Chapter 9

Treatment of drug-susceptible and drug-resistant tuberculosis

Christoph Lange [1,2,3,4], Thomas Theo Brehm[5,6], Dumitru Chesov [1,2,3,7], Yousra Kherabi[8,9] and Lorenzo Guglielmetti [8,10]

[1]Division of Clinical Infectious Diseases, Research Center Borstel, Borstel, Germany. [2]German Center for Infection Research (DZIF), Partner Site Hamburg-Lübeck-Borstel-Riems, Borstel, Germany. [3]Respiratory Medicine and International Health, University of Lübeck, Lübeck, Germany. [4]Baylor College of Medicine and Texas Childreńs Hospital, Global TB Program, Houston, TX, USA. [5]Division of Infectious Diseases, I. Department of Internal Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. [6]German Center for Infection Research (DZIF), Partner Site Hamburg-Lübeck-Borstel-Riems, Hamburg, Germany. [7]Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, Republic of Moldova. [8]Sorbonne University, INSERM, U1135, Centre d'Immunologie et des Maladies Infectieuses, Cimi-Paris, Paris, France. [9]Department of Infectious Diseases, Bichat-Claude Bernard Hospital, Assistance Publique Hôpitaux de Paris, Paris, France. [10]AP-HP, Pitié-Salpêtrière Hospital, Department of Bacteriology-Hygiene, Centre National de Référence des Mycobactéries et de la Résistance des Mycobactéries aux Antituberculeux, Paris, France.

Corresponding author: Christoph Lange (clange@fz-borstel.de)

Cite as: Lange C, Brehm TT, Chesov D, *et al.* Treatment of drug-susceptible and drug-resistant tuberculosis. *In:* García-Basteiro AL, Öner Eyüboğlu F, Rangaka MX, eds. The Challenge of Tuberculosis in the 21st Century (ERS Monograph). Sheffield, European Respiratory Society, 2023; pp. 117–138 [https://doi.org/10.1183/2312508X.10024622].

@ERSpublications
The treatment of TB has been revolutionised in recent years. This chapter presents an historical perspective and an update for the clinical management of patients with drug-susceptible and drug-resistant TB.
https://bit.ly/ERSM101

 Print ISBN: 978-1-84984-169-6. Online ISBN: 978-1-84984-170-2. Print ISSN: 2312-508X. Online ISSN: 2312-5098.

Recent advances have enabled the use of shorter TB treatment regimens. Key changes in the management of TB are: 1-month preventive treatment with rifapentine and isoniazid; 4-month treatment for paucibacillary TB in children; 4-month treatment for PTB in adults based on rifapentine; and 6-month treatment for MDR/RR-TB with bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM). However, the history of TB drug resistance, and limited capacity worldwide for DST, are cause for caution.

Introduction

TB is a preventable and treatable infectious disease. According to the latest estimates from the WHO [1], more than 85% of patients affected by TB achieve a successful outcome with anti-TB therapies. Presently there are 21 medicines from several drug classes available for the treatment of TB [2].

Until 2022, the standard duration of anti-TB therapies was 6 months for adults and children with pulmonary disease and 18 months for those affected by RR-TB or MDR-TB [3, 4]. Recently, important achievements have been made for effective, safe and shorter treatment regimens for patients affected by drug-susceptible TB (DS-TB) and by DR-TB, which have led to revisions of WHO treatment recommendations [5–7]. With 19 compounds in clinical phase 1

and 2 of drug development as of the first quarter of the year 2023 and several ongoing clinical trials evaluating novel combinations of medicines in different regimens, there is prospect for even shorter, safer and more effective treatments in the near future [8]. However, emergence of *Mycobacterium tuberculosis* drug resistance is challenging the success of anti-TB therapies [9]. Recent history teaches us that soon after the marketing of novel anti-TB medicines drug-resistant strains of *M. tuberculosis* can be found [10, 11]. In this chapter we present a brief history of the treatments against TB, we inform about drugs and their mode of action and we review current treatment recommendations against DS-TB and DR-TB.

History of the medical treatment of TB

The sanatorium movement, from the Latin word *sanare*, "to heal", started decades before the discovery of *M. tuberculosis* by Robert Koch in 1882 (figure 1). In 1840, George Bodington, a British physician, published an essay entitled "On the Treatment and Cure of Pulmonary Consumption" in which he advocated for a treatment based on fresh air and a balanced diet [12]. In 1862, Hermann Brehmer inaugurated the first high-altitude sanatorium specifically dedicated to PTB patients at Görbersdorf (now Sokołowsko in Poland) [13]. Though the pathophysiology of TB was not yet understood at that time, a physiological substratum could be found in bed rest. Gravity indeed affects the distribution of ventilation and blood flow in the lung. Lying in a horizontal position could help by reducing oxygen tension in the apices and therefore the multiplication of the TB bacilli. This process would specially be emphasised at high altitudes given the low amount of oxygen in the air [14].

With the advent of the sanatorium era, several therapeutic protocols were introduced to treat TB [15, 16]. In 1881, Professor Jaccoud (France) published "The Curability and Treatment of Pulmonary Phthisis", in which he described the most popular TB treatments at that time [17]. Associated with hygienic measures, Jaccoud mentioned among others the use of chest massages, salts of iron, cod liver oil, arsenic, antimony, quinine salts and inhalations of carbolic acid, iodine, creosote and turpentine [18]. TB treatment by gold compounds became popular in the 1920s based on the fact that gold cyanide was found effective *in vitro* against cultures of TB bacilli, despite its absence of effectiveness *in vivo* [19]. Medical treatments were also supported by surgical procedures. These included, for instance, artificial pneumothorax proposed by Forlanini since 1882, lung resection since Block's works in 1883, thoracoplasty first performed by De Cérenville in 1885 and phrenic nerve crush proposed by Stuertz in 1911 [20]. Though frequently used in selected patients, none of these interventions was ever properly evaluated to assess their efficacy.

Overall, no scientific evidence exists that sanatorium treatment had any efficacy against TB, and with the discovery of effective antibiotic therapies, sanatoria became progressively obsolete [21, 22]. In 1943, streptomycin, purified from *Streptomyces griseus*, was isolated in the laboratory of Selman Waksman at Rutgers University (USA) [23]. In 1944, a TB patient was declared cured after a streptomycin treatment, soon followed by other case series [24, 25]. In 1948, the British Medical Research Council conducted the first large-scale clinical trial to assess the efficacy of streptomycin [26]. The results showed efficacy at 6 months (7% mortality rate in the streptomycin arm compared to 27% in the "bed rest" arm), but not after a 5-year follow up (58% in the streptomycin arm compared to 76% in the "bed rest" arm), and the majority of *M. tuberculosis* strains from streptomycin-treated patients developed streptomycin resistance [27].

Available anti-TB medicines

Streptomycin discovery and development was soon followed by the advent of several anti-TB drugs in the late 1940s and 1950s [28]. Researchers rapidly demonstrated the benefits of

 https://doi.org/10.1183/2312508X.10024622

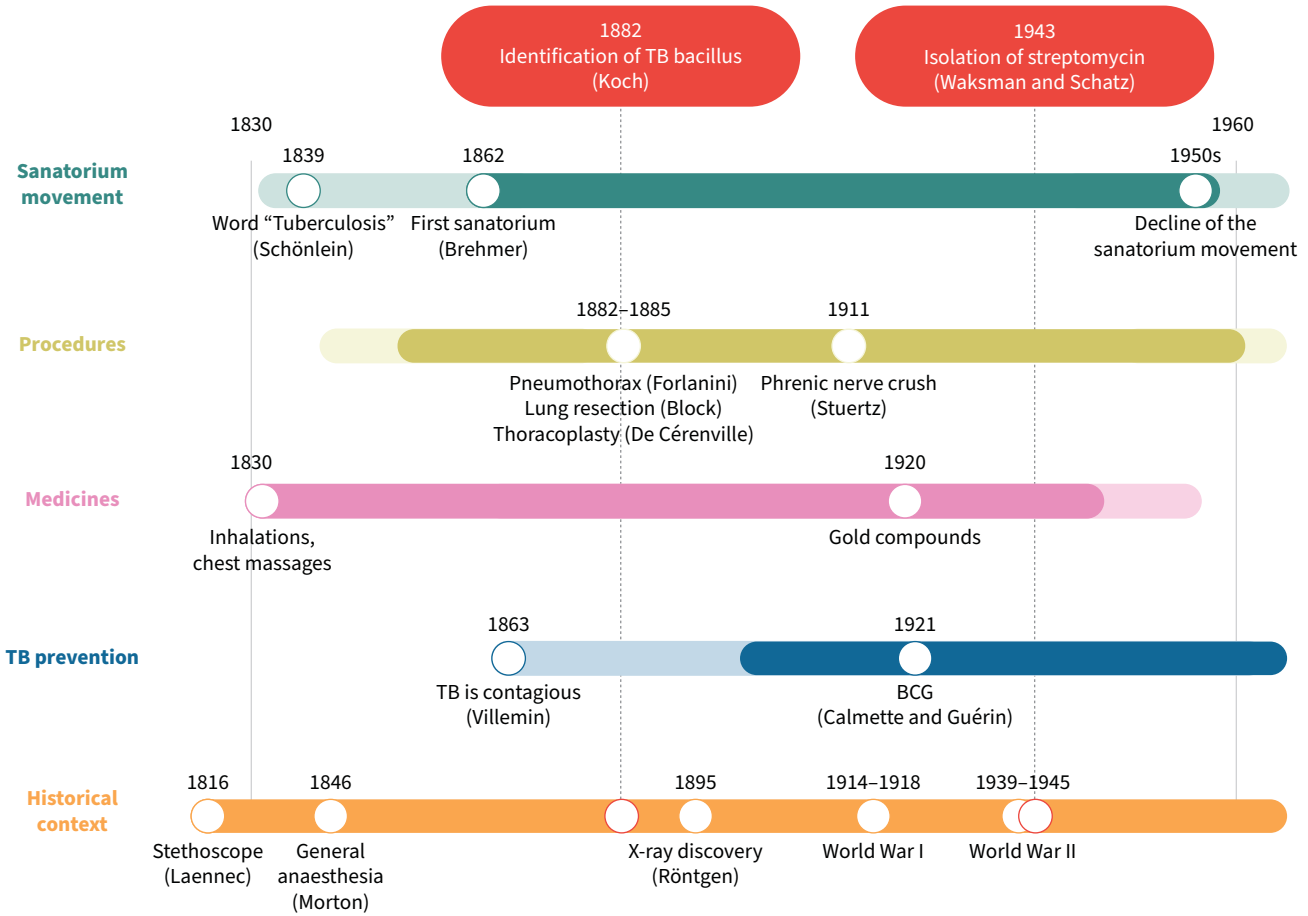

FIGURE 1 TB sanatorium treatment in the pre-antibiotic era.

combination therapy to prevent selection of drug resistance and relapse due to persisting bacilli [29]. The development of rifampicin was a major breakthrough because it allowed treatment duration to be shortened to 9 months. The discovery of ethambutol in the 1960s and the introduction of pyrazinamide at a lower dose led to the currently used 6-month regimen. Table 1 summarises the main advances in shortening treatment duration.

Currently, there are 21 drugs from several classes available for the treatment of TB. Figure 2 presents the mechanisms of action of the currently used anti-TB drugs. Rifamycins (rifampicin, rifabutin, rifapentine) block the RNA polymerase enzyme and thus inhibit gene transcription of mRNA [32]. Unlike rifamycins which are used to treat other bacterial infections, the antimicrobial spectrum of isoniazid is selective for mycobacteria. Isoniazid's exact mechanism of action is not completely understood yet. It blocks cell wall synthesis by interfering in mycolic acid synthesis. Isoniazid is converted by a catalase peroxidase within *M. tuberculosis* into an active metabolite able to inhibit *inhA*, an enzyme necessary to bacterial survival [33]. Thioamide drugs, ethionamide and prothionamide also seem to inhibit *inhA* [34]. Pyrazinamide interferes with multiple mechanisms such as energy production, intracellular acidification and plasma membrane disruption [28, 35]. Ethambutol blocks arabinosyltransferases *embA*, *embB*, and *embC*, enzymes involved in the generation of arabinogalactan, a mycobacterial cell wall constituent [18].

Fluoroquinolones (levofloxacin and moxifloxacin) increase levels of DNA breaks produced by *M. tuberculosis* DNA gyrase, a type II topoisomerase necessary to shape double-stranded DNA [36]. Aminoglycosides (amikacin, capreomycin, kanamycin, streptomycin) and oxazolidinones (linezolid) bind to the mycobacterial ribosome and inhibit protein synthesis [37, 38]. *Para*-aminosalicylic acid (PAS) disrupts folate metabolism through competitive binding with dihydrofolate reductase, thus stopping the growth of *M. tuberculosis* [39]. Bedaquiline inhibits the mycobacterial adenosine 5′-triphosphate (ATP) synthase [40]. Delamanid interferes in the synthesis of methoxymycolate and ketomycolate [41]. Pretomanid inhibits the oxidation of hydroxymycolate to ketomycolate [42]. Terizidone and cycloserine inhibit L-alanine racemase and D-alanine ligase involved in cell wall synthesis [43]. Clofazimine affects intracellular redox cycling and membrane destabilisation [44]. Carbapenems, though weak substrates for *M. tuberculosis* β-lactamase, are efficient when associated with clavulanate which inactivates the β-lactamase encoded by the *blaC* gene [28, 45].

TABLE 1 Main steps in the development of treatment protocols for drug-susceptible TB

Year	[Ref.]	Drug(s)	Consequence
1948	[26] [29]	Streptomycin	First anti-TB antibiotic therapy Monotherapy leads to drug resistance and relapses
1951	[29]	Streptomycin+PAS>streptomycin	Drug combination prevents drug resistance
1962	[30]	Isoniazid+streptomycin+PAS	First anti-TB regimen: 18 months' treatment
1970s	[30]	Isoniazid+rifampicin+ethambutol	Treatment length divided by 2: 9 months
1980s	[30]	Isoniazid+rifampicin+pyrazinamide +ethambutol	Current treatment of drug-susceptible TB: 6 months
2021	[31]	Isoniazid+rifapentin+moxifloxacin +pyrazinamide	4-month regimen

PAS: *para*-aminosalicylic acid.

 https://doi.org/10.1183/2312508X.10024622

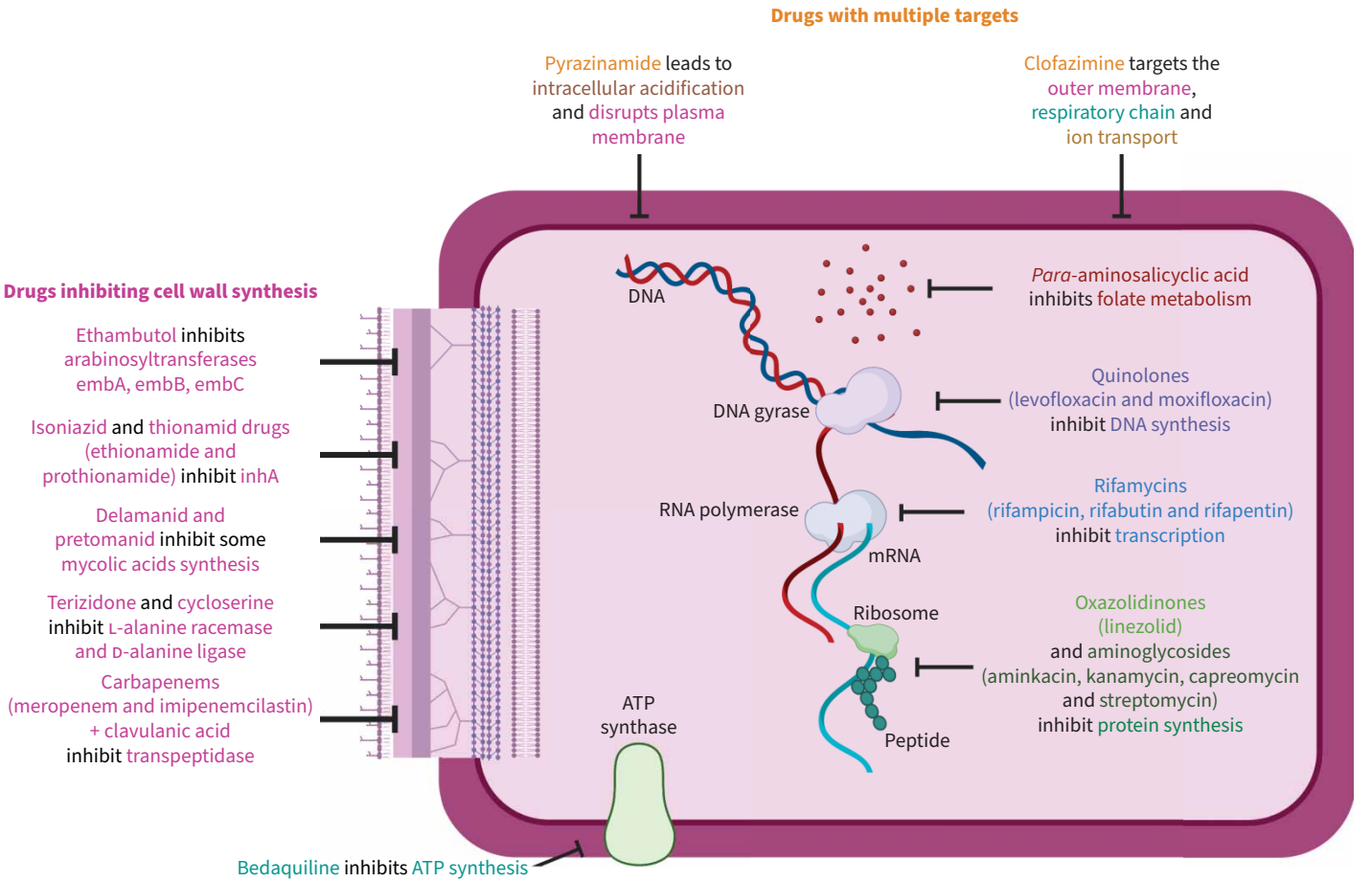

FIGURE 2 Mechanisms of action of the currently used anti-TB medicines. ATP: adenosine 5'-triphosphate; mRNA: messenger ribonucleic acid. Created with BioRender.com. Reproduced and modified from [28] with permission.

Treatment against DS-TB in children and adults

The traditional regimen for treating adults with TB caused by organisms that are not known or that are suspected to be drug-resistant consists of a 2-month intensive phase with isoniazid, rifampicin, pyrazinamide and ethambutol, followed by a 4-month continuation phase with isoniazid and rifampicin (table 2) [46–48]. However, it is advised to continue the quadruple therapy if acid-fast bacilli are still detectable from sputum at the end of the second month until drug susceptibility to isoniazid and rifampicin is confirmed or until acid-fast bacilli are no longer detectable in a sputum specimen.

Patients with extensively advanced or cavitary disease and/or those with a delayed culture conversion may benefit from prolongation of the continuation phase to reduce the chance of a relapse. It has been recommended to extend the continuation phase of treatment for at least 4 months beyond the time when acid-fast bacilli become undetectable from sputum specimen [49].

Approximately 85% of patients achieve a successful treatment outcome with this regimen, which has been widely used worldwide for decades [1]. These recommendations also apply to patients with EPTB, except for central nervous system disease and bone and joint disease, for which longer treatment durations are recommended by some expert groups. Whenever feasible, fixed-drug combination tablets are preferred over separate drug formulations [50]. Daily therapy is favoured over intermittent therapy since it provides higher cure rates and a lower risk of disease relapse and drug-acquired resistance than thrice-weekly or twice-weekly dosing regimens [51–57]. Dosagesof different medicines are shown in table 3. An open-label, randomised controlled trial in 2021 indicated that a 4-month regimen with rifapentine, moxifloxacin, isoniazid, and pyrazinamide was non-inferior to the standard 6-month regimen in terms of efficacy and safety [58]. Consequently, the WHO endorsed this 4-month regimen as a treatment option for nonpregnant patients aged ⩾12 years with body weight ⩾40 kg, with drug-susceptible PTB [5]. This shorter treatment regimen has the potential to reduce the burden on healthcare systems, increase treatment adherence and allow faster cure. However, implementation and uptake are hampered by the limited availability of rifapentine. As of March 2020, rifapentine has been registered only in 13 countries worldwide [59]. A recent survey within the TB Network European Trials group (TBnet) showed that by October 2021,

TABLE 2 Treatment regimens for drug-susceptible PTB

Regimen	Intensive phase		Continuation phase		Comment
	Drugs	Duration, months	Drugs	Duration, months	
Regimen 1	H R Z E	2	H R	4	Traditional regimen
Regimen 2	H Rpt Z Mfx	4			Endorsed for nonpregnant patients aged ⩾12 years with body weight ⩾40 kg with drug-susceptible PTB by the WHO
Regimen 3	H R Z (E)	2	H R	2	Endorsed for children and adolescents between 3 months and 16 years of age with presumed drug-susceptible non-severe disease by the WHO

H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol; Rpt: rifapentine; Mfx: moxifloxacin.

 https://doi.org/10.1183/2312508X.10024622

TABLE 3 Dosage for drugs used in TB regimens for adults and children

Drug	Age	Daily dose	Maximum dose	Comments
Amikacin	⩾15 years <15 years	15–20 mg·kg^{-1} 15–20 mg·kg^{-1}	1000 mg 1000 mg	Amikacin may be included in the treatment of MDR-/RR-TB patients aged ⩾18 years on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions.
Bedaquiline	⩾15 years <15 years	400 mg once daily for 2 weeks, then 200 mg M/W/F for 22 weeks >29 kg: 400 mg once daily for 2 weeks, then 200 mg M/W/F for 22 weeks 15–29 kg: 200 mg once daily for 2 weeks, then 100 mg once daily M/W/F for 22 weeks	400 mg	Bedaquiline should be included in longer MDR-TB regimens for patients aged ⩾18 years. (Strong recommendation, moderate certainty of evidence.) Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years. (Conditional recommendation, very low certainty of evidence.) In children with MDR-/RR-TB aged <6 years, an all-oral treatment with bedaquiline may be used.
Clavulanic acid	⩾15 years <15 years	125 mg as amoxicillin/clavulanate 500/125 mg 62.5 mg as amoxicillin/clavulanate 250/62.5 mg		Clavulanic acid should not be included in the treatment of MDR-/RR-TB patients on longer regimens. Only to be used with carbapenems. Given orally 30 min before each infusion.
Clofazimine	⩾15 years <15 years	100 mg 2–5 mg·kg^{-1}	100 mg 100 mg	Clofazimine may be included in the treatment of MDR-/RR-TB patients on longer regimens.
Cycloserine	⩾15 years <15 years	10–15 mg·kg^{-1} 15–20 mg·kg^{-1}	1000 mg 1000 mg	Cycloserine may be included in the treatment of MDR-/RR-TB patients on longer regimens.
Delamanid	⩾15 years <15 years	100 mg twice daily 3–5 years: 25 mg twice daily; 6–11 years: 50 mg twice daily; 12–17 years: 100 mg twice daily	200 mg 200 mg	Delamanid may be included in the treatment of MDR-/RR-TB patients aged ⩾3 years on longer regimens. In children with MDR-/RR-TB aged <3 years delamanid may be used as part of longer regimens.
Ethambutol	⩾15 years <15 years	15–20 mg·kg^{-1} 15–25 mg·kg^{-1}		Ethambutol may be included in the treatment of MDR-/RR-TB patients on longer regimens.
Ethionamide	⩾15 years <15 years	15–20 mg·kg^{-1} 15–20 mg·kg^{-1}		Ethionamide may be included in the treatment of MDR-/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible.

Continued

TABLE 3 Continued

Drug	Age	Daily dose	Maximum dose	Comments
Imipenem–cilastatin	⩾15 years <15 years	1 g/1 g twice daily Not used in patients aged <15 years		Imipenem–cilastatin may be included in the treatment of MDR-/RR-TB patients on longer regimens.
Isoniazid	⩾15 years <15 years	Standard dose: 4–6 mg·kg^{-1} High dose: 10–15 mg·kg^{-1} 7–15 mg·kg^{-1}	300 mg 300 mg	Pyridoxine is given with isoniazid in patients at risk (*e.g.* those with HIV or malnutrition).
Levofloxacin	⩾15 years <15 years	⩽45 kg: 750 mg >45 kg: 1000 mg 10–15 mg·kg^{-1}	1500 mg 1500 mg	Levofloxacin should be included in the treatment of MDR-/RR-TB patients on longer regimens.
Linezolid	⩾15 years <15 years	600 mg 1–15 kg: 15 mg·kg^{-1} >15 kg: 10–12 mg·kg^{-1}	1200 mg 600 mg	Linezolid should be included in the treatment of MDR-/RR-TB patients on longer regimens.
Meropenem	⩾15 years <15 years	1 g three times daily or 2 g twice daily 20–40 mg·kg^{-1} three times daily		Meropenem may be included in the treatment of MDR-/RR-TB patients on longer regimens. Must be administered with clavulanic acid (only available in combination with amoxicillin or ampicillin).
Moxifloxacin	⩾15 years <15 years	Standard dose: 400 mg High dose: 600–800 mg ⩾6 months: 10–15 mg·kg^{-1} <6 months: 10 mg·kg^{-1}	400 mg 800 mg 400 mg	Moxifloxacin should be included in the treatment of MDR-/RR-TB patients on longer regimens.
***Para*-aminosalicylic acid**	⩾15 years <15 years	8–12 g per day in 2–3 divided doses 200–300 mg·kg^{-1} in 2 divided doses	12 g	*Para*-aminosalicylic acid may be included in the treatment of MDR-/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible.
Pretomanid	⩾15 years <15 years	200 mg Not recommended	200 mg	Pretomanid is the newest anti-TB drug on the market and is part of the BPaL(M) regimen. Clinical experience is as yet limited.
Protionamid	⩾15 years <15 years	15–20 mg·kg^{-1} 15–20 mg·kg^{-1}	1000 mg	Prothionamide may be included in the treatment of MDR-/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible.
Pyrazinamide	⩾15 years <15 years	20–30 mg·kg^{-1} 30–40 mg·kg^{-1}		Pyrazinamide may be included in the treatment of MDR-/RR-TB patients on longer regimens.

Continued

https://doi.org/10.1183/2312508X.10024622

TABLE 3 Continued

Drug	Age	Daily dose	Maximum dose	Comments
Rifampicin	⩾15 years <15 years	8–12 mg·kg^{-1} 10–20 mg·kg^{-1}	600 mg 600 mg	High-dosage rifampicin therapy is currently evaluated to reduce the duration of anti-TB therapy.
Rifapentin	⩾15 years <15 years	1200 mg 1200 mg (>12 years of age)		Rifapentin-based regimens can reduce the duration of therapy for TB prevention to 1 month (rifapentin and isoniazid) and active TB to 4 months (rifapentin, isoniazid, moxifloxacin and pyrazinamide (pyrazinamid for 2 months only)).
Streptomycin	⩾15 years <15 years	12–18 mg·kg^{-1} 20–40 mg·kg^{-1}	1000 mg 1000 mg	Streptomycin may replace amikacin if amikacin is not available in the treatment of MDR-/RR-TB for patients aged ⩾18 years on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured.
Terizidon	⩾15 years <15 years	10–15 mg·kg^{-1} 15–20 mg·kg^{-1}	1000 mg 1000 mg	Terizidone is a condensation product of two cycloserine molecules. Terizidone may be included in the treatment of MDR-/RR-TB patients on longer regimens.

M/W/F: Monday/Wednesday/Friday; BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin. Data from [46] and [58].

rifapentine was available in only 6 (14%) out of 43 participating countries of the WHO European region [60]. In March 2023, the TRUNCATE-TB trial demonstrated that a treatment strategy with an 8-week intensified treatment regimen of bedaquiline (400 mg once daily for 2 weeks, then 200 mg three times a week), linezolid (600 mg), isoniazid, pyrazinamide, and ethambutol and treatment extension only in patients with persistent clinical disease was non-inferior to standard treatment for rifampicin-susceptible PTB with respect to clinical outcomes [61]. These promising results document that shorter treatment durations are possible for many patients. For paediatric patients, the 6-month regimen has been the standard of care [46–48]. In 2022, the open-label, randomised controlled SHINE trial showed that 6 months of anti-TB treatment with isoniazid, rifampicin and pyrazinamide, with or without ethambutol was non-inferior to 6 months of treatment in children younger than 16 years weighing ⩾3 kg with drug-susceptible, non-severe, smear-negative TB [62]. Non-severe TB was defined as non-cavitary PTB confined to one lobe without a miliary patern or complex pleural effusion, intrathoracic lymph node TB without airway obstruction, and peripheral lymph node TB. The WHO conditionally endorsed this shortened treatment regimen for children and adolescents between 3 months and 16 years of age with presumed drug-susceptible non-severe disease [5]. The use of ethambutol is recommended in settings with a high prevalence of isoniazid resistance as defined by the national TB programmes, or a high HIV prevalence (defined as ⩾1% among adult pregnant women or ⩾5% among TB patients) [46, 63]. In other settings, patients receiving the shortened regimen may be treated with a three-drug regimen for the first 2 months without ethambutol, if *M. tuberculosis* susceptibility to isoniazid and rifampicin is ensured by rapid molecular testing [64].

Treatment for rifampicin-susceptible, isoniazid-resistant TB

A recent meta-analysis comprising 5418 patients with rifampicin-susceptible, isoniazid-resistant TB suggests that the addition of a fluoroquinolone is linked to improved treatment success [65]. Therefore, 6-month treatment with rifampicin, ethambutol, pyrazinamide, and levofloxacin is recommended in patients with confirmed rifampicin-susceptible, isoniazid-resistant TB (table 4) [46]. Levofloxacin is generally the fluoroquinolone of choice since it has frequently been used in studies and has fewer drug interactions than other fluoroquinolones. For example, moxifloxacin plasma concentration significantly decreases when combined with rifampicin [66]. In cases of noncavitary disease, low disease burden, or pyrazinamide toxicity, the American Thoracic Society (ATS), US Centers for Disease Control and Prevention (CDC), European Respiratory Society (ERS), and Infectious Diseases Society of America (IDSA) suggest that treatment with pyrazinamide may be reduced to 2 months [48]. Patients with fluoroquinolone resistance or contraindications for fluoroquinolone treatment are generally recommended to be treated with 6 months of rifampicin, ethambutol, and pyrazinamide [46]. The use of high-dose isoniazid is not recommended in geographic regions where isoniazid resistance is based on *katG* mutations in the great majority of patients, *e.g.* the WHO European region [9, 67]. When additional drug resistance is suspected or confirmed, individual treatment regimens need to be designed.

TABLE 4 Treatment regimen for rifampicin-susceptible, isoniazid-resistant PTB

Drugs	Duration months
R Lfx Z E	6

R: rifampicin; Lfx: levofloxacin; Z: pyrazinamide; E: ethambutol.

 https://doi.org/10.1183/2312508X.10024622

Treatment for MDR-/RR-TB, pre-XDR-TB and XDR-TB

For the past decades, treatment against DR-TB was recommended for a duration of at least 18 months with a combination of at least four active compounds [3, 68], was associated with a high rate of adverse drug events [69] and high costs [60], and resulted in not more than 60% treatment success overall [1].

The outcome of the Nix-TB trial changed the prospect for the treatment of patients with DR-TB substantially in 2020. The Nix-TB trial was an open-label, single-group phase 3 study in which the safety and efficacy of an all-orally available drug regimen with three compounds: bedaquiline at a dose of 400 mg once daily for 2 weeks followed by 200 mg three times a week for 24 weeks; pretomanid at a dose of 200 mg daily for 26 weeks; and linezolid at a dose of 1200 mg daily for up to 26 weeks (BPaL), was evaluated [70]. Patients with XDR-TB or those who failed MDR-TB regimens were included. At the end of 6 months of treatment 98 patients (90%; 95% CI 83–95%) had a favourable outcome. However, 81% of patients developed peripheral neuropathy and 48% developed anaemia and/or thrombocytopenia, adverse events that were attributed to the high dose of linezolid.

Subsequently, results from two phase 2–3 trials have been published aiming to confirm the efficacy of the BPaL regimen and to find the optimal dosage of linezolid with the best efficacy/toxicity balance [71, 72]. In the ZeNiX-TB trial, published 2022 [71], patients with MDR/RR-TB were randomly assigned to receive bedaquiline for 26 weeks (200 mg daily for 8 weeks, then 100 mg daily for 18 weeks), pretomanid (200 mg daily for 26 weeks), and daily linezolid at a dose of 1200 mg for 26 weeks or 9 weeks or 600 mg for 26 weeks or 9 weeks. There was no internal control arm. Among 181 participants who received BPaL with linezolid at a dose of 1200 mg for 26 weeks or 9 weeks or 600 mg for 26 weeks or 9 weeks, 93%, 89%, 91%, and 84%, respectively, had a favourable outcome. Peripheral neuropathy occurred in 38%, 24%, 24%, and 13%, respectively and myelosuppression occurred in 22%, 15%, 2%, and 7%, respectively. Although the trial was not powered to draw conclusions on the comparison between arms, the overall risk–benefit ratio seemed to favour the group that received BPaL with linezolid at a dose of 600 mg for 26 weeks, with a lower incidence of adverse events reported and fewer linezolid dose modifications.

The TB PRACTECAL trial, also published in 2022 [72], was a multicentre, randomised, controlled, non-inferiority multi-arm multi-stage trial evaluating the efficacy and safety of three 24-week, BpaL-based treatment regiment with linezolid at a daily dosage of 600 mg for 16 weeks, followed by linezolid at 300 mg for 8 weeks. In the second stage of the trial, a 24-week regimen with BPaL plus moxifloxacin (BPaLM) was compared to a 9–20-month standard-of-care arm. 89% of the patients in the BPaLM arm and 52% of patients in the standard-of-care arm experience treatment success. The incidence of adverse events of grade 3 or higher or serious adverse events was significantly higher in the standard-of-care arm (59% *versus* 19%) than in the BPaLM arm.

In 2022, the WHO summoned a guideline development group of international experts to independently review data from the ZeNix-TB and TB PRACTECAL trials. As a result of this process, the WHO issued a rapid communication in May 2022 with key changes for the treatment of DR-TB [6]. These recommendations were further consolidated in official WHO guidelines on DR-TB in December 2022 [46], recommending the BPaLM regiment as the preferred regimen for patients with MDR/RR-TB. This is a revolution for the management of DR-TB [73, 74].

The current recommendations for the selection of treatment regimens for patients affected by MDR-/RR-TB, pre-XDR-TB and XDR-TB are (table 5) [75]:

1. BPaLM regimen (6 months all-oral treatment regimen of bedaquiline, pretomanid, linezolid and moxifloxacin): In patients with MDR-/RR-TB where fluoroquinolone susceptibility is presumed or documented this regimen should be the treatment of choice. It is possible to omit moxifloxacin and continue with the BPaL regimen for MDR-/RR-TB patients with confirmed fluoroquinolone resistance (based on the results of the ZeNiX-TB [71] and TB PRACTECAL [72] trials). When the regimen is BPaL from the start or is changed to BPaL, it can be extended to a total of 39 weeks (counting from the start of the therapy with BPaLM/BPaL). This extension is justified in cases of failure to convert culture between months 4 and 6 while on treatment; alternatively, it can be based on the clinical judgement of the treating physician. Up to 1 month can be added to the overall treatment duration if there is a need to make up the missed doses [75].

2. For those who are not eligible for the shorter BPaLM/BPaL regiments (table 5): 9-month all-oral treatment regimen consisting of bedaquiline (used for 6 months), in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide and clofazimine (for 4 months, with the possibility of extending to 6 months if acid-fast bacilli are still detectable in the patient's sputum at the end of 4 months), followed by treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide (for 5 months).

TABLE 5 Factors to be considered for selection of treatment regimens for patients with MDR-/RR-TB

Regimen	MDR-/RR-TB fluoroquinolone susceptible	Pre-XDR-TB	XDR-TB	Extensive PTB	EPTB	Age <14 years
6-month BPaLM/BPaL	Yes (BPaLM)	Yes (BPaL)	No	Yes	Yes – except TB involving CNS, miliary TB and osteoarticular TB	No
9-month all-oral	Yes	No	No	No	Yes – except TB meningitis, miliary TB, osteoarticular TB and pericardial TB	Yes
Longer individualised 18-month	Yes[#]/No	Yes[#]/No	Yes	Yes	Yes	Yes
Additional factors to be considered if several regimens are possible	Drug intolerance or adverse events Treatment history, previous exposure to regimen component drugs or likelihood of drug effectiveness Patient or family preference Access to and cost of regimen component drugs					

BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; CNS: central nervous system. [#]: when 6-month BPaLM/BPaL and 9-month regimens cannot be used. Reproduced and modified from [75] with permission.

 https://doi.org/10.1183/2312508X.10024622

Ethionamide can be replaced by 2 months of linezolid (600 mg daily). Patients with MDR-/RR-TB are eligible for this regimen if resistance to fluoroquinolones has been excluded (based on operational data from South Africa [46]).

3. Longer individualised regimens: for patients with MDR-/RR-TB who are not eligible for or had no favourable treatment outcome using the above 6-month or 9-month regimens, have TB disease caused by *M. tuberculosis* strains with extensive drug resistance (*e.g.* XDR-TB) or have intolerance to key components of the above-mentioned regiments (table 5). These regimens have a duration of at least 18 months and are individually designed based on a hierarchical grouping of second-line TB medicines, the drug-resistance profile and the patient's medical history (based on the results of an individual patient data analysis [76]).

Patients with XDR-TB or those who have failed treatments with MDR-/RR-TB therapies should be managed in referral centres. The management of difficult-to-treat patients should be discussed in interdisciplinary boards (consilia).

Anti-TB medicines in clinical evaluation

Currently the pipeline of new TB drugs candidate is flourishing like never before. Thus, 19 new or repurposed compounds for treatment of DS-TB and DR-TB are at present in phase 1 or 2 clinical trials (table 6). Of these new drugs, 10 are of new classes or with a new mechanism of action. Particularly these new medicines target *QcrB* cytochrome complex (an essential components of the respiratory electron transport chain required for ATP synthesis), *DprE1* and *MmpL3* (enzymes important for cell wall synthesis), *LeuRS* (enzyme involved in protein synthesis), *gyrB* (a gyrase taking part in DNA replication), and cholesterol catabolism (nospecific target fully determined yet) [77–81].

Apart of the conceptually novel drugs, the pipeline of TB compounds in clinical development includes four oxazolidinones (delpazolid, sutezolid, tedizolid, TBI-223), three diarylquinoline (TBAJ-587, TBAJ-876, Sudapyridine) and one riminophenazine (pyrifazimine), of interest as potential effective alternatives to the existing TB drugs such as linezolid, bedaquiline and clofazimine respectively [82].

Novel compounds are evaluated in phase 2a clinical trials to demonstrate the potential for these medicines to be components of simpler TB treatment regimens in the future [83]. GSK-656 in particular showed early bactericidal activity with a low, once-daily oral dose after 14 days of treatment in participants with drug-susceptible PTB [84]. Treatment was generally well tolerated with no serious adverse events identified. Similarly, Telacebec and BTZ-043 demonstrated good dose-dependent early bactericidal activity, with increasing doses of the drug associated with greater reductions in viable TB bacteria measured in sputum and reported acceptable adverse-event rates [85, 86]. In addition, a phase 2b study on sutezolid (SUDOCU) has been completed and reporting of its results is expected.

The new TB drugs in clinical development are oral formulations: this is particularly relevant for further design of full-oral TB treatment regimens which usually are preferred by doctors and patients and ensure better adherence [7].

Drugs that have new targets and/or mechanisms of action are important for constructing effective regimens and to overcome emerging drug resistance. However, despite the unprecedented recent

TABLE 6 Novel anti-TB medicines in phase 1 and 2 clinical development

Class	Mechanism of action	Trial phase			
		Phase 1A	Phase 1B	Phase 2A	Phase 2B/C
Diarylquinolines	Inhibits ATP synthase and bacterial respiration	TBAJ-587 TBAJ-876			
				Sudapyridine (WX-081)	
Riminophenazine	Inhibits ion transport and bacterial respiration			Pyrifazimine (TBI-166)	
Oxozalidone	Inhibits protein synthesis (23S ribosome)				Delpazolid (LCB01-0371) Sutezolid (PNU-100480)
				Tedizolid	
			TBI-223		
Carbapenem	Inhibits cell wall synthesis			Sanfetrinem	
Amido-piperidine	Inhibits cell wall synthesis *via* boosting ethionamide			BVL-GSK098	
DprE1 inhibitors	Inhibits cell wall synthesis		BTZ-043 Macozinone (PBTZ169)		
					OPC-167832
				TBA-7371	
QcrB inhibitor	Inhibits ATP synthesis			Telacebec (Q203)	
MmpL3 inhibitor	Inhibits cell wall synthesis				SQ109
GyrB inhibitor	Inhibits bacterial DNA synthesis	SPR720			
Cholesterol catabolism inhibitor		GSK-286			
LeuRS inhibitor	Inhibits protein synthesis			GSK-656	

ATP: adenosine 5'-triphosphate.

advances, the overall process of TB drug development is relatively slow in view of the therapeutic needs and speed of the drug resistance emergency. Thus, no new drugs have reached phase 3 trials or been approved for market regulation since the approval of pretomanid in 2019. Acceleration of clinical assessment of novel TB drugs is expected in the coming years as a result of new clinical trial platforms such as UNITE4TB and PAN-TB [87, 88].

Ongoing clinical trials

The global pipeline of clinical research on TB treatment is evolving [89, 90]. The majority of trials aim to show non-inferiority of an experimental regimen with a shorter treatment duration compared to a control, which is usually standardised for DS-TB and individualised for RR-TB.

For DS-TB, ongoing trials (table 7) focus on different approaches. A few trials implement high-dose rifampicin, with or without a fluoroquinolone (OptiRiMoxTB, and RIFASHORT and Hi-DoRi-3, respectively), building on growing evidence on rifampicin dose [91–95] optimisation. A high-dose rifampicin-based regimen, if non-inferior to the standard of care, could be more readily accessible than the current WHO-recommended 4-month rifapentine-based regimen [75], given rifapentine access and pricing issues [60, 96, 97]. Other

 https://doi.org/10.1183/2312508X.10024622

TABLE 7 Main ongoing and planned phase 2/3/4 TB therapeutic clinical trials

Trial	Phase	Control arm	Country	Experimental treatment regimen(s)	Experimental treatment duration, months	Notes	ClinicalTrials.gov identifier
Rifampicin-susceptible TB							
Beijing Chest Hospital	4	Yes	China	Isoniazid, rifampicin, pyrazinamide, ethambutol, and levofloxacin for the full course; or isoniazid, rifampicin, pyrazinamide, and ethambutol for the full course	4.5		NCT02901288
CLO-Fast (ACTG 5362)	2	Yes	Multicountry	Clofazimine, ethambutol, isoniazid, pyrazinamide, and rifapentine for 8 weeks, followed by clofazimine, isoniazid, pyrazinamide, and rifapentine for 8 weeks	3		NCT04311502
Hi-DoRi-3	3	Yes	South Korea	Isoniazid, rifampicin 30 $mg \cdot kg^{-1}$, and pyrazinamide	3 months after culture conversion	Treatment duration based on sputum culture conversion	NCT04485156
OptiRiMoxTB	3	Yes	Multicountry	Ethambutol, isoniazid, pyrazinamide, and rifampicin 35 $mg \cdot kg^{-1}$, or isoniazid, moxifloxacin, pyrazinamide, and rifampicin 35 $mg \cdot kg^{-1}$	4		NCT05575518
ORIENT	3	Yes	China	Isoniazid, moxifloxacin, and pyrazinamide, plus: rifapentine 600 $mg \cdot day^{-1}$, or rifapentine 1200 $mg \cdot day^{-1}$, or rifapentine 1800$mg \cdot day^{-1}$	4–6	Multi-arm, multi-stage clinical trial	NCT05401071
PredictTB	2	Yes	Multicountry	2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 2 months of isoniazid and rifampicin	4	Strategy trial; only participants with moderate disease are randomised	NCT02821832
PRESCIENT	2	Yes	Multicountry	Bedaquiline, clofazimine, delamanid, and pyrazinamide	2		NCT05556746

Continued

TABLE 7 Continued

Trial	Phase	Control arm	Country	Experimental treatment regimen(s)	Experimental treatment duration, months	Notes	ClinicalTrials.gov identifier
RIAlta	2	No	Multicountry	Rifampicin (35 $mg \cdot kg^{-1}$ per day), isoniazid, pyrazinamide and ethambutol	6	Comparison to historical controls	NCT04768231
RIFASHORT	3	Yes	Multicountry	Standard regimen with rifampicin at 1200 $mg \cdot day^{-1}$; or standard regimen with rifampicin at 1800 $mg \cdot day^{-1}$	4		NCT02581527
SimpliciTB	2/3	Yes	Multicountry	Bedaquiline, pretomanid, moxifloxacin, and pyrazinamide	4	Includes a non-randomised arm with RR-TB patients	NCT03338621
TRUNCATE-TB	2/3	Yes	Multicountry	Isoniazid, high-dose rifampicin, pyrazinamide, ethambutol, and linezolid; isoniazid, high-dose rifampicin, pyrazinamide, ethambutol, and clofazimine; isoniazid, rifapentine, pyrazinamide, levofloxaxin, and linezolid; bedaquiline, isoniazid, pyrazinamide, ethambutol, and linezolid	2	Multi-arm, multi-stage clinical trial	NCT03474198
RR-TB							
ACTG A5356	2	No	Multicountry	Bedaquiline, clofazimine, delamanid, plus linezolid at different dosages	6		NCT05007821
BEAT Tuberculosis	3	Yes	South Africa	Bedaquiline, delamanid, and linezolid, plus levofloxacin or clofazimine	6	Strategy trial; experimental regimen adapted according to rapid molecular testing	NCT04062201
DRAMATIC	2	No	Multicountry	Levofloxacin, bedaquiline, linezolid, delamanid, and clofazimine	4–9	Duration-randomised clinical trial	NCT03828201

Continued

https://doi.org/10.1183/2312508X.10024622

TABLE 7 Continued

Trial	Phase	Control arm	Country	Experimental treatment regimen(s)	Experimental treatment duration, months	Notes	ClinicalTrials.gov identifier
endTB	3	Yes	Multicountry	Bedaquiline, moxifloxacin, linezolid, and pyrazinamide; or bedaquiline, clofazimine, levofloxacin, linezolid, and pyrazinamide; or bedaquiline, delamanid, levofloxacin, linezolid, and pyrazinamide; or delamanid, clofazimine, levofloxacin, linezolid, and pyrazinamide; or delamanid, clofazimine, moxifloxacin, and pyrazinamide	9	Trial implementing Bayesian adaptive randomisation	NCT02754765
GRACE-TB	NS	Yes	China	Individualised regimens	NS	Individualised regimen guided by rapid molecular tests	NCT03604848
InDEX	4	Yes	South Africa	Individualised regimens	NS	Gene-derived individualised regimen	NCT03237182
PROSPECT	4	No	China	Clofazimine, cycloserine, levofloxacin, linezolid, and prothionamide; or bedaquiline, clofazimine, cycloserine, levofloxacin, and linezolid	6 (first regimen), 9 (second regimen)		NCT05306223
TB-TRUST	3	Yes	China	Levofloxacin, linezolid, cycloserine, and pyrazinamide (or clofazimine if resistant to pyrazinamide)	6–9		NCT03867136
Rifampicin-resistant, fluoroquinolone-resistant tuberculosis							
endTB-Q	3	Yes	Multicountry	Bedaquiline, clofazimine, delamanid, and linezolid	6–9	Strategy trial; duration adapted to extent of disease and treatment response.	NCT03896685
mBPaL	3	No	India	Bedaquiline, pretomanid, and linezolid at different dosages	6		NCT05040126

NS: not stated. Reproduced and modified from [8] and [82] with permission. Data from [91].

trials aim to optimise the successful TBTC S31/ACTG 5349 regimen [31] by identifying the optimal dosageof rifapentine (ORIENT) or by adding clofazimine (CLO-Fast). Another common design is testing experimental regimens that include new/repurposed drugs in combination with fluoroquinolones and first-line drugs (PRESCIENT, SimpliciTB, TRUNCATE-TB). Finally, one trial adds a fluoroquinolone to the standard regimen (NCT02901288), similarly to previous trials which failed to show non-inferiority [98]. Overall, the duration of the experimental regimens in these trials ranges from 2 to 4 months. The trial design is conventional in most cases, with a few exceptions including Phase 2C (CLO-FAST, PRESCIENT) [99], and multi-arm multi-stage designs (TRUNCATE-TB).

Ongoing trials on DR-TB (table 7) enrol all patients with rifampicin-resistance (*i.e.* A5356) or only those with susceptibility to fluoroquinolones (*i.e.* endTB). Another approach, exemplified by BEAT TB, is to include all RR-TB patients and adapt the regimen to results of rapid molecular testing for fluoroquinolone resistance. Almost all experimental regimens include a bedaquiline–linezolid backbone, with the possible addition of a nitroimidazole (delamanid or pretomanid), clofazimine, a fluoroquinolone, and/or pyrazinamide. Tested durations range between 4 and 9 months. Novel trial designs are increasingly frequent, including Bayesian adaptive [100, 101] (endTB) and duration-randomised designs (DRAMATIC) [102, 103]. Two trials (GRACE-TB and InDEX) compare individualised treatment guided by next-generation sequencing to a control. Concerningly, clinical research on the most advanced forms of DR-TB is lacking. No more than a couple of trials specifically target pre-XDR-TB, only one including an internal control arm [104]. To date, no trials are ongoing/planned on XDR-TB.

Overall, a wealth of clinical trial results will be available in the coming years. Further innovations in trial methodology [105], increased resources [106], and harmonisation of trial conduct, implementation, and assessments [107, 108], will optimise the impact of future clinical research.

Conclusion

Recent years have seen much-awaited improvements in TB treatment. The historical paradigm of the 6-month “short course” treatment for DS-TB has fallen [31] and treatment duration for RR-TB has been reduced to one-third of the previous time [71, 72, 109]. In addition, recent reports suggest that further treatment shortening may be possible [61]. This news has been welcomed by the scientific community with understandable excitement. However, a few reasons for concern exist. History has shown how quickly new TB drugs can be followed by the emergence of drug resistance [110]. By introducing new regimens with scarce global capacity for DST, past mistakes are being repeated [74]. Furthermore, implementation of conditional recommendations based on very low certainty of evidence, like the recent WHO DR-TB guidelines, should be performed carefully and considering patient choice among treatment options [46]. Finally, access to new drugs and regimens is a global emergency that requires commitment and adequate investments. Future efforts should be directed to protect these recent advances, while striving for further breakthroughs.

References

1 World Health Organization. Global tuberculosis report 2022. Geneva, World Health Organization, 2022.
2 Horsburgh CR, Jr, Barry CE 3rd, Lange C. Treatment of tuberculosis. *N Engl J Med* 2015; 373: 2149–2160.
3 World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. 2019.
4 World Health Organization. Guidelines for treatment of drug-susceptible tuberculosis and patient care (2017 update). Geneva, World Health Organization, 2017.

 https://doi.org/10.1183/2312508X.10024622

5 World Health Organization. Treatment of drug-susceptible tuberculosis: rapid communication. Geneva, World Health Organization, 2021.
6 World Health Organization. Rapid communication: key changes to the treatment of drug-resistant tuberculosis. Geneva, World Health Organization, 2022.
7 World Health Organization. WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents. Geneva, World Health Organization, 2022.
8 Lange C, Barry CE3rd, Horsburgh CR, Jr. Treatments of multidrug-resistant tuberculosis: light at the end of the tunnel. *Am J Respir Crit Care Med* 2022; 205: 1142–1144.
9 Lange C, Dheda K, Chesov D, *et al.* Management of drug-resistant tuberculosis. *Lancet* 2019; 394: 953–966.
10 Bloemberg GV, Keller PM, Stucki D, *et al.* Acquired resistance to bedaquiline and delamanid in therapy for tuberculosis. *N Engl J Med* 2015; 373: 1986–1988.
11 Koehler N, Andres S, Merker M, *et al.* Pretomanid-resistant tuberculosis. *J Infect* 2023; 86: 520–524.
12 Keers RY. Two forgotten pioneers. James Carson and George Bodington. *Thorax* 1980; 35: 483–489.
13 Daniel TM. Hermann Brehmer and the origins of tuberculosis sanatoria. *Int J Tuberc Lung Dis* 2011; 15: 161–162, i.
14 Murray JF. Bill Dock and the location of pulmonary tuberculosis: how bed rest might have helped consumption. *Am J Respir Crit Care Med* 2003; 168: 1029–1033.
15 Murray JF, Schraufnagel DE, Hopewell PC. Treatment of tuberculosis. A historical perspective. *Ann Am Thorac Soc* 2015; 12: 1749–1759.
16 Rosenblatt MB. Pulmonary tuberculosis: evolution of modern therapy. *Bull N Y Acad Med* 1973: 49: 163–196.
17 Bignall JR. A century of treating tuberculosis. *Tubercle* 1982; 63: 19–22.
18 Riva MA. From milk to rifampicin and back again: history of failures and successes in the treatment for tuberculosis. *J Antibiot (Tokyo)* 2014: 67: 661–665.
19 Benedek TG. The history of gold therapy for tuberculosis. *J Hist Med Allied Sci* 2004; 59: 50–89.
20 Odell JA. The history of surgery for pulmonary tuberculosis. *Thorac Surg Clin* 2012; 22: 257–269.
21 Martini M, Gazzaniga V, Behzadifar M, *et al.* The history of tuberculosis: the social role of sanatoria for the treatment of tuberculosis in Italy between the end of the 19th century and the middle of the 20th. *J Prev Med Hyg* 2018; 59: E323–E327.
22 Tuberculosis Chemotherapy Centre. A concurrent comparison of home and sanatorium treatment of pulmonary tuberculosis in South India. *Bull World Health Organ* 1959; 21: 51–144.
23 Keshavjee S, Farmer PE. Tuberculosis, drug resistance, and the history of modern medicine. *N Engl J Med* 2012; 367: 931–936.
24 Hinshaw HC, Feldman WH, Pfuetze KH. Treatment of tuberculosis with streptomycin; a summary of observations on one hundred cases. *J Am Med Assoc* 1946; 132: 778–782.
25 Jellinek K. Streptomycin in the treatment of extrapulmonary tuberculosis; early results. *N Engl J Med* 1949; 240: 680–683.
26 Medical Research Council. STREPTOMYCIN treatment of pulmonary tuberculosis. *Br Med J* 1948; 2: 769–782.
27 Fox W, Sutherland I, Daniels M. A five-year assessment of patients in a controlled trial of streptomycin in pulmonary tuberculosis; report to the Tuberculosis Chemotherapy Trials Committee of the Medical Research Council. *Q J Med* 1954; 23: 347–366.
28 Zumla AI, Gillespie SH, Hoelscher M, *et al.* New antituberculosis drugs, regimens, and adjunct therapies: needs, advances, and future prospects. *Lancet Infect Dis* 2014; 14: 327–340.
29 Tempel CW, Hughes FJ, Jr, Mardis RE, *et al.* Combined intermittent regimens employing streptomycin and para-aminosalicylic acid in the treatment of pulmonary tuberculosis; a comparison with daily and intermittent dosage schedules. *Am Rev Tuberc* 1951; 63: 295–311.
30 Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946–1986, with relevant subsequent publications. *Int J Tuberc Lung Dis* 1999; 3: 10 Suppl 2, S231–S279-.
31 Dorman SE, Nahid P, Kurbatova EV, *et al.* Four-month rifapentine regimens with or without moxifloxacin for tuberculosis. *N Engl J Med* 2021; 384: 1705–1718.
32 Campbell EA, Korzheva N, Mustaev A, *et al.* Structural mechanism for rifampicin inhibition of bacterial rna polymerase. *Cell* 2001; 104: 901–912.
33 Bernardes-Genisson V, Deraeve C, Chollet A, *et al.* Isoniazid: an update on the multiple mechanisms for a singular action. *Curr Med Chem* 2013; 20: 4370–4385.
34 Wang F, Langley R, Gulten G, *et al.* Mechanism of thioamide drug action against tuberculosis and leprosy. *J Exp Med* 2007; 204: 73–78.
35 Zhang Y, Shi W, Zhang W, *et al.* Mechanisms of pyrazinamide action and resistance. *Microbiol Spectr* 2013; 2: 1–12.
36 Aldred KJ, Blower TR, Kerns RJ, *et al.* Fluoroquinolone interactions with *Mycobacterium tuberculosis* gyrase: enhancing drug activity against wild-type and resistant gyrase. *Proc Natl Acad Sci USA* 2016; 113: E839–E846.

37 Krause KM, Serio AW, Kane TR, *et al.* Aminoglycosides: an overview. *Cold Spring Harb Perspect Med* 2016; 6: a027029.
38 Dietze R, Hadad DJ, McGee B, *et al.* Early and extended early bactericidal activity of linezolid in pulmonary tuberculosis. *Am J Respir Crit Care Med* 2008; 178: 1180–1185.
39 Minato Y, Thiede JM, Kordus SL, *et al. Mycobacterium tuberculosis* folate metabolism and the mechanistic basis for *para*-aminosalicylic acid susceptibility and resistance. *Antimicrob Agents Chemother* 2015; 59: 5097–5106.
40 Hards K, Robson JR, Berney M, *et al.* Bactericidal mode of action of bedaquiline. *J Antimicrob Chemother* 2015; 70: 2028–2037.
41 Khoshnood S, Taki E, Sadeghifard N, *et al.* Mechanism of action, resistance, synergism, and clinical implications of delamanid against multidrug-resistant *Mycobacterium tuberculosis*. *Front Microbiol* 2021; 12: 717045.
42 Gils T, Lynen L, de Jong BC, *et al.* Pretomanid for tuberculosis: a systematic review. *Clin Microbiol Infect* 2022: 28: 31–42.
43 Alghamdi WA, Alsultan A, Al-Shaer MH, *et al.* Cycloserine population pharmacokinetics and pharmacodynamics in patients with tuberculosis. *Antimicrob Agents Chemother* 2019; 63: e00055-19.
44 Gopal M, Padayatchi N, Metcalfe JZ, *et al.* Systematic review of clofazimine for the treatment of drug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2013: 17: 1001–1007.
45 Davies Forsman L, Giske CG, Bruchfeld J, *et al.* Meropenem-clavulanate has high in vitro activity against multidrug-resistant *Mycobacterium tuberculosis*. *Int J Mycobacteriol* 2015; 4: Suppl 1, 80–81.
46 World Health Organization. WHO consolidated guidelines on tuberculosis. Module 4: Treatment – Drug-susceptible tuberculosis treatment. Geneva, World Health Organization, 2022.
47 National Institute for Health and Care Excellence. Tuberculosis: NICE guideline 33. 2016 edition. www.nice.org.uk/guidance/ng33
48 Nahid P, Mase SR, Migliori GB, *et al.* Treatment of Drug-Resistant Tuberculosis. An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline. *Am J Respir Crit Care Med* 2019; 200: e93–e142.
49 Caminero JA, Scardigli A, van der Werf T, *et al.* Treatment of drug-susceptible and drug-resistant tuberculosis. *In:* Migliori GB, Bothamley G, Duarte R, *et al.* eds. Tuberculosis (ERS Monograph). Sheffield, European Respiratory Society, 2018; pp. 152–178.
50 Gallardo CR, Rigau Comas D, Valderrama Rodríguez A, *et al.* Fixed-dose combinations of drugs versus single-drug formulations for treating pulmonary tuberculosis. *Cochrane Database Syst Rev* 2016; 2016: CD009913.
51 Menzies D, Benedetti A, Paydar A, *et al.* Effect of duration and intermittency of rifampin on tuberculosis treatment outcomes: a systematic review and meta-analysis. *PLoS Med* 2009; 6: e1000146.
52 Swaminathan S, Narendran G, Venkatesan P, *et al.* Efficacy of a 6-month versus 9-month intermittent treatment regimen in HIV-infected patients with tuberculosis: a randomized clinical trial. *Am J Respir Crit Care Med* 2010; 181: 743–751.
53 Lienhardt C, Cook SV, Burgos M, *et al.* Efficacy and safety of a 4-drug fixed-dose combination regimen compared with separate drugs for treatment of pulmonary tuberculosis: the Study C randomized controlled trial. *JAMA* 2011; 305: 1415–1423.
54 Johnson JL, Hadad DJ, Dietze R, *et al.* Shortening treatment in adults with noncavitary tuberculosis and 2-month culture conversion. *Am J Respir Crit Care Med* 2009; 180: 558–563.
55 Blanc FX, Sok T, Laureillard D, *et al.* Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med* 2011; 365: 1471–1481.
56 Gillespie SH, Crook AM, McHugh TD, *et al.* Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *N Engl J Med* 2014; 371: 1577–1587.
57 Merle CS, Fielding K, Sow OB, *et al.* A four-month gatifloxacin-containing regimen for treating tuberculosis. *N Engl J Med* 2014; 371: 1588–1598.
58 World Health Organization. WHO operational handbook on tuberculosis. Module 4: Treatment - Drug-resistant tuberculosis treatment. Geneva, World Health Organization, 2020.
59 Treatment Action Group. An Activist's Guide to Rifapentine for the Treatment of TB Infection. Date last accessed: 12 February 2023; date last updated: April 2020. www.treatmentactiongroup.org/publication/an-activists-guide-to-rifapentine-for-the-treatment-of-tb-infection/
60 Günther G, Guglielmetti L, Leu C, *et al.* Availability and costs of medicines for the treatment of tuberculosis in Europe. *Clin Microbiol Infect* 2023; 29: 77–84.
61 Paton NI, Cousins C, Suresh C, *et al.* Treatment strategy for rifampin-susceptible tuberculosis. *N Engl J Med* 2023; 388: 873–887.
62 Turkova A, Wills GH, Wobudeya E, *et al.* Shorter treatment for nonsevere tuberculosis in African and Indian children. *N Engl J Med* 2022; 386: 911–922.

 https://doi.org/10.1183/2312508X.10024622

63 World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2nd edn. Geneva, World Health Organization, 2014.
64 De Castro N, Mechai F, Bachelet D, *et al.* Treatment with a three-drug regimen for pulmonary tuberculosis based on rapid molecular detection of isoniazid resistance: a noninferiority randomized trial (FAST-TB). *Open Forum Infect Dis* 2022; 9: ofac353.
65 Fregonese F, Ahuja SD, Akkerman OW, *et al.* Comparison of different treatments for isoniazid-resistant tuberculosis: an individual patient data meta-analysis. *Lancet Respir Med* 2018; 6: 265–275.
66 Ramachandran G, Hemanth Kumar AK, Srinivasan R, *et al.* Effect of rifampicin & isoniazid on the steady state pharmacokinetics of moxifloxacin. *Indian J Med Res* 2012; 136: 979–984.
67 Lempens P, Meehan CJ, Vandelannoote K, *et al.* Isoniazid resistance levels of Mycobacterium tuberculosis can largely be predicted by high-confidence resistance-conferring mutations. *Sci Rep* 2018; 8: 3246.
68 World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, WHO, 2008.
69 Lan Z, Ahmad N, Baghaei P, *et al.* Drug-associated adverse events in the treatment of multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Lancet Respir Med* 2020; 8: 383–394.
70 Conradie F, Diacon AH, Ngubane N, *et al.* Treatment of highly drug-resistant pulmonary tuberculosis. *N Engl J Med* 2020; 382: 893–902.
71 Conradie F, Bagdasaryan TR, Borisov S, *et al.* Bedaquiline–pretomanid–linezolid regimens for drug-resistant tuberculosis. *N Engl J Med* 2022; 387: 810–823.
72 Nyang'wa BT, Berry C, Kazounis E, *et al.* A 24-week, all-oral regimen for rifampin-resistant tuberculosis. *N Engl J Med* 2022; 387: 2331–2343.
73 Dheda K, Lange C. A revolution in the management of multidrug-resistant tuberculosis. *Lancet* 2022; 400: 1823–1825.
74 Lange C, Kohler N, Gunther G. Regimens for drug-resistant tuberculosis. *N Engl J Med* 2023; 388: 190.
75 World Health Organization. WHO operational handbook on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, update. Geneva, World Health Organization, 2022.
76 Collaborative Group for the Meta-Analysis of Individual Patient Data in MDRTB treatment-2017, Ahmad N, Ahuja SD, *et al.* Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Lancet* 2018; 392: 821–834.
77 Harrison GA, Mayer Bridwell AE, Singh M, *et al.* Identification of 4-amino-thieno[2,3-d]pyrimidines as QcrB inhibitors in *Mycobacterium tuberculosis*. *mSphere* 2019; 4: e00606-19.
78 Mali SN, Pandey A, Bhandare RR, *et al.* Identification of hydantoin based Decaprenylphosphoryl-beta-D-Ribose Oxidase (DprE1) inhibitors as antimycobacterial agents using computational tools. *Sci Rep* 2022; 12: 16368.
79 Poce G, Consalvi S, Biava M. MmpL3 inhibitors: diverse chemical scaffolds inhibit the same target. *Mini Rev Med Chem* 2016; 16: 1274–1283.
80 Zhang P, Ma S. Recent development of leucyl-tRNA synthetase inhibitors as antimicrobial agents. *Medchemcomm* 2019; 10: 1329–1341.
81 P SH, Solapure S, Mukherjee K, *et al.* Optimization of pyrrolamides as mycobacterial GyrB ATPase inhibitors: structure-activity relationship and in vivo efficacy in a mouse model of tuberculosis. *Antimicrob Agents Chemother* 2014; 58: 61–70.
82 McKenna L. Treatment Action Group Pipeline report 2022. www.treatmentactiongroup.org/resources/pipeline-report/2022-pipeline-report/
83 Koele SE, Phillips PPJ, Upton CM, *et al.* Early bactericidal activity studies for pulmonary tuberculosis: A systematic review of methodological aspects. *Int J Antimicrob Agents* 2023; 61: 106775.
84 GlaxoSmithKline. GSK announces positive Phase IIa study results for a new first-in-class candidate medicine for patients with tuberculosis. Date last updated: 14 November 2022. www.gsk.com/en-gb/media/press-releases/gsk-announces-positive-phase-iia-study-results-for-a-new-first-in-class-candidate-medicine/.
85 de Jager VR, Dawson R, van Niekerk C, *et al.* Telacebec (Q203), a new antituberculosis agent. *N Engl J Med* 2020; 382: 1280–1281.
86 Heinrich N. BTZ-043 drug development programme. Date last updated: 13 November 2022. www.newtbdrugs.org/sites/default/files/meetings/files/13_Norbert%20Heinrich_LMU%20Munich.pdf.
87 Boeree MJ, Lange C, Thwaites G, *et al.* UNITE4TB: a new consortium for clinical drug and regimen development for TB. *Int J Tuberc Lung Dis* 2021; 25: 886–889.
88 New TB Drugs Working Group. PAN-TB collaboration announces novel tb drug regimens trial. Date last updated: 23 August 2022. https://www.newtbdrugs.org/news/pan-tb-collaboration-announces-novel-tb-drug-regimens-trial
89 Lee A, Xie YL, Barry CE, *et al.* Current and future treatments for tuberculosis. *BMJ* 2020; 368: m216.
90 Phillips PPJ, Mitnick CD, Neaton JD, *et al.* Keeping phase III tuberculosis trials relevant: adapting to a rapidly changing landscape. *PLoS Med* 2019; 16: e1002767.

91 RESIST-TB. DR-TB Clinical Trial Progress Report. Date last accessed: 3 July 2023. www.resisttb.org/clinical-trials-progress-report
92 Te Brake LHM, de Jager V, Narunsky K, *et al.* Increased bactericidal activity but dose-limiting intolerability at 50 mg.kg^{-1} rifampicin. *Eur Respir J* 2021; 58: 2000955.
93 Velasquez GE, Brooks MB, Coit JM, *et al.* Efficacy and safety of high-dose rifampin in pulmonary tuberculosis. a randomized controlled trial. *Am J Respir Crit Care Med* 2018; 198: 657–666.
94 Boeree MJ, Heinrich N, Aarnoutse R, *et al.* High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised controlled trial. *Lancet Infect Dis* 2017; 17: 39–49.
95 Boeree MJ, Diacon AH, Dawson R, *et al.* A dose-ranging trial to optimize the dose of rifampin in the treatment of tuberculosis. *Am J Respir Crit Care Med* 2015; 191: 1058–1065.
96 Guglielmetti L, Gunther G, Leu C, *et al.* Rifapentine access in Europe: growing concerns over key tuberculosis treatment component. *Eur Respir J* 2022; 59: 2200388.
97 Masini T, Kanchar A, Mirzayev F, *et al.* Wider access to quality-assured rifapentine-based regimens is needed to accelerate tuberculosis prevention and care globally. *Eur Respir J* 2022; 60: 2201227.
98 Nimmo C, Lipman M, Phillips PP, *et al.* Shortening treatment of tuberculosis: lessons from fluoroquinolone trials. *Lancet Infect Dis* 2015; 15: 141–143.
99 Phillips PP, Dooley KE, Gillespie SH, *et al.* A new trial design to accelerate tuberculosis drug development: the Phase IIC Selection Trial with Extended Post-treatment follow-up (STEP). *BMC Med* 2016; 14: 51.
100 Cellamare M, Ventz S, Baudin E, *et al.* A Bayesian response-adaptive trial in tuberculosis: The endTB trial. *Clin Trials* 2017; 14: 17–28.
101 Cellamare M, Milstein M, Ventz S, *et al.* Bayesian adaptive randomization in a clinical trial to identify new regimens for MDR-TB: the endTB trial. *Int J Tuberc Lung Dis* 2016; 20: 8–12.
102 Horsburgh CR, Shea KM, Phillips P, *et al.* Randomized clinical trials to identify optimal antibiotic treatment duration. *Trials* 2013; 14: 88.
103 Quartagno M, Walker AS, Carpenter JR, *et al.* Rethinking non-inferiority: a practical trial design for optimising treatment duration. *Clin Trials* 2018; 15: 477–488.
104 Guglielmetti L, Low M, McKenna L. Challenges in TB regimen development: preserving evidentiary standards for regulatory decisions and policymaking. *Expert Rev Anti Infect Ther* 2020; 18: 701–704.
105 Lienhardt C, Vernon AA, Cavaleri M, *et al.* Development of new TB regimens: harmonizing trial design, product registration requirements, and public health guidance. *PLoS Med* 2019; 16: e1002915.
106 Nyang'wa BT, LaHood AN, Mitnick CD, *et al.* TB research requires strong protections, innovation, and increased funding in response to COVID-19. *Trials* 2021; 22: 371.
107 Hills NK, Lyimo J, Nahid P, *et al.* A systematic review of endpoint definitions in late phase pulmonary tuberculosis therapeutic trials. *Trials* 2021; 22: 515.
108 Bonnett LJ, Ken-Dror G, Koh G, *et al.* Comparing the efficacy of drug regimens for pulmonary tuberculosis: meta-analysis of endpoints in early-phase clinical trials. *Clin Infect Dis* 2017; 65: 46–54–.
109 Goodall RL, Meredith SK, Nunn AJ, *et al.* Evaluation of two short standardised regimens for the treatment of rifampicin-resistant tuberculosis (STREAM stage 2): an open-label, multicentre, randomised, non-inferiority trial. *Lancet* 2022; 400: 1858–1868-.
110 Guglielmetti L. Bedaquiline for the treatment of multidrug-resistant tuberculosis: another missed opportunity? *Eur Respir J* 2017; 49: 1700738.

Disclosures: C. Lange reports the following, outside the submitted work: receipt of consulting fees from INSMED; receipt of speaker's honoraria from INSMED and GILEAD; membership of the data safety board of trails for MSF. L. Guglielmetti reports receiving grants or contracts from Unitaid, outside the submitted work. The remaining authors have nothing to disclose.

 https://doi.org/10.1183/2312508X.10024622