New and repurposed drugs to treat multidrug- and extensively drug-resistant tuberculosis

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ABSTRACT

Multidrug-resistant and extensively drug-resistant tuberculosis (MDR-TB and XDR-TB, respectively) continue to represent a challenge for clinicians and public health authorities. Unfortunately, although there have been encouraging reports of higher success rates, the overall rate of favorable outcomes of M/XDR-TB treatment is only 54%, or much lower when the spectrum of drug resistance is beyond that of XDR-TB. Treating M/XDR-TB continues to be a difficult task, because of the high incidence of adverse events, the long duration of treatment, the high cost of the regimens used, and the drain on health care resources. Various trials and studies have recently been undertaken (some already published and others ongoing), all aimed at improving outcomes of M/XDR-TB treatment by changing the overall approach, shortening treatment duration, and developing a universal regimen. The objective of this review was to summarize what has been achieved to date, as far as new and repurposed drugs are concerned, with a special focus on delamanid, bedaquiline, pretomanid, clofazimine, carbapenems, and linezolid. After more than 40 years of neglect, greater attention has recently been paid to the need for new drugs to fight the "white plague", and promising results are being reported.

Keywords: Tuberculosis/therapy; Tuberculosis, multidrug-resistant; Extensively drug-resistant tuberculosis; Antitubercular agents.

INTRODUCTION

In its 2017 Global Tuberculosis Report, the World Health Organization (WHO) estimated that there were 1.67 million deaths attributable to tuberculosis in 2016, indicating that the so-called "white plague" continues to be a public health priority.[1] Given that 490,000 cases of multidrug-resistant tuberculosis (MDR-TB, resistant to at least isoniazid and rifampin) were reported in 2016, and that 6.2% of those cases were attributed to infection with extensively drug-resistant tuberculosis (XDR-TB) strains (i.e., MDR-TB strains with additional resistance to fluoroquinolones and at least one of the second-line injectable drugs), there is grave concern that the global epidemic is becoming resistant to the existing treatments. Unfortunately, although there have been encouraging reports of higher success rates,[2] the overall rate of favorable outcomes of M/XDR-TB treatment is only 54%,[1] or much lower when the spectrum of drug resistance is beyond that of XDR-TB.[3]

Treating M/XDR-TB continues to be a difficult task for clinicians, because of the high incidence of adverse events, the long duration of treatment, the high cost of the regimens used, and the drain on health care resources.[4-9] Various trials and studies have recently been undertaken (some already published and others ongoing), all aimed at improving outcomes of M/XDR-TB treatment by changing the overall approach and perhaps even shortening treatment duration.[1,4,10-12] The objective of this review was to summarize what has been achieved to date, as far as new and repurposed drugs are concerned.

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METHODS

We performed a nonsystematic review of the literature, using Google, Google Scholar, PubMed, and ClinicalTrials. gov to identify reports in English, Spanish, or Portuguese published between November 1, 2014 and November 1, 2017. Numerous searches were performed using the following keywords: "TB", "MDR-TB", "XDR-TB", "drugs", "trials", and "drug development". Individual searches were also performed for the following new or repurposed tuberculosis drugs: bedaquiline, delamanid, clofazimine, levofloxacin, moxifloxacin, pretomanid (previously known as Pa-824), pyrazinamide, rifapentine, rifampin, linezolid, delpazolid, sutezolid, carbapenems, imipenem, meropenem, ertapenem, and faropenem. We also performed a search for information on new and repurposed drugs in the WHO Global Tuberculosis Report 2017, as well as from relevant websites: the Global Alliance for Tuberculosis Drug Development (TB Alliance); Unitaid; the Treatment Action Group; and the Stop TB Partnership Working Group on New Drugs. Oral presentations and posters presented at the 2017 conference of the International Union Against Tuberculosis and Lung Disease (IUATLD) were also reviewed.

We have employed WHO-accepted definitions.[13] The search results are divided into three main topics: repurposed drugs, new drugs, and trials.

REPURPOSED DRUGS

Clofazimine is a riminophenazine originally used to treat leprosy. It has not traditionally been used against tuberculosis, because it has little bactericidal activity. However, recent studies have shown that it has sterilizing and treatment-shortening potentials, although the mechanism of action has yet to be fully elucidated. Clofazimine darkens the skin (a side effect that is unacceptable to a significant proportion of patients). Clofazimine can also cause gastrointestinal distress and prolongs the QT interval (the time between the start of the Q wave and the end of the T wave on an electrocardiogram). In addition, cross-resistance between clofazimine and bedaquiline can occur. A phase 1 trial of a modified molecule, TBI-166, designed to reduce the occurrence of skin darkening, is currently underway.[14] The largest study of clofazimine conducted in Brazil achieved a 62% success rate, confirming previous results in smaller cohorts.[15] Clofazimine, which was in drug group 5 in the previous WHO classification, is presently classified as a WHO Group C drug (other core second-line agents), as shown in Chart 1.

Because of their potent beta lactamase, BlaC, carbapenems are not active against *Mycobacterium tuberculosis*; they become active in the presence of clavulanic acid, causing cell wall disruption via peptidoglycan modulation and thus becoming strongly bactericidal. They are presently in WHO Group D3 (non-core drugs), and the combination of a carbapenem with clavulanate has proven to be active against M/XDR-TB, with excellent tolerability.[16-18] The main drawbacks of carbapenems are their high cost, their possible contribution to greater antimicrobial resistance in commensal bacteria, and the need to administer them parenterally. Unfortunately, faropenem, an oral carbapenem, has not been found to be active against *M. tuberculosis*. However, ertapenem has recently been shown to be a suitable "switch therapy" option to be administered intramuscularly or intravenously once daily at home.[19]

Linezolid, an oxazolidinone, inhibits the 50S ribosomal subunit in protein synthesis, has demonstrated antimycobacterial efficacy, and is included in many drug trial regimens[20] However, its toxicity profile limits its use beyond drug-resistant tuberculosis. In the past, the WHO classified linezolid as a Group 5 drug, whereas it is now considered a core second-line agent, in the new WHO Group C (Chart 1). Sutezolid and delpazolid are two newer generation oxazolidinones used in early clinical trials; the hope is that they will be just as effective as linezolid and less toxic. Although not yet recommended by the WHO, efflux pump inhibitors such as verapamil and thioridazine might play a role in lowering resistance to and boosting the antimicrobial activity of drugs like bedaquiline.[21,22]

NEW DRUGS

Bedaquiline

Bedaquiline is a novel diarylquinoline with specific activity against mycobacteria, because it inhibits mitochondrial adenosine triphosphate synthase. Currently, the WHO recommends using bedaquiline to treat M/XDR-TB only in combination with three other effective drugs, excluding delamanid (Charts 1 and 2). A recent systematic review of bedaquiline use was published in the European Respiratory Journal in 2017, updating the results of a review carried out in 2016.[23,24]

By September of 2017, over 10,000 MDR-TB cases were estimated to have been treated with bedaquiline, the vast majority in South Africa.[25] Concerns about the safety of bedaquiline were based on the 10 (late) deaths occurring in the interventional arm of the phase 2b (C208) trial and on the risk of QT prolongation.[26]

Recently, a large, retrospective observational study reported the outcomes of 428 cases of MDR-TB treated with bedaquiline-containing regimens in 15 countries under specific conditions.[2] Sputum smear and culture conversion rates achieved at the end of treatment were 88.7% and 91.2%, respectively; the success rate in the cohort as a whole was 77%, 10% higher than that reported in the study conducted in South Africa.[25] The risk of QT prolongation appears to be lower than initially thought: bedaquiline was interrupted due to side effects in only 5.8% of cases. One patient died after having presented with electrocardiographic abnormalities, which were found not to be bedaquiline-related.[2]

Bedaquiline, which is currently being studied in the TB Alliance Nix-TB trial, is effective in the treatment

Chart 1. World Health Organization categorization of second-line antituberculosis drugs recommended for the treatment of rifampin-resistant and multidrug-resistant tuberculosis.[4]

Group A	Fluoroquinolones	Levofloxacin*
		Moxifloxacin*
		Gatifloxacin*,†
Group B	Aminoglycosides	Amikacin*
		Capreomycin
		Kanamycin
		(Streptomycin)‡
Group C	Other core second-line agents	Ethionamide/prothionamide
		Cycloserine/terizidone
		Linezolid*
		Clofazimine*
Group D	Add-on agents (non-core MDR-TB regimen)	D1
		Pyrazinamide
		Ethambutol
		High-dose isoniazid
		D2
		Bedaquiline§
		Delamanid§
		D3
		Para-aminosalicylic acid
		Imipenem plus cilastatin (requires clavulanate)*
		Meropenem (requires clavulanate)*
		Amoxicillin plus clavulanate*
		Thioacetazone*,‖

MDR-TB: Multidrug-resistant tuberculosis. *Repurposed antibiotics. †Not on the market. ‡Significant resistance, not recommended. §Approved but still under investigation. ‖Not for use in people living with HIV.

of cases of XDR-TB and pre-XDR-TB (resistance to fluoroquinolones or injectable drugs), as well as in the treatment of patients suffering drug intolerance or not responding to the treatment prescribed. The Nix-TB trial is a single-arm, open-label trial evaluating the regimen of 6 months of bedaquiline, pretomanid, and linezolid (600 mg twice daily); if patients are still sputum culture-positive at 4 months, the drugs are administered for an additional 3 months.[27] The most recent Nix-TB trial data (reported in 2017) show that 26 (86.7%) of the 30 patients who completed the treatment remained relapse-free during the subsequent 6 months of follow-up, although 4 patients died in the initial phase of treatment. It is of note that culture conversion was achieved in all patients by month 4, occurring in the first 8 weeks of treatment in 65%.[28] In November of 2017, the Nix-TB trial rolled over into the new ZeNix trial, which is aimed at evaluating different doses of linezolid.

Among the existing trials evaluating bedaquiline, the most relevant are the Standard Treatment Regimen of Anti-Tuberculosis Drugs for Patients With MDR-TB (STREAM) trial, which is ongoing (in stage II), results being expected by 2021[29]; the NEXT trial[30]; the Pragmatic Clinical Trial for a More Effective Concise and Less Toxic MDR-TB Treatment Regimen (TB-PRACTECAL) trial[31]; and the Evaluating Newly Approved Drugs for Multidrug-resistant TB (endTB) trial.[32] The NEXT (open-label) trial evaluates an injection-free regimen consisting of 6-9 months of treatment with bedaquiline,

ethionamide (or high-dose isoniazid), linezolid, levofloxacin, and pyrazinamide, in comparison with the recently introduced shorter WHO regimen available for use in MDR-TB patients who meet specific criteria. The TB-PRACTECAL trial, which is a phase 2-3 trial with an adaptive design, is aimed at evaluating the safety and efficacy of a 6-month regimen of treatment with bedaquiline, pretomanid, and linezolid, with or without moxifloxacin or clofazimine, administered in adult patients with M/XDR-TB. The endTB trial, a phase 3 trial, is designed to evaluate different regimens (containing bedaquiline, delamanid, or both; moxifloxacin or levofloxacin; and pyrazinamide plus linezolid, clofazimine, or both), in various combinations, in comparison with the standard individualized regimen, in terms of their efficacy in treating M/XDR-TB.

The early findings of the ongoing NC-005 phase 2 trial, as reported in 2017, suggested that the combination of bedaquiline, pretomanid, moxifloxacin, and pyrazinamide (the BPaMZ regimen) has good bactericidal activity and appears to be well tolerated.[33] Another phase 3 trial,[34] conducted by the TB Alliance, is further evaluating this regimen by studying the effects of different doses of linezolid (ranging from 600 to 1,200 mg/day) to determine the optimal dose and treatment duration.

Through its A5343 study, the AIDS Clinical Trials Group (ACTG) aims to evaluate the combination of delamanid and bedaquiline within the WHO shorter regimen for MDR-TB. In its three arms, it evaluates the

use of bedaquiline, delamanid, and a combination of the two; clofazimine is removed to prevent increased QT prolongation.

A recent systematic review of published cases treated with bedaquiline provided, for the first time, details on QT prolongation.[26] The authors of that review found that information on QT prolongation ≥ 450 ms was available for only 35 (10.6%) of 329 cases, and that information on QT prolongation ≥ 500 ms was available for only 42 (3.2%) of 1,293 cases. Although bedaquiline was discontinued because of side effects in 44 (3.4%) of 1,293 cases, it was discontinued specifically because of QT prolongation in only 8 (0.9%) of 857 cases. It is of note that bedaquiline was restarted in 2 of those 8 cases.

Delamanid

Delamanid, which is in the same drug class as metronidazole (that of the nitroimidazoles), inhibits the biosynthesis of mycolic acid. For the treatment of M/XDR-TB, the WHO recommends delamanid only if it is used in combination with three other drugs of proven efficacy, excluding bedaquiline (Charts 1 and 2).

It has been estimated that approximately 700 patients underwent delamanid treatment by the end of 2017, either through the *Médecins sans Frontières* (Doctors without Borders) projects or the compassionate use program of the European Respiratory Society/WHO TB Consilium.[25,35,36] The Otsuka phase 3 delamanid trial appears as "completed" on ClinicalTrials.gov, and the final results are expected to be submitted for publication in the first or second quarter of 2018. Encouraging results were presented at the IUATLD Conference in Guadalajara, Mexico, in October of 2017. [37-40] The Otsuka delamanid studies provided consistent results with a high proportion of favorable outcomes: 74.5% (192 cases) in phase 2 trial 204[37]; 81.4% (339 cases) in phase 2 trial 213[38]; and 84.2% (19 cases) in a programmatic study conducted in Latvia.[39] The results of the compassionate use cases are encouraging, sputum culture conversion having been achieved in 53 (80.3%) of the 66 cases evaluated.[40]

There are data to support the efficacy and safety of delamanid in children over 6 years of age. Trial 232, which evaluates 18-day pharmacokinetic and safety profiles in a specific weight group, is expected to deliver results in 2018.[41,42] Otsuka Trial 233 is ongoing, evaluating 6-month pharmacokinetic and safety profiles in all pediatric weight groups, with results expected in 2020. Delamanid is also being tested in a number of new trials, most notably the endTB trial (Chart 2). The MDR-END trial is evaluating 9- and 12-month regimens comprising delamanid, linezolid, levofloxacin, and pyrazinamide. The H-35265 trial will evaluate the same regimens as those evaluated in the MDR-END trial, with arms for various shorter durations.

Combination treatment with bedaquiline and delamanid has recently been evaluated, although, in the absence of trial data, it is not yet recommended.

However, recent evidence suggests that the bedaquiline-delamanid combination might be better tolerated than previously considered. In one study, QT prolongation was reported in only 1 of 5 cases,[43] and the condition was transient, being reduced after a short interruption of the drug and the inclusion of verapamil in the regimen, without clinical consequences, as reported in a second study of that same case.[44] There are two trials that are currently recruiting patients for a study of the bedaquiline-delamanid combination, although results are not expected until 2020 or 2021.[45] Although the WHO does not recommend the use of the bedaquiline-delamanid combination, it recognizes that physicians might require guidance and has provided recommendations, including active drug safety monitoring, that could provide for more rapid and robust phase 4 safety data collection.[46,47]

Pretomanid

Pretomanid is a nitroimidazole (in the same class as delamanid), developed by the TB Alliance to test three different regimens for the treatment of drug-susceptible tuberculosis as well as MDR-TB. Promising results from the NC-005 trial support the use of the BPaMZ regimen.[33] In the Shortening Treatments by Advancing Novel Drugs (STAND) trial, a phase 3 trial, pretomanid is being combined with moxifloxacin and pyrazinamide in treatment regimens of two different durations (4 and 6 months). In the Nix-TB trial, pretomanid is one of the core drugs. The TB Alliance has also planned to study the bedaquiline-moxifloxacin combination and pyrazinamide within the NC-008 trial. The NC-008 SimpliciTB trial is a phase 3 trial that tests a regimen including pretomanid and bedaquiline. Pretomanid is being studied in multiple arms of the phase 2-3 TB-PRACTECAL trial.

EXISTING TRIALS

A summary of the most important trials is presented in Chart 2. There are various ongoing trials aimed at identifying the best means of managing infection with isoniazid mono-resistant strains of tuberculosis.[48-50] The ACTG 5312 and NEXT trials are evaluating the effects of high-dose isoniazid when low-level drug resistance is identified. The RIFASHORT and STAND trials are focused on shortening the current pan-sensitive treatment regimen while looking at the role of rifapentine, high-dose rifampin, and a completely new regimen. A recent phase 2 trial demonstrated that a high dose of rifampin (20 mg/kg) did not increase the rate of adverse events, although efficacy remained the same.[51]

The PanACEA trial tested three different rifampin doses (35, 20, and 10 mg/kg) in comparison with the standard regimen. The authors found that the time to culture conversion was shorter in the 35 mg/kg arm and that inclusion of SQ109 and moxifloxacin did not increase the efficacy of the regimen.[52]

In the TBTC S31/ACTG A5349 trial, a phase 3 trial, rifapentine is being tested at the standard dose of 1,200

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Chart 2. Tuberculosis drug development pipeline: class of drug, target, and phase of trial.

Class	Drug(s)	Target	Phase	Notes
Diarylquinoline	Bedaquiline	ATP synthase	3	Conditional marketing approval
Imidazopyridine amide	Q203	Targets the cytochrome b subunit of the cytochrome bc1 complex, essential for the respiratory electron chain, also depletes intracellular ATP	1	Phase 1b safety studies completed in the United States
				Phase 1 dose-escalation study underway (NCT02858973)
		Activity similar to that of bedaquiline		Early bactericidal activity study expected to have started before the end of 2017
Nitroimidazole	Delamanid	Inhibit cell wall synthesis and cell respiration	3	Conditional marketing approval
	Pretomanid		3	Awaiting regulatory approval
Oxazolidinone	Sutezolid	Protein synthesis 23s ribosome	2a	Significant reduction in counts of colony-forming units in an early bactericidal activity study
				Phase 1a completed only recently (NCT03199313), due to licensing problems
	Delpazolid (LCB01-0371)		2	A phase 2 safety and early bactericidal activity study of the drug expected to be completed in late 2017
1,2-ethylenediamine	SQ109	Inhibit cell wall synthesis (MmpL3)	2-3	May be synergic with bedaquiline
				Two SQ109-containing arms in a PanACEA trial testing high-dose rifampin stopped early because pre-specified efficacy thresholds were not met
Benzothiazinone	PBTZ169	DprE1 inhibitors (inhibit cell wall synthesis)	2	Synergies with bedaquiline and clofazimine
	OPC-167832		1	Co-developed as a companion drug for delamanid in view of a pan-tuberculosis regimen
	TBA-7371		1	Phase 1a trial has begun (NCT03199339)
Riminophenazine	TBI-166	Outer membrane, bacterial respiratory chain and ion transporters	1	Improved analogue of clofazimine
				Phase 1 to commence in China in October of 2017
Oxaborole	GSK 070, GSK 3036656	Protein synthesis (leucyl-tRNA synthetase)	1	Phase 1 completed (NCT03075410)

ATP: adenosine triphosphate.

mg/day.[53] The TRUNCATE-TB strategy phase 2c trial will test the possibility of shortening the treatment of drug-susceptible tuberculosis to 2 months by combining new and repurposed drugs, including rifamycins.[54] Recently, the use of rifabutin was shown to improve treatment outcomes.[55]

The Opti-Q phase 2 trial has been designed to identify the optimal daily dose of levofloxacin (11, 14, 17, or 20 mg/kg) for the treatment of MDR-TB.[56] Levofloxacin is also being studied in the H-35265 trial, the NEXT trial, the STREAM trial, and the MDR-END trial.[57]

Moxifloxacin is under evaluation in different trials as a replacement for isoniazid or ethambutol in mono-resistant cases or in patients with tolerability problems. The WHO has recently launched the so called "shorter regimen", also known as the "Bangladesh regimen", which is a 9- to 11-month standardized

regimen—consisting of 4-6 months of treatment with gatifloxacin/moxifloxacin, kanamycin/amikacin, ethionamide/prothionamide, clofazimine, high-dose isoniazid (10 mg/kg, maximum 600 mg/day), ethambutol, and pyrazinamide, followed by 5 months of treatment with gatifloxacin/moxifloxacin, clofazimine, ethambutol, and pyrazinamide.[58,59] The shorter regimen is indicated for all patients with pulmonary MDR-TB or rifampin-resistant tuberculosis (excluding pregnant women and patients with extrapulmonary tuberculosis), not previously treated with second-line drugs, that is susceptible to fluoroquinolones and aminoglycosides.[4] It is important that adequate resistance testing be performed, to avoid selecting further resistance.[60-62] A recent meta-analysis reported that shorter regimens are effective, although failure and relapse were found to be associated with fluoroquinolone resistance (OR = 46).[63]

There are limited data available on the use of shorter regimens.[64-67] Interim results of the STREAM trial, presented at the IUATLD Conference in Guadalajara, demonstrated no inferiority of the shorter regimens in comparison with the individualized WHO longer regimen, favorable outcomes being achieved in approximately 78.1% of the patients treated with the shorter regimen, compared with 80.6% of those treated with the longer regimen.[68] The proportion of patients showing prolongation of the corrected QT was higher in the patients treated with the shorter regimen than in those treated with the longer regimen. The second stage of the trial is evaluating the role of bedaquiline within the shorter regimen.

In conclusion, after more than 40 years of neglect, the WHO and partner organizations are now giving greater attention to the need for new, better drugs and regimens to fight the "white plague". Favorable results are expected.

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REFERENCES

1. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; c2017 [cited 2017 Oct 30]. Global tuberculosis report 2017; [about 2 screens]. Available from: http://www.who.int/tb/publications/global_report/en/

2. Borisov SE, Dheda K, Enwerem M, Romero Leyet R, D'Ambrosio L, Centis R, et al. Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study. Eur Respir J. 2017;49(5). pii: 1700387. https://doi.org/10.1183/13993003.00387-2017

3. Migliori GB, Sotgiu G, Gandhi NR, Falzon D, DeRiemer K, Centis R, et al. Drug resistance beyond extensively drug-resistant tuberculosis: individual patient data meta-analysis. Eur Respir J. 2013;42(1):169-179. https://doi.org/10.1183/09031936.00136312

4. Falzon D, Schünemann HJ, Harausz E, González-Angulo L, Lienhardt C, Jaramillo E, et al. World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. Eur Respir J. 2017;49(3). pii: 1602308. https://doi.org/10.1183/13993003.02308-2016

5. Winters N, Butler-Laporte G, Menzies D. Efficacy and safety of World Health Organization group 5 drugs for multidrug-resistant tuberculosis treatment. Eur Respir J. 2015;46(5):1461-70. https://doi.org/10.1183/13993003.00649-2015

6. Diel R, Rutz S, Castell S, Schaberg T. Tuberculosis: cost of illness in Germany. Eur Respir J. 2012;40(1):143-51. https://doi.org/10.1183/09031936.00204611

7. Diel R, Vandeputte J, de Vries G, Stillo J, Wanlin M, Nienhaus A. Costs of tuberculosis disease in the European Union: a systematic analysis and cost calculation. Eur Respir J. 2014;43(2):554-65. https://doi.org/10.1183/09031936.00079413

8. D'Ambrosio L, Bothamley G, Caminero Luna JA, Duarte R, Guglielmetti L, Mu-oz Torrico M, et al. Team approach to manage difficult-to-treat TB cases: experiences in Europe and beyond. Rev Port Pneumol (2006). 2017. pii: S2173-5115(17)30163-X. [Epub ahead of print] https://doi.org/ 10.1016/j.rppnen.2017.10.005

9. Blasi F, Dara M, van der Werf MJ, Migliori GB. Supporting TB clinicians managing difficult cases: the ERS/WHO Consilium. Eur Respir J. 2013;41(3):491-4. https://doi.org/10.1183/09031936.00196712

10. Caminero JA, Piubello A, Scardigli A, Migliori GB. Proposal for a standardised treatment regimen to manage pre- and extensively drug-resistant tuberculosis cases. Eur Respir J. 2017;50(1). pii: 1700648. https://doi.org/10.1183/13993003.00648-2017

11. Global Alliance for Public Relations and Communications Management [homepage on the Internet]. Lugano: the Alliance. [updated 2017 Nov 19; cited 2017 Nov 21]. Available from: http://www.globalalliancepr.org/

12. ClinicalTrials.gov [database on the Internet]. Bethesda: National Library of Medicine (US). [updated 2017 Nov 19; cited 2017 Nov 21]. Available from: https://clinicaltrials.gov/

13. World Health Organization. Compendium of WHO guidelines and associated standards: ensuring optimum delivery of the cascade of care for patients with tuberculosis. Geneva: World Health Organization; 2017.

14. Lu Y, Zheng M, Wang B, Fu L, Zhao W, Li P, et al. Clofazimine analogs with efficacy against experimental tuberculosis and reduced potential for accumulation. Antimicrob Agents Chemother. 2011;(55):5185-93. https://doi.org/10.1128/AAC.00699-11

15. Dalcolmo M, Gayoso R, Sotgiu G, D'Ambrosio L, Rocha JL, Borga L, et al. Effectiveness and safety of clofazimine in multidrug-resistant tuberculosis: a nationwide report from Brazil. Eur Respir J. 2017;49(3). pii: 1602445. https://doi.org/10.1183/13993003.02445-2016

16. Tiberi S, Sotgiu G, D'Ambrosio L, Centis R, Abdo Arbex M, Alarcon Arrascue E, et al. Comparison of effectiveness and safety of imipenem/clavulanate- versus meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB. Eur Respir J. 2016;47(6):1758-66. https://doi.org/10.1183/13993003.00214-2016

17. Tiberi S, Payen MC, Sotgiu G, D'Ambrosio L, Alarcon Guizado V, Alffenaar JW, et al. Effectiveness and safety of meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB. Eur Respir J. 2016;47(4):1235-43. https://doi.org/10.1183/13993003.02146-2015

18. Diacon AH, van der Merwe L, Barnard M, von Groote-Bidlingmaier F, Lange C, García-Basteiro AL, et al. β-Lactams against Tuberculosis--New Trick for an Old Dog? N Engl J Med. 2016;375(4):393-4. https://doi.org/10.1056/NEJMc1513236

19. Tiberi S, D'Ambrosio L, De Lorenzo S, Viggiani P, Centis R, Sotgiu G, et al. Ertapenem in the treatment of multidrug-resistant tuberculosis: first clinical experience. Eur Respir J. 2016;47(1):333-6. https://doi.org/10.1183/13993003.01278-2015

20. Sotgiu G, Pontali E, Migliori GB. Linezolid to treat MDR-/XDR-tuberculosis: available evidence and future scenarios. Eur Respir J. 2015;45(1):25-9. https://doi.org/10.1183/09031936.00145014

21. Te Brake LHM, de Knegt GJ, de Steenwinkel JE, van Dam TJP, Burger DM, Russel FGM, et al. The Role of Efflux Pumps in Tuberculosis Treatment and Their Promise as a Target in Drug Development: Unraveling the Black Box. Annu Rev Pharmacol Toxicol. 2018;58:271-291. https://doi.org/10.1146/annurev-pharmtox-010617-052438

22. Amaral K, Viveiros M. Thioridazine: A Non-Antibiotic Drug Highly Effective, in Combination with First Line Anti-Tuberculosis Drugs, against Any Form of Antibiotic Resistance of Mycobacterium tuberculosis Due to Its Multi-Mechanisms of Action. Antibiotics (Basel). 2017;6(1). pii: E3. https://doi.org/10.3390/antibiotics6010003

23. Pontali E, Sotgiu G, D'Ambrosio L, Centis R, Migliori GB. Bedaquiline and multidrug-resistant tuberculosis: a systematic and critical analysis of the evidence. Eur Respir J. 2016;47(2):394-402. https://doi.org/10.1183/13993003.01891-2015

24. Pontali E, D'Ambrosio L, Centis R, Sotgiu G, Migliori GB. Multidrug-resistant tuberculosis and beyond: an updated analysis of the current evidence on bedaquiline. Eur Respir J. 2017;49(3). pii: 1700146. https://doi.org/10.1183/13993003.00146-2017

25. DR-TB Scale-Up Treatment Action Team (DR-TB STAT) [homepage on the Internet]. [updated 2017 Sep; cited 2017 Nov 21]. Country Updates. Available from: http://drtb-stat.org/country-updates/

26. Pontali E, Sotgiu G, Tiberi S, D'Ambrosio L, Centis R, Migliori GB. Cardiac safety of bedaquiline: a systematic and critical analysis of the evidence. Eur Respir J. 2017;50(5). pii: 1701462. https://doi.org/10.1183/13993003.01462-2017

27. ClinicalTrials.gov [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2000. [updated 2018 Jan 26; cited 2017 Nov 21]. A Phase 3 Study Assessing the Safety and Efficacy of Bedaquiline Plus PA-824 Plus Linezolid in Subjects With Drug

Resistant Pulmonary Tuberculosis; Identifier NCT02333799; [about 13 screens]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02333799?term=NCT02333799&rank=1

28. Conradie F, Diacon AH, Everitt D, Mendel C, van Niekerk C, Howell P, et al. The NIX-TB trial of pretomanid, bedaquiline and linezolid to treat XDR-TB. In: Conference on Retroviruses and Opportunistic Infections [proceedings on the Internet]; 2017 Feb 13-16; Seattle (WA), USA. Abstract Number 80LB. [cited 2017 Nov 21]. Available from: http://www.croiconference.org/sessions/nix-tb-trial-pretomanid-bedaquiline-and-linezolid-treat-xdr-tb

29. ClinicalTrials.gov [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2000. [updated 2018 Jan 11; cited 2017 Nov 21].The Evaluation of a Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients With MDR-TB (STREAM); Identifier NCT02409290; [about 22 screens]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02409290?term=NCT02409290&rank=1

30. ClinicalTrials.gov [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2000. [updated 2016 Oct 26; cited 2017 Nov 21]. An Open-label RCT to Evaluate a New Treatment Regimen for Patients With Multi-drug Resistant Tuberculosis (NEXT); Identifier NCT02454205; [about 14 screens]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02454205?term=NCT02454205&rank=1

31. ClinicalTrials.gov [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2000. [updated 2017 Jan 18; cited 2017 Nov 21]. Pragmatic Clinical Trial for a More Effective Concise and Less Toxic MDR-TB Treatment Regimen(s) (TB-PRACTECAL); Identifier NCT02589782; [about 14 screens]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02589782?term=NCT02589782&rank=1

32. ClinicalTrials.gov [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2000. [updated 2017 Nov 17; cited 2017 Oct 15]. Evaluating Newly Approved Drugs for Multidrug-resistant TB (endTB); Identifier NCT02754765; [about 16 screens]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02754765?term=NCT02754765&rank=1

33. Dawson R, Harris K, Conradie A, Burger D, Murray S, Mendel C, et al. Efficacy Of Bedaquiline, Pretomanid, Moxifloxacin & PZA (BPAMZ) Against DS- & MDR-TB. In: Conference on Retroviruses and Opportunistic Infections [proceedings on the Internet]; 2017 Feb 13-16; Seattle, Washington. Abstract Number 724LB. [cited 2017 Oct 18]. Available from: http://www.croiconference.org/sessions/efficacy-bedaquiline-pretomanid-moxifloxacin-pza-bpamz-against-ds-mdr-tb

34. ClinicalTrials.gov [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2000. [updated 2018 Feb 8; cited 2017 Oct 15]. Safety and Efficacy of Various Doses and Treatment Durations of Linezolid Plus Bedaquiline and Pretomanid in Participants With Pulmonary TB, XDR-TB, Pre- XDR-TB or Non-responsive/Intolerant MDR-TB (ZeNix); Identifier NCT03086486. [about 20 screens]. Available from: https://clinicaltrials.gov/ct2/show/NCT03086486

35. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; c2014 [cited 2017 Oct 18]. The use of delamanid in the treatment of multidrug-resistant tuberculosis: interim policy guidance [Adobe Acrobat document, 80p.]. Available from: http://apps.who.int/iris/bitstream/10665/137334/1/WHO_HTM_TB_2014.23_eng.pdf

36. Tadolini M, Garcia-Prats AJ, D'Ambrosio L, Hewison C, Centis R, Schaaf HS, et al. Compassionate use of new drugs in children and adolescents with multidrug-resistant and extensively drug-resistant tuberculosis: early experiences and challenges. Eur Respir J. 2016;48(3):938-43. https://doi.org/10.1183/13993003.00705-2016

37. Skripconoka V, Danilovits M, Pehme L, Tomson T, Skenders G, Kummik T, et al. Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. Eur Respir J. 2013;41(6):1393-400. https://doi.org/10.1183/09031936.00125812

38. McKay B. New Treatments for Drug-Resistant TB Get a Boost. Posted on October 23, 2017 The Wall Street Journal. 2017 Oct 13.

39. Kuksa L, Barkane L, Hittel N, Gupta R. Final treatment outcomes of multidrug- and extensively drug-resistant tuberculosis patients in Latvia receiving delamanid-containing regimens. Eur Respir J. 2017;50(5). pii: 1701105. https://doi.org/10.1183/13993003.01105-2017

40. Hafkin J, Hittel N, Martin A, Gupta R. Early outcomes in MDR-TB and XDR-TB patients treated with delamanid under compassionate use. Eur Respir J. 2017 Jul 27;50(1). pii: 1700311. https://doi.org/10.1183/13993003.00311-2017

41. Hafkin J, Frias M, Hesseling A, Garcia-Prats AJ, Schaaf HS, Gler M, et al. Pharmacokinetics and safety of delamanid in pediatric MDR-TB patients: ages 6–17 years. In: Proceedings of the 55th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2015 Sep 17-21; San Diego (CA), USA.

42. Hafkin J, Frias M, De Leon A, Hittel N, Geiter L, Wells C, et al. Long-term safety, tolerability and pharmacokinetics of delamanid in pediatric MDR-TB patients, ages 12–17 years. In: Proceedings of the 46th Union World Conference on Lung Health; 2015 Dec 2-6; Cape Town, South Africa.

43. Maryandyshev A, Pontali E, Tiberi S, Akkerman O, Ganatra S, Sadutshang TD, et al. Bedaquiline and Delamanid Combination Treatment of 5 Patients With Pulmonary Extensively Drug-Resistant Tuberculosis. Emerg Infect Dis. 2017;23(10). https://doi.org/10.3201/eid2310.170834

44. Tadolini M, Lingtsang RD, Tiberi S, Enwerem M, D'Ambrosio L, Sadutshang TD, et al. First case of extensively drug-resistant tuberculosis treated with both delamanid and bedaquiline. Eur Respir J. 2016;48(3):935-8. https://doi.org/10.1183/13993003.00637-2016

45. ClinicalTrials.gov [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2000. [updated 2017 Dec 7; cited 2017 Sep 28]. Evaluating the Safety, Tolerability, and Pharmacokinetics of Bedaquiline and Delamanid, Alone and in Combination, For Drug-Resistant Pulmonary Tuberculosis; Identifier NCT02583048 [about 12 screens]. Available from: https://clinicaltrials.gov/ct2/show/NCT02583048?term=NCT02583048&rank=1

46. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; c2017 [cited 2017 Oct 5]. WHO best-practice statement on the off-label use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis. [Adobe Acrobat document, 9p.]. Available from: http://apps.who.int/iris/bitstream/10665/258941/1/WHO-HTM-TB-2017.20-eng.pdf

47. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; c2015 [cited 2017 Oct 5]. Active tuberculosis drug-safety monitoring and management (aDSM). Framework for implementation. [Adobe Acrobat document, 28p.]. Available from: http://apps.who.int/iris/bitstream/10665/204465/1/WHO_HTM_TB_2015.28_eng.pdf

48. Santos G, Oliveira O, Gaio R, Duarte R. Effect of Isoniazid Resistance on the Tuberculosis Treatment Outcome. Arch Bronconeumol. 2018;54(1):48-51.

49. Gegia M, Winters N, Benedetti A, van Soolingen D, Menzies D. Treatment of isoniazid-resistant tuberculosis with first- line drugs: a systematic review and meta-analysis. Lancet Infect Dis. 2017 Feb;17(2):223-234. https://doi.org/10.1016/S1473-3099(16)30407-8

50. Stagg HR, Lipman MC, McHugh TD, Jenkins HE. Isoniazid-resistant tuberculosis: a cause for concern? Int J Tuberc Lung Dis. 2017;21(2):129-139. https://doi.org/10.5588/ijtld.16.0716

51. Jindani A, Borgulya G, de Pati-o IW, Gonzales T, de Fernandes RA, Shrestha B, et al. A randomised Phase II trial to evaluate the toxicity of high-dose rifampicin to treat pulmonary tuberculosis. Int J Tuberc Lung Dis. 2016;20(6):832-8. https://doi.org/10.5588/ijtld.15.0577

52. Boeree MJ, Heinrich N, Aarnoutse R, Diacon AH, Dawson R, Rehal S, et al. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomized controlled trial. Lancet Infect Dis. 2017;17(1):39-49. https://doi.org/10.1016/S1473-3099(16)30274-2

53. ClinicalTrials.gov [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2000. [updated 2016 Jul 11; cited 2017 Oct 15]. BTC Study 31: Rifapentine-containing Tuberculosis Treatment Shortening Regimens (S31/A5349); Identifier NCT02410772 Available from: https://www.clinicaltrials.gov/ct2/show/NCT02410772?term=NCT02410772&rank=1

54. Papineni P; Phillips P; Lu Q; Cheung YB; Nunn A; Paton N. TRUNCATE-TB: an innovative trial design for drug-sensitive tuberculosis. Int J Infect Dis. 2016;45 Suppl 1:404. https://doi.org/10.1016/j.ijid.2016.02.863

55. Lee H, Ahn S, Hwang NY, Jeon K, Kwon OJ, Huh HJ, et al. Treatment outcomes of rifabutin-containing regimens for rifabutin-sensitive multidrug-resistant pulmonary tuberculosis Int J Infect Dis. 2017;65:135-141. https://doi.org/10.1016/j.ijid.2017.10.013

56. ClinicalTrials.gov [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2000. [updated 2017 Jul 18; cited 2017 Oct 20]. Efficacy and Safety of Levofloxacin for the Treatment of MDR-TB (Opti-Q); Identifier NCT01918397; [about 12 screens]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT01918397?term=NCT01918397&rank=1

57. ClinicalTrials.gov [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2000. [updated 2016 May 3; cited 2017 Oct 20]. Treatment Shortening of MDR-TB Using Existing and New Drugs (MDR-END); Identifier NCT02619994; [about 10 screens]. Available at: https://www.clinicaltrials.gov/ct2/show/NCT02619994?term=NCT02619994&rank=1

58. Aung K, Van Deun A, Declerq E, Sarker MR, Das PK, Hossain MA, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. Int J Tuberc Lung Dis. 2014(18):1180-7. https://doi.org/10.5588/ijtld.14.0100

59. Piubello A, Harouna S, Souleymane MB, Boukary I, Morou S, Daouda M, et al. High cure rate with standardized short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. Int J Tuber Lung Dis. 2014(18):1188-94.

60. Sotgiu G, Tiberi S, D'Ambrosio L, Centis R, Zumla A, Migliori GB. WHO recommendations on shorter treatment of multidrug-resistant tuberculosis. Lancet. 2016;387(10037):2486-7. https://doi.org/10.1016/S0140-6736(16)30729-2

61. Sotgiu G, Tiberi S, Centis R, D'Ambrosio L, Fuentes Z, Zumla A, et al. Applicability of the shorter 'Bangladesh regimen' in high multidrug-resistant tuberculosis settings. Int J Infect Dis. 2017;56:190-193. https://doi.org/10.1016/j.ijid.2016.10.021

62. Sotgiu G, Tiberi S, D'Ambrosio L, Centis R, Alffenaar JW, Caminero JA, et al. Faster for less: the new "shorter" regimen for multidrug-resistant tuberculosis. Eur Respir J. 2016;48(5):1503-1507. https://doi.org/10.1183/13993003.01249-2016

63. Ahmad Khan F, Salim MAH, du Cros P, Casas EC, Khamraev A, Sikhondze W, et al. Effectiveness and safety of standardised shorter regimens for multidrug-resistant tuberculosis: individual patient data and aggregate data meta-analyses. Eur Respir J. 2017;50(1). pii: 1700061. https://doi.org/10.1183/13993003.00061-2017

64. van der Werf MJ, Ködmön C, Catchpole M. Shorter regimens for multidrug-resistant tuberculosis should also be applicable in Europe. Eur Respir J. 2017;49(6). pii: 1700463. https://doi.org/10.1183/13993003.00463-2017

65. Yassin MA, Jaramillo E, Wandwalo E, Falzon D, Scardigli A, Kunii O, et al. Investing in a novel shorter treatment regimen for multidrug-resistant tuberculosis: to be repeated. Eur Respir J. 2017;49(3). pii: 1700081. https://doi.org/10.1183/13993003.00081-2017

66. Barry PM, Lowenthal P, True L, Henry L, Schack G, Wendorf K, et al. Benefit of the Shorter Multidrug-Resistant Tuberculosis Treatment Regimen in California and Modified Eligibility Criteria. Am J Respir Crit Care Med. 2017;196(11):1488-1489. https://doi.org/10.1164/rccm.201701-0013LE

67. Chee CBE, KhinMar KW, Sng LH, Jureen R, Cutter J, Lee VJM, et al. The shorter multidrug-resistant tuberculosis treatment regimen in Singapore: are patients from South-East Asia eligible? Eur Respir J. 2017;50(2). pii: 1700753. https://doi.org/10.1183/13993003.00753-2017

68. Medical Research Council Clinical Trials Unit [homepage on the Internet]. London: MRC Clinical Trials Unit; c2014 [cited 2017 Oct 18]. Preliminary results from STREAM trial provide insight into shorter treatment for multidrug-resistant tuberculosis [about 3 screens]. Available from: http://www.ctu.mrc.ac.uk/news/2017/preliminary_results_from_stream_trial_provide_insight_into_shorter_treatment_for_multidrug_resistant_tuberculosis