# Shortened tuberculosis treatment regimens: what is new?

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## ABSTRACT

Given the global burden of tuberculosis, shortened treatment regimens with existing or repurposed drugs are needed to contribute to tuberculosis control. The long duration of treatment of drug-susceptible tuberculosis (DS-TB) is associated with nonadherence and loss to follow up, and the treatment success rate of multidrug-resistant tuberculosis (MDR-TB) is low (approximately 50%) with longer regimens. In this review article, we report recent advances and ongoing clinical trials aimed at shortening regimens for DS-TB and MDR-TB. We discuss the role of high-dose rifampin, as well as that of clofazimine and linezolid in regimens for DS-TB. There are at least 5 ongoing clinical trials and 17 observational studies and clinical trials evaluating shorter regimens for DS-TB and MDR-TB, respectively. We also report the results of observational studies and clinical trials evaluating a standardized nine-month moxifloxacin-based regimen for MDR-TB. Further studies, especially randomized clinical trials, are needed to evaluate regimens including newer drugs, drugs proven to be or highly likely to be efficacious, and all-oral drugs in an effort to eliminate the need for injectable drugs.

Keywords: Tuberculosis/drug therapy; Tuberculosis, multidrug-resistant/drug therapy; Drug resistance, bacterial.

## INTRODUCTION

Given the global burden of tuberculosis, shortened regimens with existing or repurposed drugs are needed to contribute to tuberculosis control. The current standard antituberculosis chemotherapy treatment regimen currently recommended by the World Health Organization (WHO) consists of a 2-month intensive phase with isoniazid, rifampin, pyrazinamide, and ethambutol, followed by a 4-month continuation phase with isoniazid and rifampin. Isoniazid and rifampin are the drugs with the greatest early bactericidal activity, and rifampin and pyrazinamide are the drugs with the greatest sterilizing power. Ethambutol is bacteriostatic and is strategically associated with the more potent drugs to prevent the emergence of resistant bacilli. The major justification for using this longer treatment regimen is to reduce recurrence.[1] In addition, previously published data do not support the use of shortened treatment regimens in adults with newly diagnosed pulmonary drug-susceptible tuberculosis (DS-TB). However, the long duration of DS-TB treatment is associated with nonadherence and loss to follow-up. Four-month treatment regimens that replace ethambutol with moxifloxacin or gatifloxacin, or those that replace isoniazid with moxifloxacin, increase relapse substantially when compared with standard 6-month treatment regimens.[2] However, the treatment success rate of multidrug-resistant tuberculosis (MDR-TB) is low (approximately 50%) with longer regimens, although recent studies involving new drugs have suggested that

better results are possible also at the programmatic level.[3] The development of efficacious, safe, and shorter treatment regimens for both DS-TB and MDR-TB could significantly improve tuberculosis management and treatment success rates.[4]

In the present review article, we report recent advances and ongoing clinical trials aimed at shortening regimens for DS-TB and MDR-TB.

## METHODS

In this nonsystematic review we searched PubMed, Google, Google Scholar, and ClinicalTrials.gov for studies evaluating short regimens for DS-TB and MDR-TB and published in English, Spanish, Portuguese, Italian, or French, published between January 1, 2014 and December 20, 2019. The following search terms were used: "treatment" AND "tuberculosis" OR "drug-susceptible tuberculosis" OR "MDR-TB".

## SHORTENED REGIMENS FOR DS-TB

The treatment currently recommended by the WHO for patients with DS-TB lasts at least 6 months: a 2-month intensive phase (isoniazid, rifampin, pyrazinamide, and ethambutol) followed by a continuation phase of 4 months with isoniazid and rifampin. The long duration of this treatment regimen is a major barrier to adherence and has a significant negative impact on tuberculosis control.[5]

Current evidence from in vitro, animal, and human studies suggests that high-dose rifampin can shorten the duration of tuberculosis treatment.[6] In a multicenter, randomized, controlled, triple-blinded clinical trial[7,8] involving 180 treatment-naïve adults diagnosed with pulmonary tuberculosis (positive sputum smear) were allocated to receiving rifampin at 10 mg/kg per day (control group), 15 mg/kg per day, or 20 mg/kg per day during the intensive phase. Higher rifampin doses were associated with more rapid sputum sterilization, and toxicity was similar to that of the standard dose.

Finding the optimal higher-than-standard dose of rifampin and avoiding toxicity is a challenge. Svensson et al.[9] evaluated 336 patients with newly diagnosed pulmonary tuberculosis from seven sites in Tanzania and South Africa who were treated with rifampin at 10, 20, or 35 mg/kg. Higher rifampin doses increased the probability of a reduction in time to culture conversion, with no maximal limit of the effect, suggesting that doses > 35 mg/kg could be more effective.[9]

Clofazimine, an antileprosy agent, showed significant bactericidal and sterilizing activity in a mouse model of MDR-TB treatment[10] and enabled significant shortening of treatment duration in MDR-TB patients.[11-14] Recently, clofazimine was repurposed in the new short-course MDR-TB regimen.[11] When added to the first-line regimen for DS-TB in a mouse model of tuberculosis, clofazimine demonstrated greatest activity when used continuously throughout the treatment together with the first-line drugs, doses at 12.5 mg/kg and 25 mg/kg being equivalent.[15] However, the optimal dose of clofazimine in the first-line regimen is uncertain, especially as it may cause dose-dependent skin discoloration.[16,17] Also, adding clofazimine and replacing rifampin with high-dose rifapentine in the first-line regimen was associated with greater bactericidal and sterilizing activity when compared with either modification alone in another mouse model.[18] In a large program-based Brazilian study,[19] clofazimine was well tolerated, with a low proportion of adverse events, such as gastrointestinal complaints (10.5%) and neurological disturbances (9-13%); however, hyperpigmentation was present in 50.2%.

Linezolid, an oxazolidinone currently recommended for MDR-TB treatment,[11] could have a potential role in shortening DS-TB treatment. Previous studies[20,21] suggested that a reduction in the dose from 1,200 to 600 mg/day was able to reduce the proportion of serious adverse events.

In a recent phase 2, multicenter, randomized, open-label trial[22] for patients with pulmonary tuberculosis at three hospitals in South Korea, the authors evaluated the substitution of linezolid for ethambutol during the intensive phase of treatment. The use of linezolid at 600 mg once daily for 2 weeks was associated with a higher proportion of 8-week culture negativity when compared with control arms.[22] Nevertheless, linezolid has a narrow therapeutic window, and its prolonged use could result in peripheral/optic neuropathy and bone marrow suppression.[23] In a recent active drug-safety monitoring and management global study by the Global Tuberculosis Network, the proportion of serious adverse events attributed to linezolid, such as peripheral neuropathy, optic neuritis, severe urticaria, anemia, and bone marrow depression, was 2.8% (15/536).[24,25]

Table 1 shows details of ongoing clinical trials evaluating shortened regimens for DS-TB. A trial designated S31/A5349 (NCT02410772)[26] is currently underway to determine whether one or two 4-month regimens for tuberculosis treatment are as effective as the standard 6-month regimen. The first short regimen is a single substitution of rifapentine for rifampin: isoniazid, rifapentine, ethambutol, and pyrazinamide for 2 months, followed by isoniazid and rifapentine for 2 months. The second short regimen is a double substitution of rifapentine for rifampin and of moxifloxacin for ethambutol: isoniazid, rifapentine, moxifloxacin, and pyrazinamide for 2 months, followed by isoniazid, rifapentine, and moxifloxacin for 2 months.[26]

The trial designated TRUNCATE-TB (NCT03474198) [27] is a randomized, open-label, multi-arm, multistage trial to test the hypothesis that treatment for 2 months (8 weeks, extended to 12 weeks if there is inadequate clinical response) with four potentially boosted regimens is non-inferior to the standard management strategy.[27]

The designated RIFASHORT trial (NCT02581527)[28] is an open-label three-arm trial in order to compare a standard 6-month control regimen with two 4-month treatment regimens (with increased doses of rifampin—1,200 mg or 1,800 mg) for the treatment of tuberculosis. The objective is to assess whether high doses of rifampin for 4 months will result in greater and faster killing of tuberculous bacilli in the lungs, as well as in relapse rates similar to those obtained with the standard 6-month regimen.

## SHORTENED REGIMENS FOR MDR-TB

From 2005 to 2011, 515 patients were enrolled in a prospective, observational study from the Damien Foundation in Bangladesh[29] in order to evaluate the first treatment for MDR-TB using a standardized regimen, consisting of high-dose gatifloxacin, ethambutol, pyrazinamide, and clofazimine for at least 9 months, supplemented during the intensive phase (for 4 months at least) with kanamycin, prothionamide, and isoniazid. The 4-month intensive phase was extended until sputum smear conversion. Due to extensive disease with delayed sputum conversion, only half of the patients completed treatment within 9 months; however, 95% were able to complete

**Table 1.** Ongoing clinical trials evaluating shortened regimens for drug-susceptible tuberculosis.

| ClinicalTrials.gov Identifier (study name) | Phase | Study population | Study groups | Status | Results expected in (year) |
|---|---|---|---|---|---|
| NCT02410772 (TBTC 31/A5349) | 3 | 2,500 adults and children (≥ 12 years), HIV+ and HIV- | 2 months of isoniazid, rifapentine, ethambutol, and pyrazinamide, followed by 2 months of isoniazid and rifapentine, or 2 months of isoniazid, rifapentine, moxifloxacin, and pyrazinamide, followed by 2 months of isoniazid, rifapentine, and moxifloxacin vs. standard 6-month therapy | Active, not recruiting | 2020 |
| NCT03474198 (TRUNCATE-TB) | 2/3 | 900 adults, HIV+ and HIV- | Standard 6-month therapy vs. Regimen B: rifampin (35 mg/kg), isoniazid, pyrazinamide, ethambutol, and linezolid; or Regimen C: rifampin (35 mg/kg), isoniazid, pyrazinamide, ethambutol, and clofazimine; or Regimen D: rifapentine, isoniazid, pyrazinamide, linezolid, and levofloxacin; or Regimen E: isoniazid, pyrazinamide, ethambutol, linezolid, and bedaquiline | Recruiting | 2022 |
| NCT02581527 (RIFASHORT) | 3 | 654 adults, HIV- | 2 months of ethambutol, isoniazid, rifampin (1,200 mg or 1,800 mg), and pyrazinamide daily, followed by 2 months of isoniazid and rifampin (1,200 mg or 1,800 mg) daily vs. standard 6-month therapy | Recruiting | 2021 |
| NCT03338621 | 2c/3 | 450 adults, HIV+ and HIV- | BPaMZ regimen: bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 9 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1,500 mg daily for 17 weeks (total treatment duration: 4 months) vs. standard 6-month therapy | Recruiting | 2022 |
| NCT03561753 | 2b | 300 adults, HIV- | PRS regimen: 4 months of daily clofazimine, ethambutol, prothionamide, and high dose pyrazinamide vs. standard 6-month therapy | Enrolling by invitation | 2021 |

treatment within 12 months, and 84.4% had a bacteriologically favorable outcome. An external review of that project[29] conducted in 2007 by the WHO concluded that additional data from a clinical trial were needed.[30] The 2011 WHO guidelines recommended an intensive treatment phase of 8 months and a total treatment duration of 20 months.[31]

A clinical trial initiated in 2012 (designated STREAM) compared a 9-month moxifloxacin-based regimen with the WHO-recommended 20-24 month regimen.[32]

In 2016, the WHO introduced new guidelines for the treatment of MDR-TB, including recommendations for isolated use of bedaquiline or delamanid and a shorter MDR-TB treatment regimen.[11] They recommended that in patients with rifampin-resistant tuberculosis or MDR-TB who had not previously been treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable drugs was excluded or considered as highly unlikely, a shorter (9-12 months) MDR-TB regimen might be used instead of longer regimens.[11]

In 2018, Trébucq et al.[12] reported the results of a prospective observational study in nine African countries that evaluated a standardized 9-month moxifloxacin-based regimen in 1,006 MDR-TB patients. The treatment success rate was 81.6% and did not differ by HIV status. Despite being an observational study, its results support the efficacy and good tolerability of the regimen. However, hearing loss was reported in 7.1% of the patients.

In March of 2019, the initial results of the abovementioned trial[32] were published.[33] The authors found that, in patients with rifampin-resistant tuberculosis that was susceptible to fluoroquinolones and aminoglycosides, a shorter regimen (9-11 months, including high-dose moxifloxacin) was non-inferior to the longer regimen (20 months, following the 2011 WHO guidelines) with respect to the primary efficacy outcome (negative cultures at week 132) and was similar to the longer regimen in terms of safety. However, the participants in the short-regimen group had more adverse events (grade 3 or more), prolongation of either the QT interval or the QTc to 500 milliseconds, acquired resistance to fluoroquinolones or aminoglycosides, and death; nevertheless, the differences were not significant. A development of that clinical trial,[32] also designated STREAM (NCT02409290),[34] is currently evaluating the efficacy of a short, fully oral regimen containing bedaquiline; the results are expected in 2022.[35] Recently, a study on individual patient data meta-analysis[36] compared longer and shorter regimens in

terms of safety and efficacy, substantially confirming the results of that trial.[33]

A regimen approved by the U.S. Food and Drug Administration in mid-2019 (bedaquiline, pretomanid, and linezolid for 6-9 months) was recommended by the WHO in a rapid communication published in December of 2019.[37] The regimen improved treatment outcomes in patients with extensively drug-resistant tuberculosis and can be used under operational research conditions in those patients for whom design of an effective regimen based on existing recommendations is not possible, as well as in those who have not had previous exposure to bedaquiline and linezolid (defined as < 2 weeks). However, further evidence on efficacy and safety is needed to consider its programmatic use worldwide.[37]

Table 2 shows details of ongoing clinical trials evaluating shortened regimens for MDR-TB. A phase 2/3, multicenter, randomized, open-label clinical trial of non-inferiority design designated MDR-END (NCT02619994)[38] aims at comparing a new shorter regimen including delamanid, linezolid, levofloxacin, and pyrazinamide for 9 or 12 months (depending on the time to sputum culture conversion) with a conventional treatment regimen with second-line drugs, including injected drugs, for 20-24 months. The primary outcome is treatment success rate at 24 months after treatment initiation, and the results are expected by 2021.[38]

The designated endTB clinical trial (NCT02754765)[39] is a phase 3, randomized, controlled, open-label, non-inferiority, multi-country trial evaluating the efficacy and safety of five new, all-oral, shortened regimens for MDR-TB. The regimens examined combine the newly approved drugs bedaquiline and/or delamanid with existing drugs known to be active against *Mycobacterium tuberculosis* (linezolid, clofazimine, moxifloxacin or levofloxacin, and pyrazinamide). Results are expected by 2021.

The designated TB-PRACTECAL trial (NCT02589782)[40] is a multicenter, open-label, multi-arm, randomized, controlled phase 2/3 trial, aimed at evaluating short treatment regimens containing bedaquiline and pretomanid in combination with existing and repurposed antituberculosis drugs for MDR-TB treatment. The study will be divided into two stages: the primary outcome measures in stage 1 are the proportion of patients with culture conversion in liquid media and the proportion of patients who discontinue treatment for any reason or die at 8 weeks after randomization; the primary outcome measure in stage 2 is the proportion of patients with an unfavorable outcome at week 72.

The designated GRACE-TB trial (NCT03604848)[41] is a multicenter, open-label, randomized, controlled clinical trial involving patients with MDR-TB. The objective is to assess the feasibility and effects of individualized regimens for MDR-TB based on rapid molecular drug susceptibility tests of key second-line drugs by means of next-generation sequencing. The trial will evaluate a shorter course regimen (pyrazinamide, amikacin, moxifloxacin, prothionamide, and cycloserine for 9 or 12 months) among patients whose MDR-TB is proven to be susceptible to fluoroquinolones, second-line injectable drugs, or pyrazinamide by next-generation sequencing.

The designated TB-TRUST trial (NCT03867136)[42] is a phase 3, multicenter, open-label, randomized controlled trial aiming at assessing the efficacy, safety and tolerability of an ultra-short treatment regimen of all-oral antituberculosis drugs (levofloxacin, linezolid, cycloserine, and pyrazinamide [or clofazimine if pyrazinamide-resistant]) compared with the WHO standardized shorter regimen of 9-11 months. The primary outcome measure is the treatment success rate without relapse in 24 months. The results are expected by 2022.

## FINAL CONSIDERATIONS

The present review shows that many observational studies and clinical trials have demonstrated the potential of shortened regimens for the treatment of both DS-TB and MDR-TB. In addition to reducing costs, the use of shorter regimens can improve adherence and, consequently, treatment completion. However, further studies, especially randomized clinical trials[32] and pragmatic clinical trials, are needed to evaluate regimens including newer drugs, drugs drugs proven to be or highly likely to be efficacious, and all-oral drugs in an effort to eliminate the need for injectable drugs.[43,44] The potential of using programmatic data and individual patient data meta-analysis has recently been highlighted.[43]

New approaches need to be identified to shorten treatment duration, including the possibility of administering new drugs (e.g., bedaquiline and delamanid) together, as recent evidence suggests that it can be safer than it was initially considered.[45]

Importantly, active drug-safety monitoring and management, which is recommended by the WHO for new drugs and regimens for drug-resistant tuberculosis, should be integrated into tuberculosis programs.[24,25,46] In addition, drug susceptibility testing should be available where new regimens are to be implemented in order to allow the identification of resistance patterns and to avoid selecting strains resistant to promising new regimens.[37,44]

## ACKNOWLEDGMENTS

**Table 2.** Ongoing clinical trials evaluating shortened regimens for multidrug-resistant tuberculosis.

| ClinicalTrials.gov Identifier (study name) | Phase | Study population | Study groups | Status | Results expected in (year) |
|---|---|---|---|---|---|
| NCT02619994 (MDR-END) | 2/3 | 238 adults, HIV+ and HIV- | Delamanid, linezolid, levofloxacin, and pyrazinamide for 9 or 12 months (depending on time to sputum culture conversion) vs. locally-used WHO-approved MDR-TB regimen (intensive phase regimen consists of four effective second-line antituberculosis drugs, including injectable second-line drugs, and pyrazinamide for at least 20 months) | Recruiting | 2021 |
| NCT02409290 (STREAM stage 2) | 3 | 530 adults and children (≥ 15 years), HIV+ and HIV- | Moxifloxacin, clofazimine, ethambutol, and pyrazinamide daily for 9 months, with initial isoniazid, kanamycin, and prothionamide daily for 2 months; or bedaquiline, clofazimine, ethambutol, levofloxacin, and pyrazinamide daily for 9 months, with initial isoniazid (high dose) and prothionamide daily for 2 months (all oral); or bedaquiline, clofazimine, levofloxacin, and pyrazinamide daily for 6 months, with initial isoniazid (high dose) and kanamycin for 2 months vs. 20-24-month local regimen | Recruiting | 2022 |
| NCT02754765 (endTB) | 3 | 750 adults and children (≥ 15 years), HIV+ and HIV- | Bedaquiline, linezolid, moxifloxacin, and pyrazinamide daily for 9 months; or bedaquiline, linezolid, clofazimine, levofloxacin, and pyrazinamide daily for 9 months; or bedaquiline, linezolid, delamanid, levofloxacin, and pyrazinamide daily for 9 months, or delamanid, linezolid, clofazimine, levofloxacin, and pyrazinamide daily for 9 months; or delamanid, clofazimine, moxifloxacin, and pyrazinamide daily for 9 months vs. local regimen | Recruiting | 2021 |
| NCT02589782 (TB PRACTECAL) | 2/3 | 630 adults and children (≥ 15 years), HIV+ and HIV- | Bedaquiline, pretomanid, moxifloxacin, and linezolid daily for 6 months; or bedaquiline, pretomanid, linezolid, and clofazimine daily for 6 months; or bedaquiline, pretomanid, and linezolid daily for 6 months (all oral) vs. local regimen | Recruiting | 2021 |
| NCT01918397 (Opti-Q) | 2 | 111 adults (> 18 years), HIV+ and HIV- | Levofloxacin (14, 17, or 20 mg/kg daily) plus optimized background regimen for 6 months vs. levofloxacin (11 mg/kg daily) plus optimized background regimen for 6 months | Active, not recruiting | 2020 |
| NCT02333799 | 3 | 109 adults and children (≥ 14 years), HIV+ and HIV- | Single arm study: bedaquiline (200 mg daily for 2 weeks, then 200 mg three times weekly), pretomanid (200 mg daily), and linezolid (600 mg twice daily) for 6 months | Active, not recruiting | 2021 |
| NCT02454205 (NEXT) | 2/3 | 154 adults (> 18 years), HIV+ and HIV- | Bedaquiline, linezolid, levofloxacin, pyrazinamide, and either high-dose isoniazid or ethionamide or terizidone daily (all oral) for 6-9 months vs. conventional treatment (kanamycin, moxifloxacin, pyrazinamide, ethionamide, and terizidone for 21-24 months) | Active, not recruiting | 2020 |
| NCT03141060 | 1/2 | 48 children (<18 years), HIV+ and HIV- | Single arm study: bedaquiline (100 mg twice daily) plus optimized background regimen for 6 months | Recruiting | 2021 |
| NCT03338621 | 2c/3 | 450 adults, HIV+ and HIV- | Single arm study: bedaquiline, pretomanid, moxifloxacin, and pyrazinamide for 6 months | Recruiting | 2022 |

WHO: World Health Organization; and MDR-TB: multidrug-resistant tuberculosis.

**Table 2.** Continued...

| ClinicalTrials.gov Identifier (study name) | Phase | Study population | Study groups | Status | Results expected in (year) |
|---|---|---|---|---|---|
| NCT03086486 (ZeNix) | 3 | 180 adults and children (≥ 14 years), HIV+ and HIV- | Linezolid (600 or 1,200 mg daily, double-blinded), bedaquiline (200 mg daily for 2 weeks, then 100 mg daily), and pretomanid (200 mg daily) for 2 or 6 months | Recruiting | 2021 |
| NCT02354014 | 2 | 60 children (< 18 years), HIV- | Single arm study: bedaquiline (daily for 2 weeks, then 3 times a week) plus optimized background regimen for 6 months | Recruiting | 2025 |
| NCT02583048 | 2 | 84 adults (> 18 years), HIV+ and HIV- | Bedaquiline plus optimized background regimen for 6 months; or delamanid plus optimized background regimen for 6 months, or bedaquiline and delamanid plus optimized background regimen for 6 months | Active, not recruiting | 2021 |
| NCT03604848 (GRACE-TB) | 3 | 488 adults (≥ 18 years), HIV- | Pyrazinamide, amikacin, moxifloxacin, prothionamide, and cycloserine for 9 or 12 months vs. WHO-approved MDR-TB regimen for 24 months | Not yet recruiting | 2024 |
| NCT03867136 (TB-TRUST) | 3 | 354 adults (≥ 18 years), HIV- | Levofloxacin, linezolid, cycloserine and pyrazinamide(or clofazimine if resistant to pyrazinamide) for 6 to 8 months vs. WHO standardized shorter regimen of 9-11 months | Not yet recruiting | 2022 |
| NCT01859923 | 2 | 37 children (<18 years), HIV+ and HIV- | Delamanid plus optimized background regimen for 6 months | Active, not recruiting | 2020 |
| NCT03896685 (endTB-Q) | 3 | 324 adults and children (≥ 15 years), HIV+ and HIV- | BeDeCLi regimen: bedaquiline-delamanid-linezolid-clofazimine for 24 or 39 weeks vs. local regimen according to WHO guidelines | Not yet recruiting | 2022 |
| NCT04062201 (BEAT) | 3 | 400 adults and children (≥ 12 years), HIV+ and HIV- | Bedaquiline, delamanid, and linezolid plus levofloxacin and clofazimine for 6 months vs. local regimen for 9 months | Recruiting | 2023 |

WHO: World Health Organization; and MDR-TB: multidrug-resistant tuberculosis.

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