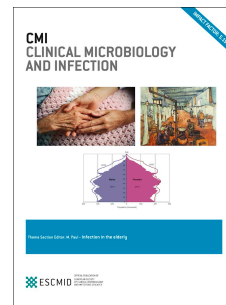


# Journal Pre-proof

Recent advances in the treatment of tuberculosis

Ilaria Motta, Martin Boeree, Dumitru Chesov, Keertan Dheda, Gunar Günther, C. Robert Horsburgh JR, Yousra Kherabi, Christoph Lange, Christian Lienhardt, Helen M. McIlleron, Nicholas I. Paton, Helen R. Stagg, Guy Thwaites, Zarir Udwadia, Reinout Van Crevel, Gustavo E. Velásquez, Robert J. Wilkinson, Lorenzo Guglielmetti



PII: S1198-743X(23)00339-7

DOI: <https://doi.org/10.1016/j.cmi.2023.07.013>

Reference: CMI 3362

To appear in: *Clinical Microbiology and Infection*

Received Date: 30 April 2023

Revised Date: 12 July 2023

Accepted Date: 18 July 2023

Please cite this article as: Motta I, Boeree M, Chesov D, Dheda K, Günther G, Horsburgh JR CR, Kherabi Y, Lange C, Lienhardt C, McIlleron HM, Paton NI, Stagg HR, Thwaites G, Udwadia Z, Van Crevel R, Velásquez GE, Wilkinson RJ, Guglielmetti L, Recent advances in the treatment of tuberculosis, *Clinical Microbiology and Infection*, <https://doi.org/10.1016/j.cmi.2023.07.013>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2023 Published by Elsevier Ltd on behalf of European Society of Clinical Microbiology and Infectious Diseases.

# 1 Recent advances in the treatment of tuberculosis

2

## 3 Title page

4

## 5 Authors:

6 Ilaria Motta<sup>1\*</sup>, Martin Boeree<sup>2</sup>, Dumitru Chesov<sup>3,4,5</sup>, Keertan Dheda<sup>6,7,8</sup>, Gunar Günther<sup>9,10</sup>, C.  
7 Robert Horsburgh JR<sup>11</sup>, Yousra Kherabi<sup>12\*</sup>, Christoph Lange<sup>13,14,15,16</sup>, Christian Lienhardt<sup>17,18</sup>,  
8 Helen M. McIlleron<sup>19,20</sup>, Nicholas I. Paton<sup>18,21</sup>, Helen R. Stagg<sup>22</sup>, Guy Thwaites<sup>23,24</sup>, Zarir  
9 Udawadia<sup>25</sup>, Reinout Van Crevel<sup>2,24\*</sup>, Gustavo E. Velásquez<sup>26,27</sup>, Robert J. Wilkinson<sup>28,29</sup>, Lorenzo  
10 Guglielmetti<sup>30,31\*</sup>

11

## 12 Affiliations:

13 \*These authors are members of the Study Group on Mycobacteria (ESGMYC) of the European  
14 Society of Clinical Microbiology and Infectious Diseases (ESCMID).

15

- 16 1. Médecins Sans Frontières, Manson Unit, United Kingdom
- 17 2. Department of Internal Medicine and Radboud Center for Infectious Diseases, Radboud  
18 University Medical Center, Nijmegen, the Netherlands
- 19 3. Chiril Draganiuc Phthisiopneumology Institute, Chisinau, Moldova
- 20 4. Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, Moldova

- 21 5. Research Center Borstel, Borstel, Germany
- 22 6. Centre for Lung Infection and Immunity, Division of Pulmonology, Department of  
23 Medicine and UCT Lung Institute and South African MRC/UCT Centre for the Study of  
24 Antimicrobial Resistance, University of Cape Town, Cape Town, South Africa
- 25 7. Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, Cape  
26 Town, South Africa
- 27 8. Faculty of Infectious and Tropical Diseases, Department of Immunology and Infection,  
28 London School of Hygiene and Tropical Medicine, London, United Kingdom
- 29 9. Department of Pulmonology and Allergology, Inselspital, Bern University Hospital, Bern,  
30 Switzerland
- 31 10. Department of Medical Sciences, Faculty of Health Sciences, University of Namibia,  
32 Windhoek, Namibia
- 33 11. Departments of Epidemiology, Biostatistics, Global Health and Medicine, Boston  
34 University, Boston MA USA
- 35 12. Infectious, and Tropical Diseases Department, Bichat-Claude Bernard Hospital, Assistance  
36 Publique-Hôpitaux de Paris, Paris, France
- 37 13. Division of Clinical Infectious Diseases, Research Center Borstel, Borstel, Germany
- 38 14. German Center for Infection Research (DZIF), Respiratory Medicine & International  
39 Health, University of Lübeck, Lübeck, Germany
- 40 15. University of Lübeck, Lübeck, Germany
- 41 16. Baylor College of Medicine and Texas Children's Hospital, Houston, Texas, USA
- 42 17. Institut de Recherche pour le Développement, Montpellier, France
- 43 18. London School of Hygiene and Tropical Medicine, London, United Kingdom

- 44 19. Division of Clinical Pharmacology, Department of Medicine, University of Cape Town,  
45 Cape Town, South Africa
- 46 20. Wellcome Centre for Infectious Diseases Research in Africa (CIDRI-Africa), Institute of  
47 Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South  
48 Africa
- 49 21. Department of Medicine, National University of Singapore
- 50 22. Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical  
51 Medicine, London, United Kingdom
- 52 23. Oxford University Clinical Research Unit, Ho Chi Minh city, Vietnam
- 53 24. Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, Oxford  
54 University, Oxford, United Kingdom
- 55 25. Hinduja Hospital & Research Centre, Mumbai, India.
- 56 26. UCSF Center for Tuberculosis, University of California, San Francisco, San Francisco,  
57 California, USA
- 58 27. Division of HIV, Infectious Diseases, and Global Medicine, University of California, San  
59 Francisco, San Francisco, California, USA
- 60 28. Francis Crick Institute, London, NW1 1AT, United Kingdom
- 61 29. Department of Infectious Diseases, Imperial College London, W12 0NN, United Kingdom
- 62 30. Sorbonne Université, INSERM, U1135, Centre d'Immunologie et des Maladies  
63 Infectieuses (CIMI-Paris), Paris, France
- 64 31. AP-HP Sorbonne Université, Hôpital Pitié-Salpêtrière, Laboratoire de Bactériologie-  
65 Hygiène, Centre National de Référence des Mycobactéries et de la Résistance des  
66 Mycobactéries aux Antituberculeux, Paris, France

67

68 **Word Count:** 3083; Figures/Tables: 4; References: 78

69

70 **Corresponding Author:** Lorenzo Guglielmetti, Pitié-Salpêtrière Hospital, Laboratoire de  
71 Bactériologie-Hygiène, AP-HP, Centre National de Référence des Mycobactéries et de la  
72 Résistance des Mycobactéries aux Antituberculeux, 91 Boulevard de l'hôpital, Paris Cedex 13  
73 75634, France. E-mail: lorenzo.guglielmetti@aphp.fr

74

75 **Abstract:**

76 **Background**

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

86 **Objectives**

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

## 90 **Sources**

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

## 95 **Content**

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

## 102 **Implications**

103 Future research should be directed to individualize regimens and protect these recent  
104 breakthroughs by preventing and identifying the selection of drug resistance and providing  
105 widespread, affordable, patient-centered access to new treatment options for all people affected by  
106 tuberculosis.

107 **Main article**

108

109 **Introduction**

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

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

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

## 121 **Treatment of drug-susceptible TB**

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

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

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



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

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

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

167 diverse populations. Of note, the definition of TB severity is heterogeneous among the  
168 aforementioned studies and would greatly benefit from consensus on validated criteria.[8, 9]

169

### 170 **Treatment of isoniazid-resistant, rifampicin-susceptible TB**

171 Isoniazid resistance without concurrent rifampicin resistance is the most common type of *M.*  
172 *tuberculosis* resistance worldwide, present among an estimated 10.6% of all TB cases in 2019.[18]

173 In 2018, WHO recommended a regimen consisting of six months of rifampicin, ethambutol,  
174 pyrazinamide, and levofloxacin to treat isoniazid-resistant TB, following an individual patient data

175 (IPD) meta-analysis containing 3,923 patients with isoniazid-resistant, rifampicin-susceptible TB

176 which indicated that the addition of a fluoroquinolone, compared to six months of standard

177 treatment with or without isoniazid, increased the likelihood of treatment success (adjusted odds

178 ratio: 2,8 [95% confidence interval: 1,1-7,3]).[12, 19] This recommendation was, however,

179 conditional, based on a very low certainty of evidence. In instances of noncavitary disease, low

180 bacillary burden, or pyrazinamide toxicity, European-American guidelines have suggested that

181 pyrazinamide may be given only during the first two months of treatment, provided the

182 fluoroquinolone used is later-generation.[20] Patients with fluoroquinolone resistance or

183 contraindications are generally recommended to be treated with rifampicin, ethambutol and

184 pyrazinamide only for six months. However, these two latter recommendations lack clinical trial

185 evidence and are based on expert opinion. When additional drug resistance is detected or highly

186 likely, individualised regimens are needed.

187 At the time of the WHO guidelines, there was no clear evidence if using high-dose isoniazid within

188 such regimens was beneficial. This is likely to be influenced by the resistance mutation(s) present

189 (for example, mutations in *inhA* and its promoter are usually associated with lower-level resistance  
190 than *katG* mutations) and the patient's acetylase status.[21] There is recognition that isoniazid  
191 may be included in regimens simply due to the use of fixed-dose combination pills. As the majority  
192 of the evidence for the treatment of isoniazid-resistant TB derives from secondary observational  
193 data, bespoke clinical trials (potentially drawing from emulated target trials) would be needed to  
194 strengthen the evidence base.[22]

195

### 196 **Treatment of MDR/RR-TB**

197 In 2018, the results of an IPD analysis with more than 12,000 patients with MDR/RR-TB, and an  
198 observational cohort about the impact of bedaquiline on TB mortality in South Africa, led to  
199 substantial changes in the recommendations for management of patients with MDR/RR-  
200 TB.[20,21] The recommendation to change from 18-20 months of treatment to an all-oral, shorter,  
201 9-12 month regimen, as well as the recommendation against the use of injectables (namely  
202 capreomycin and kanamycin), marked a drastic shift in the management of patients with MDR/RR-  
203 TB.[25, 26] STREAM Stage 2 trial was a phase III trial that compared a nine-month injectable  
204 containing regimen (four months of kanamycin, isoniazid, prothionamide, and nine months of  
205 moxifloxacin, clofazimine, ethambutol, pyrazinamide) with a nine-month all-oral regimen where  
206 bedaquiline replaced kanamycin. The primary endpoint, favourable treatment outcome, was  
207 reached with the injectable-containing regimen in 71% of participants and with the all-oral regimen  
208 in 83%.[27] Most importantly, grade 3/4 hearing loss was documented in only 2% of participants  
209 receiving the all-oral regimen vs. 9% in the injectable-containing regimen. The WHO  
210 recommended the nine- to twelve-month regimen with bedaquiline (and the option of replacing  
211 ethionamide with linezolid given for two months) in 2022 for the treatment of MDR/RR-TB

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

230 Unfortunately, despite all progress with new regimens, the scarcity of drug resistance testing  
231 against bedaquiline, linezolid, pretomanid, delamanid, and other key drugs is a substantial threat  
232 to all the progress made in the treatment of MDR/RR-TB.[35] The lack of user-friendly,  
233 standardized phenotypic drug susceptibility testing limits not only the scale-up of diagnostics, but  
234 also undermines the trust of treating physicians in their implementation in clinical practice. It is

235 crucial to implement widespread routine surveillance systems for drug resistance.[36] Moreover,  
236 drugs included in these regimens are not accessible everywhere and their availability is jeopardized  
237 by unacceptably high costs in many countries.[37]

238

### 239 **Treatment of MDR/RR and fluoroquinolone-resistant TB**

240 Challenges that clinicians face when managing patients with pre extensively drug-resistant (pre-  
241 XDR) TB, defined as RR/MDR-TB with additional fluoroquinolone resistance, include limited  
242 efficacy with current regimens, a high adverse event profile, unaffordable costs for most settings,  
243 and the potential to amplify drug resistance given the limited availability of registered novel  
244 drugs.[38] The only ongoing trial is reported in **Table 3**. The BEAT-India trial specifically  
245 recruited persons with pre-XDR-TB and used a six to nine-month four-drug regimen (bedaquiline,  
246 linezolid at 600 mg daily, clofazimine, and delamanid), 139/153 participants (91%) had a  
247 favourable outcome, though linezolid-associated toxicity was considerable.[39] Over half of the  
248 participants developed myelosuppression (85, 52%) or neurotoxicity (69, 42%) of any grade,  
249 although 34 patients were able to take a lower (300 mg) dose of linezolid. NiX-TB and ZeNix  
250 trials used a three-drug 6 months BPaL regimen in pre-XDR-TB or MDR-TB with previous failure  
251 (linezolid was dosed 1200 mg daily for 6 months in NiX-TB and 600 mg or 1200 mg daily for 2  
252 or 6 months in ZeNix). Neither study had a control arm and the number of participants included  
253 was relatively small. Nix-TB showed ~90% favourable outcome rate in 109 participants, with 81%  
254 experiencing peripheral neuropathy and 48% myelosuppression. ZeNix confirmed the efficacy  
255 results (favourable outcome ranged between 84% and 93% across different linezolid doses groups)  
256 and the risk-benefit ratio seemed in favour of the group that received linezolid at 600mg daily for  
257 six months. Nine participants had baseline phenotypic bedaquiline resistance, of whom six had a

258 favourable outcome.[40, 41] The BPaL regimen can be prescribed in case of proven  
259 fluoroquinolone resistance, according to WHO recommendations (very low certainty of  
260 evidence).[42] The optimal linezolid dosing posology remains to be established, as current WHO  
261 recommended dosing (600 mg daily throughout the treatment) is based on very low certainty of  
262 evidence; ongoing efforts may inform policies on reduced/intermittent linezolid administration[43,  
263 44]. In patients with more extensive disease and with unfavourable linezolid pharmacokinetics  
264 (sub-optimal linezolid levels relative to minimal inhibitory concentration (MIC)),[45] there are  
265 concerns about the amplification of resistance, even if evidence is still lacking. Moreover,  
266 monitoring linezolid side effects outside clinical trial settings in high-endemic, low-resource areas  
267 may be challenging.

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

278

279 **Host-directed therapy**

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

290 Whilst there has been considerable activity recently on preclinical evaluation of HDT, clinical trial  
291 evidence is lacking. Interferon-gamma modestly increased bacterial clearance and resolution of  
292 fever in patients with cavitary TB in a single randomized-controlled trial,[50] and TNF- and  
293 interleukin-1 antagonists have shown to be effective in steroid-refractory paradoxical  
294 reactions.[51, 52] Vitamin D3 potentially has both antimicrobial and anti-inflammatory actions  
295 through promotion of autophagy and the induction of antimicrobial cathelicidin:[53] however,  
296 clinical trial evidence of the benefit of systematic addition of vitamin D3 has been modest or non-  
297 existent. Metformin therapy of diabetes mellitus associates epidemiologically with benefit, but did  
298 not lead to earlier sputum conversion in a recent trial.[54] A type 4 phosphodiesterase inhibitor  
299 and everolimus, a mTOR inhibitor, both modestly enhanced recovery of lung function at end of  
300 therapy in a recent trial in South Africa.[55] The clearest evidence of anti-inflammatory benefit  
301 exists for corticosteroids, which are associated with 30% lower mortality of HIV-1 uninfected TB  
302 meningitis,[56] and reduce constriction and hospitalization in TB pericarditis,[57] and both

303 prevent and improve outcome of TB-IRIS.[58, 59] However, this benefit may vary according to  
304 different patient genotypes (i.e. leukotriene A(4) hydrolase) and pro-inflammatory cytokine  
305 concentrations (i.e. in cerebrospinal fluid of TB meningitis patients).[60, 61]

306

### 307 **Pharmacokinetics and pharmacogenomics**

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

321 Pharmacogenetic evaluations have not yet gained guideline endorsements in the treatment for TB.  
322 The best described pharmacogenetic signal to date, for isoniazid acetylator status, has been  
323 considered—but not recommended—by the WHO to inform the use of high-dose isoniazid for the  
324 treatment of DR-TB for rapid acetylators.[69, 70] The recent development of a cartridge-based



325 multiplex quantitative PCR assay on the GeneXpert platform that differentiates NAT2 acetylator  
326 genotype signals raises hope that the personalization of treatment, based on host genetic  
327 polymorphisms, may be within grasp.[71]

328

### 329 **Future research priorities**

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

343 Implementation research remains critically important to evaluate and optimise outcomes in  
344 programmatic settings. There is a need to improve treatment outcome definitions based on long-  
345 term outcome benchmarks.[76] Research on the optimal approaches to roll out molecular  
346 diagnostic drug susceptibility tests accompanying the availability of new regimens is important to

347 ensure that affected patients receive appropriate therapy.[35] Barriers accessing new drugs  
348 (including rifapentine) and regimens are significant, [77, 78] and there is a need for research into  
349 how these can be overcome to ensure rapid translation of new findings into practice. This  
350 particularly applies to special populations, such as children of all ages and pregnant women:  
351 inclusion of these groups in future clinical trials should be prioritized. **Table 4** summarizes  
352 research priorities.

Journal Pre-proof

**353 Conclusions**

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

364 **Tables**

365

366 **Table 1: Registered, unpublished clinical trials for the treatment of drug-susceptible**  
 367 **tuberculosis (as of July 6<sup>th</sup>, 2023).**

368

Therapeutic approach	Trial (adult TB patients)	Experimental regimen(s)	Clinical trials registration	Phase	Status
<b>Optimizing rifampicin</b>	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
	CRUSH-TB	Bdq+Mfx+Z+Rbt or Dlm – 4 months	NCT05766267	IIC	Final preparation

<b>Regimens including new drugs</b>	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

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

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

<b>Trial</b>	<b>Phase</b>	<b>Control Arm</b>	<b>Country</b>	<b>Experimental treatment regimen(s)</b>	<b>Treatment duration (months)</b>	<b>Notes</b>	<b>Clinicaltrials.gov identifier</b>
<b>Recently completed trials</b>							
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 individualized regimen	NCT03237182
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

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

378



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

381

Name of trial	Regimen	Duration of trial regimen	Site	Inclusion criteria	Status	Participants enrolled
endTB-Q [44] (NCT038 96685)	Bdq-Lzd-Dlm- Cfz	24-39 weeks	India, Kazakhstan, Lesotho, Pakistan, Peru and Vietnam	Pre-XDR TB (FQ-resistant TB) in $\geq 15$ year-old with pulmonary tuberculosis according to a validated rapid molecular test	ongoing	Enrolment completed in March 2023

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

384 **Table 4. Research priorities**

385

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

386

387 **Author contributions:**

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

391

392 **Transparency declaration:**

393 *Conflict of interest disclosure:*

394 **IM, MB, DC, KD, GG, CRH, YK, CLa, CLi, HM, GT, ZU, RvC, GEV, RJW, and LG** have  
395 nothing to declare

396 **HRS** reports honoraria in 2018 for speaking at and attending an event organised by the Latvian  
397 Society Against Tuberculosis, which was sponsored by Otsuka and Johnson and Johnson; **NIP**  
398 has received grant funding paid to institution from Janssen, drug donation for trials from Pfizer  
399 and Sanofi, and speaker fees from Janssen.

400 *Funding:*

401 **GT** and **CLi** are supported by the Wellcome Trust. **HRS** is supported by the Medical Research  
402 Council (MRC), UK [MR/R008345/1].

403 **GEV** is supported the National Institute of Allergy and Infectious Diseases at the U.S. National  
404 Institutes of Health grant number K08 AI141740.

405 **RJW** is funded by the Francis Crick Institute which receives funding from Wellcome (CC2112),  
406 Cancer Research UK (CC2112) and the Medical Research Council (CC2112). He is also funded

407 by Wellcome (203135). For the purposes of open access, the author has applied a CC-BY public  
408 copyright licence to any author-accepted manuscript arising from this submission.

409 *Acknowledgements:*

410 **IM, LG** and **RvC** are part of the Study Group on Mycobacteria (ESGMYC) of the European  
411 Society of Clinical Microbiology and Infectious Diseases and would like to acknowledge the  
412 support from the Study Group.

Journal Pre-proof

413 **Bibliography:**

- 414 1. World Health Organization. Global tuberculosis report 2022. *Geneva. Licence: CC BY-NC-*  
415 *SA 3.0 IGO. 2022; .*
- 416 2. Fox W. Studies on the treatment of tuberculosis undertaken by the British Medical Research  
417 Council Tuberculosis Units, 1946–1986, with relevant subsequent publications. *Int J Tuberc*  
418 *Lung Dis* 1998; 280: 1200-a-1200.
- 419 3. Rustomjee R, Lienhardt C, Kanyok T, Davies GR, Levin J, Mthiyane T, Reddy C, Sturm  
420 AW, Sirgel FA, Allen J, Coleman DJ, Fourie B, Mitchison DA. A Phase II study of the  
421 sterilising activities of ofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis.  
422 *Int J Tuberc Lung Dis* 2008; 12: 128–138.
- 423 4. Conde MB, Efron A, Loreda C, De Souza GRM, Graça NP, Cezar MC, Ram M, Chaudhary  
424 MA, Bishai WR, Kritski AL, Chaisson RE. Moxifloxacin versus ethambutol in the initial  
425 treatment of tuberculosis: a double-blind, randomised, controlled phase II trial. *Lancet* 2009;  
426 373: 1183–1189.
- 427 5. Merle CS, Fielding K, Sow OB, Gninafon M, Lo MB, Mthiyane T, Odhiambo J, Amukoye  
428 E, Bah B, Kassa F, N’Diaye A, Rustomjee R, de Jong BC, Horton J, Perronne C, Sismanidis  
429 C, Lapujade O, Olliaro PL, Lienhardt C. A Four-Month Gatifloxacin-Containing Regimen  
430 for Treating Tuberculosis. *N Engl J Med* 2014; 371: 1588–1598.
- 431 6. Jindani A, Harrison TS, Nunn AJ, Phillips PPJ, Churchyard GJ, Charalambous S, Hatherill  
432 M, Geldenhuys H, McIlleron HM, Zvada SP, Mungofa S, Shah NA, Zizhou S, Magweta L,  
433 Shepherd J, Nyirenda S, van Dijk JH, Clouting HE, Coleman D, Bateson ALE, McHugh TD,  
434 Butcher PD, Mitchison DA. High-Dose Rifapentine with Moxifloxacin for Pulmonary  
435 Tuberculosis. *N Engl J Med* 2014; 371: 1599–1608.
- 436 7. Gillespie SH, Crook AM, McHugh TD, Mendel CM, Meredith SK, Murray SR, Pappas F,  
437 Phillips PPJ, Nunn AJ. Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive  
438 Tuberculosis. *N Engl J Med* 2014; 371: 1577–1587.
- 439 8. Imperial MZ, Nahid P, Phillips PPJ, Davies GR, Fielding K, Hanna D, Hermann D, Wallis  
440 RS, Johnson JL, Lienhardt C, Savic RM. A patient-level pooled analysis of treatment-  
441 shortening regimens for drug-susceptible pulmonary tuberculosis. *Nat Med* 2018; 24: 1708–  
442 1715.
- 443 9. Imperial MZ, Phillips PPJ, Nahid P, Savic RM. Precision-enhancing Risk Stratification  
444 Tools for Selecting Optimal Treatment Durations in Tuberculosis Clinical Trials. *Am J*  
445 *Respir Crit Care Med* 2021; : rccm.202101-01170C.
- 446 10. Te Brake LHM, de Jager V, Narunsky K, Vanker N, Svensson EM, Phillips PPJ, Gillespie  
447 SH, Heinrich N, Hoelscher M, Dawson R, Diacon AH, Aarnoutse RE, Boeree MJ,  
448 PanACEA Consortium. Increased bactericidal activity but dose-limiting intolerability at 50  
449 mg·kg<sup>-1</sup> rifampicin. *Eur Respir J* 2021; 58: 2000955.

- 450 11. Dorman SE, Nahid P, Kurbatova EV, Phillips PPJ, Bryant K, Dooley KE, Engle M,  
 451 Goldberg SV, Phan HTT, Hakim J, Johnson JL, Lourens M, Martinson NA, Muzanyi G,  
 452 Narunsky K, Nerette S, Nguyen NV, Pham TH, Pierre S, Purfield AE, Samaneka W, Savic  
 453 RM, Sanne I, Scott NA, Shenje J, Sizemore E, Vernon A, Waja Z, Weiner M, Swindells S, et  
 454 al. Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis. *N*  
 455 *Engl J Med* 2021; 384: 1705–1718.
- 456 12. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 4:  
 457 treatment - drug-susceptible tuberculosis treatment. *Geneva. Licence: CC BY-NC-SA 3.0*  
 458 *IGO. 2022; .*
- 459 13. Dooley KE, Hendricks B, Gupte N, Barnes G, Narunsky K, Whitelaw C, Smit T, Ignatius  
 460 EH, Friedman A, Dorman SE, Dawson R, Assessing Pretomanid for Tuberculosis (APT)  
 461 Study Team. Assessing Pretomanid for Tuberculosis (APT), a Randomized Phase 2 Trial of  
 462 Pretomanid-Containing Regimens for Drug-Sensitive Tuberculosis: 12-Week Results. *Am J*  
 463 *Respir Crit Care Med* 2023; 207: 929–935.
- 464 14. Eristavi M, Variava E, Haraka F. SimpliciTB Results and Hepatic Safety of Pretomanid  
 465 Regimens +/1 Pyrazinamide [OA-109]. *Presented at the 2023 Conference on Retroviruses*  
 466 *and Opportunistic Infections during Oral Abstracts Session-02 TB and Hepatitis. 20 Feb*  
 467 *2023; Seattle, Washington.*
- 468 15. Sputum-smear-negative pulmonary tuberculosis: controlled trial of 3-month and 2-month  
 469 regimens of chemotherapy. *Lancet* 1979; 1: 1361–1363.
- 470 16. Turkova A, Wills GH, Wobudeya E, Chabala C, Palmer M, Kinikar A, Hissar S, Choo L,  
 471 Musoke P, Mulenga V, Mave V, Joseph B, LeBeau K, Thomason MJ, Mboizi RB, Kapasa  
 472 M, van der Zalm MM, Raichur P, Bhavani PK, McIlleron H, Demers A-M, Aarnoutse R,  
 473 Love-Koh J, Seddon JA, Welch SB, Graham SM, Hesseling AC, Gibb DM, Crook AM.  
 474 Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children. *New England*  
 475 *Journal of Medicine* Massachusetts Medical Society; 2022; 386: 911–922.
- 476 17. Paton NI, Cousins C, Suresh C, Burhan E, Chew KL, Dalay VB, Lu Q, Kusmiati T, Balanag  
 477 VM, Lee SL, Ruslami R, Pokharkar Y, Djaharuddin I, Sugiri JJR, Veto RS, Sekaggya-  
 478 Wiltshire C, Avihingsanon A, Sarin R, Papineni P, Nunn AJ, Crook AM. Treatment Strategy  
 479 for Rifampin-Susceptible Tuberculosis. *N Engl J Med* Massachusetts Medical Society; 2023;  
 480 388: 873–887.
- 481 18. WHO. Global tuberculosis report 2020. *Geneva: World Health Organization 2020; :*  
 482 *Licence: CC BY-NC-SA 3.0 IGO.*
- 483 19. Fregonese F, Ahuja SD, Akkerman OW, Arakaki-Sanchez D, Ayakaka I, Baghaei P, Bang  
 484 D, Bastos M, Benedetti A, Bonnet M, Cattamanchi A, Cegielski P, Chien J-Y, Cox H,  
 485 Dedicoat M, Erkens C, Escalante P, Falzon D, Garcia-Prats AJ, Gegia M, Gillespie SH,  
 486 Glynn JR, Goldberg S, Griffith D, Jacobson KR, Johnston JC, Jones-López EC, Khan A,  
 487 Koh W-J, Kritski A, et al. Comparison of different treatments for isoniazid-resistant  
 488 tuberculosis: an individual patient data meta-analysis. *The Lancet Respiratory Medicine*  
 489 2018; 6: 265–275.

- 490 20. Nahid P, Mase SR, Migliori GB, Sotgiu G, Bothamley GH, Brozek JL, Cattamanchi A,  
491 Cegielski JP, Chen L, Daley CL, Dalton TL, Duarte R, Fregonese F, Horsburgh CR, Ahmad  
492 Khan F, Kheir F, Lan Z, Lardizabal A, Lauzardo M, Mangan JM, Marks SM, McKenna L,  
493 Menzies D, Mitnick CD, Nilsen DM, Parvez F, Peloquin CA, Raftery A, Schaaf HS, Shah  
494 NS, et al. Treatment of Drug-Resistant Tuberculosis. An Official ATS/CDC/ERS/IDSA  
495 Clinical Practice Guideline. *Am J Respir Crit Care Med* American Thoracic Society -  
496 AJRCCM; 2019; 200: e93–e142.
- 497 21. Dooley KE, Miyahara S, von Groote-Bidlingmaier F, Sun X, Hafner R, Rosenkranz SL,  
498 Ignatius EH, Nuermberger EL, Moran L, Donahue K, Swindells S, Vanker N, Diacon AH,  
499 the A5312 Study Team. Early Bactericidal Activity of Different Isoniazid Doses for Drug  
500 Resistant TB (INHindsight): A Randomized Open-label Clinical Trial. *Am J Respir Crit*  
501 *Care Med* 2020; : rccm.201910-19600C.
- 502 22. Stagg HR, Lipman MC, McHugh TD, Jenkins HE. Isoniazid-resistant tuberculosis: a cause  
503 for concern? *Int J Tuberc Lung Dis* 2017; 21: 129–139.
- 504 23. Collaborative Group for the Meta-Analysis of Individual Patient Data in MDRTB treatment,  
505 Ahmad N, Ahuja SD, Akkerman OW, Alffenaar JC, Anderson LF, Baghaei P, Bang D,  
506 Barry PM, Bastos ML, Behera D, Benedetti A, Bisson GP, Boeree MJ, Bonnet M, Brode SK,  
507 Brust JCM, Cai Y, Caumes E, Cegielski JP, Centis R, Chan PC, Chan ED, Chang KC,  
508 Charles M, Cirule A, Dalcolmo MP, D'Ambrosio L, de Vries G, Dheda K, et al. Treatment  
509 correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an  
510 individual patient data meta-analysis. *Lancet* 2018/09/15 ed. 2018; 392: 821–834.
- 511 24. Schnippel K, Ndjeka N, Maartens G, Meintjes G, Master I, Ismail N, Hughes J, Ferreira H,  
512 Padanilam X, Romero R, Te Riele J, Conradie F. Effect of bedaquiline on mortality in South  
513 African patients with drug-resistant tuberculosis: a retrospective cohort study. *Lancet Respir*  
514 *Med* 2018/07/14 ed. 2018; 6: 699–706.
- 515 25. Organization WH. WHO consolidated guidelines on tuberculosis. Module 4: treatment -  
516 drug-resistant tuberculosis treatment. World Health Organization; 2020. Licence: CC BY-  
517 NC-SA 3.0 IGO.; 2020 Geneva.
- 518 26. Organisation WorldH. Rapid communication: key changes to treatment of drug-resistant  
519 tuberculosis. Geneva: World Health Organization; 2019 (WHO/CDS/TB/2019.26). Licence:  
520 CC BY-NC-SA 3.0 IGO. 2019; .
- 521 27. Goodall RL, Meredith SK, Nunn AJ, Bayissa A, Bhatnagar AK, Bronson G, Chiang C-Y,  
522 Conradie F, Gurumurthy M, Kirenga B, Kiria N, Meressa D, Moodliar R, Narendran G,  
523 Ngubane N, Rassool M, Sanders K, Solanki R, Squire SB, Torrea G, Tsogt B, Tudor E, Deun  
524 AV, Rusen ID, Adilaa O, Alexandru S, Bellenger K, Bennet J, Bennet D, Bindroo P, et al.  
525 Evaluation of two short standardised regimens for the treatment of rifampicin-resistant  
526 tuberculosis (STREAM stage 2): an open-label, multicentre, randomised, non-inferiority  
527 trial. *The Lancet* Elsevier; 2022; 400: 1858–1868.

- 528 28. WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant  
529 tuberculosis treatment, 2022 update. Geneva: World Health Organization; 2022. Licence: CC  
530 BY-NC-SA 3.0 IGO. .
- 531 29. Nyang'wa B-T, Berry C, Kazounis E, Motta I, Parpieva N, Tigay Z, Solodovnikova V,  
532 Liverko I, Moodliar R, Dodd M, Ngubane N, Rassool M, McHugh TD, Spigelman M, Moore  
533 DAJ, Ritmeijer K, du Cros P, Fielding K. A 24-Week, All-Oral Regimen for Rifampin-  
534 Resistant Tuberculosis. *N Engl J Med* 2022; 387: 2331–2343.
- 535 30. Nyang'wa B-T. TB-PRACTECAL final efficacy and safety results. *Presented at the 27th*  
536 *annual conference of the Union-North America Region 2023*; .
- 537 31. Esmail A, Oelofse S, Lombard C, Perumal R, Mbuthini L, Goolam Mahomed A, Variava E,  
538 Black J, Oluboyo P, Gwentshu N, Ngam E, Ackerman T, Marais L, Mottay L, Meier S,  
539 Pooran A, Tomasicchio M, Te Riele J, Derendinger B, Ndjeka N, Maartens G, Warren R,  
540 Martinson N, Dheda K. An All-Oral 6-Month Regimen for Multidrug-Resistant  
541 Tuberculosis: A Multicenter, Randomized Controlled Clinical Trial (the NExT Study). *Am J*  
542 *Respir Crit Care Med* 2022; 205: 1214–1227.
- 543 32. Conradie F, Phillips P, Badet T, et al. High rate of successful outcomes treating RR-TB with  
544 a delamanid-bedaquiline regimen in BEAT Tuberculosis: an interim analysis. Presented at  
545 the Union World Conference on Lung health during LBTB The Union/CDC late-breaker  
546 session on TB. 2022 November. .
- 547 33. Mok J, Lee M, Kim DK, Kim JS, Jhun BW, Jo K-W, Jeon D, Lee T, Lee JY, Park JS, Lee  
548 SH, Kang YA, Lee J-K, Kwak N, Ahn JH, Shim TS, Kim SY, Kim S, Kim K, Seok K-H,  
549 Yoon S, Kim YR, Kim J, Yim D, Hahn S, Cho SN, Yim J-J, MDR-END investigators. 9  
550 months of delamanid, linezolid, levofloxacin, and pyrazinamide versus conventional therapy  
551 for treatment of fluoroquinolone-sensitive multidrug-resistant tuberculosis (MDR-END): a  
552 multicentre, randomised, open-label phase 2/3 non-inferiority trial in South Korea. *Lancet*  
553 2022; 400: 1522–1530.
- 554 34. World Health Organization. Companion handbook to the WHO guidelines for the  
555 programmatic management of drug-resistant tuberculosis [Internet]. Geneva: World Health  
556 Organization; 2014 [cited 2023 Mar 11]. Available from:  
557 <https://apps.who.int/iris/handle/10665/130918>.
- 558 35. Günther G, Guglielmetti L, Leu C, Lange C, Leth F van, Hafizi H, Khachatryan N, Aroyan  
559 H, Kabasakalyan E, Knappik M, Skrahina A, Klimuk D, Nikolenka A, Muylle I, Milanov V,  
560 Velkovska D, Tarinska N, Bachiyiska E, Jankovic M, Pieridou D, Adamide T, Nicolaou N,  
561 Vasakova M, Sukholytka M, Kopeckà E, Folkvardsen DB, Svensson E, Danilovits M,  
562 Kummik T, Vasankari T, et al. Availability and costs of medicines for the treatment of  
563 tuberculosis in Europe. *Clinical Microbiology and Infection* Elsevier; 2023; 29: 77–84.
- 564 36. Saluzzo F, Maria Cirillo D. Mind the gap. Rolling out new drug resistant tuberculosis  
565 regimens with limited diagnostic tools. *Journal of Clinical Tuberculosis and Other*  
566 *Mycobacterial Diseases* 2023; : 100350.



- 567 37. DR-TB Drugs Under the Microscope, 8th Edition [Internet]. Médecins Sans Frontières  
 568 Access Campaign [cited 2023 Jan 16]. Available from: [https://msfaccess.org/dr-tb-drugs-](https://msfaccess.org/dr-tb-drugs-under-microscope-8th-edition)  
 569 [under-microscope-8th-edition](https://msfaccess.org/dr-tb-drugs-under-microscope-8th-edition).
- 570 38. Dheda K, Gumbo T, Gandhi NR, Murray M, Theron G, Udwadia Z, Migliori GB, Warren R.  
 571 Global control of tuberculosis: from extensively drug-resistant to untreatable tuberculosis.  
 572 *The Lancet Respiratory Medicine* 2014; 2: 321–338.
- 573 39. Padmapriyadarsini C, Vohra V, Bhatnagar A, Solanki R, Sridhar R, Anande L,  
 574 Muthuvijayalakshmi M, Rana MB, Jeyadeepa B, Taneja G, Balaji S, Shah P, Saravanan N,  
 575 Chavan V, Kumar H, Ponnuraja C, Livchits V, Bahl M, Alavadi U, Sachdeva KS,  
 576 Swaminathan S, for the BEAT India Team. Bedaquiline, Delamanid, Linezolid, and  
 577 Clofazimine for Treatment of Pre-extensively Drug-Resistant Tuberculosis. *Clinical*  
 578 *Infectious Diseases* 2023; 76: e938–e946.
- 579 40. Conradie F, Bagdasaryan TR, Borisov S, Howell P, Mikiashvili L, Ngubane N, Samoilo  
 580 A, Skorniykova S, Tudor E, Variava E, Yablonskiy P, Everitt D, Wills GH, Sun E, Olugbosi  
 581 M, Egizi E, Li M, Holsta A, Timm J, Bateson A, Crook AM, Fabiane SM, Hunt R, McHugh  
 582 TD, Tweed CD, Foraida S, Mendel CM, Spigelman M. Bedaquiline–Pretomanid–Linezolid  
 583 Regimens for Drug-Resistant Tuberculosis. *New England Journal of Medicine*  
 584 Massachusetts Medical Society; 2022; 387: 810–823.
- 585 41. Conradie F, Diacon AH, Ngubane N, Howell P, Everitt D, Crook AM, Mendel CM, Egizi E,  
 586 Moreira J, Timm J, McHugh TD, Wills GH, Bateson A, Hunt R, Van Niekerk C, Li M,  
 587 Olugbosi M, Spigelman M. Treatment of Highly Drug-Resistant Pulmonary Tuberculosis. *N*  
 588 *Engl J Med* 2020; 382: 893–902.
- 589 42. WHO. Rapid communication: key changes to the treatment of drug-resistant tuberculosis.  
 590 (*WHO/UCN/TB/2022.2*). Licence: CC BY-NC-SA 3.0 IGO. 2022; .
- 591 43. Guglielmetti L, Varaine F, Mitnick C. Evaluating newly approved drugs for multidrug-  
 592 resistant tuberculosis (endTB): an adaptive, multi-country randomized controlled trial. *Trials*  
 593 2021; 22: 1–15.
- 594 44. Evaluating newly approved drugs in combination regimens for multidrug-resistant TB with  
 595 fluoroquinolone resistance (endtb-Q). *ClinicalTrials.gov*. [accessed April 4th 2023].  
 596 Available from: <https://clinicaltrials.gov/ct2/show/NCT03896685>.
- 597 45. Wasserman S, Denti P, Brust JCM, Abdelwahab M, Hlungulu S, Wiesner L, Norman J,  
 598 Sirgel FA, Warren RM, Esmail A, Dheda K, Gandhi NR, Meintjes G, Maartens G. Linezolid  
 599 Pharmacokinetics in South African Patients with Drug-Resistant Tuberculosis and a High  
 600 Prevalence of HIV Coinfection. *Antimicrob. Agents Chemother.* 2019; 63.
- 601 46. Ismail F, Kachingwa E, He Z. Bedaquiline resistance among patients not responding to a  
 602 drug resistant treatment regimen in South Africa. *7th SA TB Conference; Sept 13–16 2022; .*
- 603 47. Derendinger B, Dippenaar A, Vos M de, Huo S, Alberts R, Tadokera R, Limberis J, Sirgel F,  
 604 Dolby T, Spies C, Reuter A, Folkerts M, Allender C, Rie AV, Gagneux S, Rigouts L, Riele J

- 605 te, Dheda K, Engelthaler D, Warren R, Metcalfe J, Cox H, Theron G. High frequency of  
 606 bedaquiline resistance in programmatically treated drug-resistant TB patients with sustained  
 607 culture-positivity in Cape Town, South Africa [Internet]. medRxiv; 2022 [cited 2023 Apr  
 608 28]. p. 2022.11.14.22282167 Available from:  
 609 <https://www.medrxiv.org/content/10.1101/2022.11.14.22282167v1>.
- 610 48. Chesov E, Chesov D, Maurer FP, Andres S, Utpatel C, Barilar I, Donica A, Reimann M,  
 611 Niemann S, Lange C, Crudu V, Heyckendorf J, Merker M. Emergence of bedaquiline  
 612 resistance in a high tuberculosis burden country. *European Respiratory Journal* [Internet]  
 613 European Respiratory Society; 2022 [cited 2022 Sep 6]; 59 Available from: [https://erj-](https://erj-ersjournals-com.proxy.insermbiblio.inist.fr/content/59/3/2100621)  
 614 [ersjournals-com.proxy.insermbiblio.inist.fr/content/59/3/2100621](https://erj-ersjournals-com.proxy.insermbiblio.inist.fr/content/59/3/2100621).
- 615 49. Kaniga K, Hasan R, Jou R, Vasiliauskienė E, Chuchottaworn C, Ismail N, Metchock B,  
 616 Miliauskas S, Viet Nhung N, Rodrigues C, Shin S, Simsek H, Smithtikarn S, Ngoc ALT,  
 617 Boonyasopun J, Kazi M, Kim S, Kamolwat P, Musteikiene G, Sacopon CA, Tahseen S,  
 618 Vasiliauskaitė L, Wu M-H, Vally Omar S. Bedaquiline Drug Resistance Emergence  
 619 Assessment in Multidrug-Resistant Tuberculosis (MDR-TB): a 5-Year Prospective In Vitro  
 620 Surveillance Study of Bedaquiline and Other Second-Line Drug Susceptibility Testing in  
 621 MDR-TB Isolates. *J Clin Microbiol* 2022; 60: e0291920.
- 622 50. Dawson R, Condos R, Tse D, Huie ML, Ress S, Tseng C-H, Brauns C, Weiden M, Hoshino  
 623 Y, Bateman E, Rom WN. Immunomodulation with recombinant interferon-gamma1b in  
 624 pulmonary tuberculosis. *PLoS One* 2009; 4: e6984.
- 625 51. Armange L, Lacroix A, Petitgas P, Arvieux C, Piau-Couapel C, Poubeau P, Revest M,  
 626 Tattevin P. The use of TNF- $\alpha$  antagonists in tuberculosis to control severe paradoxical  
 627 reaction or immune reconstitution inflammatory syndrome: a case series and literature  
 628 review. *Eur J Clin Microbiol Infect Dis* 2023; 42: 413–422.
- 629 52. van Arkel C, Boeree M, Magis-Escurra C, Hoefsloot W, Carpaij N, van Ingen J, Pegge S,  
 630 Wielders P, Smeenk F, Aarnoutse R, Netea MG, van Crevel R, van Laarhoven A.  
 631 Interleukin-1 receptor antagonist anakinra as treatment for paradoxical responses in HIV-  
 632 negative tuberculosis patients: A case series. *Med* 2022; 3: 603-611.e2.
- 633 53. Chung C, Silwal P, Kim I, Modlin RL, Jo E-K. Vitamin D-Cathelicidin Axis: at the  
 634 Crossroads between Protective Immunity and Pathological Inflammation during Infection.  
 635 *Immune Netw* 2020; 20: e12.
- 636 54. Padmapriyadarsini C, Mamulwar M, Mohan A, Shanmugam P, Gomathy NS, Mane A, Singh  
 637 UB, Pavankumar N, Kadam A, Kumar H, Suresh C, Reddy D, Devi P, Ramesh PM, Sekar L,  
 638 Jawahar S, Shandil RK, Singh M, Menon J, Guleria R. Randomized Trial of Metformin With  
 639 Anti-Tuberculosis Drugs for Early Sputum Conversion in Adults With Pulmonary  
 640 Tuberculosis. *Clin Infect Dis* 2022; 75: 425–434.
- 641 55. Wallis RS, Ginindza S, Beattie T, Arjun N, Likoti M, Edward VA, Rassool M, Ahmed K,  
 642 Fielding K, Ahidjo BA, Vangu MDT, Churchyard G. Adjunctive host-directed therapies for  
 643 pulmonary tuberculosis: a prospective, open-label, phase 2, randomised controlled trial. *The*  
 644 *Lancet Respiratory Medicine* Elsevier; 2021; 9: 897–908.

- 645 56. Thwaites GE, Nguyen DB, Nguyen HD, Hoang TQ, Do TTO, Nguyen TCT, Nguyen QH,  
646 Nguyen TT, Nguyen NH, Nguyen TNL, Nguyen NL, Nguyen HD, Vu NT, Cao HH, Tran  
647 THC, Pham PM, Nguyen TD, Stepniewska K, White NJ, Tran TH, Farrar JJ. Dexamethasone  
648 for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med* 2004;  
649 351: 1741–1751.
- 650 57. Mayosi BM, Ntsekhe M, Bosch J, Pandie S, Jung H, Gumedze F, Pogue J, Thabane L,  
651 Smieja M, Francis V, Joldersma L, Thomas KM, Thomas B, Awotedu AA, Magula NP,  
652 Naidoo DP, Damasceno A, Chitsa Banda A, Brown B, Manga P, Kirenga B, Mondo C,  
653 Mntla P, Tsitsi JM, Peters F, Essop MR, Russell JBW, Hakim J, Matenga J, Barasa AF, et al.  
654 Prednisolone and *Mycobacterium indicus pranii* in tuberculous pericarditis. *N Engl J Med*  
655 2014; 371: 1121–1130.
- 656 58. Meintjes G, Stek C, Blumenthal L, Thienemann F, Schutz C, Buyze J, Ravinetto R, van Loen  
657 H, Nair A, Jackson A, Colebunders R, Maartens G, Wilkinson RJ, Lynen L. Prednisone for  
658 the Prevention of Paradoxical Tuberculosis-Associated IRIS. *N Engl J Med* 2018; 379:  
659 1915–1925.
- 660 59. Meintjes G, Wilkinson RJ, Morroni C, Pepper DJ, Rebe K, Rangaka MX, Oni T, Maartens  
661 G. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-  
662 associated immune reconstitution inflammatory syndrome. *AIDS* 2010; 24: 2381–2390.
- 663 60. Tobin DM, Roca FJ, Oh SF, McFarland R, Vickery TW, Ray JP, Ko DC, Zou Y, Bang ND,  
664 Chau TTH, Vary JC, Hawn TR, Dunstan SJ, Farrar JJ, Thwaites GE, King M-C, Serhan CN,  
665 Ramakrishnan L. Host genotype-specific therapies can optimize the inflammatory response  
666 to mycobacterial infections. *Cell* 2012; 148: 434–446.
- 667 61. Whitworth LJ, Troll R, Pagán AJ, Roca FJ, Edelstein PH, Troll M, Tobin DM, Phu NH,  
668 Bang ND, Thwaites GE, Thuong NTT, Sewell RF, Ramakrishnan L. Elevated cerebrospinal  
669 fluid cytokine levels in tuberculous meningitis predict survival in response to  
670 dexamethasone. *Proc Natl Acad Sci U S A* 2021; 118: e2024852118.
- 671 62. Savic RM, Weiner M, MacKenzie WR, Engle M, Whitworth WC, Johnson JL, Nsubuga P,  
672 Nahid P, Nguyen NV, Peloquin CA, Dooley KE, Dorman SE, Tuberculosis Trials  
673 Consortium of the Centers for Disease Control and Prevention. Defining the optimal dose of  
674 rifapentine for pulmonary tuberculosis: Exposure-response relations from two phase II  
675 clinical trials. *Clin Pharmacol Ther* 2017; 102: 321–331.
- 676 63. Boeree MJ, Diacon AH, Dawson R, Narunsky K, du Bois J, Venter A, Phillips PPJ, Gillespie  
677 SH, McHugh TD, Hoelscher M, Heinrich N, Rehal S, van Soolingen D, van Ingen J, Magis-  
678 Ecurra C, Burger D, Plemper van Balen G, Aarnoutse RE. A Dose-Ranging Trial to  
679 Optimize the Dose of Rifampin in the Treatment of Tuberculosis. *Am J Respir Crit Care*  
680 *Med* 2015; 191: 1058–1065.
- 681 64. Peloquin CA, Velásquez GE, Lecca L, Calderón RI, Coit J, Milstein M, Osso E, Jimenez J,  
682 Tintaya K, Sanchez Garavito E, Vargas Vasquez D, Mitnick CD, Davies G. Pharmacokinetic  
683 Evidence from the HIRIF Trial To Support Increased Doses of Rifampin for Tuberculosis.  
684 *Antimicrob Agents Chemother* 2017; 61: e00038-17.

- 685 65. Boeree MJ, Heinrich N, Aarnoutse R, Diacon AH, Dawson R, Rehal S, Kibiki GS,  
686 Churchyard G, Sanne I, Ntinginya NE, Minja LT, Hunt RD, Charalambous S, Hanekom M,  
687 Semvua HH, Mpagama SG, Manyama C, Mtafya B, Reither K, Wallis RS, Venter A,  
688 Narunsky K, Mekota A, Henne S, Colbers A, van Balen GP, Gillespie SH, Phillips PPJ,  
689 Hoelscher M. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a  
690 multi-arm, multi-stage randomised controlled trial. *The Lancet Infectious Diseases* 2017; 17:  
691 39–49.
- 692 66. Velásquez GE, Brooks MB, Coit JM, Pertinez H, Vargas Vásquez D, Sánchez Garavito E,  
693 Calderón RI, Jiménez J, Tintaya K, Peloquin CA, Osso E, Tierney DB, Seung KJ, Lecca L,  
694 Davies GR, Mitnick CD. Efficacy and Safety of High-Dose Rifampin in Pulmonary  
695 Tuberculosis. A Randomized Controlled Trial. *Am J Respir Crit Care Med* 2018; 198: 657–  
696 666.
- 697 67. Chabala C, Turkova A, Hesselning AC, Zimba KM, van der Zalm M, Kapasa M, Palmer M,  
698 Chirehwa M, Wiesner L, Wobudeya E, Kinikar A, Mave V, Hissar S, Choo L, LeBeau K,  
699 Mulenga V, Aarnoutse R, Gibb D, McIlleron H. Pharmacokinetics of First-Line Drugs in  
700 Children With Tuberculosis, Using World Health Organization-Recommended Weight Band  
701 Doses and Formulations. *Clin Infect Dis* 2022; 74: 1767–1775.
- 702 68. Denti P, Wasmann RE, van Rie A, Winckler J, Bekker A, Rabie H, Hesselning AC, van der  
703 Laan LE, Gonzalez-Martinez C, Zar HJ, Davies G, Wiesner L, Svensson EM, McIlleron  
704 HM. Optimizing Dosing and Fixed-Dose Combinations of Rifampicin, Isoniazid, and  
705 Pyrazinamide in Pediatric Patients With Tuberculosis: A Prospective Population  
706 Pharmacokinetic Study. *Clin Infect Dis* 2022; 75: 141–151.
- 707 69. World Health Organization. Technical report on the pharmacokinetics and  
708 pharmacodynamics (PK/PD) of medicines used in the treatment of drug-resistant  
709 tuberculosis. 2018; WHO/CDS/TB/2018.6.
- 710 70. Gausi K, Ignatius EH, Sun X, Kim S, Moran L, Wiesner L, von Groote-Bidlingmaier F,  
711 Hafner R, Donahue K, Vanker N, Rosenkranz SL, Swindells S, Diacon AH, Nuermberger  
712 EL, Dooley KE, Denti P. A Semimechanistic Model of the Bactericidal Activity of High-  
713 Dose Isoniazid against Multidrug-Resistant Tuberculosis: Results from a Randomized  
714 Clinical Trial. *Am J Respir Crit Care Med* American Thoracic Society - AJRCCM; 2021;  
715 204: 1327–1335.
- 716 71. Verma R, Patil S, Zhang N, Moreira FMF, Vitorio MT, Santos A da S, Wallace E,  
717 Gnanashanmugam D, Persing DH, Savic RM, Croda J, Andrews JR. A Rapid  
718 Pharmacogenomic Assay to Detect NAT2 Polymorphisms and Guide Isoniazid Dosing for  
719 Tuberculosis Treatment. *Am J Respir Crit Care Med* 2021; 204: 1317–1326.
- 720 72. Heyckendorf J, Marwitz S, Reimann M, Avsar K, DiNardo A, Günther G, Hoelscher M,  
721 Ibraim E, Kalsdorf B, Kaufmann SHE, Kontsevaya I, van Leth F, Mandalakas AM, Maurer  
722 FP, Müller M, Nitschkowski D, Olaru ID, Popa C, Rachow A, Rolling T, Rybniker J, Salzer  
723 HJF, Sanchez-Carballo P, Schuhmann M, Schaub D, Spinu V, Suárez I, Terhalle E,

- 724 Unnewehr M, Weiner J, et al. Prediction of anti-tuberculosis treatment duration based on a  
725 22-gene transcriptomic model. *Eur Respir J* 2021; 58: doi: 10.1183/13993003.03492-2020.
- 726 73. Heyckendorf J, Georghiou SB, Frahm N, Heinrich N, Kontsevaya I, Reimann M, Holtzman  
727 D, Imperial M, Cirillo DM, Gillespie SH, Ruhwald M, UNITE4TB Consortium.  
728 Tuberculosis Treatment Monitoring and Outcome Measures: New Interest and New  
729 Strategies. *Clin Microbiol Rev* 2022; 35: e0022721.
- 730 74. DiNardo AR, Gandhi T, Heyckendorf J, Grimm SL, Rajapakshe K, Nishiguchi T, Reimann  
731 M, Kirchner HL, Kahari J, Dlamini Q, Lange C, Goldmann T, Marwitz S, DZIF-TB cohort  
732 study group, Abhimanyu null, Cirillo JD, Kaufmann SHE, Netea MG, van Crevel R,  
733 Mandalakas AM, Coarfa C. Gene expression signatures identify biologically and clinically  
734 distinct tuberculosis endotypes. *Eur Respir J* 2022; 60: 2102263.
- 735 75. DiNardo AR, Nishiguchi T, Grimm SL, Schlesinger LS, Graviss EA, Cirillo JD, Coarfa C,  
736 Mandalakas AM, Heyckendorf J, Kaufmann SHE, Lange C, Netea MG, Van Crevel R.  
737 Tuberculosis endotypes to guide stratified host-directed therapy. *Med* 2021; 2: 217–232.
- 738 76. Maier C, Chesov D, Schaub D, Kalsdorf B, Andres S, Friesen I, Reimann M, Lange C.  
739 Long-term treatment outcomes in multidrug-resistant tuberculosis. *Clinical Microbiology  
740 and Infection* [Internet] 2023 [cited 2023 Feb 28]; Available from:  
741 <https://www.sciencedirect.com/science/article/pii/S1198743X23000836>.
- 742 77. Guglielmetti L, Günther G, Leu C, Cirillo D, Duarte R, Garcia-Basteiro AL, Goletti D,  
743 Jankovic M, Kuksa L, Maurer FP, Méchaï F, Tiberi S, van Leth F, Veziris N, Lange C.  
744 Rifapentine access in Europe: growing concerns over key tuberculosis treatment component.  
745 *Eur Respir J* 2022; 59: 2200388.
- 746 78. Lange C, Köhler N, Günther G. Regimens for Drug-Resistant Tuberculosis. *N Engl J Med*  
747 2023; 388: 190.
- 748