



New anti-tuberculosis drugs and regimens: 2015 update

Lia D'Ambrosio^{1,6}, Rosella Centis^{1,6}, Giovanni Sotgiu², Emanuele Pontali³, Antonio Spanevello^{4,5} and Giovanni Battista Migliori¹

Affiliations: ¹WHO Collaborating Centre for Tuberculosis & Lung Diseases, Fondazione S. Maugeri, IRCCS, Tradate, Italy. ²Clinical Epidemiology and Medical Statistics Unit, Department of Biomedical Sciences, University of Sassari - Research, Medical Education and Professional Development Unit, AOU Sassari, Sassari, Italy. ³Department of Infectious Diseases, Galliera Hospital, Genoa, Italy. ⁴Pneumology Unit, Fondazione Maugeri, IRCCS, Tradate, Italy. ⁵Dept of Clinical and Experimental Medicine, University of Insubria, Varese, Italy. ⁶These authors contributed equally.

Correspondence: Giovanni Battista Migliori, World Health Organization Collaborating Centre for Tuberculosis and Lung Diseases, Fondazione S. Maugeri, IRCCS, Via Roncaccio 16, 21049, Tradate, Italy.
E-mail: giovannibattista.migliori@fsm.it

ABSTRACT Over 480 000 cases of multidrug-resistant (MDR) tuberculosis (TB) occur every year globally, 9% of them being affected by extensively drug-resistant (XDR) strains of *Mycobacterium tuberculosis*. The treatment of MDR/XDR-TB is unfortunately long, toxic and expensive, and the success rate largely unsatisfactory (<20% among cases with resistance patterns beyond XDR).

The aim of this review is to summarise the available evidence-based updated international recommendations to manage MDR/XDR-TB, and to update the reader on the role of newly developed drugs (delamanid, bedaquiline and pretomanid) as well as repurposed drugs (linezolid and meropenem clavulanate, among others) used to treat these conditions within new regimens.

A nonsystematic review based on historical trials results as well as on recent literature and World Health Organization (WHO) guidelines has been performed, with special focus on the approach to managing MDR/XDR-TB.

The new, innovative global public health interventions, recently approved by WHO and known as the "End TB Strategy", support the vision of a TB-free world with zero death, disease and suffering due to TB. Adequate, universally accessed treatment is a pre-requisite to reach TB elimination. New shorter, cheap, safe and effective anti-TB regimens are necessary to boost TB elimination.



@ERSpublications

The new WHO post-2015 End TB Strategy will support the efforts that research on new drugs and regimens requires <http://ow.ly/LnJER>



Introduction

In 2014, the World Health Organization (WHO) estimated 9 million new tuberculosis (TB) cases had occurred globally in 2013, 480 000 of them being affected by multidrug-resistant (MDR) *Mycobacterium tuberculosis* strains [1]. MDR-TB is defined as resistance *in vitro* to at least isoniazid and rifampicin, while extensively drug-resistant (XDR)-TB is resistant to at least one fluoroquinolone and one injectable second-line anti-TB drug in addition to isoniazid and rifampicin [2–5].

In “hot spots” (e.g. in some former Soviet Union countries), between 20% and 30% of the new TB cases are infected by MDR-TB strains (the global average is 3.5%) [1], while a proportion up to 50% is observed among retreated cases (figs 1 and 2) [3, 6, 7]. As MDR/XDR-TB clinical outcomes are largely suboptimal and their treatment very long, toxic and expensive, these difficult-to-treat cases are considered a serious threat to TB control and elimination [4, 5, 8, 9].

A recent study demonstrated that while in Germany the MDR-TB treatment-related costs exceed €50 000 [8], in Europe, the average cost to treat a single XDR-TB case is over €160 000 [8]. The largest meta-analytic study presently available revealed that MDR-TB treatment success is only 54% (with 15% death, 8% failure/relapse and 23% default). When the drug resistance profile is beyond XDR (with increasing complexity), the outcomes are unfortunately lower: treatment success ranges from 40% to 19%, failure/relapse from 15% to 54% and death from 15% to 35% [4, 5].

Every day, clinicians managing these cases face relevant challenges that include frequent occurrence of adverse events, problems in patients' adherence, lack of clinical experience, and limited availability of adequate diagnostics and second-line anti-TB drugs (in some countries). The risk of acquiring further drug resistance is therefore real.

WHO has recently launched its innovative “End TB Strategy” [1], supporting the TB elimination strategy and the vision of a TB-free world with zero death, disease and suffering due to TB [10–12]. The new strategy clearly supports universal access to high-quality MDR-TB diagnosis and treatment. However, since the market launch of rifampicin in the early 1960s, no new anti-TB drug has been specifically developed until recently, while significant progress has been achieved in the area of diagnostics (e.g. Xpert MTB/RIF test; Cepheid, Sunnyvale, CA, USA) [1, 13]. The need for new drugs and regimens is obvious [14–16].

The aim of this review is to summarise, based on evidence, how to design an anti-TB regimen, and the updated international recommendations to manage MDR/XDR-TB, and to update the reader on the role of newly developed drugs (delamanid, bedaquiline and pretomanid) as well as repurposed drugs (linezolid and meropenem clavulanate, among others) used to treat these conditions within new regimens. A nonsystematic review based on historical trials results as well as on recent literature and WHO guidelines has been performed, with special focus on the approach to managing MDR/XDR-TB.

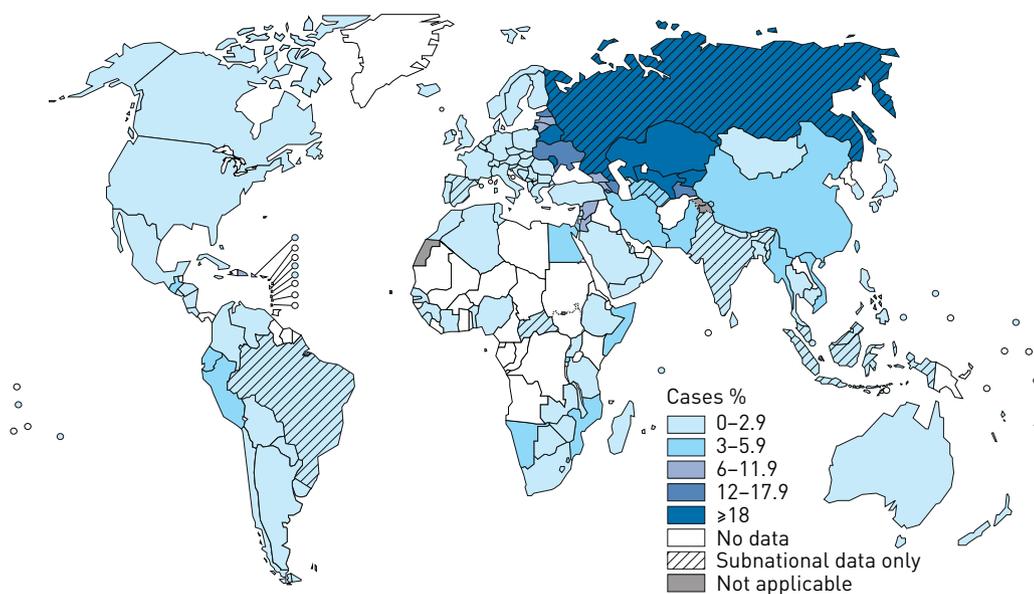


FIGURE 1 Percentage of new tuberculosis (TB) cases with multidrug-resistant TB. Figures are based on the most recent year for which data have been reported, which varies among countries. Reproduced from [1] with permission from the publisher.

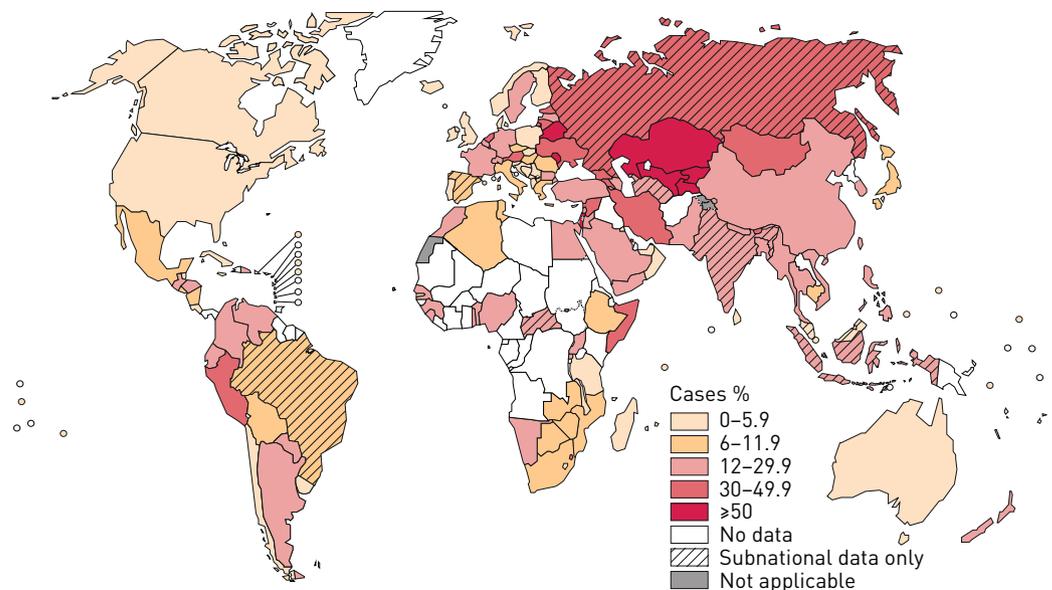


FIGURE 2 Percentage of previously treated tuberculosis (TB) cases with multidrug-resistant (MDR)-TB. Figures are based on the most recent year for which data have been reported, which varies among countries. The high percentages of previously treated TB cases with MDR-TB in Bahrain, Bonaire, Israel, Saint Eustatius and Saba, and Sao Tomé and Príncipe refer to only small numbers of notified cases (range 1–8 notified previously treated TB cases). Reproduced from [1] with permission from the publisher.

Designing a regimen to treat TB

The treatment regimens, approved TB drugs and the dosage of anti-TB drugs recommended by the evidence-based WHO guidelines (presently under revision) are summarised in tables 1 and 2. “New” and “retreatment” cases are clearly separated, 30 days of previous anti-TB treatment being the cut-off [17]. New TB cases (irrespective of HIV status) should be treated for the first 2 months (intensive phase) with isoniazid, rifampicin, pyrazinamide and ethambutol, followed by isoniazid and rifampicin for the remaining 4 months (continuation phase) [17]. The daily dosage is recommended (although the three times weekly dosing can be used during the continuation phase under directly observed therapy) as well as the fixed-dose combinations [18].

Drug susceptibility testing (DST) (rapid and/or conventional) is strongly recommended by WHO in all cases and particularly for those previously treated [1]. While awaiting DST results, in settings with a

TABLE 1 World Health Organization recommended treatment regimens for new patients

Intensive phase		Continuation phase	
Drug	Duration months	Drug	Duration months
Ethambutol [#] Isoniazid Pyrazinamide Rifampicin	2	Isoniazid [¶] Rifampicin [¶]	4
Ethambutol [#] Isoniazid Pyrazinamide Rifampicin	2	Ethambutol [¶] Isoniazid [¶] Rifampicin [¶]	4 [*]

[#]: ethambutol has to be prescribed in individuals with noncavitary, sputum smear-negative pulmonary tuberculosis (TB) or with extrapulmonary TB who are known to be HIV negative; in TB meningitis, it should be replaced by streptomycin. [¶]: the World Health Organization considers the three times per week continuation phase as an acceptable alternative for any new TB patient receiving directly observed therapy. ^{*}: when the level of isoniazid resistance among new cases is elevated and *in vitro* isoniazid drug susceptibility testing is not available, isoniazid (H)–rifampicin (R)–ethambutol regimen may be an acceptable alternative to HR regimen. Information from [17].

TABLE 2 World Health Organization recommended treatment regimens for previously treated patients, pending drug susceptibility testing (DST) results[#]

Probability of MDR-TB		
Medium or low [¶]		High [*]
Drug	Duration months (phase)	
Ethambutol Isoniazid Pyrazinamide Rifampicin Streptomycin	2 (intensive)	Empirical MDR-TB regimen
Ethambutol Isoniazid Pyrazinamide Rifampicin Ethambutol Isoniazid Rifampicin	1 (intensive)	
To be changed once DST testing results are available	5 (continuation)	To be changed once DST testing results are available

MDR: multidrug-resistant; TB: tuberculosis. [#]: up to 2–3 months after the start of treatment; [¶]: relapse, lost to follow-up; ^{*}: failure. Information from [17].

medium or low probability of MDR-TB, retreatment cases could initially be treated with an empiric regimen including isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin for 2 months, followed by isoniazid, rifampicin, pyrazinamide and ethambutol for 1 month, and isoniazid, rifampicin, and ethambutol for 5 months.

Designing a regimen to treat MDR-TB

Based on their effectiveness and safety, WHO identified five groups of anti-TB drugs (table 3) [9]. A stepwise approach is recommended to design treatment regimens for MDR-TB cases (table 4) [9, 19, 20]. Although DST-guided individualised regimens have to be preferred, standardised regimens are used in setting where DST is not available. They are based on representative patient population data, ensuring that treatment regimens are likely to include a sufficient number of active drugs (four) to ensure treatment success.

Rational MDR-TB treatment should include a minimum of four active drugs: a later-generation fluoroquinolone (moxifloxacin, gatifloxacin or levofloxacin) plus an injectable aminoglycoside (amikacin, capreomycin or kanamycin) plus any first-line drug to which the isolate is susceptible (*e.g.*, pyrazinamide) plus the addition of one drug from group 4 (cycloserine, p-aminosalicylic acid (PAS), terizidone, prothionamide or ethionamide) (table 4). The drugs belonging to group 5 should be included whenever four active drugs are not available from previous groups. When using injectables, the minimum duration of the intensive phase is 8 months, the continuation phase lasting for 12–18 months, for a total treatment duration of at least 20 months. As a rule, 18 months need to be added to the date of the first negative culture to define the final treatment duration. In the case of failure to achieve culture conversion, the underlying causes (incorrect drug dosage, quality of drug supply, nonadherence factors, malabsorption and comorbidity) need to be identified and, possibly, corrected.

Unfortunately, the TB armamentarium is presently based on a limited number of effective drugs and the “optimised background regimens” (OBRs) used in clinical practice have not been tested in randomised controlled trials: clinicians are often forced to add some toxic old drugs (*e.g.* PAS, ethionamide and cycloserine) to more effective drugs that have been developed for indications other than TB.

Repurposed drugs

Linezolid

Linezolid was prescribed “off label” before reliable data from multicentre observational studies were made available [21]. At a later stage, systematic (individual and nonindividual) reviews and experimental data further defined the linezolid profile [22–27].

TABLE 3 World Health Organization groups of first- and second-line anti-TB drugs

Group	Anti-TB drugs
1) First-line oral anti-TB drugs	Isoniazid (H) Rifampicin (R) Ethambutol (E) Pyrazinamide (Z) Rifabutin (Rfb) Rifapentine (Rpt)
2) Injectable anti-TB drugs (injectable or parenteral agents)	Streptomycin (S) Kanamycin (Km) Amikacin (Am) Capreomycin (Cm)
3) Fluoroquinolones (FQs)	Levofloxacin (Lfx) Moxifloxacin (Mfx) Gatifloxacin (Gfx) Ofloxacin (Ofx)
4) Oral bacteriostatic second-line anti-TB drugs	Ethionamide (Eto) Prothionamide (Pto) Cycloserine (Cs) Terizidone (Trd) p-Aminosalicylic acid (PAS) p-Aminosalicylate sodium (PAS-Na)
5) Anti-TB drugs with limited data on efficacy and/or long-term safety in the treatment of drug-resistant TB	Bedaquiline (Bdq) Delamanid (Dlm) Linezolid (Lzd) Clofazimine (Cfz) Amoxicillin/clavulanate (Amx/Clv) Imipenem/cilastatin (Ipm/Cln) Meropenem (Mpm) High-dose isoniazid (high-dose H) Thioacetazone (T) Clarithromycin (Clr)

TB: tuberculosis. Reproduced and modified from [19] with permission from the publisher.

Linezolid, a first-generation oxazolidinone, demonstrated clinical effectiveness in most difficult-to-treat drug-resistant cases, although the frequency and severity of adverse events (*i.e.* peripheral neuropathy, optic neuropathy, gastrointestinal disorders and myelosuppression) limit its long-term use [23]. A recent prospective randomised trial enrolling XDR-TB patients failing previous chemotherapy demonstrated the efficacy of a reduced linezolid dosage (300–600 mg per day), confirming previous findings [21]: 87% of all enrolled patients achieved bacteriological conversion within 6 months [24]. As four patients acquired resistance during treatment (three of them receiving 300 mg per day), additional evidence is necessary to assess the optimal dose and adequate duration of treatment. Interesting studies have been conducted to prevent adverse events while maintaining the efficacy of linezolid using intermittent dosing and of increasing linezolid concentration in combination with clarithromycin (table 5) [28, 29]. An innovative study from the Netherlands [29] suggested that clarithromycin can boost the blood levels of linezolid, allowing administration of lower doses with fewer adverse events and economic savings. A recent individual-data meta-analysis [23] provided updated evidence on efficacy, safety and tolerability of linezolid, and indirect evidence that a proper treatment drug monitoring (TDM) approach to drug dosage can reduce linezolid toxicity (fig. 3) [31].

Recently, although not yet approved by regulatory authorities, another oxazolidinone drug (sutezolid) is attracting interest, being better tolerated [32].

As of today, a daily linezolid dose ranging between 300 and 600 mg seems to be adequate to treat MDR/XDR-TB when added to OBR [21–29, 31–35].

Meropenem/clavulanate

Meropenem clavulanate is active *in vitro* against *M. tuberculosis*, showing a good tolerability profile. Meropenem and clavulanate together have a potent *in vitro* activity against *M. tuberculosis*, as clavulanate

TABLE 4 World Health Organization recommended treatment regimen for multidrug-resistant (MDR) tuberculosis (TB)

1	Chose an injectable (group 2)	Kanamycin Amikacin Capreomycin	Choose a drug based on DST and treatment history Streptomycin is generally not used because of high rates of resistance in patients with MDR-TB
2	Choose a higher-generation fluoroquinolone (group 3)	Levofloxacin Moxifloxacin	Use a later-generation fluoroquinolone If levofloxacin (or ofloxacin) resistance is documented, use moxifloxacin Avoid moxifloxacin if possible when using bedaquiline
3	Add group 4 drugs	Cycloserine/ terizidone PAS Ethionamide/ prothionamide	Add two or more group 4 drugs until there are at least four second-line anti-TB drugs likely to be effective Ethionamide/prothionamide is considered the most effective group 4 drug Consider treatment history, side-effect profile and cost DST is not considered reliable for the drugs in this group
4	Add group 1 drugs	Pyrazinamide Ethambutol	Pyrazinamide is routinely added in most regimens Ethambutol can be added in the case of full sensitivity If isoniazid DST is unknown or pending it, can be added to the regimen until DST results become available
5	Add group 5 drugs	Bedaquiline Linezolid Clofazimine Amoxicillin/ clavulanate Imipenem/cilastatin plus clavulanate Meropenem plus clavulanate High-dose isoniazid Clarithromycin Thioacetazone	Consider adding group 5 drugs if four second-line anti-TB drugs are not likely to be effective from groups 2–4 If drugs are needed from this group, it is recommended to add two or more DST is not standardised for the drugs in this group

DST: drug susceptibility testing; PAS: p-aminosalicylic acid. Information from [19].

inhibits the extended-spectrum β -lactamase (BlaC) produced by TB bacilli, which generally hamper the activity of β -lactam antibiotics like meropenem. In a recently published case-control study, meropenem/clavulanate added to an OBR regimen containing linezolid (at the dose of 1 g three times a day) achieved high smear and culture conversion in MDR/XDR-TB (table 5) [30]. Further studies are presently ongoing to define the role of meropenem/clavulanate within the group 5 drugs.

Other drugs

Anecdotal reports suggest that other repurposed drugs, including sulfamethoxazole and mefloquine, showed activity against *M. tuberculosis* in difficult-to-treat cases, although high-quality evidence, based on randomised clinical trials, is necessary [37–38].

New drugs

Currently, as a result of a multi-stakeholder initiative, two new anti-TB drugs were approved by the US Food and Drug Administration and by the European Medicines Agency: bedaquiline and delamanid [39, 40]. In addition, pretomanid, sutezolid (mentioned earlier), SQ109 and benzothiazinones will be discussed.

Bedaquiline

Bedaquiline, belonging to the diarylquinoline class of antibiotics (table 6), selectively targets the proton pump of ATP synthesis, leading to inadequate ATP synthesis, which is necessary for bacterial metabolism

TABLE 5 Summary of the main repurposed antituberculosis drugs with the most relevant studies and related findings

Drug	Class	Main findings	[Ref.]
Linezolid	Oxazolidinone	Systematic review and meta-analysis of efficacy, safety and tolerability of linezolid-containing regimens based on individual data analysis of 12 studies (11 countries from three continents) reporting complete information on safety, tolerability, efficacy of linezolid-containing regimens in treating MDR-TB cases. Most MDR-TB cases achieved SS (86 (92.5%) out of 93) and C (100 (93.5%) out of 107) conversion after treatment with individualised regimens containing linezolid (median [interquartile range] times for SS and C conversions were 43.5 [21–90] and 61 [29–119] days, respectively) and 99 (81.8%) out of 121 patients were successfully treated. No significant differences were detected in the subgroup efficacy analysis [daily linezolid dosage ≤ 600 versus >600 mg]. AEs were observed in 63 (58.9%) out of 107 patients, of which 54 (68.4%) out of 79 were major AEs that included anaemia (38.1%), peripheral neuropathy (47.1%), gastrointestinal disorders (16.7%) optic neuritis (13.2%) and thrombocytopenia (11.8%). The proportion of adverse events was significantly higher when the linezolid daily dosage exceeded 600 mg. The study results suggest an excellent efficacy but also the necessity for caution in the prescription of linezolid.	[23]
		Retrospective, nonrandomised, unblinded observational study evaluating safety and tolerability of linezolid (600 mg once or twice daily). In MDR/XDR-TB treatment in four European countries. Out of 195 MDR/XDR-TB patients, 85 were treated with linezolid for a mean of 221 days. Of these, 35 (41.2%) out of 85 experienced major AEs attributed to linezolid (anaemia, thrombocytopenia and/or polyneuropathy), requiring discontinuation in 27 (77%) cases. Most AEs occurred after 60 days of treatment. Twice-daily administration produced more major AEs than once-daily dosing ($p=0.0004$), with no difference in efficacy found. Outcomes were similar in patients treated with/without linezolid ($p=0.8$), although linezolid-treated cases had more first-line ($p=0.002$) and second-line ($p=0.02$) drug resistance and a higher number of previous treatment regimens (4.5 versus 2.3; $p=0.07$). Linezolid 600 mg once daily added to an individualised multidrug regimen may improve the chance of bacteriological conversion, providing a better chance of treatment success in only the most complicated MDR/XDR-TB cases. Its safety profile does not warrant use in cases for which there are other, safer, alternatives.	[21]
		41 patients were enrolled, who had C-positive XDR-TB and who had not had a response to any available chemotherapeutic option during the previous 6 months. Patients were randomly assigned to linezolid therapy that started immediately or after 2 months, at a dose of 600 mg per day, without a change in their OBR. The primary end-point was the time to SS/C conversion on solid medium, with data censored 4 months after study entry. By 4 months, 15 (79%) out of 19 patients in the immediate-start group and seven (35%) out of 20 in the delayed-start group had C conversion ($p=0.001$). 34 (87%) out of 39 patients had a negative C within 6 months after linezolid had been added to their drug regimen. Of the 38 patients with exposure to linezolid, 31 (82%) had clinically significant AEs that were possibly or probably related to linezolid, including three patients who discontinued therapy. Patients who received 300 mg per day after the second randomisation had fewer AEs than those who continued taking 600 mg per day. 13 patients completed therapy and did not relapse. Four cases of acquired resistance to linezolid were observed. Linezolid is effective at achieving C conversion among patients with treatment-refractory pulmonary XDR-TB but patients must be monitored carefully for AEs.	[24]
		The authors evaluated treatment with linezolid (800 mg once daily for 1–4 months as guided by SS/C status and tolerance, and then at 1200 mg thrice weekly until ≥ 1 year after C conversion) in addition to OBD among 10 consecutive patients with XDR-TB or fluoroquinolone-resistant MDR-TB. All achieved stable cure, with anaemia corrected and neuropathy stabilised, ameliorated, or avoided after switching to intermittent dosing. Serum linezolid profiles appeared better optimised.	[28]
		Prospective pharmacokinetic study aimed at quantifying the effect of clarithromycin on the exposure of linezolid. All subjects received 300 mg linezolid twice daily during the entire study, consecutively co-administered with 250 and 500 mg clarithromycin once daily. Linezolid exposure increased by a median (interquartile range) of 44% [23–102%, $p=0.043$] after co-administration of 500 mg clarithromycin ($n=5$) compared to baseline, whereas 250 mg clarithromycin had no statistically significant effect. Co-administration was well tolerated by most patients; none experienced severe AEs. One patient reported common toxicity criteria grade 2 gastrointestinal AE. Clarithromycin significantly increased linezolid serum exposure after combining clarithromycin with linezolid in MDR-TB patients. The drug–drug interaction is possibly P-glycoprotein-mediated. Due to large interpatient variability, TDM is advisable to determine individual effect size.	[29]

Continued

TABLE 5 Continued

Drug	Class	Main findings	[Ref.]
Meropenem/ clavulanate	Carbapenem/ clavulanic acid	The study aimed to evaluate the contribution of meropenem/clavulanate when added to linezolid-containing regimens in terms of efficacy and safety/tolerability in treating MDR/XDR-TB cases after 3 months of second-line treatment. The clinical severity of cases was worse than that of controls (drug susceptibility profile, proportion of SS positive and of re-treatment cases). The group of cases yielded a higher proportion of SS converters (28 [87.5%] out of 32 <i>versus</i> nine [56.3%] out of 16; $p=0.02$) and C converters (31 [83.8%] out of 37 <i>versus</i> 15 [62.5%] out of 24; $p=0.06$). Excluding XDR-TB patients (11 [11.2%] out of 98), cases scored a significantly higher proportion of C converters than controls ($p=0.03$). One case had to withdraw from meropenem/clavulanate due to increased transaminase levels. The results of our study provide: 1) preliminary evidence on effectiveness and safety/tolerability of meropenem-clavulanate; 2) reference to design further trials; and 3) a guide to clinicians for its rationale use within salvage/compassionate regimens.	[30]

MDR: multidrug-resistant; TB: tuberculosis; SS: sputum smear; C: culture; AE: adverse event; XDR: extensively drug-resistant; OBR: optimised background regimen; SS/C: sputum smear and culture; TDM: therapeutic drug monitoring.

[50]. The minimal inhibitory concentration (MIC) of bedaquiline against *M. tuberculosis* is very low, and its bactericidal activity in the murine model is superior to that of that of isoniazid and rifampicin [50]. The results of two trials (phase II) suggested that a standard 2-month treatment regimen with bedaquiline yielded high culture conversion rates, rapid sputum culture conversion and low acquired resistance to companion drugs in newly diagnosed MDR-TB cases [41, 51].

Based on the available evidence, both WHO and the US Centers for Disease Control and Prevention recently issued recommendations that support the use of bedaquiline, at a dose of 400 mg daily for 2 weeks, then 200 mg three times a week for 22 weeks, added to OBR (as per WHO recommendations) to treat MDR-TB in adults when the following conditions are met: pharmacovigilance is in place, informed consent is ensured and QT monitoring is possible [52, 53]. As safety concerns for this drug remain because of an increased risk of death and QT prolongation, in the absence of additional evidence, the simultaneous use of bedaquiline and delamanid is not recommended [52, 53].

Delamanid and pretomanid

Delamanid and pretomanid belong to the nitroimidazole class of antibiotics, presently undergoing phase II and phase III clinical trials (table 6). They inhibit the synthesis of mycolic acids, which are components of the cell envelope of *M. tuberculosis*. Delamanid showed, both *in vitro* and *in vivo*, a high activity (and significant early bactericidal activity (EBA)) in adult cases affected by pulmonary TB [54, 55]. In a phase II randomised, placebo-controlled, multinational clinical trial in patients with MDR-TB, delamanid administered for 2 months at two different drug doses (100 and 200 mg twice daily) in addition to OBR achieved a significant increase in culture conversion compared with placebo (45% in the 100-mg group *versus* 42% in the 200-mg group and 29% in the placebo group) [42]. In a subsequent open-label extension trial for MDR/XDR-TB, the mortality rates in patients receiving delamanid for at least 6 months were 1% *versus* 8.3%, in those treated for 2 months or less [43]. Although delamanid was well tolerated, QT prolongation was more frequently reported in patients receiving delamanid against those receiving placebo [42]. Based on the available evidence, WHO recommends the use of delamanid at the dose of 100 mg twice daily for 6 months, added to OBR in adults, when pharmacovigilance is in place and informed consent ensured [56].

A recent retrospective analysis of clinical studies carried out so far showed that the greatest reduction in mortality (around four-fold) occurred among patients treated with delamanid for ≥ 6 months *versus* those treated for ≤ 2 months [57]. Although anecdotal evidence suggests that delamanid is effective and safe in children [14], two clinical trials (www.clinicaltrials.gov identifier numbers NCT01859923 and NCT01856634) are studying delamanid in the treatment of paediatric MDR-TB.

Pretomanid (previously known as PA-824) has a low MIC for *M. tuberculosis*, comparable to that of isoniazid. This drug was studied as part of different potential new regimens. DIACON and co-workers [40, 41, 44, 46] assessed the 14-day early bactericidal activity of a regimen composed of pretomanid, moxifloxacin and pyrazinamide, which proved to be significantly higher than that of bedaquiline alone, bedaquiline plus pyrazinamide and bedaquiline plus pretomanid (but not to pretomanid plus pyrazinamide), and comparable to that of the standard treatment regimen (isoniazid, rifampicin and

TABLE 6 Summary of the main new antituberculosis drugs with the most relevant studies and related findings

Drug	Class	Study ID number	Clinical trial phase	Registration number	Main findings	[Ref.]
Bedaquiline	Diarylquinoline	TMC207-TIDP13-C208	II	NCT00449644	The addition of delamanid (TMC207) to OBR reduced the time to C conversion, as compared with OBR (HR 11.8, 95% CI 2.3–61.3; p=0.003) and increased the proportion of C converters (48% versus 9%). The mean log ₁₀ CFU count in SS declined more rapidly in the TMC207 group than in OBR group. No significant differences in average plasma TMC207 concentrations were noted between patients with and those without C conversion. Most AEs were mild to moderate.	[41]
Delamanid (OPC 67683)	Nitroimidazole	242-07-204	II	NCT00685360	Among patients who received OBR plus 100 mg of delamanid twice daily, 45.4% had C conversion at 2 months, as compared with 29.6% of patients receiving OBR (p=0.008). As compared with OBR, the group receiving OBR plus delamanid 200 mg twice daily had a higher proportion of SS and C conversion (41.9%, p=0.04). Most AEs were mild to moderate and evenly distributed across groups. Although no clinical events due to QT prolongation on ECG were observed, QT prolongation was reported significantly more frequently in the delamanid groups.	[42]
		242-09-213	III	NCT01424670	Patients who participated in the above trial of delamanid and the subsequent open-label extension trial were eligible to participate in a 24-month observational study designed to capture treatment outcomes. Favourable outcomes were observed in 143 (74.5%) out of 192 patients receiving delamanid for ≥6 months, compared to 126 (55%) out of 229 patients who received delamanid for ≤2 months. Mortality was reduced to 1.0% among those receiving long-term delamanid versus short-term/no delamanid (8.3%; p<0.001). Treatment benefit was also seen among XDR-TB patients.	[43]
Pretomanid (PA-824)	Nitroimidazole	NC-001-(J-M-Pa-Z)	II	NCT01215851	The 14-day EBA of PaMZ (n=13; mean±SD 0.233±0.128) was significantly higher than that of bedaquiline (n=14; 0.061±0.068), bedaquiline-pyrazinamide (n=15; 0.131±0.102), bedaquiline-Pa (n=14; 0.114±0.050) but not PaZ (n=14; 0.154±0.040) and comparable with that of standard treatment (n=10; 0.140±0.094). Treatments were well tolerated and appeared safe. One patient on PaMZ was withdrawn because of corrected QT interval changes exceeding pre-specified criteria.	[44]
		NC-002-(M-Pa-Z)	II	NCT01498419	The study evaluated a novel regimen for efficacy and safety in DS-TB and MDR-TB during the first 8 weeks of treatment. Smear positive DS, treatment-naïve PTB patients randomised were enrolled to receive 8 weeks of M, Pa (100 mg) and Z (MPa100Z, regimen 1) or M, Pa (200 mg) and Z (MPa200Z, regimen 2) or the current standard regimen for DS-PTB (HRZE) as positive control. A group of MDR-TB participants received M 400 mg, Pa 200 mg and Z 1500 mg (DRMPa200Z). The regimen 1 BA days 0–56 (n=54; 0.155, 95% BCI 0.133–0.178) in DS-TB patients was significantly greater than for standard regimen (n=54; 0.112, 95% BCI 0.093–0.131). Regimen 2 had similar BA to the standard regimen. The day 7–14 BA correlated well with days 7–56. AEs were equally distributed among group and control subjects. The most common AE was hyperuricaemia in 59 (28.5%) patients spread similarly across treatment groups. Other common AEs were nausea in 37 (17.9%) and vomiting in 25 (12.1%) patients. No patient had corrected QT interval exceeding 500 ms. No phenotypic resistance developed. The MPaZ combination, previously found to have promising activity over 14 days in DS-TB, was safe, well tolerated and demonstrated superior BA in DS-TB during 8 weeks treatment. Results were consistent between DS-TB and MDR-TB.	[45]
		NC-003-(C-J-Pa-Z)	II	NCT01691534	Experimental and clinical evidence suggests that the new drugs Bdq and Pa, combined with an existing drug, Z, and a repurposed drug, Cfz, may assist treatment shortening of both DS-TB and DR-TB. The study evaluated the 14-day EBA of Cfz and Z in monotherapy and in combinations with Pa and Bdq. Groups of 15 treatment-naïve, SS-positive PTB patients were randomised to receive combinations of Bdq with ZCfz, PaZ, PaZCfz and PaCfz, or Cfz or Z alone, or standard combination treatment for 14 days. The primary end-point was the mean daily fall in log ₁₀ CFU·mL ⁻¹ SS estimated by joint nonlinear mixed effects Bayesian regression modelling. Results: estimated activities were 0.167 [95% CI 0.075–0.257] for BdqPaZ, 0.151 [95% CI 0.071–0.232] for standard treatment, 0.124 [95% CI 0.035–0.214] for BdqZCfz, 0.115 [95% CI 0.039–0.189] for BdqPaZCfz and 0.076 [95% CI 0.005–0.145] for BdqPaCfz. Z alone had modest activity [0.036, 95% CI –0.026–0.099]. Cfz had no activity alone [–0.017, 95% CI –0.085–0.053] or in combinations. Treatments were well tolerated and safe. BdqPaZ, including two novel agents without resistance in prevalent <i>M. tuberculosis</i> strains, is a potential	[46]

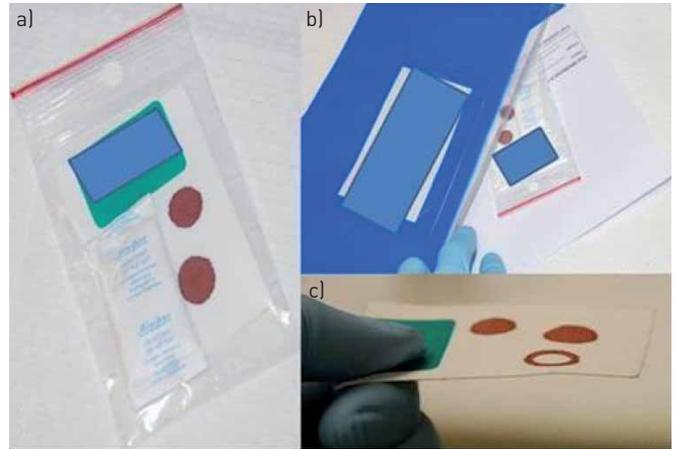
Continued

TABLE 6 Continued

Drug	Class	Study ID number	Clinical trial phase	Registration number	Main findings	[Ref.]
Sutezolid (PNU-100480)	Oxazolidinone	B1171003	II	NCT01225640	new TB treatment regimen. Cfz had no measurable activity in the first 14 days of treatment. All patients completed assigned treatments and began subsequent standard TB treatment according to protocol. The 90% CI for bactericidal activity in sputum over the 14-day interval excluded zero for all treatments and both monitoring methods, as did those for cumulative WBA. There were no treatment-related serious AEs, premature discontinuations or dose reductions due to laboratory abnormalities. There was no effect on the QT interval. Seven (14%) sutezolid-treated patients had transient, asymptomatic ALT elevations to 173 ± 34 U·L ⁻¹ on day 14 that subsequently normalised promptly; none met Hy's criteria for serious liver injury. The mycobactericidal activity of sutezolid 600 mg twice daily or 1200 mg once daily was readily detected in sputum and blood. Both schedules were generally safe and well tolerated.	[47]
SQ109	Ethylenediamine	LMU-IMPH-SQ109-01	II	NCT01218217	Study to determine safety, tolerability, pharmacokinetics and bacteriological effect of different doses of SQ109 alone and in combination with rifampicin when administered over 14 days. SQ109 was safe and generally well tolerated. Mild-to-moderate dose-dependent gastrointestinal complaints were the most frequent AE. No relevant QT prolongation was noted. Maximum SQ109 plasma concentrations were lower than MICs. Exposure to SQ109 (AUC ₀₋₂₄) increased by drug accumulation upon repeated administration in the SQ109 monotherapy groups. Co-administration of SQ109 150 mg with R resulted in decreasing SQ109 exposures from day 1 to day 14. A higher (300 mg) dose of SQ109 largely outweighed the evolving inductive effect of R. The daily fall in log ₁₀ CFU·mL ⁻¹ of sputum (95% CI) was 0.093 [0.126-0.059] with R, 0.133 [0.166-0.100] with R plus 150 mg of SQ109 and 0.089 [0.121-0.057] with R plus 300 mg of SQ109. Treatments with SQ109 alone showed no significant activity. SQ109 alone or with rifampicin was safe over 14 days. Upon co-administration with R, 300 mg of SQ109 yielded a higher exposure than the 150-mg dose. SQ109 did not appear to be active alone or to enhance the activity of rifampicin during the 14 days of treatment.	[48]
Benzothiazinones (BTZ043)	2-[(2S)-2-methyl-1,4-dioxo-8-azaspiro[4.5]dec-8-yl]-8-nitro-6-trifluoromethyl-4H-1,3-benzothiazin-4-one/Rv3790	Pre-clinical development phases			Studied the interaction profiles of BTZ043 with several anti-TB drugs or drug candidates against <i>M. tuberculosis</i> strain H37Rv, namely, R, H, E, delamanid, Pa, M, meropenem with or without clavulanate and SQ-109. No antagonism was found between BTZ043 and the tested compounds, and most of the interactions were purely additive. BTZ043 acts synergistically with delamanid, with a fractional inhibitory concentration index of 0.5. TMC207 at a quarter of the MIC (20 ng·mL ⁻¹) used in combination with BTZ043 (quarter MIC 0.375 ng·mL ⁻¹) had a stronger bactericidal effect on <i>M. tuberculosis</i> than delamanid alone at a concentration of 80 ng·mL ⁻¹ . This synergy was not observed when the combination was tested on a BTZ-resistant <i>M. tuberculosis</i> mutant, suggesting that DprE1 inhibition is the basis for the interaction. This finding excludes the possibility of synergy occurring through an off-target mechanism. Hypothesis that sub-MICs of BTZ043 weaken the bacterial cell wall and allow improved penetration of delamanid to its target. Synergy between two new antimycobacterial compounds (delamanid and BTZ043) with novel targets offers an attractive foundation for a new anti-TB regimen	[49]

OBR: optimised background regimen; C: culture; HR: hazard ratio; CFU: colony-forming unit; SS: sputum smear; AE: adverse event; XDR: extensively drug-resistant; TB: tuberculosis; EBA: early bactericidal activity; Pa: pretomanid; M: moxifloxacin; Z: pyrazinamide; DS: drug-susceptible; MDR: multidrug-resistant; PTB: pulmonary tuberculosis; H: isoniazid; R: rifampicin; E: ethambutol; BA: bactericidal activity; BCI: Bayesian credibility interval; Bdq: bedaquiline; Cfz: clofazimine; DR-TB: drug-resistant; WBA: whole-blood bactericidal activity; ALT: alanine transaminase; MIC: minimum inhibitory concentrations; AUC₀₋₂₄: area under the curve in the first 24 h.

FIGURE 3 Dried blood spot for therapeutic drug monitoring. a). Blood is collected on paper strips and packed in a plastic bag with a desiccant to keep the strip dry. b). Sample can be transported via regular post or any other suitable means. c). Dried blood spot is collected from the strip, drug is extracted and concentration measured using validated method. Reproduced from [31].



pyrazinamide with streptomycin or ethambutol). Interestingly, the addition of pyrazinamide increased the activity of both bedaquiline and pretomanid.

In a new phase IIb trial, the bactericidal activity of a new 8-week regimens including moxifloxacin, pretomanid (100 or 200 mg, according to the arm), pyrazinamide and clofazimine was compared to that of the standard anti-TB regimen to treat sputum smear positive patients with both drug-susceptible and drug-resistant TB. The new regimen yielded higher bactericidal activity than the current WHO-recommended regimen after 2 months of treatment and was well tolerated (no episode of QT interval exceeding 500 ms was identified) [45].

Sutezolid

Sutezolid (PNU-100480), like linezolid (see section on repurposed drugs), belongs to the oxazolidinone class of antibiotics. Their mechanism of action prevents the initiation of protein synthesis by binding to 23S RNA in the 50S ribosomal subunit of bacteria.

Having shown potent action against *M. tuberculosis* in the murine model [58], it was studied in phase I trials in humans, and appeared to be safe and well tolerated [59, 60]. Recently, a phase II clinical trial (NCT01225640) assessing safety and efficacy using EBA and whole-blood bactericidal activity was completed (table 6) [47].

SQ109

SQ109, a 1,2-ethylenediamine, is an analogue of ethambutol. The drug is active against both drug-susceptible and drug-resistant TB by targeting MmpL3 in *M. tuberculosis* and specifically inhibiting the protein synthesis [61]. *In vitro*, it has some synergic effects with bedaquiline and favourable interactions with sutezolid. SQ109 is presently undergoing phase II clinical trials (table 6) [48].

Benzothiazinones

This new class of anti-TB drugs, in the pre-clinical development phase, are able to inhibit the synthesis of decaprenylphosphoarabinose, the precursor of the arabinans in the mycobacterial cell wall [62]. Preliminary evidence suggests that BTZ043 is potent, with activity against 240 clinical isolates of *M. tuberculosis*, including drug-susceptible, MDR-TB and XDR-TB strains. Additive interactions and no antagonism were found between BTZ043 and rifampicin, isoniazid, ethambutol, pretomanid, moxifloxacin, meropenem with or without clavulanate, and SQ109, while synergic effects were found combining BTZ043 and bedaquiline (table 6) [62].

Improving the individualised approach to drug dosing: TDM

TDM is well known among clinical pharmacologists although it is not yet very popular among TB clinicians [63–65]. Based on the collection of blood samples, it allows the evaluation *ex vivo* of the blood concentration of a given drug, and consequently, the potential quantitative effect on the pharmacological target. The causes leading to the development of drug resistance in *M. tuberculosis* are well known, and include inadequate treatment (inadequate dose or dosing frequency) [66, 67], nonadherence to the prescribed regimen and pharmacokinetic (PK) variability [49, 68]. TDM has not yet been used to its full potential to improve therapy management when second-line anti-TB drugs are used of [65, 59].

Dose adjustments are important when treating patients who are slow to respond to treatment (because of inaccurate dosing, malabsorption or altered metabolism, drug–drug interactions [64] and PK variability [49]), have MDR/XDR-TB with adverse events or are intolerant to a given drug. TDM prevents, for example, the development of further drug resistance due to exposure to drug concentrations below the MIC. When managing XDR-TB and no more than four or five effective drugs are available, TDM is potentially life-saving as it can detect malabsorption and allow dose re-adjustment. Furthermore, TDM can reduce linezolid toxicity by reducing the dose necessary [23, 31].

While TDM is still considered an experimental procedure, a simple and cheap dried blood spot (DBS) method allows us to take advantage of the test even from remote settings [70]. It needs only a small blood volume while allowing easy sampling, storage and transportation (fig. 3).

Some laboratories in the USA perform drug testing in-house (C.A. Peloquin, College of Pharmacy and Emerging Pathogens Institute, University of Florida, Gainesville, FL, USA; personal communication) [6]; in Europe, a proficiency testing programme is under development under the lead of the Nijmegen group in the Netherlands (C.A. Peloquin, personal communication). In the near future, a system of reference laboratories adequately covering clinical needs globally might receive the DBS by ordinary mail and rapidly send back the answer by e-mail. Although TDM is still expensive, a gradual decrease in cost is likely to occur in the future as a consequence of an enlarged market. In addition, the reduction of the dose of drug used will pay back the TDM cost in a few days.

Improving the clinical management of MDR/XDR-TB: the European Respiratory Society/WHO TB Consilium

WHO recommends that management of MDR-TB cases is supported by a specialised team, which usually includes diverse professional perspectives (clinical, in adults and children; surgical; radiological; public health; psychological; nursing, *etc.*). The existence of WHO guidelines and European Standards of TB Care does not automatically guarantee appropriate treatment of MDR/XDR-TB, while rapid advice from a multidisciplinary team with clinical and management experience at national or supranational level would help to ensure proper treatment [9, 71, 72]. Similar consultation bodies do not exist or are not used in the majority of the countries.

The European Respiratory Society (ERS), which is in the frontline of TB elimination in Europe [73–78], launched the electronic ERS/WHO TB Consilium in Vienna, Austria, in September 2012, under a Memorandum of Understanding signed with the WHO Regional Office for Europe. The overall aim of this initiative is to provide scientifically sound, evidence-based advice to national consilia and individual clinicians on how to manage drug-resistant TB and other difficult-to-treat TB cases, including co-infection with HIV and paediatric cases [14, 15, 79], in order to prevent development of further drug resistance, and ensure monitoring and evaluation of clinical practices in the different countries (prevention, diagnosis and treatment). The platform ensures a cost-free, multilingual (English, Portuguese, Russian and Spanish), Internet-based consultation system able to provide suggestions on clinical management of complicated TB cases in less than 3 days.

In collaboration with the WHO Regional Office for Europe, a new function aimed at supporting clinicians treating trans-border migrants affected by TB has been recently launched. Furthermore, new functionality is under development (in collaboration with public organisations), aimed at allowing patients to request specific advice directly for their TB infection or disease to a physician, a nurse or a psychologist, and/or to ask for motivational support from other patients who survived, in order to support the TB elimination roadmap [73–75].

The pipeline to design new regimens

Fluoroquinolones are considered pivotal in reducing treatment duration. A recent randomised trial, however, showed a higher relapse rate of 15% and 11% in the 4-month thrice-weekly regimens of gatifloxacin or moxifloxacin with isoniazid, rifampicin and pyrazinamide (2GHRZ3/2GHR3 or 2MHRZ3/2MHR3), respectively, compared with 6% in the standard 6-month regimen (2EHRZ3/4HR3) during the 24 months after the end of treatment [80].

Three noninferiority trials are presently assessing the use of fluoroquinolones to shorten the treatment duration to 4 months. The OFLOTUB Trial (NCT00216385) is comparing the standard 6-month regimen with a regimen consisting of a 2-month intensive phase with gatifloxacin substituting ethambutol, followed by a 2-month maintenance phase of gatifloxacin, isoniazid and rifampicin (2GHRZ/2GHR). Follow-up data have been obtained but the results have not yet been published [81–83]. REMox TB (NCT00864383) is comparing standard 6-month therapy with two study regimens (2 months of moxifloxacin, isoniazid, rifampicin and pyrazinamide followed by 2 months of moxifloxacin, isoniazid and rifampicin (2MHRZ/

2MHR) or 2 months of ethambutol, moxifloxacin, rifampicin and pyrazinamide followed by 2 months of moxifloxacin and rifampicin (2EMRZ/2MR)). RIFAQUIN (ISRCTN44153044) is comparing the standard 6-month regimen with two study regimens (2 months of daily ethambutol, moxifloxacin, rifampicin and pyrazinamide followed by 2 months of twice-weekly moxifloxacin and rifapentine (2EMRZ/2PM2) or 4 months of once-weekly moxifloxacin and rifapentine (2EMRZ/4PM1) in a maintenance phase).

The very recent study by Dawson *et al.* [45] opens new perspectives on what regimens can be designed with the newly available anti-TB drugs [84]. This new phase IIb trial compared the bactericidal activity of 8-week regimens including moxifloxacin and pretomanid (100 or 200 mg, according to the arm) plus pyrazinamide against the standard anti-TB regimen to treat sputum smear positive patients with both drug-susceptible and drug-resistant TB.

The bactericidal activity of the of the 8-week regimens was higher than that of the current WHO-recommended regimen in both drug-susceptible and drug-resistant TB after 2 months of treatment. The experimental treatment was well tolerated and no episode of QT interval exceeding 500 ms was identified.

The study showed that rifampicin-sparing regimen might work (allowing easier and safer treatment of HIV-positive cases with protease inhibitors) while achieving rapid sputum culture conversion and reduced transmission *M. tuberculosis* with the community. Given the potential to shorten treatment duration, hopes exist to improve patient adherence.

Conclusions

In spite of the progress achieved so far, much needs still to be done to improve our approach to clinical trials of new anti-TB drugs and regimens. The surrogate markers currently adopted to measure the efficacy of a given drug are old and need complicated statistical approaches to interpolate the scientific evidence [85]. Furthermore, the time necessary to assess the pharmacological profile of a new drug is still very long and the possibility of enrolling vulnerable persons into the trials is a barrier we need to overcome soon [86]. The new WHO post-2015 End TB Strategy will support the efforts that research on new drugs and regimens requires.

References

- 1 World Health Organization. Global tuberculosis report 2014. WHO/HTM/TB2014.08. Geneva, World Health Organization, 2014.
- 2 Migliori GB, Dara M, de Colombani P, *et al.* Multidrug-resistant tuberculosis in Eastern Europe: still on the increase? *Eur Respir J* 2012; 39: 1290–1291.
- 3 Skrahina A, Hurevich H, Zalutskaya A, *et al.* Alarming levels of drug-resistant tuberculosis in Belarus: results of a survey in Minsk. *Eur Respir J* 2012; 39: 1425–1431.
- 4 Falzon D, Gandhi N, Migliori GB, *et al.* Resistance to fluoroquinolones and second-line injectable drugs: impact on multidrug-resistant TB outcomes. *Eur Respir J* 2013; 42: 156–168.
- 5 Migliori GB, Sotgiu G, Gandhi NR, *et al.* Drug resistance beyond extensively drug-resistant tuberculosis: individual patient data meta-analysis. *Eur Respir J* 2013; 42: 169–179.
- 6 Zignol M, Dara M, Dean AS, *et al.* Drug-resistant tuberculosis in the WHO European Region: an analysis of surveillance data. *Drug Resist Updat* 2013; 16: 108–115.
- 7 Ulmasova DJ, Uzakova G, Tillyashayhov MN, *et al.* Multidrug-resistant tuberculosis in Uzbekistan: results of a nationwide survey, 2010 to 2011. *Euro Surveill* 2013; 18: 20609.
- 8 Diel R, Rutz S, Castell S, *et al.* Tuberculosis: cost of illness in Germany. *Eur Respir J* 2012; 40: 143–151.
- 9 Falzon D, Jaramillo E, Schünemann HJ, *et al.* WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. *Eur Respir J* 2011; 38: 516–528.
- 10 Sotgiu G, Migliori GB. Is tuberculosis elimination a reality? *Lancet Infect Dis* 2014; 14: 364–365.
- 11 Migliori GB, Sotgiu G. Measuring the effect of tuberculosis control: a step forward. *Lancet* 2014; 383: 2026–2028.
- 12 Tanimura T, Jaramillo E, Weil D, *et al.* Financial burden for tuberculosis patients in low- and middle-income countries: a systematic review. *Eur Respir J* 2014; 43: 1763–1775.
- 13 Weyer K, Mirzayev F, Migliori GB, *et al.* Rapid molecular TB diagnosis: evidence, policy making and global implementation of Xpert MTB/RIF. *Eur Respir J* 2013; 42: 252–271.
- 14 Esposito S, D'Ambrosio L, Tadolini M, *et al.* ERS/WHO Tuberculosis Consilium assistance with extensively drug-resistant tuberculosis management in a child: case study of compassionate delamanid use. *Eur Respir J* 2014; 44: 811–815.
- 15 Codecasa LR, Ciconali G, Mazzola E, *et al.* Managing an XDR-TB outbreak: the public health face of the medal. *Eur Respir J* 2015; 45: 25–29.
- 16 Daskapan A, de Lange WCM, Akkerman OW, *et al.* The role of therapeutic drug monitoring in individualised drug dosage and exposure measurement in tuberculosis and HIV co-infection. *Eur Respir J* 2015; 45: 569–571.
- 17 World Health Organization. The treatment of tuberculosis: guidelines – 4th ed. Document WHO/HTM/TB/2009.420. Geneva, World Health Organization, 2010.
- 18 Albanna AS, Smith BM, Cowan D, *et al.* Fixed-dose combination antituberculosis therapy: a systematic review and meta-analysis. *Eur Respir J* 2013; 42: 721–732.
- 19 World Health Organization. WHO Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. WHO/HTM/TB/2014.11. Geneva, World Health Organization, 2014.

- 20 Dara M, Kluge H. Roadmap to prevent and combat drug-resistant tuberculosis. Copenhagen, World Health Organization Regional Office for Europe, 2011. www.euro.who.int/__data/assets/pdf_file/0014/152015/e95786.pdf Date last accessed: March 31, 2015.
- 21 Migliori GB, Eker B, Richardson MD, et al. A retrospective TBNET assessment of linezolid safety, tolerability and efficacy in multidrug-resistant tuberculosis. *Eur Respir J* 2009; 34: 387–393.
- 22 Cox H, Ford N. Linezolid for the treatment of complicated drug-resistant tuberculosis: a systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2012; 16: 447–454.
- 23 Sotgiu G, Centis R, D'Ambrosio L, et al. Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. *Eur Respir J* 2012; 40: 1430–1442.
- 24 Lee M, Lee J, Carroll MW, et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. *N Engl J Med* 2012; 367: 1508–1518.
- 25 Sotgiu G, Centis R, D'Ambrosio L, et al. Linezolid to treat extensively drug-resistant TB: retrospective data are confirmed by experimental evidence. *Eur Respir J* 2013; 42: 288–290.
- 26 Tang S, Yao L, Hao X, et al. Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. *Eur Respir J* 2015; 45: 161–170.
- 27 Sotgiu G, Pontali M, Migliori GB. Linezolid to treat M/XDR-TB: available evidence and future scenarios. *Eur Respir J* 2015; 45: 25–29.
- 28 Chang KC, Yew WW, Cheung SW, et al. Can intermittent dosing optimize prolonged linezolid treatment of difficult multidrug-resistant tuberculosis? *Antimicrob Agents Chemother* 2013; 57: 3445–3449.
- 29 Bolhuis MS, Altena RV, Soolingen DV, et al. Clarithromycin increases linezolid exposure in multidrug-resistant tuberculosis patients. *Eur Respir J* 2013; 42: 1614–1621.
- 30 De Lorenzo S, Alffenaar JW, Sotgiu G, et al. Efficacy and safety of meropenem- clavulanate added to linezolid-containing regimens in the treatment of MDR/XDR-TB. *Eur Respir J* 2013; 41: 1386–1392.
- 31 Srivastava S, Peloquin CA, Sotgiu G, et al. Therapeutic drug management: is it the future of multidrug-resistant tuberculosis treatment? *Eur Respir J* 2013; 42: 1449–1453.
- 32 Engohang-Ndong J. Antimycobacterial drugs currently in Phase II clinical trials and preclinical phase for tuberculosis treatment. *Expert Opin Investig Drugs* 2012; 21: 1789–1800.
- 33 Villar M, Sotgiu G, D'Ambrosio L, et al. Linezolid safety, tolerability and efficacy to treat multidrug- and extensively drug-resistant tuberculosis. *Eur Respir J* 2011; 38: 730–733.
- 34 De Lorenzo S, Centis R, D'Ambrosio L, et al. On linezolid efficacy and tolerability. *Eur Respir J* 2012; 39: 770–772.
- 35 Sotgiu G, Lange C, Richardson MD, et al. Comment on: Daily 300 mg dose of linezolid for the treatment of intractable multidrug-resistant and extensively drug-resistant tuberculosis. *J Antimicrob Chemother* 2009; 64: 879–883.
- 36 Sotgiu G, Centis R, D'Ambrosio L, et al. Low minimal inhibitory concentrations of linezolid against multidrug-resistant tuberculosis strains. *Eur Respir J* 2015; 45: 287–289.
- 37 Alsaad N, Wilffert B, van Altena R, et al. Potential antimicrobial agents for the treatment of multidrug-resistant tuberculosis. *Eur Respir J* 2014; 43: 884–897.
- 38 Alsaad N, van Altena R, Pranger AD, et al. Evaluation of co-trimoxazole in the treatment of multidrug-resistant tuberculosis. *Eur Respir J* 2013; 42: 504–512.
- 39 Skripconoka V, Danilovits M, Pehme L, et al. Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. *Eur Respir J* 2013; 41: 1393–1400.
- 40 Diacon AH, Pym A, Grobusch MP, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N Engl J Med* 2014; 371: 723–732.
- 41 Diacon AH, Pym A, Grobusch M, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. *N Engl J Med* 2009; 360: 2397–2405.
- 42 Gler MT, Skripconoka V, Sanchez-Garavito E, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. *N Engl J Med* 2012; 366: 2151–2160.
- 43 Skripconoka V, Danilovits M, Pehme L, et al. Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. *Eur Respir J* 2013; 41: 1393–1400.
- 44 Diacon AH, Dawson R, von Groote-Bidingmaier F, et al. 14-day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial. *Lancet* 2012; 380: 986–993.
- 45 Dawson R, Diacon AH, Everitt D, et al. The anti-tuberculosis activity of the combination of moxifloxacin, pretomanid (PA-824) and pyrazinamide during the first eight weeks of therapy: a Phase 2b open label, partially randomized trial of efficacy, tolerability and safety in patients with drug-susceptible and drug-resistant pulmonary tuberculosis. *Lancet* 2015 [In press DOI: 10.1016/S0140-6736(14)62002-X].
- 46 Diacon AH, Dawson R, von Groote-Bidingmaier F, et al. Bactericidal activity of pyrazinamide and clofazimine alone and in combinations with pretomanid and bedaquiline. *Am J Respir Crit Care Med* 2015 [In press DOI: 10.1164/rccm.201410-1801OC].
- 47 Wallis RS, Dawson R, Friedrich SO, et al. Mycobactericidal activity of sutezolid (PNU-100480) in sputum (EBA) and blood (WBA) of patients with pulmonary tuberculosis. *PLoS One* 2014; 9: e94462.
- 48 Heinrich N, Dawson R, du Bois J, et al. Early phase evaluation of SQ109 alone and in combination with rifampicin in pulmonary TB patients. *J Antimicrob Chemother* 2015 [In press DOI: 10.1093/jac/dku553].
- 49 Srivastava S, Pasipanodya JG, Meek C, et al. Multidrug-resistant tuberculosis not due to noncompliance but to between-patient pharmacokinetic variability. *J Infect Dis* 2011; 204: 1951–1959.
- 50 Andries K, Verhasselt P, Guillemont J, et al. A diarylquinoline drug active on the ATP synthase of *Mycobacterium tuberculosis*. *Science* 2005; 307: 223–227.
- 51 Diacon AH, Donald PR, Pym A, et al. Randomized pilot trial of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: longterm outcome, tolerability, and effect on emergence of drug resistance. *Antimicrob Agents Chemother* 2012; 56: 3271–3276.
- 52 World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance. Document WHO/HTM/TB/2013.6. Geneva, World Health Organization, 2013.
- 53 Mase S, Chorba T, Lobue P, et al. Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate (Sirturo) for the treatment of multidrug-resistant tuberculosis. *MMWR Recomm Rep* 2013; 62: 1–12.

- 54 Matsumoto M, Hashizume H, Tomishige T, *et al.* OPC-67683, a nitro-dihydroimidazoazole derivative with promising action against tuberculosis *in vitro* and in mice. *PLoS Med* 2006; 3: e466.
- 55 Diacon AH, Dawson R, Hanekom M, *et al.* Early bactericidal activity of delamanid (OPC-67683) in smear-positive pulmonary tuberculosis patients. *Int J Tuberc Lung Dis* 2011; 15: 949–954.
- 56 World Health Organization. The use of delamanid in the treatment of multidrug-resistant tuberculosis. Interim policy guidance. Document WHO/HTM/TB2014.23. Geneva, World Health Organization, 2014.
- 57 Wells CD, Gupta R, Hittel N, *et al.* Long-term mortality assessment of multidrug-resistant tuberculosis patients treated with delamanid. *Eur Respir J* 2015 [In press DOI: 10.1183/09031936.00176314].
- 58 Williams KN, Stover CK, Zhu T, *et al.* Promising antituberculosis activity of the oxazolidinone PNU-100480 relative to that of linezolid in a murine model. *Antimicrob Agents Chemother* 2009; 53: 1314–1319.
- 59 Wallis RS, Jakubiec WM, Kumar V, *et al.* Pharmacokinetics and whole-blood bactericidal activity against *Mycobacterium tuberculosis* of single doses of PNU-100480 in healthy volunteers. *J Infect Dis* 2010; 202: 745–751.
- 60 Wallis RS, Jakubiec W, Kumar V, *et al.* Biomarker-assisted dose selection for safety and efficacy in early development of PNU-100480 for tuberculosis. *Antimicrob Agents Chemother* 2011; 55: 567–574.
- 61 Sacksteder KA, Protopopova M, Barry CEIII, *et al.* Discovery and development of SQ109: a new antitubercular drug with a novel mechanism of action. *Future Microbiol* 2012; 7: 823–837.
- 62 Lechartier B, Hartkoorn RC, Cole ST. *In vitro* combination studies of benzothiazinone lead compound BTZ043 against *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother* 2012; 56: 5790–5793.
- 63 Haysell SK, Moore JL, Keller SJ, *et al.* Therapeutic drug monitoring for slow response to tuberculosis treatment in a state control program, Virginia, USA. *Emerging Infect Dis* 2010; 16: 1546–1553.
- 64 Peloquin CA. Pharmacological issues in the treatment of tuberculosis. *Ann NY Acad Sci* 2001; 953: 157–164.
- 65 Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis. *Drugs* 2002; 62: 2169–2183.
- 66 Migliori GB, Sotgiu G, D'Ambrosio L, *et al.* TB and MDR/XDR-TB in European Union and European Economic Area countries: managed or mismanaged? *Eur Respir J* 2012; 39: 619–625.
- 67 Raviglione MC, Lange C, Migliori GB. Preventing and managing antimicrobial resistance: imperative for chest physicians. *Eur Respir J* 2011; 37: 978–981.
- 68 Van der Werf MJ, Langendam MW, Huitric E, *et al.* Multidrug resistance after inappropriate tuberculosis treatment: a meta-analysis. *Eur Respir J* 2012; 39: 1511–1519.
- 69 Tortoli E, Russo C, Piersimoni C, *et al.* Clinical validation of Xpert MTB/RIF for the diagnosis of extrapulmonary tuberculosis. *Eur Respir J* 2012; 40: 442–447.
- 70 Vu DH, Alffenaar JWC, Edelbroek PM, *et al.* Dried blood spots: a new tool for tuberculosis treatment optimization. *Curr Pharm Des* 2011; 17: 2931–2939.
- 71 Migliori GB, Zellweger JP, Abubakar I, *et al.* European Union Standards for Tuberculosis Care. *Eur Respir J* 2012; 39: 807–819.
- 72 van der Werf MJ, Sandgren A, D'Ambrosio L, *et al.* The European Union standards for tuberculosis care: do they need an update? *Eur Respir J* 2014; 43: 933–942.
- 73 World Health Organization. Framework for tuberculosis elimination in low-incidence countries. Document WHO/HTM/TB/2014.13. Geneva, World Health Organization, 2014.
- 74 Diel R, Loddenkemper R, Zellweger JP, *et al.* Old ideas to innovate tuberculosis control: preventive treatment to achieve elimination. *Eur Respir J* 2013; 42: 785–801.
- 75 D'Ambrosio L, Dara M, Tadolini M, *et al.* TB Elimination: theory and practice in Europe. *Eur Respir J* 2014; 43: 1410–1420.
- 76 Voniatis C, Migliori GB, Voniatis M, *et al.* Tuberculosis elimination: dream or reality? The case of Cyprus. *Eur Respir J* 2014; 44: 543–546.
- 77 Blasi F, Barnes PJ, Gaga M, *et al.* Future directions for the ERS: presidential plans. *Eur Respir J* 2013; 42: 875–880.
- 78 Blasi F, Reichman LB, Migliori GB. Presenting the European Forum for TB Innovation: innovative thinking in progressing towards TB elimination in Europe. *Eur Respir J* 2012; 40: 806–808.
- 79 D'Ambrosio L, Tadolini M, Dupasquier S, *et al.* ERS/WHO TB consilium: reporting on initial 10 cases. *Eur Respir J* 2014; 43: 286–289.
- 80 Jawahar MS, Banurekha VV, Paramasivan CN, *et al.* Randomized clinical trial of thrice-weekly 4-month moxifloxacin or gatifloxacin containing regimens in the treatment of new sputum positive pulmonary tuberculosis patients. *PLoS One* 2013; 8: e67030.
- 81 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.
- 82 Merle CS, Sismanidis C, Sow OB, *et al.* A pivotal registration phase III, multicenter, randomized tuberculosis controlled trial: design issues and lessons learnt from the Gatifloxacin for TB (OFLOTUB) project. *Trials* 2012; 13: 61.
- 83 Smythe W, Merle CS, Rustomjee R, *et al.* Evaluation of initial and steady-state gatifloxacin pharmacokinetics and dose in pulmonary tuberculosis patients by using Monte Carlo simulations. *Antimicrob Agents Chemother* 2013; 57: 4164–4171.
- 84 Sotgiu G, Migliori GB. New effective antituberculosis regimens. *Lancet* 2015 [In press DOI: 10.1016/S0140-6736(14)62303-5].
- 85 Kurbatova EV, Cegielski JP, Lienhardt C, *et al.* Sputum culture conversion as a prognostic marker for end-of-treatment outcome in patients with multidrug-resistant tuberculosis: a secondary analysis of data from two observational cohort studies. *Lancet Respir Med* 2015; 3: 201–209.
- 86 Zumla AI, Schito M, Maeurer M. Advancing the portfolio of tuberculosis diagnostics, drugs, biomarkers, and vaccines. *Lancet Infect Dis* 2014; 14: 7–9.