [Control]	For Treatment of	Number of Participants	Phase	Status [Est. Completion Date]
Drug-Sensitive TB					
HIGHSHORT-RP NCT04694586	$2HR_{Hd}ZE/2HR_{Hd}$ [2HRZE/4HR]	DS-TB	40	II	Suspended recruitment
STEP2C-01 NCT05807399	$3R_{Hd}HZM_{600}$ $3R_{Hd}HZHdM_{600}$ $3BDMS_{1200}$ [2HRZE/4HR]	DS-TB	360	IIb/c	Recruiting [Feb 2025]
OptiRiMoxTB NCT05575518	$4HR_{Hd}ZE$ $4HR_{Hd}MZ$ [2HRZE/4HR]	DS-TB	414	III	Recruiting [Mar 2026]
ORIENT NCT05401071	$2HP_{600}MZ/2HP_{600}M$ $2HP_{900}MZ/2HP_{900}M$ $2HP_{1200}MZ/2HP_{1200}M$ [2HRZE/4HR]	DS-TB	2,442	II/III	Recruiting [Nov 2027]
Hi-DoRi-3 NCT04485156	$1–2HR_{Hd}Z/3HR_{Hd}$ [2HRZE/4HR]	DS-TB	926	III	Not yet recruiting
PORT NCT06057519	$2HR_{Hd}ZE/4HR_{Hd}$ [2HRZE/4HR]	DS-TB	164	III	Not yet recruiting
A5406 NCT05630872	PK and DDI study of DTG given BID with HPMZ	DS-TB	30	II	Recruiting [May 2025]
A5414 / SPECTRA	Stratified medicine approach to shortening HPMZ	DS-TB	900	IIc	Protocol in development

* The WHO also recommends that the standard regimen can be given for just four months (2HRZ[E]/2HR) to children with nonsevere forms of drug-sensitive TB based on data from the SHINE study.

Study Name	Experimental Arms [Control]	For Treatment of	Number of Participants	Phase	Status [Est. Completion Date]
Drug-Sensitive TB					
yzhang207 NCT05454345	13wkSxHPZ 6wkSxHPZ/7wkSxHP+SMZ/TMP [2HRZE/4HR] [2HPMZ/2HPM]	DS-TB	620	III	Not yet recruiting
A5362 / CLO-FAST NCT04311502	2CHPZE/1CHPZ [2HRZE/4HR]	DS-TB	104	IIc	Closed early
TBTC Study 38 / CRUSH-TB NCT05766267	4BMZRb 4BMZD [2HRZE/4HR]	DS-TB	288	IIc	Recruiting [Dec 2026]
PRESCIENT NCT05556746	3BDZC [2HRZE/4HR]	DS-TB	156	IIc	Recruiting [Jan 2027]
SURE ISRCTN40829906	6HRZLx ± aspirin [2HRZE/10HR ± aspirin]	TBM (children)	400	III	Active, not recruiting [Dec 2025]
INTENSE-TBM NCT04145258	$2HR_{Hd}ZELz/7HR$ ± aspirin [2HRZE/7HR ± aspirin]	TBM	768	III	Recruiting [Apr 2026]
A5384 / IMAGINE-TBM NCT05383742	$2HR_{Hd}ZLz/4HR_{Hd}$ 2HRZE/7HR]	TBM	330	II	Recruiting [Aug 2026]
INSHORT NCT05917340	$2HR_{Hd}ZM/4HRZ$ + aspirin, steroid $2HR_{Hd}ZM/4HRZ$ + steroid [2HRZE/7HR]	TBM	372	III	Not yet recruiting
Drug-Resistant TB					
BEAT-Tuberculosis NCT04062201	6BDLz (Lx or C) [9–20mo South Africa SOC]	RR-, MDR-, Pre-XDR-TB	402	III	Results presented, Union 2022
endTB NCT02754765	9BLzMZ 9BLzLxCZ 9BDLzLxZ 9DLzLxCZ 9DMCZ [9–20mo SOC] *Lz dose reduced from 600 mg QD to 300 mg QD or 600 mg TIW after 4 months	MDR-TB	754	III	Results presented, Union 2023
K21-024 NCT05278988	6–9BDCZ [9–20mo SOC]	MDR-TB	60	IV	Recruiting [Sept 2024]
endTB-Q NCT03896685	6BDLzC 9BDLzC [9–20mo SOC] *6- vs. 9-month duration assigned using stratified medicine approach; Lz dose reduced from 600 mg QD to 300 mg QD or 600 mg TIW after 4 months	Pre-XDR-TB	323	III	Active, not recruiting [Nov 2024]

Study Name	Experimental Arms [Control]	For Treatment of	Number of Participants	Phase	Status [Est. Completion Date]
Drug-Resistant TB					
mBPaL NCT05040126	$2BPaLz_{600}/4BPaLz_{300}$ $3BPaLz_{600}/3BPaLz_{300}$ [$6BPaLz_{600}$]	Pre-XDR-, TI-NR-MDR-TB	400	III	Active, not recruiting [Dec 2024]
SMART4TB PRISM-TB	Stratified medicine approach to shortening BPaL/M	MDR-, Pre-XDR-TB	840	III	Protocol in development
DRAMATIC NCT03828201	$16wkBDCLxLz_{8wk}$ $24wkBDCLxLz_{8wk}$ $32wkBDCLxLz_{8wk}$ $40wkBDCLxLz_{8wk}$ [none]	MDR-TB	220	IIc	Recruiting [July 2025]
ACTG A5356 NCT05007821	$1BDCLz_{1200\ QD}/5BDCLz_{1200\ TIW}$ $6BDCLz_{600\ QD}$ [none]	RR-, MDR-, pre-XDR-TB	132	II	Recruiting [Sept 2025]

- Post-2021 definitions for pre-extensively drug-resistant TB (pre-XDR-TB) and extensively drug-resistant TB (XDR-TB) are used in Table 2, i.e., pre-XDR-TB: multidrug-resistant TB (MDR-TB) with additional resistance to the fluoroquinolones; XDR-TB: MDR-TB with additional resistance to the fluoroquinolones and other group A drugs (bedaquiline or linezolid)
- DDI = drug-drug interaction, DTG = dolutegravir, DS-TB = drug-sensitive TB, RR-TB = rifampicin-resistant TB, PK = pharmacokinetics, SOC = standard of care, TBM = tuberculous meningitis, TI-NR-MDR-TB = treatment-intolerant or nonresponsive MDR-TB
- 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, unless otherwise specified (i.e., wk = weeks); letters represent the individual drugs comprising each regimen
- Subscripts indicate dosing in mg; Hd = high dose, BID = twice daily, QD = once daily, TIW = thrice weekly
- Letters indicate TB drugs: B = bedaquiline, C = clofazimine, D = delamanid, E = ethambutol, H = isoniazid, Lx = levofloxacin, Lz = linezolid, M = moxifloxacin, P = rifapentine, Pa = pretomanid, R = rifampicin, S = sutezolid, Sx = sitafloxacin, SMZ/TMP = sulfamethoxazole/ trimethoprim, Z = pyrazinamide

This year, the Pipeline Report also covers trials that appear stuck in the past (see Table 3). These include trials attempting to breathe new life into old drugs that have otherwise been largely discarded by the global community due to an unacceptable safety and tolerability profile, i.e., amikacin, as well as trials that are potentially unethical due to the unlikelihood of them generating any social value and/or because they are unmoored from current standards of care.

Table 3. Trials Attempting to Breathe New Life into Old Drugs and/or Anticipated to Have Limited Social Value

Study Name	Experimental Arms [Control]	For Treatment of	Number of Participants	Phase	Status [Est. Completion Date]
Tri-Do-Re NCT04260477	$6H_{Hd}R_{Hd}ZE$ [6HRZE]	Previously treated DS-TB	370	III	Recruiting [Nov 2024]
TB-TRUST NCT03867136	6LxLzCsZCz with Z or Cz discontinued based on PZA-R [4–6AmkPtoH$_{HD}$MCzEZ/5MCzEZ]	MDR-TB	354	IV	Active, not recruiting [Nov 2023]
TB-TRUSTplus NCT04717908	6BLzCsZCz with Z or Cz discontinued and duration extended based on PZA-R	MDR-TB	89	IV	Active, not recruiting [Nov 2023]
STAKE NCT05555303	4–6BLzH_{Hd}LxCzZE/5LxCzZE + 2 doses of Amk during the first week of treatment	MDR-TB	20	II	Recruiting [Mar 2024]
PROSPECT NCT05306223	9BLxCsCzLz [6LxCsCzZPtoLz]	MDR-TB	212	IV	Recruiting [Aug 2025]
PACTR202203645724919	4–6BLzPtoH$_{Hd}$LxCzZ/5BLxCzZ [4–6AmkPtoH$_{Hd}$MCzEZ/5MCzEZ]	MDR-TB	230	IV	Recruiting [Jan 2026]

- DS-TB = drug-sensitive TB, MDR-TB = multidrug-resistant TB, PZA-R = pyrazinamide resistance
- 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, unless otherwise specified; letters represent the individual drugs comprising each regimen
- Subscripts indicate dosing in mg; Hd = high dose
- Letters indicate TB drugs: Amk = amikacin, B = bedaquiline, Cs = cycloserine, Cz = clofazimine, E = ethambutol, H = isoniazid, Lx = levofloxacin, Lz = linezolid, M = moxifloxacin, Pto = prothionamide, R = rifampicin, Z = pyrazinamide

Pediatric Investigations of TB Drugs

A single-dose pediatric study of pretomanid finally opened to enrollment in 2023 (IMPAACT 2034; NCT05586230). This is just the first step for children to be able to benefit from access to the six-month BPaL/M regimen for drug-resistant TB. IMPAACT 2034 will need to be followed by a multidose pretomanid study.

The single-dose study of pretomanid is currently only enrolling female children because reduced fertility was observed in male rats and mice treated with pretomanid. A meta-analysis of human male hormone data from pretomanid studies has already been published.[22,23] Additional data are expected soon from a reproductive safety study focused on sperm count (PaSEM; NCT04179500). The U.S. Food and Drug Administration (FDA) will review these data to determine whether the inclusion of male children in IMPAACT 2034 and other planned studies of pretomanid in children can proceed.

In the meantime, each of the components of the endTB and BEAT Tuberculosis regimens are already indicated for use in children, and pediatric formulations are available. The efficacy of these regimens proven in adults can be extrapolated to children. As such, programs do not need to wait for pretomanid data in children to treat drug-resistant TB in kids with evidence-based shorter regimens. The NIH-funded International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) network and U.S. Agency for International Development (USAID)-funded SMART4TB Consortium are planning studies to evaluate similar regimens in children. IMPAACT P2020 will evaluate a six-month bedaquiline- and delamanid-containing regimen that includes levofloxacin or clofazimine (depending on fluoroquinolone resistance) and linezolid for the first eight weeks. In P2020, all of the study medications will be dosed once daily. The SMART4TB PRISM Kids study will explore the potential of a stratified medicine approach to shorten treatment with this regimen to four months for children with easier-to-treat TB.

At the end of 2023, a pediatric rifapentine formulation finally became available, enabling the treatment of younger children with rifapentine-based TB preventive treatment (TPT) regimens.[24] This formulation will also be important for facilitating future access to the four-month rifapentine- and moxifloxacin-containing regimen for treating active, drug-sensitive TB in children. The U.S. Centers for Disease Control and Prevention (CDC) Tuberculosis Trials Consortium (TBTC) is planning a phase II pediatric pharmacokinetics and safety study of the four-month rifapentine- and moxifloxacin-containing regimen for drug-sensitive TB (Study 39/ Radiant Kids). And the SMART4TB Consortium is planning a phase III trial to evaluate whether the same regimen can be reduced to just two months for children under ten years old (SMILE-TB).

In terms of new TB drugs, there are six compounds in phase IIb studies in adults: TBAJ-876, quabodepistat, BTZ-043, sutezolid, delpazolid, and ganfeborole. There are also two new and one repurposed compound in phase III: sudapyridine, contezolid, and sitafloxacin. Phase IIb is the latest stage at which pediatric investigational planning should begin. The sponsors of these compounds are in different places with respect to the planning and execution of preclinical and clinical investigations necessary to inform the use and licensure of these new drugs for children. If these efforts are not accelerated soon, developers will fall into an all too familiar pattern — one that perpetuates long and life-threatening delays between when new TB medicines are approved for use in adults versus children.

Updates on New Drugs in Clinical Development for TB

Twenty-two new or repurposed compounds are in clinical development for TB (see Figure 1 and Table 4). This includes 11 compounds from a new class or with a new mechanism of action and 11 potentially advantaged alternatives to existing TB drugs, including two that are approved for other indications and are now under investigation for TB. In 2023, several phase II trials reported results including for sutezolid (an oxazolidinone like linezolid), TBAJ-876 (a diarylquinoline like bedaquiline), and TBA-7371 (a DprE1 inhibitor).[25,26,27] Results are expected imminently from a phase IIb/c study of the DprE1 inhibitor that's the furthest along — quabodepistat (formerly OPC-167832). And phase IIb/c trials sponsored by the Gates Medical Research Institute Project to Accelerate New Treatments for Tuberculosis (PAN-TB) and UNITE4TB (academia and industry united innovation and treatment for tuberculosis) are finally actively recruiting participants. These trials will evaluate regimens that include quabodepistat and another DprE1 inhibitor, BTZ-043, as well as sutezolid and ganfeborole.

Figure 1. Global Pipeline of Medicines in Clinical Development for TB

Figure adapted from Stop TB Partnership Working Group on New Drugs.
Diarylquinoline; Oxazolidinone; DprE1 inhibitor; Riminophenazine Nitroimidazole; Fluroquinolone.
Drugs that appear in black font are from classes and/or with mechanisms of action not otherwise represented by the other colors.

Table 4. New (and Repurposed) Drugs in Clinical Development for TB

Drug	Class	Mechanism of Action	Sponsor	Phase	Clinical Trial(s)	
Energy Production						
GSK2556286 (GSK-286)	Pyrimidine	Inhibits cholesterol catabolism (target to be determined)	GSK	Ia/Ib	NCT04472897	
pyrifazimine (TBI-166)	Riminophenazine	Inhibits ion transport and bacterial respiration	IMM/CAMS/ PUMC	IIa	ChiCTR1800018780 NCT04670120	
sudapyridine (WX-081)	Diarylquinoline	Inhibits ATP synthase	Shanghai Jiatan Pharmatech Co.	III	NCT06117514 NCT04608955 NCT05824871	← NEW
TBAJ-587	Diarylquinoline	Inhibits ATP synthase	TB Alliance/ ERA4TB	Ia/Ib	NCT04890535	

Drug	Class	Mechanism of Action	Sponsor	Phase	Clinical Trial(s)	
Energy Production						
TBAJ-876	Diarylquinoline	Inhibits ATP synthase and bacterial respiration	TB Alliance	IIb	NCT04493671 NCT05526911 NCT06058299	← NEW
telacebec (Q203)	Imidazopyridine	Inhibits ATP synthesis (QcrB) and bacterial respiration	Qurient/ TB Alliance /Infectex	IIa	NCT02530710 NCT02858973 NCT03563599	
Cell Wall Synthesis						
BTZ-043	Benzothiazinone	Inhibits cell wall synthesis (DprE1)	University of Munich/DZIF	IIb/c	NCT03590600 NCT04044001 NCT04874948 NCT05926466 NCT06114628	← NEW ← NEW
alpibectir (BVL-GSK098)	Amido-piperidine	Inhibits cell wall synthesis via boosting ethionamide	BioVersys/GSK	IIa	NCT04654143 NCT05473195	
macozinone (PBTZ169)	Benzothiazinone	Inhibits cell wall synthesis (DprE1)	iM4TB/Nearmedic	Ib/IIa	NCT03036163 NCT03423030 NCT03776500 NCT03334734	
quabodepistat (OPC-167832)	Carbostyril	Inhibits cell wall synthesis (DprE1)	Otsuka	IIb/c	NCT03678688 NCT05221502 NCT05971602	← NEW
sanfetrinem cilexetil	Carbapenem	Inhibits cell wall synthesis	GSK/GMRI	IIa	NCT05388448	
SQ109	Ethylenediamine	Inhibits cell wall synthesis (MmpL3)	Sequella	IIb	NCT01585636 NCT00866190 NCT01358162 NCT01218217 NCT01785186	
TBA-7371	Azaindole	Inhibits cell wall synthesis (DprE1)	TB Alliance/ GMRI	IIa	NCT03199339 NCT04176250	
Protein Synthesis						
contezolid	oxazolidinone	Inhibits protein synthesis (23S ribosome)	MicuRx	III	NCT03033342 NCT03033329 NCT03747497 NCT06081361	← NEW

Drug	Class	Mechanism of Action	Sponsor	Phase	Clinical Trial(s)	
Protein Synthesis						
delpazolid (LCB01-0371)	Oxazolidinone	Inhibits protein synthesis (50S ribosomal subunit)	LegoChem Biosciences	IIb	NCT01554995 NCT01842516 NCT02540460 NCT02836483 NCT04550832	
sutezolid (PNU-100480)	Oxazolidinone	Inhibits protein synthesis (50S ribosomal subunit)	Sequella/TB Alliance	IIb/c	NCT00871949 NCT00990990 NCT01225640 NCT03199313 NCT03959566 NCT06192160 NCT05971602 NCT05686356	← NEW ← NEW ← NEW
tedizolid *repurposed	Oxazolidinone	Inhibits protein synthesis (50S ribosomal subunit)	Assistance Publique – Hôpitaux de Paris	IIa	NCT05534750	
TBI-223	Oxazolidinone	Inhibits protein synthesis (50S ribosomal subunit)	TB Alliance/IMM	IIa	NCT03758612 NCT04865536 NCT06192160	← NEW
NEW → MK-7762 (TBD09)	Oxazolidinone	Inhibits protein synthesis (50S ribosomal subunit)	GMRI/Merck	Ia/b	NCT05824091	
ganfeborole (GSK-656)	Oxaborole	Inhibits protein synthesis (LeuRS)	GSK	IIb	NCT03075410 NCT03557281 NCT05382312 NCT06114628	← NEW
DNA Synthesis						
SPR720	Benzimidazole	Inhibits bacterial DNA synthesis (GyrB)	Spero Therapeutics/ GMRI	Ia/Ib	NCT03796910	
Sitafloxacin *repurposed	Fluoroquinolone	Inhibit bacterial DNA synthesis	Daiichi Sankyo	III	NCT05454345	

Phase listed represents the most advanced trial that is ongoing/completed.

ATP = adenosine triphosphate
CAMS = Chinese Academy of Medical Sciences
DprE1 = Decaprenylphosphoryl-β-d-ribose 2′-epimerase, an enzyme involved in cell wall synthesis
DZIF = German Center for Infection Research
GMRI = Bill & Melinda Gates Medical Research Institute
GSK = GlaxoSmithKline
GyrB = DNA gyrase subunit B, an enzyme involved in DNA synthesis
iM4TB = Innovative Medicines for Tuberculosis
IMM = Institute of Materia Medica, China
LeuRS = leucyl-tRNA synthetase, an enzyme involved in protein synthesis
MmpL3 = mycobacterial membrane protein large 3, mycolic acid and lipid transporter required for cell growth and viability
PUMC = Peking Union Medical College, China
QcrB = Cytochrome b subunit of the cytochrome bc1 complex, an essential component of the respiratory electron transport chain required for ATP synthesis

Table 5. Trials of Investigational Regimens That Advance New Drugs

Study Name	Experimental Arms [Control]	For Treatment of	Number of Participants	Phase	Status [Est. Completion]
A5409/RAD-TB NCT06192160	2BPaS_{800}/4HR 2BPaS_{1600}/4HR 2BPa$TBI\text{-}223_{1200}$/4HR 2BPa$TBI\text{-}223_{2400}$/4HR 2BPaL/4HR [2HRZE/4HR]	DS-TB	315	IIa+	Not yet recruiting [Apr 2026]
NC-009 NCT06058299	2J_{25}PaL/2–4HR 2J_{50}PaL/2–4HR 2J_{100}PaL/2–4HR 6BPaL [2HRZE/4HR]	DS-TB	300	IIb	Recruiting [June 2026]
SUDOCU NCT03959566	3BDMS_{600}/3HR 3BDMS_{1200}/3HR 3BDM$S_{600\ BID}$/3HR 3BDM$S_{800\ BID}$/3HR [3BDM/3HR]	DS-TB	75	IIb	Results presented, CROI 2023
STEP2C-01 NCT05807399	3$R_{Hd}HZM_{600}$ 3$R_{Hd}HZ_{Hd}M_{600}$ 3BDMS_{1200} [2HRZE/4HR]	DS-TB	360	IIb/c	Recruiting [Feb 2025]
DECODE NCT04550832	4BDMDzd_{400} 4BDMDzd_{800} 4BDMDzd_{1200} 4BDM$Dzd_{800\ BID}$ [4BDM]	DS-TB	76	IIb	Fully enrolled [Mar 2024]
DECISION/ UNITE4TB-02 NCT05926466	4BDT_{500}/2HR 4BDT_{1000}/2HR 4BDT_{1500}/2HR [4BDM/2HR]	DS-TB	90	IIb	Recruiting [Aug 2024]
Trial 323-201-00006 NCT05221502	4BDQ_{10} 4BDQ_{30} 4BDQ_{90} [2HRZE/4HR]	DS-TB	122	IIb/c	*Results forthcoming, CROI 2024
Gates MRI-TBD06-201 NCT05971602	2–4PaBQS 2–4DBQS [2HRZE/4HR]	DS-TB + RR/MDR obs. cohort	514	IIb/c	Recruiting [Mar 2027]

Study Name	Experimental Arms [Control]	For Treatment of	Number of Participants	Phase	Status [Est. Completion]
PARADIGM4TB / UNITE4TB-01 NCT06114628	2–4BDGM 2–4BPaGM 2–4BDGZ 2–4BDGL 2–4BDTM 2–4BPaTM 2–4BDTZ 2–4BDTL 2–4BDGT 2–4BMTZ 2–4BDM [2HRZE/4HR] *L for the first 8 weeks only	DS-TB	2,500	IIb/c	Recruiting [Aug 2027]
panTB-HM NCT05686356	4BPaS_{1200} 4BPaS_{1600} 4BPaS_{1600} + $NAC_{1800\ BID}$ [2HRZE/4HR]	DS-TB	352	II/III	Recruiting [Sept 2025]
INSPIRE-CODA NCT06081361	6BDCzd (Lx or Cz) [6BLzCsCzLx/12CsCz Lx]* *For FQ-R, Lx will be replaced by Pto, Z, PAS or E	MDR-TB, pre-XDR-TB	186	III	Not yet recruiting
WISH NCT05824871	6W + OBR [6B + OBR] *OBR given for up to 18 months	MDR-TB	450	III	Recruiting [Mar 2025]

- CROI = Conference on Retroviruses and Opportunistic Infections, DS-TB = drug-sensitive TB, FQ-R = fluoroquinolone-resistant TB, MDR-TB = multidrug-resistant TB, RR-TB = rifampicin-resistant TB, XDR-TB = extensively drug-resistant TB
- 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, unless otherwise specified; letters represent the individual drugs comprising each regimen
- Subscripts indicate dosing in mg; BID = twice daily; TIW = thrice weekly
- NAC = N-acetyl cysteine (a repurposed host-directed therapy)
- OBR = optimized background regimen
- Letters indicate TB drugs: B = bedaquiline, D = delamanid, Dzd = delpazolid, Czd = contezolid, Cs = cycloserine, Cz = clofazimine, E = ethambutol, G = ganfeborole, H = isoniazid, J = TBAJ-876, L = linezolid, Lx = levofloxacin, M = moxifloxacin, Pa = pretomanid, PAS = para-aminosalicylic acid, Pto = prothionamide, Q = quabodepistat, R = rifampicin, S = sutezolid, T = BTZ-043, TBI-223 = TBI-223, W = WX-081, Z = pyrazinamide

Conclusion

With collaborative approaches being initiated earlier in the development pathway, we will more quickly figure out how to optimally combine the next generation of new drugs to improve treatment and preserve the longevity of new agents and drug classes. To support the rapid advancement of this work and adoption of the next generation of new treatment regimens, three areas demand urgent attention:

Person-centered outcomes: As research and product sponsors prepare for new drugs to advance to phase III, clinical trialists, TB-affected communities, and normative bodies need to work together to establish person-centered trial outcomes and determine a set of standardized tools (existing and/or new) that can be used to measure them.[28] Person-centered outcomes will be especially important as new regimens perform better and gains in efficacy and safety become increasingly incremental. These novel outcomes will help distinguish the benefits of next-generation regimens beyond their noninferiority to existing standards of care. This information and methods that support indirect comparisons across regimens evaluated in different randomized controlled trials will be necessary to inform guidelines and adoption.

Regulatory preparation and communication: Regulatory authorities should also prepare to review applications for new drugs that have been developed in the context of regimens containing more than one novel agent. While the approach the TB Alliance took to developing and filing for pretomanid's approval tested these waters, the other components of the regimen in the context of which pretomanid was reviewed, i.e., bedaquiline and linezolid, were already approved by stringent regulatory authorities (SRAs). Just as the WHO is developing guidance for TB drug and regimen developers regarding the evidence required for global guidelines, regulatory authorities should update the guidance they provide to industry, especially regarding what evidence will be required to demonstrate the individual contributions of each novel component to the overall efficacy and safety of new TB treatment regimens.[29,30]

Planning for access: Research and product sponsors need to think about access much earlier and consider lessons learned from the development and introduction of bedaquiline, delamanid, and pretomanid. Among these lessons are the importance of: (1) inclusive trials and early planning for pediatric investigations; (2) addressing the unmet medical needs of communities and individuals affected by extensively drug-resistant TB through pre-approval access programs; and (3) attaching access conditionalities to public and philanthropic funding.[31,32,33] To expedite equitable access to the next generation of TB treatment innovations and end TB by 2030, we must do things differently.

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