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Recent advances in the treatment of tuberculosis

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1 **Recent advances in the treatment of tuberculosis**

2

3 **Title page**

4

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75

76 **Abstract:**

77 **Background**

78 Tuberculosis is a global health challenge and one of the leading causes of death worldwide. In
79 the last decade, the tuberculosis treatment landscape has dramatically changed. After long years
80 of stagnation, new compounds entered the market (bedaquiline, delamanid and pretomanid) and
81 phase III clinical trials have shown promising results towards shortening duration of treatment
82 for both drug-susceptible (Study 31/A5349, TRUNCATE-TB, SHINE) and drug-resistant
83 tuberculosis (STREAM, NiX-TB, ZeNix, TB-PRACTECAL). Dose optimization of rifamycins
84 and repurposed drugs have also brought hopes of further development of safe and effective

85 regimens. Consequently, international and World Health Organization clinical guidelines have
86 been updated multiple times in the last years to keep pace with these advances.

87 **Objectives**

88 This narrative review aims to summarize the state-of-the-art on treatment of drug-susceptible and
89 drug-resistant tuberculosis, as well as recent trials results and an overview of ongoing clinical
90 trials.

91 **Sources**

92 A non-systematic literature review was conducted in PubMed and MEDLINE, focusing on the
93 treatment of tuberculosis. Ongoing clinical trials were listed according to the authors'
94 knowledge, and completed consulting clinicaltrials.gov and other publicly available websites
95 (www.resisttb.org/clinical-trials-progress-report, www.newtbdugs.org/pipeline/trials).

96 **Content**

97 This review summarizes the recent, major changes in the landscape for drug-susceptible and
98 drug-resistant treatment, with a specific focus on their potential impact on patient outcomes and
99 programmatic TB management. Moreover, insights in host-directed therapies, and advances in
100 pharmacokinetic and pharmacogenomics are discussed. A thorough outline of ongoing
101 therapeutic clinical trials is presented, highlighting different approaches and goals in current TB
102 clinical research.

103 **Implications**

104 Future research should be directed to individualize regimens and protect these recent
105 breakthroughs by preventing and identifying the selection of drug resistance and providing

106 widespread, affordable, patient-centered access to new treatment options for all people affected
107 by tuberculosis.

108 **Main article**

109

110 **Introduction**

111 Tuberculosis (TB) remains a global health challenge, with an estimated incidence of 10.6 million
112 new cases occurring in 2021, according to the 2022 World Health Organization (WHO) Global
113 TB Report.[1] The incidence of multidrug-resistant/rifampicin-resistant TB (MDR/RR-TB) is
114 increasing, with an estimated 450,000 new cases in 2021.

115 Existing treatments for drug-susceptible (DS) and drug-resistant (DR) TB for adult and children
116 have saved millions of lives. However, TB is still a leading infectious cause of death with 1.6
117 million deaths (including 187,000 people living with HIV) occurring in 2021 and in the near
118 future could replace again COVID-19 as the leading cause of death by a single infectious
119 agent.[1]

120 Recent therapeutic advances have dramatically renewed the landscape for DS- and DR-TB
121 treatment. This review aims to highlight these major changes and their potential impact on
122 patient outcomes and programmatic TB management.

123 **Treatment of drug-susceptible TB**

124 For much of the last 50 years, DS-TB has been treated with the so-called ‘short-course
125 chemotherapy’ regimen. Administered over six months, the regimen was the result of a series of
126 clinical trials conducted between 1946 and 1986 by the British Medical Research Council.[2]
127 These trials demonstrated that an ‘intensive’ phase of two months of rifampicin, isoniazid, and
128 pyrazinamide, followed by a ‘continuation’ phase of four months of rifampicin and isoniazid,
129 could cure most patients. Pyrazinamide was added to the regimen in the intensive phase to permit
130 treatment shortening from nine to six months.[2] This ‘one-size-fits-all’ regimen subsequently
131 became the global standard, recommended for treating all forms of DS-TB.

132 Short-course chemotherapy has saved millions of lives, but six months of pill-taking challenges
133 patients and TB treatment programmes alike. There has, therefore, been much interest in
134 shortening the regimen. There were early signals that the addition of fluoroquinolones might
135 shorten treatment, with trials suggesting that these drugs reduced the time-to-sterilisation of
136 sputum when added to the standard therapy.[3, 4] However, three independent phase III trials
137 published in 2014 showed that four-month regimens containing moxifloxacin or gatifloxacin did
138 not meet the pre-defined non-inferiority margins when compared to the standard six-month
139 regimen.[5–7] Nonetheless, subsequent analyses of the results of these trials have shown that
140 specific subgroups of patients may benefit from less than six months of treatment.[8, 9]

141 Investigators turned to shorten treatment by optimising the pharmacokinetics of the drugs used,
142 especially the rifamycins (rifampicin, rifabutin, rifapentine). Clinical studies have confirmed that
143 rifampicin doses up to 40mg/kg/day were well-tolerated and increased early bactericidal
144 activity,[10] but whether high rifampicin doses can safely shorten therapy, or improve outcomes
145 from TB meningitis, remains the subject of ongoing trials (**Table 1**). Recent data from a large

146 phase III trial (Study 31/A5349) showed that rifapentine – a rifamycin with a longer half-life –
147 used in combination with isoniazid, pyrazinamide and moxifloxacin, can shorten therapy to four
148 months.[11] In May 2022, the WHO conditionally recommended that eligible persons aged ≥ 12
149 years with pulmonary DS-TB may receive this four-month regimen.[12]

150 A reinvigorated anti-TB drug pipeline has enabled new approaches to treatment (**Table 1**). A
151 recent phase II trial compared pretomanid - a new nitroimidazole - with either rifampicin or
152 rifabutin, in combination with isoniazid and pyrazinamide, against the standard 6-month
153 regimen.[13] The pretomanid-rifabutin regimen induced faster bacterial killing in sputum than
154 the other regimens, but with more frequent hepatic adverse events, probably due to the
155 pretomanid/pyrazinamide combination, which may temper the use of this combination for future
156 DS-TB treatment.[14]

157 It has long been recognised that there is a subset of patients, often with less severe TB, that may
158 be cured with less than six months of therapy.[15] The SHINE trial showed that sixteen weeks
159 was non-inferior to six months of treatment in children with DS, non-severe, smear-negative
160 TB.[16] The TRUNCATE-TB trial investigated a strategy of giving eight-week treatment
161 regimens to adults with mild or moderately severe pulmonary TB, with the possibility to extend
162 treatment in those with poor response and retreatment for relapses. [17] One strategy arm using
163 an initial eight-week combination of bedaquiline, linezolid, isoniazid, pyrazinamide, and
164 ethambutol met the 12% non-inferiority margin, with marked reduction in total time on
165 treatment, and without major safety concerns. Overall, 3 (2%) participants out of 189 in the
166 successful strategy arm extended regimen and 24 (13%) started a second treatment course. Two
167 participants in the bedaquiline-, linezolid-containing arm relapsed with confirmed acquired
168 phenotypic drug resistance to bedaquiline (and clofazimine). Implementation research is needed

169 to evaluate the outcome of such strategy in diverse populations. Of note, the definition of TB
170 severity is heterogeneous among the aforementioned studies and would greatly benefit from
171 consensus on validated criteria.[8, 9]

172

173 **Treatment of isoniazid-resistant, rifampicin-susceptible TB**

174 Isoniazid resistance without concurrent rifampicin resistance is the most common type of *M.*
175 *tuberculosis* resistance worldwide, present among an estimated 10.6% of all TB cases in
176 2019.[18] In 2018, WHO recommended a regimen consisting of six months of rifampicin,
177 ethambutol, pyrazinamide, and levofloxacin to treat isoniazid-resistant TB, following an
178 individual patient data (IPD) meta-analysis containing 3,923 patients with isoniazid-resistant,
179 rifampicin-susceptible TB which indicated that the addition of a fluoroquinolone, compared to
180 six months of standard treatment with or without isoniazid, increased the likelihood of treatment
181 success (adjusted odds ratio: 2,8 [95% confidence interval: 1,1-7,3]).[12, 19] This
182 recommendation was, however, conditional, based on a very low certainty of evidence. In
183 instances of noncavitary disease, low bacillary burden, or pyrazinamide toxicity, European-
184 American guidelines have suggested that pyrazinamide may be given only during the first two
185 months of treatment, provided the fluoroquinolone used is later-generation.[20] Patients with
186 fluoroquinolone resistance or contraindications are generally recommended to be treated with
187 rifampicin, ethambutol and pyrazinamide only for six months. However, these two latter
188 recommendations lack clinical trial evidence and are based on expert opinion. When additional
189 drug resistance is detected or highly likely, individualised regimens are needed.

190 At the time of the WHO guidelines, there was no clear evidence if using high-dose isoniazid
191 within such regimens was beneficial. This is likely to be influenced by the resistance mutation(s)
192 present (for example, mutations in *inhA* and its promoter are usually associated with lower-level
193 resistance than *katG* mutations) and the patient's acetylase status.[21] There is recognition that
194 isoniazid may be included in regimens simply due to the use of fixed-dose combination pills. As
195 the majority of the evidence for the treatment of isoniazid-resistant TB derives from secondary
196 observational data, bespoke clinical trials (potentially drawing from emulated target trials) would
197 be needed to strengthen the evidence base.[22]

198

199 **Treatment of MDR/RR-TB**

200 In 2018, the results of an IPD analysis with more than 12,000 patients with MDR/RR-TB, and an
201 observational cohort about the impact of bedaquiline on TB mortality in South Africa, led to
202 substantial changes in the recommendations for management of patients with MDR/RR-
203 TB.[20,21] The recommendation to change from 18-20 months of treatment to an all-oral,
204 shorter, 9-12 month regimen, as well as the recommendation against the use of injectables
205 (namely capreomycin and kanamycin), marked a drastic shift in the management of patients with
206 MDR/RR-TB.[25, 26] STREAM Stage 2 trial was a phase III trial that compared a nine-month
207 injectable containing regimen (four months of kanamycin, isoniazid, prothionamide, and nine
208 months of moxifloxacin, clofazimine, ethambutol, pyrazinamide) with a nine-month all-oral
209 regimen where bedaquiline replaced kanamycin. The primary endpoint, favourable treatment
210 outcome, was reached with the injectable-containing regimen in 71% of participants and with the
211 all-oral regimen in 83%.[27] Most importantly, grade 3/4 hearing loss was documented in only
212 2% of participants receiving the all-oral regimen vs. 9% in the injectable-containing regimen.

213 The WHO recommended the nine- to twelve-month regimen with bedaquiline (and the option of
214 replacing ethionamide with linezolid given for two months) in 2022 for the treatment of
215 MDR/RR-TB without fluoroquinolone resistance as second option.[28] The TB-PRACTECAL
216 trial consolidated the evidence that MDR/RR-TB can be treated successfully with a six-month
217 regimen.[29] A regimen with bedaquiline, linezolid, pretomanid and moxifloxacin (BPaLM) was
218 documented in the modified intention to treat analysis to be superior to the standard of care (89%
219 favourable outcomes in BPaLM group versus 51% in standard of care). At least as important as
220 the efficacy of the regimen were the safety results: only 25% patients on BPaLM, compared to
221 60% on standard of care suffered a grade 3/4 adverse event within 108 weeks after
222 randomization.[30] The trial was stopped early due to the superiority of the BPaLM regimen and
223 the WHO recommended it (very low certainty of evidence) as the preferred treatment option for
224 fluoroquinolone-susceptible MDR/RR-TB in 2022 guidelines, even if the trial included also
225 participants with fluoroquinolone-resistant TB.[28] The NExT trial supports the potential of
226 bedaquiline, linezolid (600 mg daily) and fluoroquinolones to shorten MDR/RR-TB treatment to
227 six months.[31] An interim analysis of the BEAT-Tuberculosis trial with bedaquiline, linezolid
228 and delamanid for 6 months showed also high efficacy with 87% obtaining a favourable
229 outcome.[32] The MDR-END trial, using a non-bedaquiline based regimen with delamanid,
230 linezolid, levofloxacin and pyrazinamide for 9-12 months, showed 75% success and the regimen
231 was non-inferior to a 20-24 month regimen based on WHO 2014 MDR-TB guidelines.[33, 34]
232 **Table 2** shows completed and ongoing trials not yet published concerning treatment of
233 MDR/RR-TB.

234 Unfortunately, despite all progress with new regimens, the scarcity of drug resistance testing
235 against bedaquiline, linezolid, pretomanid, delamanid, and other key drugs is a substantial threat

236 to all the progress made in the treatment of MDR/RR-TB.[35] The lack of user-friendly,
237 standardized phenotypic drug susceptibility testing limits not only the scale-up of diagnostics,
238 but also undermines the trust of treating physicians in their implementation in clinical practice. It
239 is crucial to implement widespread routine surveillance systems for drug resistance.[36]
240 Moreover, drugs included in these regimens are not accessible everywhere and their availability
241 is jeopardized by unacceptably high costs in many countries.[37]

242

243 **Treatment of MDR/RR and fluoroquinolone-resistant TB**

244 Challenges that clinicians face when managing patients with pre extensively drug-resistant (pre-
245 XDR) TB, defined as RR/MDR-TB with additional fluoroquinolone resistance, include limited
246 efficacy with current regimens, a high adverse event profile, unaffordable costs for most settings,
247 and the potential to amplify drug resistance given the limited availability of registered novel
248 drugs.[38] The only ongoing trial is reported in **Table 3**. The BEAT-India trial specifically
249 recruited persons with pre-XDR-TB and used a six to nine-month four-drug regimen
250 (bedaquiline, linezolid at 600 mg daily, clofazimine, and delamanid), 139/153 participants (91%)
251 had a favourable outcome, though linezolid-associated toxicity was considerable.[39] Over half
252 of the participants developed myelosuppression (85, 52%) or neurotoxicity (69, 42%) of any
253 grade, although 34 patients were able to take a lower (300 mg) dose of linezolid. NiX-TB and
254 ZeNix trials used a three-drug 6 months BPaL regimen in pre-XDR-TB or MDR-TB with
255 previous failure (linezolid was dosed 1200 mg daily for 6 months in NiX-TB and 600 mg or
256 1200 mg daily for 2 or 6 months in ZeNix). Neither study had a control arm and the number of
257 participants included was relatively small. Nix-TB showed ~90% favourable outcome rate in 109
258 participants, with 81% experiencing peripheral neuropathy and 48% myelosuppression. ZeNix

259 confirmed the efficacy results (favourable outcome ranged between 84% and 93% across
260 different linezolid doses groups) and the risk-benefit ratio seemed in favour of the group that
261 received linezolid at 600mg daily for six months. Nine participants had baseline phenotypic
262 bedaquiline resistance, of whom six had a favourable outcome.[40, 41] The BPaL regimen can
263 be prescribed in case of proven fluoroquinolone resistance, according to WHO recommendations
264 (very low certainty of evidence).[42] The optimal linezolid dosing posology remains to be
265 established, as current WHO recommended dosing (600 mg daily throughout the treatment) is
266 based on very low certainty of evidence; ongoing efforts may inform policies on
267 reduced/intermittent linezolid administration[43, 44]. In patients with more extensive disease and
268 with unfavourable linezolid pharmacokinetics (sub-optimal linezolid levels relative to minimal
269 inhibitory concentration (MIC)),[45] there are concerns about the amplification of resistance,
270 even if evidence is still lacking. Moreover, monitoring linezolid side effects outside clinical trial
271 settings in high-endemic, low-resource areas may be challenging.

272 In summary, the available findings seem to indicate that a six to nine-month, three- to four-drug
273 regimen to treat fluoroquinolone-resistant MDR/rifampicin-resistant disease is feasible.
274 Although there is no solid evidence base, where appropriate (multiple poor prognostic features),
275 it would be reasonable for clinicians to opt for a four-drug regimen (i.e. bedaquiline-linezolid-
276 delamanid-clofazimine as in the BEAT-India regimen) or to extend the duration of the regimen
277 in case of culture positivity at the four-month time point when using a six-month regimen.
278 Overall, it is imperative that capacity for drug-susceptibility testing of Group A drugs
279 (fluoroquinolones, bedaquiline and linezolid), and pretomanid, is urgently developed and rolled
280 out. Concerningly, emerging bedaquiline resistance acquisition has been reported in
281 programmatic setting in South Africa, Moldova and other countries.[46–49]

282

283 **Host-directed therapy**

284 Host-directed therapy (HDT) for TB may either boost host defence ('antimicrobial') or control
285 an exuberant inflammatory phenotype ('anti-inflammatory'). Determining the correct timing of
286 HDT is a challenge. It is equally complicated to identify underlying TB endotypes, defined as
287 distinct immune, epigenetic, metabolic, molecular and transcriptional profiles. In addition,
288 recognised immune risk factors include Mendelian susceptibility to mycobacteria, untreated
289 HIV-1 infection, or TNF inhibitors use. In HIV-1 infection, provision of antiretroviral therapy
290 reduces individual risk for developing TB by 60-80% and reduces mortality, and is thus the most
291 effective HDT widely in use. Conversely, excessive dysregulated immune responses may
292 contribute to tissue damage and even death, such as in tuberculous meningitis, or HIV-
293 tuberculosis immune reconstitution inflammatory syndrome (TB-IRIS).

294 Whilst there has been considerable activity recently on preclinical evaluation of HDT, clinical
295 trial evidence is lacking. Interferon-gamma modestly increased bacterial clearance and resolution
296 of fever in patients with cavitary TB in a single randomized-controlled trial,[50] and TNF- and
297 interleukin-1 antagonists have shown to be effective in steroid-refractory paradoxical
298 reactions.[51, 52] Vitamin D3 potentially has both antimicrobial and anti-inflammatory actions
299 through promotion of autophagy and the induction of antimicrobial cathelicidin:[53] however,
300 clinical trial evidence of the benefit of systematic addition of vitamin D3 has been modest or
301 non-existent. Metformin therapy of diabetes mellitus associates epidemiologically with benefit,
302 but did not lead to earlier sputum conversion in a recent trial.[54] A type 4 phosphodiesterase
303 inhibitor and everolimus, a mTOR inhibitor, both modestly enhanced recovery of lung function
304 at end of therapy in a recent trial in South Africa.[55] The clearest evidence of anti-inflammatory

305 benefit exists for corticosteroids, which are associated with 30% lower mortality of HIV-1
306 uninfected TB meningitis,[56] and reduce constriction and hospitalization in TB pericarditis,[57]
307 and both prevent and improve outcome of TB-IRIS.[58, 59] However, this benefit may vary
308 according to different patient genotypes (i.e. leukotriene A(4) hydrolase) and pro-inflammatory
309 cytokine concentrations (i.e. in cerebrospinal fluid of TB meningitis patients).[60, 61]

310

311 **Pharmacokinetics and pharmacogenomics**

312 Advances in pharmacokinetics have accelerated the pace of TB drug development. In a salient
313 example, pharmacometric analyses of two clinical trials optimized rifapentine dosing from an
314 initial posology of 10 mg/kg daily to a fixed 1200 mg daily dose of rifapentine as part of the
315 newly-approved four-month regimen.[11, 12, 62] While pharmacokinetic studies have
316 demonstrated that rifampicin exposure increases at least dose-proportionally,[63, 64] and that
317 higher rifampicin doses exhibit dose- and exposure-response relationships,[65, 66] clinical trials
318 have yet to confirm whether treatment shortening is possible with high-dose rifampicin (**Table**
319 **1**). [16] The pharmacokinetic analysis of SHINE and results from a separate cohort study
320 indicated substantially reduced drug exposures in children in lower weight bands and in those
321 who transition onto adult doses (≥ 25 kg), underlining the need for doses to account for the higher
322 mg/kg requirement of smaller individuals.[67, 68] Despite significant gains in treatment
323 shortening for adults, adolescents, and children with DS-TB, pharmacokinetic studies suggest
324 that treatment approaches tailored to patient characteristics may be achievable.

325 Pharmacogenetic evaluations have not yet gained guideline endorsements in the treatment for
326 TB. The best described pharmacogenetic signal to date, for isoniazid acetylator status, has been

327 considered—but not recommended—by the WHO to inform the use of high-dose isoniazid for
328 the treatment of DR-TB for rapid acetylators.[69, 70] The recent development of a cartridge-
329 based multiplex quantitative PCR assay on the GeneXpert platform that differentiates NAT2
330 acetylator genotype signals raises hope that the personalization of treatment, based on host
331 genetic polymorphisms, may be within grasp.[71]

332

333 **Future research priorities**

334 There remains a pressing need to find well-tolerated, safe, short regimens for both DS and DR-
335 TB,[11, 29] including in particular a better-tolerated alternative for linezolid. Cure of most non-
336 severely affected patients with a two-month duration of treatment may be achievable. Long-
337 acting injectable drugs also have transformative potential, for both prevention and treatment of
338 TB. In parallel with the quest for new regimens, it is important to evaluate strategic, more
339 individualised, treatment approaches, or individual risk-based strategy such as those tested in the
340 TRUNCATE-TB trial.[17] Efficient testing of multiple new regimens requires identification of a
341 biomarker that is a reliable surrogate for relapse-free cure.[72] This would accelerate the
342 identification and advancement of promising regimens to testing in definitive trials, as well as
343 guide physicians decisions to individualise treatments.[73] Testing adjunctive host-directed
344 therapies, with the goals of enhancing bacterial clearance and minimising post-tuberculosis lung
345 damage, is an important but neglected research direction. Understanding TB endotypes may
346 enable a stratified approach to use such host-directed agents.[74, 75]

347 Implementation research remains critically important to evaluate and optimise outcomes in
348 programmatic settings. There is a need to improve treatment outcome definitions based on long-

349 term outcome benchmarks.[76] Research on the optimal approaches to roll out molecular
350 diagnostic drug susceptibility tests accompanying the availability of new regimens is important
351 to ensure that affected patients receive appropriate therapy.[35] Barriers accessing new drugs
352 (including rifapentine) and regimens are significant, [77, 78] and there is a need for research into
353 how these can be overcome to ensure rapid translation of new findings into practice. This
354 particularly applies to special populations, such as children of all ages and pregnant women:
355 inclusion of these groups in future clinical trials should be prioritized. **Table 4** summarizes
356 research priorities.

357 **Conclusions**

358 The last two decades have seen major changes in the management of TB. The availability of new
359 compounds, coupled with renewed interest in TB regimen development, has led to impressive
360 achievements which will have to be sustained in the coming years. While the focus in recent
361 years has been in treatment shortening with new drug combinations, future aims may include
362 improving current regimens by increasing the quality of supporting evidence (including
363 operational and programmatic data), reducing toxicity and optimizing efficacy, for instance by
364 enhancing pharmacokinetic properties, identifying optimal HDT, and further individualizing
365 regimens. In parallel, future efforts should be directed to protect these recent advances by
366 preventing and identifying the selection of drug resistance and providing widespread, affordable,
367 patient-centred access to new treatment options for all people affected by TB.

368 **Tables**

369

370 **Table 1: Registered, unpublished clinical trials for the treatment of drug-susceptible**
 371 **tuberculosis (as of July 6th, 2023).**

372

Therapeutic approach	Trial (adult TB patients)	Experimental regimen(s)	Clinical trials registration	Phase	Status
Optimizing rifampicin	IMAGINE-TBM	High-dose R and H for TB meningitis	NCT05382742	II	In preparation
	INTENSE-TBM	High-dose R and high-dose Lzd for TB meningitis	NCT04145258	III	In preparation
	ReDEFINE	High-dose R for TB meningitis	NCT02169882	II	Enrolling
	STEP2C	High-dose R and Mfx for 3 or 4 months	NCT05807399	IIC	Enrolling
	HARVEST	High-dose R for TB meningitis	ISRCTN15668391	III	Enrolling
	SURE	High-dose R, H, Z + Lfx (+/- aspirin) for children with TB meningitis	ISRCTN40829906	III	Enrolling
	RIFASHORT	Higher dose R (to 1800 mg/d) – 4 months	NCT0258152	III	Completed
Regimens including	CRUSH-TB	Bdq+Mfx+Z+Rbt or Dlm – 4 months	NCT05766267	IIC	Final preparation

new drugs	DECODE	16 weeks of experimental of Delpazolid at different doses associated with Bdq+Dlm+Mfx	NCT04550832	II	Enrolling
	Safety and Efficacy of 4-month Regimen of OPC-167832+Dlm+Bdq		NCT05221502	II	Enrolling
	CLO-FAST (ACTG A5362)	Cfz+Rpt+HZE – 13-17 weeks	NCT04311502	IIC	Enrolling
	SUDOCU	Bdq+Dlm+Mfx vs. Bdq+Dlm+Mfx+Sutezolid (3 dosages)	NCT03959566	II	Completed
	SimpliciTB	Bdq+Ptm+Mfx+Z – 4 months	NCT03338621	III	Completed

373 R = rifampicin, H = isoniazid, Lzd = linezolid, TB = tuberculosis, Z = pyrazinamide, Lfx = levofloxacin,
374 Mfx = moxifloxacin, Bdq = bedaquiline, Pa = pretomanid, Dlm = delamanid, Rbt = rifabutin, Cfz =
375 clofazimine.

376 **Table 2. Recently completed and ongoing, unpublished trials on rifampicin-resistant tuberculosis treatment (excluding**
 377 **fluoroquinolone-resistant tuberculosis) (as of July 6th, 2023).**

Trial	Phase	Control Arm	Country	Experimental treatment regimen(s)	Treatment duration (months)	Notes	Clinicaltrials.gov identifier
Recently completed trials							
OptiQ	II	No	Peru, South Africa	Lfx 11, 14, 17 or 20 mg/Kg plus background regimen	6	750-1000 mg Lfx qd achieved target AUC/MIC	NCT01918397
SimpliciTB	II	Yes (only for DS-TB)	8 countries	Bdq, Pa, Z, Mfx	4	Not non-inferior to HRZE; no comparator for MDR-TB arm	NCT03338621
SUDOCU	II	No	South Africa, Tanzania	Sutezolid, Bdq, Dlm, Mfx	3	regimen well tolerated	NCT03959566
TREAT-TB (India)	III	No	India	Bdq, Dlm, Lzd and Cfz	6-9 months	91% favourable outcomes	CTRI/2019/01/017310

Ongoing trials

ACTG A5356	II	No	Multicountry	Bdq, Cfz, Dlm, and Lzd (different posologies)	6	TIW dosing of Lzd	NCT05007821
DECODE	II	No	South Africa, Tanzania	Delpazolid, Bdq, Dlm, Mfx	3 months	Dose-ranging and tolerability	NCT04550832
DRAMATIC	II	No	Multicountry	Lfx, Bdq, Lzd, Dlm, and Cfz	4 to 9	Duration-randomized clinical trial	NCT03828201
BEAT Tuberculosis	III	Yes	South Africa	Bdq, Dlm, and Lzd, plus Lfx or Cfz	6	Experimental regimen adapted according to rapid molecular testing	NCT04062201
endTB[43]	III	Yes	Multicountry	Bdq, Mfx, Lzd, and Z; or Bdq, Cfz, Lfx, Lzd, and Z; or Bdq, Dlm, Lfx, Lzd, and Z; or Dlm, Cfz, Lfx, Lzd, and Z; or Dlm, Cfz, Mfx, and Z	9	Trial implementing Bayesian adaptive randomization	NCT02754765
TB-TRUST	III	Yes	China	Lfx, Lzd, Cs, and Z (or Cfz if resistant to Z)	6 to 9	No follow-up available	NCT03867136
TB TRUST Plus	III	No	China	Bdq, Z, Lzd, Cs, Cfz	6-9 months	Regimen guided by Z susceptibility testing	NCT04717908
InDEX	IV	Yes	South Africa	Individualized regimens	NS	WGS-derived	NCT03237182

						individualized regimen	
PROSPECT	IV	No	China	Cfz, Cs, Lfx, Lzd, and Pto; or Bdq, Cfz, Cs, Lfx, and Lzd	6 (first regimen), 9 (second regimen)	No follow-up available	NCT05306223
GRACE-TB	NA	Yes	China	Individualized regimens	NS	Individualized regimen guided by rapid molecular tests	NCT03604848
SMARTT	NA	Yes	South Africa	WGS-guided regimen	NS	Individualized regimen guided by rapid molecular tests	NCT05017324

378 DS-TB = drug-susceptible tuberculosis, Lfx = levofloxacin, Bdq = bedaquiline, Pa = pretomanid, Z = pyrazinamide, Mfx = moxifloxacin, HRZE =
379 isoniazid + rifampicin + pyrazinamide + ethambutol, MDR-TB = multidrug-resistant tuberculosis, Dlm = delamanid, Lzd = linezolid, Cfz =
380 clofazimine, Cs = cycloserine, Pto = prothionamide, NS = not specified, NA = not applicable, TIW = three times weekly, WGS = whole genome
381 sequencing.

382

383 **Table 3. Recently completed and ongoing, unpublished trials on rifampicin-resistant, fluoroquinolone-resistant tuberculosis**
 384 **treatment (as of July 6th, 2023).**

385

Name of trial	Regimen	Duration of trial regimen	Site	Inclusion criteria	Status	Participants enrolled
endTB-Q [44] (NCT03896685)	Bdq-Lzd-Dlm-Cfz	24-39 weeks	India, Kazakhstan, Lesotho, Pakistan, Peru and Vietnam	Pre-XDR TB (FQ-resistant TB) in ≥ 15 year-old with pulmonary tuberculosis according to a validated rapid molecular test	ongoing	Enrolment completed in March 2023

386 Bdq = bedaquiline, Lzd = linezolid, Dlm = delamanid, Cfz = clofazimine, Pre-XDR TB = pre-extensively drug resistant tuberculosis, FQ =
 387 fluoroquinolone.

388 **Table 4. Research priorities**

389

<p>New drugs and regimens</p> <ul style="list-style-type: none">• Shorter, well-tolerated and safer regimens for drug-susceptible and drug-resistant tuberculosis• Sustained early development pipeline of new anti-TB compounds, including long-acting injectable drugs
<p>Tailored treatment approach</p> <ul style="list-style-type: none">• Treatment strategies based on more individualised treatment, including the identification of criteria to define TB severity• Surrogate biomarker of relapse-free cure
<p>Host-directed therapies</p> <ul style="list-style-type: none">• Improved understanding of TB endotypes• Host-directed therapies to accelerate bacterial clearance or reduce post-TB morbidity
<p>Implementation research</p> <ul style="list-style-type: none">• Identify barriers to access to new drugs (including special populations, for instance children)• Optimise rollout of drug-susceptibility testing for new drugs (including rapid molecular tests and evidence on relationship between phenotypic-genotypic resistance profiles)

390

391 **Author contributions:**

392 **IM** and **LG** conceptualized and supervised the review process, wrote part of the initial draft,
393 revised the full draft, and approved the final manuscript; all other authors wrote part of the initial
394 draft, revised the full draft, and approved the final manuscript.

395

396 **Transparency declaration:**

397 *Conflict of interest disclosure:*

398 **IM, MB, DC, KD, GG, CRH, YK, CLa, CLi, HM, GT, ZU, RvC, GEV, RJW, and LG** have
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