



Pulmonary Tuberculosis Management: 2015 Update

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ABSTRACT

Tuberculosis, currently killing more than 3,500 people every day, continues to be a first-class health priority in terms of incidence and mortality. The 2014 WHO Global Report estimates that nine million incident cases of tuberculosis and 1.5 million deaths occurred in 2013. The aim of the present review is to update the reader on the principles of modern anti-tuberculosis treatment, describe the regimens recommended by the WHO for drug-resistant and multidrug-resistant/extensively drug-resistant tuberculosis cases, and describe the trials presently underway on new regimens *vis-à-vis* the availability of new drugs like delamanid, bedaquiline, and pretomanid and several re-proposed drugs including linezolid and meropenem clavulanate. We performed a non-systematic review based on historical trial results as well as on recent literature and WHO guidelines, with special focus on the approach to manage multidrug-resistant and extensively drug-resistant tuberculosis. The new, innovative, global public health interventions, recently approved by the WHO and known as “End Tuberculosis Strategy”, support the vision of a tuberculosis-free world with zero death, zero disease, and zero suffering due to tuberculosis. While rapid diagnosis and effective treatment of (infectious) cases are the pillars of tuberculosis control, a more aggressive approach based on diagnosis and treatment of latently infected individuals has been proposed in the context of tuberculosis elimination to ensure future generations free of the disease. Adequate, universally accessed treatment is a prerequisite to reach tuberculosis elimination. New shorter, cheap, safe, and effective anti-tuberculosis regimens are necessary to boost tuberculosis elimination. (BRN Rev. 2015;1:26-38)

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INTRODUCTION

Tuberculosis (TB), originating over 400 centuries ago in Africa, is caused by *Mycobacterium tuberculosis*. Killing currently > 3,500 people every day, TB continues to be a first-class health priority in terms of incidence and mortality, together with HIV/AIDS and malaria. The 2014 World Health Organization (WHO) Global Report estimates that nine million incident cases of TB and 1.5 million deaths occurred in 2013¹.

The rise in the number of *M. tuberculosis* isolates resistant to first-line (multidrug-resistant TB [MDR-TB], i.e. resistant to at least isoniazid and rifampicin) and second-line (extensively drug resistant [XDR], i.e. resistant to any fluoroquinolones and to at least one of the second-line injectable drugs, amikacin, capreomycin, and kanamycin on top of isoniazid and rifampicin) drugs is posing a real threat to global TB control and elimination efforts²⁻⁵. The WHO estimated that in 2013, the prevalence of MDR-TB among the new and re-treated cases was, respectively, 3.5 and 20.5%, with 9% of them being XDR-TB^{1,6}.

Unfortunately, at the global level, out of the estimated 300,000 MDR-TB cases, only 136,000 (45.3%) are diagnosed and 97,000 (32.3%) are treated using adequate regimens based on drug-susceptibility testing (DST). Consequently, the treatment success rate of MDR-TB is low (48%), and that of the XDR-TB cases with advanced resistance patterns is very low (< 20%)^{1,7,8}.

The aim of the present review is to update the reader on the principles of modern anti-TB treatment, describe the regimens recommended by the WHO for drug-resistant and MDR/XDR-TB cases, and describe the trials

presently ongoing on new regimens *vis-à-vis* the availability of new drugs like delamanid, bedaquiline, and pretomanid.

A non-systematic review based on historical trials results as well as on recent literature and WHO guidelines has been performed.

The rationale of modern short-course chemotherapy

Mycobacterium tuberculosis is a slow-growing aerobic organism with the capacity to remain dormant for long periods of time. Prolonged treatment with multiple drugs is then necessary to ensure both relapse-free cure and prevention of drug-resistance. The results of any treatment effort are determined by a combination of bacteriological (e.g. number and metabolic conditions of the bacilli), environmental (anatomical and biochemical; e.g. oxygen tension and pH level) and pharmacological factors (e.g. drug dosage, combination and treatment duration)⁹⁻¹¹.

Preventing the emergence of drug resistance, as early studies from 1960s have demonstrated¹¹, is of paramount importance; at least two active drugs are necessary as mono-therapy leads to treatment failure and relapse.

There are three main actions of anti-TB drugs⁹⁻¹¹:

- Bactericidal action, e.g. the ability to rapidly kill actively growing bacilli, i.e. isoniazid (H), and to a lesser extent rifampicin (R), pyrazinamide (Z) and streptomycin (S);
- Sterilizing action, e.g. the capacity to kill the semi-dormant organisms, e.g. R and Z; and

- Prevention of emergence of bacillary resistance, e.g. H and R; and, with a lower efficacy, S, ethambutol (E) and Z.

Anti-TB treatment has an intensive and a continuation phase. The intensive phase of treatment kills both actively growing and semi-dormant bacilli, ensuring individual benefit for the patient, and reducing transmission in the community as well as the probability to select resistant mutants. During the intensive phase of treatment, at least two bactericidal drugs (H and S or H and R) are necessary. Z is added because of its brilliant activity in the acidic environment of the pulmonary cavities, and its capacity to kill semi-dormant bacilli not destroyed by other drugs. E, although bacteriostatic, is helpful in case of initial resistance to a single drug or when the initial bacillary load is high.

Appropriate multidrug combinations (including 3-5 drugs) are likely to contain at least two drugs able to kill the pre-existing mono-drug-resistant spontaneous mutants among wild strains. In case of mono-resistance to a first-line drug (R excluded), the chances of a favorable outcome are reasonably high if four drugs are prescribed in the intensive phase of treatment¹².

The continuation phase (usually including H and R for new cases) eliminates most residual bacilli, reducing the probability of failure and relapse. As the bacilli are no longer replicating actively, the probability of selecting drug-resistant mutants is low¹³.

MANAGING DRUG-SUSCEPTIBLE TUBERCULOSIS

The current 2004 WHO-recommended treatment regimens for new cases, approved TB

drugs, and their dosage are summarized in table 1. The WHO has started the procedures to revise these guidelines.

The recommendations¹⁴ clearly distinguish between new cases (e.g. patients diagnosed with TB, who have never previously received anti-TB drugs for more than one month) and retreatment cases (e.g. those treated previously for more than 30 days). New TB cases (irrespective of HIV-status) should be treated with a six-month regimen of HRZE for the first two months (“intensive phase”), followed by HR for the remaining four months (“continuation phase”)¹⁴. Longer treatments are not recommended as clinical trials have not confirmed clinical superiority.

Although daily dosage is recommended for the entire duration of treatment (and particularly during the intensive phase), the three-times weekly approach is allowed if directly observed therapy is ensured.

Fixed-dose combination formulations are recommended to treat TB, based on evidence of no significant differences between fixed-dose combinations and separate TB drug formulations in acquiring drug resistance, achieving bacteriological conversion, or producing adverse events¹⁵. Furthermore, fixed-dose combinations simplify TB therapy at the programmatic level, although no evidence exists that these formulations improve treatment outcomes or patient adherence.

The WHO has recently published its new “End TB Strategy”^{1,16} based on three pillars: the first pillar includes prevention, diagnostic and treatment interventions, the second the socio-economic interventions beyond the TB

TABLE 1. WHO-recommended treatment regimens for new and previously treated patients

NEW TUBERCULOSIS CASES				PREVIOUSLY TREATED TUBERCULOSIS CASES Pending DST results (up to 2-3 months after the start of treatment) PROBABILITY OF MDR-TB				
INTENSIVE PHASE		CONTINUATION PHASE		Medium or low (relapse, lost to follow-up)				High (failure)
Duration	Anti-TB drugs	Duration	Anti-TB drugs	INTENSIVE PHASE		CONTINUATION PHASE		
				Duration	Anti-TB drugs	Duration	Anti-TB drugs	
2 months	Isoniazid (H) Rifampicin (R) Pyrazinamide (Z) Ethambutol* (E)	4 months [†]	Isoniazid (H) [‡] Rifampicin (R) [‡] or Isoniazid (H) [‡] Rifampicin (R) [‡] Ethambutol (E) [‡]	2 months	Isoniazid (H) Rifampicin (R) Pyrazinamide (Z) Ethambutol (E) Streptomycin (S)	5 months	Isoniazid (H) Rifampicin (R) Ethambutol (E)	Empirical MDR-TB regimen
				1 month	Isoniazid (H) Rifampicin (R) Pyrazinamide (Z) Ethambutol (E)			

*Ethambutol has to be prescribed in individuals with non-cavitary, sputum smear-negative pulmonary TB or with extra-pulmonary TB who are known to be HIV-negative. In TB meningitis, it should be replaced by streptomycin.

[†]When the level of isoniazid resistance among new cases is elevated and in-vitro isoniazid DST is not available, HRE regimen may be an acceptable alternative to HR regimen

[‡]WHO considers the 3 times per week continuation phase as acceptable alternative for any new TB patient receiving directly observed therapy

WHO: World Health Organization; TB: tuberculosis; MDR-TB: multidrug-resistant tuberculosis; DST: drug susceptibility testing.

Adapted from: World Health Organization. *The treatment of tuberculosis: guidelines-4th ed.*¹⁴.

programmatic level (e.g. universal access, social protection, etc.) and the third, the research priorities.

As part of pillar 1, universal drug susceptibility testing (rapid DST with, for example GeneXpert¹⁷ and/or conventional with solid or liquid culture) is strongly recommended before prescribing the anti-TB regimen; however, this is not universally available yet in several developing countries. Re-treatment patients need special attention because of the risk of inducing drug resistance. Rapid tests for DST should be used whenever available to ensure an appropriate treatment regimen from the beginning as well as adequate infection control management in a specialized MDR-TB Centre^{18,19}. While awaiting DST results, these patients could be initially treated with an empiric regimen (i.e. HRZES for two months,

followed by HRZE for one month and HRE for five months) only in settings where the prevalence of MDR-TB is medium or low.

MANAGING MULTIDRUG RESISTANT AND EXTENSIVELY DRUG RESISTANT TUBERCULOSIS

The emergence and spread of MDR-and XDR-TB has attracted interest at different levels^{1,20-23}. Recently, *M. tuberculosis* strains that are resistant to all known drugs have been described in Italy²⁴ as well as in India and Iran²⁵⁻²⁷, leading to the new definition of “total drug resistance”. However, this definition has not been approved by the WHO due to the difficulty to standardize the panel of drugs to be tested *vis-à-vis* the new drugs gradually entering in the anti-TB treatment arena.

From the public health point of view, MDR/XDR-TB is considered a serious threat for TB control and elimination^{1,21}.

The prevalence of MDR-TB is particularly high in several countries belonging to the former Soviet Union, where 9-35% of new cases and $\geq 50\%$ of previously treated cases harbor MDR-TB strains¹.

XDR-TB had been reported by 100 countries worldwide. Overall, 75 countries plus five territories globally reported representative data on the proportion of MDR-TB cases affected by XDR-TB, being 9% (95% CI: 6.5-11.5) in 2013. Fifteen of these 75 countries reported 10 or more XDR-TB cases. Among those countries, the proportion of MDR-TB cases affected by XDR-TB was highest in Georgia (20%), Kazakhstan (22.7%), Latvia (21.7%), Lithuania (24.8%), and Tajikistan (Dushanbe city and Rudaki district: 21%)¹.

To combat the MDR/XDR-TB threat, the 53 Member States of WHO European Region have endorsed the five-year Consolidated Action Plan to Prevent and Combat M/XDR-TB 2011-2015⁶.

We have mentioned above how unsatisfactory the clinical outcome of MDR-TB cases is^{1,6,29,30}. In the largest ever-published cohort of 9,153 MDR-TB cases from 32 observational cohorts supporting an individual data meta-analysis, the clinical outcomes were unacceptably poor (treatment success 54%; default 23%; failure/relapse 8%; death 15%)³¹. In XDR-TB cases and cases with resistance patterns beyond XDR, the outcomes were even worse, with treatment success ranging from 19 to 40%, failure/relapse from 15 to 54%, and death from 15 to 35%^{7,8}.

TABLE 2. WHO groups of first-and second-line anti-tuberculosis drugs

Group name	Anti-tuberculosis 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 (FQ)	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.

Adapted from: WHO Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis³³.

The challenges clinicians face when dealing with MDR-and XDR-TB cases include frequent occurrence of adverse events, limited availability of second-line anti-TB drugs, the relevant risk of acquiring further *M. tuberculosis* resistance, on top of associated conditions such as alcohol and drug abuse and problems in patient adherence.

The 2011 WHO MDR-TB guidelines³² have divided anti-TB drugs into groups, based on their efficiency and safety (Table 2).

TABLE 3. WHO-recommended treatment regimen for multidrug-resistant tuberculosis

World Health Organization recommendations		
STEP 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.
STEP 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
STEP 3	Add Group 4 drugs Group 4 – Cycloserine/terizidone – Para-aminosalicylic acid (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.
STEP 4	Add Group 1 drugs Group 1 – Pyrazinamide – Ethambutol	Pyrazinamide is routinely added in most regimens. Ethambutol can be added in case of full sensitivity. If isoniazid is unknown or pending it can be added to the regimen until DST results become available.
STEP 5	Add Group 5 drugs Group 5 – 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 standardized for the drugs in this group.

TB: tuberculosis; MDR-TB: multidrug-resistant tuberculosis; DST: drug susceptibility testing.

Adapted from: WHO Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis³³.

The strategies for the treatment of drug-resistant TB (DR-TB) have recently been updated^{32,33}. The treatment of mono- and poly-drug-resistant TB is largely based on the recommendations from the 2011 WHO Guidelines for the programmatic management of DR-TB mentioned above, which underwent systematic review and analysis of the best treatment evidence base²⁸. Table 3 summarizes the stepwise approach recommended for the design of treatment regimens. There are presently two approaches TB programs are using, including both standardized and individualized regimens.

Suspected MDR-TB cases should be confirmed by DST whenever possible. In the absence of patient-specific DST, data from representative patient populations are used to develop and design standardized empiric treatment regimens, which are likely to include a sufficient number of active drugs to ensure treatment success.

However, the individualized approach has to be preferred. Each treatment regimen is designed based on both the patient's past history of TB treatment and the individual DST results. The recommended empiric regimen

for MDR-TB treatment should include a minimum of four potentially active drugs: a later generation fluoroquinolone (moxifloxacin, gatifloxacin, or levofloxacin) and an injectable aminoglycoside (amikacin, capreomycin, or kanamycin), plus any first-line drug to which the isolate is susceptible such as pyrazinamide, plus the addition of one drug from group 4 (cycloserine, para-aminosalicylic acid, terizidone, prothionamide, or ethionamide) (Table 3). The drugs categorized as WHO class 5 should be included only if four potential active drugs are not available. The core principle is that at least four drugs to which *M. tuberculosis* is likely to be susceptible are needed.

The minimum duration of the intensive phase (using injectables) is eight months, while the continuation phase will last for 12-18 months. The total treatment duration recommended by the WHO based on the available evidence is at least 20 months. The duration of treatment should be guided by culture conversion: 18 months need to be added to the date of the first negative culture. Where patients show no clinical response and their *M. tuberculosis* cultures are consistently positive, the underlying causes should be identified. The most common causes are incorrect drug dosage, quality of drug supply, non-adherence factors, malabsorption, and comorbidities.

NEW TRIALS AND NEW DRUGS

Fluoroquinolones are being studied for their interesting bactericidal activity and potential capacity to reduce the treatment duration. Trials using new generation fluoroquinolone-containing (moxifloxacin and gatifloxacin) regimens

indicate that they are unfortunately not effective in shortening TB treatment beyond the current recommended duration of six months. The REMoxTB trial (Rapid Evaluation of Moxifloxacin in Tuberculosis) was randomized, double-blind, and placebo-controlled. It evaluated two regimens in which either E or H was substituted by moxifloxacin in a single four-month combination therapy³⁴. The OFLOTUB trial^{35,36} evaluated a standard six-month regimen including E during the two-month intensive phase against a four-month regimen in which E was replaced with gatifloxacin during the intensive phase and continued, together with R and H, during the continuation phase of treatment. The RIFAQUIN trial³⁷ evaluated two regimens in which moxifloxacin replaced H during the intensive phase of treatment. Although the results of these trials have not been as brilliant as expected, several phase III clinical trials are presently testing existing, repurposed, and new drugs. Several of these trials involve the new drugs, bedaquiline, delamanid, and pretomanid, previously known as PA-824.

Bedaquiline selectively targets the proton pump of adenosine triphosphate (ATP) synthesis, leading to inadequate ATP production and lack of intracellular energy supporting replication³⁸. The bactericidal activity of bedaquiline is superior to that of H and R³⁸. The results of phase II trials suggest that a standard two-month treatment regimen with bedaquiline added to an optimized background regimen (OBR) designed as per WHO recommendations increase culture and sputum smear conversion rates while lowering acquired resistance to companion drugs in newly diagnosed MDR-TB cases^{39,40}. Both the WHO⁴¹ and the US Centers for Disease Control and Prevention

(CDC)⁴² have published consistent recommendations supporting the use of bedaquiline under the following conditions: the dose of 400 mg daily for two weeks (then 200 mg three-times a week for 22 weeks) should be used; bedaquiline should be added to an OBR regimen to treat adult MDR-TB cases; pharmacovigilance needs to be in place; informed consent is compulsory and QT monitoring facilities have to be available^{41,42}. The simultaneous use of bedaquiline and delamanid is not recommended because of the increased risk of QT prolongation and death^{41,42}. Phase III trials of the use of bedaquiline to shorten the treatment duration are presently ongoing.

Both delamanid (previously known as OPC-67683) and pretomanid inhibit the synthesis of mycolic acids of the mycobacterial wall, being active against replicating and anaerobic, non-replicating *M. tuberculosis* persisters. They have shown potentialities to improve treatment outcomes for MDR-TB^{5,43-51}. They are currently in phase II/III clinical trials (Table 4)^{45,46,48,50,51}. Based on the available evidence, the WHO⁴⁷ recommends the use of delamanid at a dose of 100 mg twice daily for six months, added to OBR in adults, when pharmacovigilance is in place and informed consent ensured. Although anecdotal evidence suggests that delamanid is effective and safe in children⁵, two clinical trials (NCT01859923 and NCT01856634) are presently investigating delamanid in the treatment of pediatric MDR-TB.

Diacon, et al. assessed the 14-day early bactericidal activity of a regimen composed of pretomanid, moxifloxacin, and Z, which proved to be significantly higher than that of bedaquiline

alone, bedaquiline plus Z, bedaquiline plus pretomanid (but not to pretomanid plus Z) and comparable to that of the standard treatment regimen (HRZ with S or E). Interestingly, the addition of Z increased the activity of both bedaquiline and pretomanid^{39,48-50}.

In a recent phase IIb trial, the bactericidal activity of a new eight-week regimen including moxifloxacin, pretomanid, Z, and clofazimine was compared to that of the standard (WHO-recommended) anti-TB regimen for drug susceptible and DR-TB. The new regimen yielded higher bactericidal activity than the current WHO-recommended regimen after two months of treatment⁵¹.

RE-PROPOSED DRUGS

Among re-proposed anti-TB drugs, linezolid and meropenem clavulanate recently raised special interest.

Linezolid, a first-generation oxazolidinone, proved to be effective against *M. tuberculosis* when added to OBR, although adverse events were common⁵²⁻⁵⁶. A recent meta-analysis⁵⁶ based on individual data provided updated evidence on efficacy, safety, and tolerability of linezolid, as well as indirect evidence that a proper treatment drug monitoring approach to drug dosage can reduce linezolid toxicity⁵⁷.

An interesting study from The Netherlands⁵⁸ shows that clarithromycin is able to boost the blood levels of linezolid, so that a lower dose of drug can be administered; less adverse events are then expected together with economic savings. The available evidence suggest

TABLE 4. Summary of the main new anti-tuberculosis drugs with the most relevant studies and related findings

Drug	Drug class	Study ID Number/ Clinical trial registration number	Clinical trial phase	Trial findings	Reference
Bedaquiline (TMC207)	Diarylquinoline	TMC207-TIDP13-C208/ NCT00449644	Phase II	The addition of Del (TMC207) to OBR reduced the time to C conversion, vs. OBR (HR: 11.8; 95% CI: 2.3-61.3; $p = 0.003$) while increasing the proportion of C converters (48 vs. 9%). The mean CFU \log_{10} count in SS declined more rapidly in the Del group than in OBR one. No significant differences in average plasma Del concentrations were noted between patients with and without C conversion. Most observed AE were mild to moderate.	Diacon, et al. ³⁹
Delamanid Trial 204 (OPC 67683)	Nitroimidazole	242-07-204/ NCT00685360	Phase II	Among patients receiving OBR plus 100 mg of Del BID, 45.4% achieved C conversion at 2 months, vs. 29.6% of patients receiving OBR ($p = 0.008$). As compared with OBR, the group receiving OBR+ Del 200 mg BID yielded higher proportion of SS and C conversion (41.9%; $p = 0.04$). Most AE 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.	Gler, et al. ⁴⁵
Delamanid Trial 208 (OPC 67683)	Nitroimidazole	242-09-213/ NCT01424670	Phase III	Patients participating in the previously reported Del controlled trial and the subsequent open-label extension trial were eligible to participate in a 24-month observational study designed to capture treatment outcomes. Favorable outcomes were observed in 143/192 (74.5%) patients receiving Del for ≥ 6 months, vs. 126/229 (55%) patients receiving Del for ≤ 2 months. Mortality was reduced to 1.0% among those receiving long-term Del vs. short-term/no Del (8.3%; $p = 0.001$). Treatment benefit was also observed among XDR-TB patients.	Skripconoka, et al. ⁴⁶
Pretomanid Trial NC-001 (PA-824)	Nitroimidazole	NC-001-(J-M-Pa-Z)/ NCT01215851	Phase II	The mean 14-day EBA of Pto (PA-824) + moxifloxacin + Z ($n = 13$; 0.233; SD 0.128) was significantly higher than that of Bdq (14; 0.061; 0.068), Bdq + Z (15; 0.131; 0.102), Bdq + Pto (14; 0.114; 0.050), but not Pto + Z (14; 0.154; 0.040), and comparable with that of standard HRZE treatment (10; 0.140; 0.094). Treatments were well tolerated and appeared safe. One patient on Pto + moxifloxacin + Z was withdrawn because of corrected QT interval changes exceeding pre-specified criteria.	Diacon, et al. ⁴⁸

(Continue)

that a linezolid dose between 300 and 600 mg per day is adequate to treat MDR-/XDR-TB when added to OBR⁵²⁻⁶¹.

Meropenem clavulanate is also active against *M. tuberculosis* and appears to be well tolerated. In a case-control study⁶² it demonstrated, when added to linezolid-containing OBR, to improve

sputum smear and culture conversion in MDR- and XDR-TB cases. Further studies are necessary to define the role of this drug within the anti-MDR-TB armamentarium.

Other drugs, including sulfamides and mefloquine, have been used in difficult-to-treat cases, although the evidence is anecdotal⁶³⁻⁶⁵.

TABLE 4. Summary of the main new anti-tuberculosis drugs with the most relevant studies and related findings (continued)

Drug	Drug class	Study ID Number/ Clinical trial registration number	Clinical trial phase	Trial findings	Reference
Pretomanid Trial NC-002 (PA-824)	Nitroimidazole	NC-002-(M-Pa-Z)/ NCT01498419	Phase II	The study evaluated a novel regimen for efficacy and safety in DS and MDR-TB during the first 8 weeks of treatment. SS DS, treatment-naive PTB patients randomized were enrolled to receive 8 weeks of moxifloxacin + Pto (100 mg) + Z (MPa100Z, regimen 1) or moxifloxacin + Pto (200 mg) + Z (MPa200Z, regimen 2) or the current standard regimen for DS PTB (HRZE) as positive control. A group of MDR participants received moxifloxacin 400 mg, Pto 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 patients was significantly greater than for standard regimen (n = 54; 0.112, 95% BCI: 0.093; 0.131). Regimen 2 had similar BA to regimen standard. The BA days 7-14 was well correlated with BA days 7-56. AEs were equally distributed among group and control subjects. The most common AE was hyperuricemia 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 msec. No phenotypic resistance developed. The MPaZ combination, previously found to have promising activity over 14 days in DSTB, was safe, well tolerated and demonstrated superior BA in DS-TB during 8 weeks treatment. Results were consistent between DS and MDR-TB.	Dawson, et al. ⁵¹
Pretomanid Trial NC-003 (PA-824)	Nitroimidazole	NC-003-(C-J-Pa-Z)/ NCT01691534	Phase II	Experimental and clinical evidence suggests that the new drugs Bdq and Pto, combined with an existing drug, Z, and a repurposed drug, Cfz, may assist treatment shortening of both DS and DR-TB. The study evaluated the 14-day early bactericidal activity of Cfz and Z in monotherapy and in combinations with Pto and Bdq. Groups of 15 treatment-naive, SS-positive pulmonary TB patients were randomized to receive combinations of Bdq with Z-Cfz, Pto-Z, Pto-Z-Cfz and Pto-Cfz, or Cfz or Z alone, or standard combination treatment for 14 days. The primary endpoint was the mean daily fall in log ₁₀ <i>M. tuberculosis</i> CFU/ml SS estimated by joint non-linear mixed effects Bayesian regression modeling. Results: estimated activities were 0.167 (95% CI: 0.075-0.257) for Bdq-Pto-Z, 0.151 (95% CI: 0.071-0.232) for standard treatment, 0.124 (95% CI: 0.035-0.214) for Bdq-Z-Cfz, 0.115 (95% CI: 0.039-0.189) for Bdq-Pto-Z-Cfz, and 0.076 (95% CI: 0.005-0.145) for Bdq-Pto-Cfz. 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. Bdq + Pto + Z, including two novel agents without resistance in prevalent <i>M. tuberculosis</i> strains, is a potential new TB treatment regimen. Cfz had no measurable activity in the first 14 days of treatment.	Diacon, et al. ⁵⁰

OBR: optimized background regimen; C: culture; HR: hazard ratio; CI: confidence interval; CFU: colony-forming unit; SS: sputum smear; AE: adverse events; BCI: Bayesian credibility interval; BID: twice daily; QT: measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle; ECG: electrocardiogram; EBA: early bactericidal activity; DS: drug-susceptible; DR: drug-resistant; MDR-TB: multidrug-resistant tuberculosis; PTB: pulmonary tuberculosis; DR-TB: drug-resistant-tuberculosis; TB: tuberculosis; WBA: whole blood bactericidal activity; OB: once daily; MIC: minimum inhibitory concentration; H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol; Bq: bedaquiline; Pto: pretomanid; Del: delamanid; Cfz: clofazimine.

NEW EFFECTIVE ANTI-TUBERCULOSIS REGIMENS: A STEP FORWARD

The new, innovative global public health intervention recently approved by the WHO and known as “End TB Strategy”¹, supports the vision of a TB-free world with zero death, zero disease, and zero suffering due to TB⁶⁶⁻⁶⁸.

While rapid diagnosis and effective treatment of (infectious) cases are the pillars of TB control, a more aggressive approach based on diagnosis and treatment of latently infected individuals has been proposed in the context of TB elimination to ensure future, TB-free, generations.

Within the Pillar 1 adequate, universally accessed treatment is a prerequisite to reach TB elimination.

New shorter, cheap, safe, and effective anti-TB regimens are necessary to boost TB elimination^{69,70}.

The new drugs have shown promising steps toward a new universal regimen⁵¹ that, bypassing the H and R bottleneck, allows to treat all HIV-coinfected patients (with no interference with antiretrovirals) independently from their drug-susceptible or DR status⁷¹.

There are obvious potentialities to shorten the treatment duration and, consequently, to improve patient adherence and reduce the selection of resistant mutants of *M. tuberculosis*.

The rational use of the existing drugs and regimens is necessary if we want to ensure them a long life⁷².

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CONFLICT OF INTEREST

All authors have no conflict of interest to declare.

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