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Shortened Drug Regimens for the Treatment of Active Tuberculosis

Rapid Review

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Abbreviations

HRZE	isoniazid, rifampin, pyrazinamide, and ethambutol
MHR	moxifloxacin. isoniazid and rifampin
MHRE	moxifloxacin. isoniazid. rifampin, and ethambutol
MHRZE	moxifloxacin. isoniazid. rifampin, pyrazinamide, and ethambutol
RCT	randomized controlled trial
PH	rifapentine and isoniazid
PHM	rifapentine, isoniazid, and moxifloxacin
PHZE	rifapentine, isoniazid, pyrazinamide, and ethambutol
PHZM	rifapentine, isoniazid, pyrazinamide, and moxifloxacin
SR	systematic review
TB	tuberculosis

Key Messages

- For treating active tuberculosis (TB), some 4-month treatment regimens may be as effective and safe as the standard 6-month treatment regimen. However, there are also 4-month treatment regimens that seem to be less effective than the 6-month treatment regimen for treating active TB. The effectiveness of these shortened treatment regimens depends on the combination of drugs and the dose schedule.
- For treating active TB, a 3-month treatment regimen appears to be less effective than the standard 6-month regimen, as it is associated with a higher rate of TB recurring within 2 years after completing treatment.

Context and Policy Issues

The current treatments for active tuberculosis (TB) disease involve long courses of antibiotic treatments (e.g., 6 months or longer),[1] and the length of the treatments may negatively impact treatment adherence. Incomplete treatment adherence is a contributing factor to persistent TB disease and the development of drug-resistant TB.[2] New, shorter treatment regimens (e.g., 4 months) are available[3] and there is interest in comparing the effectiveness of the shorter and longer treatment regimens.

In 2019, a Cochrane systematic review (SR) was published that compared shortened versus standard treatment regimens for TB. In August 2020, CADTH searched the literature to see if any new evidence on the topic had been published since the Cochrane review. That report[4] identified the Cochrane SR[5] and 1 randomized controlled trial (RCT)[6] that was potentially relevant. In May 2021, the search was rerun to capture any articles published since the initial search date. The purpose of the current report is to summarize and critically appraise the eligible publications.

This report is a component of a larger CADTH condition-level review on TB. A condition-level review is an assessment that incorporates all aspects of a condition, from prevention and detection to treatment and management. For more information on CADTH's condition-level review on TB, please visit the project page (https://www.cadth.ca/tuberculosis).

Research Question

What is the clinical effectiveness of shortened drug regimens for the treatment of active tuberculosis?

Methods

Literature Search Methods

A limited literature search conducted for a previous CADTH report[4] was updated by an information specialist on key resources including MEDLINE, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were shortened drug regimens and people receiving drug treatment for active tuberculosis disease. Search filters were applied to limit retrieval to health technology assessments, SRs, meta-analyses, or network meta-analyses, RCTs, controlled clinical trials or any other type of clinical trial, and observational studies. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2019 and May 14, 2021. Internet links were provided, where available.

Selection Criteria and Methods

The evidence in this report was identified in a previous CADTH report,[4] where 1 reviewer screened citations and abstracts. For this report, the full-text articles were reviewed by 1 reviewer and the final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published before 2019.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[7] for SRs and the Downs and Black checklist[8] for randomized studies. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Table 1: Selection Criteria

Criteria	Description
Population	People receiving drug treatment for active tuberculosis disease
Intervention	Tuberculosis treatment regimens that are less than 6 months
Comparator	Tuberculosis treatment regimens that are 6 months or longer
Outcomes	Clinical effectiveness (e.g., eradication of tuberculosis, quality of life, treatment adherence, relapse of tuberculosis, treatment failure) and safety (e.g., adverse drug effects, acquired drug resistance, mortality)
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies

Summary of Evidence

Quantity of Research Available

For the previous CADTH report,[4] a total of 799 citations were identified in the literature search and no potentially relevant publications were retrieved from the grey literature. Seven potentially relevant reports were identified and retrieved for full-text review, of which 1 SR[5] and 2 RCTs[6,9] met the inclusion criteria and were included in this report.

The following is a summary and critical appraisal of these studies. Additional details regarding the study characteristics, the main study findings, and the authors' conclusions are provided in tables in Appendix 4.

Summary of Study Characteristics

Additional details regarding the study characteristics are provided in tables in Appendix 1.

Study Design

The SR with meta-analysis by Grace et al. [5] was published in 2019 and searched the literature up until July 2019. RCTs or quasi-RCTs were eligible for inclusion and 5 RCTs were included in the SR and meta-analysis.[5] The RCT by Dorman et al. (2021)[9] was a 3-arm, open-label RCT that used a noninferiority design, which was designed to show that new therapies are no worse than an existing treatment.[10] The RCT by Velayutham et al. (2020)[6] was a 5-arm, open-label RCT that used an equivalence design and was designed to show that new therapies are equivalent to an established therapy (i.e., absence of a meaningful difference between therapies).[10]

Country of Origin

The SR was led by authors in India and included studies with individuals from Africa, Asia, and Latin America.[5] The RCT by Dorman et al. (2021)[9] was led by authors in the US and was conducted at 34 international sites from 13 countries (i.e., Brazil, China, Haiti, India, Kenya, Malawi, Peru, South Africa, Thailand, Uganda, the US, Vietnam, and Zimbabwe). The RCT by Velayutham et al. (2020)[6] was led by authors and conducted in South India.

Patient Population

The SR and meta-analysis included individuals with drug-sensitive pulmonary TB; a total or 5,825 adult participants were included in the meta-analysis.[5] The RCT by Dorman et al. (2021)[9] included individuals with newly diagnosed drug-sensitive TB. A total of 2,516 patients were randomized across the 3 treatment arms and 2,343 patients were included in the modified intention-to-treat analysis, while1,854 patients were included in the 95% per-protocol analysis. The RCT by Velayutham et al. (2020)[6] included adults with newly diagnosed pulmonary TB and excluded individuals with HIV. A total of 1,371 patients were randomized across the 5 treatment groups;1,329 patients were included in a modified intention-to-treat analysis and 1,223 patients were included in the per-protocol analysis (i.e., patients who received at least 80% of their allocated treatment).

Interventions and Comparators

The SR and meta-analysis compared shortened anti-TB regimens (i.e., less than 6 months) to standard first-line therapy for TB.[5] All 5 RCTs included studies comparing shorter regimens

(i.e., 3 to 4 months) of fluoroquinolones (i.e., moxifloxacin [4 RCTs] or gatifloxacin [1 RCT]) compared to the standard 6-month regimen.

The RCT by Dorman et al. (2021)[9] was designed to compare 2 different, 4-month anti-TB regimens containing rifapentine to a standard 6-month anti-TB regimen. The 4-month interventions included 8 weeks of once-daily rifapentine, isoniazid, pyrazinamide, and ethambutol (PHZE) followed by 9 weeks of once-daily rifapentine and isoniazid (PH) (i.e., 2PHZE-2PH), and 8 weeks of once-daily rifapentine, isoniazid, pyrazinamide, and moxifloxacin (PHZM) followed by 9 weeks of once-daily rifapentine, isoniazid, and moxifloxacin (PHM) (i.e., 2PHZM-2PHM) — both of which were compared to the control of 8 weeks of once-daily isoniazid, rifampin, pyrazinamide, and ethambutol (HRZE) followed by 18 weeks of once-daily rifampin and isoniazid.[9]

The RCT by Velayutham et al. (2020)[6] was designed to compare 4 different shortened anti-TB regimens (i.e., 3 or 4 months) containing moxifloxacin to a standard 6-month, thrice-weekly regimen (that does not contain moxifloxacin). The interventions included 3 months of daily moxifloxacin, isoniazid. rifampin, pyrazinamide, and ethambutol (MHRZE) — i.e., M3; MHRZE daily for 2 months, then moxifloxacin, isoniazid and rifampin (MHR) daily for 2 months — i.e., M4; MHRZE daily for 2 months, then MHR 3 times a week for 2 months — i.e., M4-I; and MHRZE daily for 2 months, then moxifloxacin, isoniazid. rifampin, and ethambutol (MHRE) 3 times a week for 2 months — i.e., M4-IE; all of these were compared to the control of 2 months of HRZE 3 times a week, followed by 4 months of isoniazid and rifampin 3 times a week. Partway through the study, the 3-month regimen was suspended by the data safety and monitoring board due to a high rate of TB recurrence.[6]

Outcomes

Relevant outcomes in the SR with meta-analysis were relapse (i.e., recurrence of TB within 2 years), rate of treatment discontinuation, rate of treatment failure (i.e., persistent or recurrent positive TB culture), acquired drug resistance (i.e., development of resistance to anti-TB drugs), serious adverse events (i.e., adverse events that were fatal or life-threatening), and all-cause mortality (during treatment or within 2 years).[5]

Relevant outcomes in the RCT by Dorman et al. (2021)[9] included disease-free survival at 12 months and adverse events that were classified as Grade 3 or higher. TB disease-free survival at 12 months was measured using culture samples and classified as "cure" (favourable outcome), "absence of a cure"(unfavourable outcome), or "not assessable" (e.g., lost to follow-up, death, pregnancy, and stopping treatment).[9] Noninferiority was assessed by comparing the difference between the proportion of participants classified as having an unfavourable outcome compared to the control group and the noninferiority margin was predefined as 6.6%.[9] As lower values of this outcome are better (i.e., the proportion with unfavourable outcome), if the upper limit of the 95% confidence interval lay below 6.6%+, then noninferiority was demonstrated for the new therapy.

Relevant outcomes in the RCT by Velayutham et al. (2020)[6] included the recurrence of TB, treatment status, and adverse events. The equivalence between the test and control regimens was tested by the difference in TB recurrence (i.e., percent difference with 95% confidence intervals) and the margin of equivalence was defined as −5% to 5% (i.e., if the 95% confidence interval for the test relative to control lies within the equivalence range of −5% to 5%, equivalence is found).

Summary of Critical Appraisal

Overall, the SR by Grace et al. (2019)[5] was well-conducted and well-reported, and we have high confidence in the findings of this SR and meta-analysis. This SR followed a published protocol and included a summary and explanation of all changes between the protocol and published report, decreasing the risk of reporting bias. The research question and eligibility criteria were reported in detail and a detailed description of all relevant components of the included studies was provided, including the source of funding of the primary studies. A comprehensive search strategy was used (i.e., multiple databases were searched, as were trial registries and conference proceedings, with no language restrictions) and the full search strategy was provided. Two authors performed the study selection and data extraction in duplicate; thus, it is unlikely that relevant evidence was omitted. A full list of excluded studies and the reasons for excluding each study was also provided, thus decreasing the risk of selection bias. Risk of bias of the primary studies was assessed in duplicate using an appropriate tool and all relevant risk of bias domains were assessed and reported for each study. When reporting and discussing the findings of the SR, the authors considered the risk of bias of the primary studies and also assessed the certainty of the evidence, thus providing a more accurate summary of the findings. Multiple random- or fixed-effects meta-analyses were conducted for the various outcomes using appropriate statistical methods and sensitivity analyses were conducted that excluded a study assessed as a high risk of bias. The authors acknowledged the risk of publication bias but, because there were fewer than 10 studies, could not investigate further. The authors declared that they had no conflicts of interest and an explicit statement was made that the content of the report was not influenced by the funding agency.

The RCT by Dorman et al. (2021)[9] included a detailed protocol that clearly reported the aim and hypotheses of the study, the eligibility criteria, the characteristics of the interventions, and the outcomes. The protocol also included a statistical analysis plan, a description of the different analysis populations, and the planned subgroup analyses. The main findings are clearly reported and accompanied by 95% confidence intervals, which show the variability in the data for the main outcomes. The characteristics of the patients lost to follow-up were not described, but a similar number of patients were lost to follow-up in each group. This study used a noninferiority design and the protocol included the value of the margin of noninferiority, as well as the justification for its selection. An a priori margin of noninferiority thus reduces the risk that the selection of the margin was biased in favour of a particular treatment. For noninferiority trials, it is recommended that the analyses conducted in both the per-protocol and the intention-to-treat populations are considered when determining noninferiority.[10] In this study, the primary efficacy analysis was based on a modified intention-to-treat population, which included all patients who were microbiologically eligible (i.e., culture confirmed TB) and the "assessable" population (i.e., primary outcome could be assessed at 12 months), and did not consider a per-protocol analysis in the assessment of the primary outcome. However, secondary analyses were conducted in populations that completed 75% and 95% of the treatment (i.e., 75% and 95% per-protocol populations) and these findings support the results observed in the analyses conducted in the other populations. For this report, the findings are reported based on the modified intention-to-treat and the 95% per-protocol populations. This study was unblinded and the protocol includes a detailed rationale for not blinding the study due to differences in treatment length (i.e., not desirable to provide placebo for 2 extra months), as well as the differences in effects of food on the different drugs (i.e., knowledge of treatment is needed to optimize absorption). In addition, the primary outcome is based on culture samples, which would have been unlikely to be influenced by blinding of the patients or clinical staff. Randomization was done by a centralized, computer-generated

arm assignment and patients were allocated to a treatment after the informed consent process was complete, thus reducing the risk of selection bias. A sample size calculation was conducted based on the primary outcome and the study was adequately powered to detect differences in the primary outcome. Conflict of interest disclosure forms are available for all authors online, with 2 authors declaring funding from industry, but it is unclear how these potential conflicts were managed. The source of funding was reported and a statement was made that the funding agencies did not influence the design or conducting of the study, nor did they influence the preparation and submission of the manuscript.

The RCT by Velayutham et al. (2020)[6] clearly described the aim of the study, the eligibility criteria, the characteristics of the interventions, and the primary and secondary outcomes. This study was registered on the clinical trials registry of India; however, minimal trial information is reported (e.g., no additional details were provided regarding a priori decisions or definitions). This study used an equivalence design and, although the margin of equivalence is reported in the methods of the report, this information was not reported in the trial registry and it is unclear whether this margin was established a priori or after data collection. For equivalence trials, it is important to establish the margin of equivalence before data collection, otherwise there is a risk of bias from selecting a margin that could intentionally lead to a conclusion of equivalence. There is therefore uncertainty in the findings of this report in determining the equivalence between regimens. This RCT conducted both a modified intention-to-treat and a per-protocol analysis, which is recommended for equivalence trials, and equivalence was only established with the support of both analyses, which is appropriate for this study design. The study did not report whether any attempts were made to blind participants or outcome assessors to the interventions received and it is unclear whether this would have influenced results. The outcomes in this trial are primarily objective outcomes (e.g., sputum cultures), with some subjective aspects (e.g., clinical deterioration, adverse events), which could potentially be influenced by being unblinded. Appropriate methods were used for randomizing participants to their intervention group; however, sealed opaque envelopes were used to assign the regimens, which could contribute to a risk of selection bias if the envelopes are opened in advance of recruitment. A sample size calculation was reported based on the primary outcome (i.e., TB recurrence), including the need to recruit additional participants because of anticipated attrition. Randomization to 1 of the treatment arms (i.e., the 3-month regimen) was halted early by the data safety and monitoring board, after which the allocation ratio to the remaining treatment and control arms was altered (i.e., 1:1:1:1:1 allocation ratio modified to 2:2:2:1 ratio). The remaining 3 treatment arms (i.e., variations of a 4-month regimen) met the sample size in both the modified intention-to-treat and the per-protocol analysis. The control arm did not meet the target sample size at randomization and it unclear whether the study was adequately powered, which may have contributed to the inconclusive findings for 2 of the treatment regimens in the study. The study did not report whether any of the authors had potential conflicts of interest; thus, it is unknown whether there was any impact on the design of the study or interpretation of the findings (e.g., selection of the margin of equivalence). The source of funding was reported, but it was not explicitly stated whether the funder influenced the content of the report.

Summary of Findings

Additional details regarding the main study findings and authors' conclusions are provided in tables in Appendix 2.

Clinical Effectiveness of Shortened Drug Regimens for the Treatment of Active Tuberculosis

Treatment Failure

In the SR with meta-analysis,[5] there was no difference in the risk of treatment failure (i.e., persistent or recurrent positive TB culture) when 4-month anti-TB regimens containing either moxifloxacin or gatifloxacin were compared to standard 6-month regimens.

In 1 RCT that used a noninferiority design,[9] the 4-month rifapentine-moxifloxacin–containing regimen (i.e., 2PHZM-2PHM) was considered noninferior to the 6-month, once-daily control regimen in the proportion of patients with an "unfavourable" outcome at 12 months (i.e., absence of a cure). The 4-month rifapentine-containing regimen (i.e., 2PHZE-2PH) was not shown to be noninferior compared to the 6-month control regimen in the proportion of patients with an "unfavourable" outcome at 12 months.

Relapse

In the SR with meta-analysis,[5] when compared to a standard 6-month anti-TB regimen, the risk of the recurrence of TB within 2 years of completing treatment was statistically significantly higher in patients who were treated with a 4-month anti-TB regimen (i.e., 4-month treatment containing moxifloxacin or 4-month treatment containing gatifloxacin).

In the RCT that used an equivalence design,[6] the 4-month once-daily moxifloxacin-containing regimen (i.e., M4) was considered equivalent to the 6-month thrice-weekly control regimen (does not contain moxifloxacin) regarding the recurrence of TB. When compared to the 6-month thrice-weekly control regimen, the evidence was inconclusive and equivalence was not shown for the recurrence of TB for the 4-month moxifloxacin-containing regimens that had intermittent (i.e., thrice-weekly) continuation phases (i.e., M4-I, and M4-EI).[6] The 3-month once-daily moxifloxacin-containing regimen (i.e., M3) was considered inferior to the 6-month thrice-weekly control regimen; this regimen was suspended by the data safety and monitoring board due to a high rate of TB recurrence.[6]

Treatment Discontinuation

In the SR with meta-analysis,[5] there was no difference in the risk of discontinuing treatment when 4-month anti-TB regimens containing either moxifloxacin or gatifloxacin were compared to standard 6-month regimens.

In 1 RCT,[9] the premature discontinuation of treatment occurred statistically significantly less frequently in those treated with a 4-month rifapentine-containing once-daily regimen (i.e., 2PHZE-2PH) compared to the 6-month once-daily control regimen; there was no difference in the proportion of patients with premature discontinuation of treatment between those treated with 4-month, rifapentine-moxifloxacin–containing once-daily regimen (i.e., 2PHZM-2PHM) and the 6-month once-daily control regimen.

Acquired Drug Resistance

In the SR with meta-analysis,[5] when compared to standard 6-month regimens there was no difference in the risk of acquired drug resistance for those treated with 4-month anti-TB regimens containing either moxifloxacin or gatifloxacin.

All-Cause Mortality

In the SR with meta-analysis,[5] there was no difference in the risk of all-cause mortality when 4-month anti-TB regimens containing either moxifloxacin or gatifloxacin were compared to standard 6-month regimens.

In 1 RCT,[9] a similar proportion of patients experienced all-cause mortality (i.e., less than 1% in all 3 groups) in those treated with a 4-month, rifapentine-containing once-daily regimen (i.e., 2PHZE-2PH); a 4-month, rifapentine-moxifloxacin–containing regimen (i.e., 2PHZM-2PHM); and the 6-month, once-daily control regimen. However, no statistical tests were reported with this data.

Adverse Events

In the SR with meta-analysis,[5] there was no difference in the risk of serious adverse events when 4-month anti-TB regimens containing either moxifloxacin or gatifloxacin were compared to standard 6-month regimens.

In 1 RCT,[9] the incidence of Grade 3 or higher adverse events was statistically significantly lower in those treated with a 4-month rifapentine-containing once-daily regimen (i.e., 2PHZE-2PH) compared to the 6-month once-daily control regimen; the incidence of Grade 3 or higher adverse events was comparable between those treated with 4-month rifapentine-moxifloxacin–containing once-daily regimen (i.e., 2PHZM-2PHM) and the 6-month control regimen.

In 1 RCT,[6] the most common adverse events were arthralgia and gastrointestinal symptoms. In all of the shortened 3- and 4-month moxifloxacin-containing regimens (i.e., M3, M4, M4-I, and M4-EI), the incidence of mild arthralgia was statistically significantly higher than those treated with the 6-month thrice-weekly control regimen.[6] The incidence of mild gastrointestinal symptoms was statistically significantly higher in those treated with M4-EI (i.e., 4-month moxifloxacin-containing regimen with the intermittent ethambutol-containing continuation phase) when compared to those treated with the 6-month thrice-weekly control regimen.[6] There was no other differences between groups in the incidence of moderate to severe adverse events.[6]

Limitations

This report comprises 1 SR with meta-analysis[5] and 2 RCTs,[6,9] and it is limited by this small quantity of heterogenous evidence.

A key limitation of this report is the heterogeneity of the interventions and comparators. The shortened treatment regimens differed across the included studies and ranged in length from 3[6] to 4[5,6,9] months, included once daily[5,6,9] and thrice-weekly[5,6] dose schedules, and included the addition of fluoroquinolones (i.e., moxifloxacin[5,6,9] or gatifloxacin[5]) or rifapentine.[9] The control regimen in all 3 studies was the standard 6-month regimen (i.e., isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, then isoniazid and rifampin for 4 months) and was either taken once-daily[5,9] or 3 times a week.[5,6] The variation across drug regimens limits the ability to draw conclusions on the clinical effectiveness of shortened drug regimens for the treatment of active tuberculosis.

In addition, due to the eligibility criteria used in the RCTs within the SR[5] and in the RCTs included in this report,[6,9] the results of this report are primarily generalizable to adults with drug-sensitive pulmonary TB who are otherwise healthy, as individuals with other conditions that compromise the immune system (e.g., HIV, hepatitis, renal disease) were excluded from some of trials included in this report.

Furthermore, none of the studies in this reported were led by Canadian authors or conducted in Canada. Thus, it is unclear if the findings of this report are generalizable to the Canadian clinical practice, as there may be differences between countries in the availability of drugs for the treatment of active TB.

Conclusions

This report comprised 1 SR with meta-analysis[5] and 2 RCTs[6,9] with clinical evidence regarding the use of shortened drug regimens for the treatment of active tuberculosis.

Regarding shortened 4-month regimens that contained moxifloxacin, the findings were mixed. The findings from the 2019 SR with meta-analysis, which combined evidence from 3 RCTs that used different 4-month moxifloxacin-containing regimens, suggest that the risk of recurrence of TB within 2 years of completing treatment was higher compared to a 6-month control regimen. But there was no difference in the risk of treatment failure, of discontinuing treatment, of acquired drug resistance, of all-cause mortality, or of serious adverse events between the shortened and control regimens.[5] This finding was associated with a moderate degree of statistical heterogeneity, which may be due to the clinical differences in which drugs were administered in both the treatment and the continuation phases, as well as the dose schedule (i.e., once-daily, thrice-weekly). The findings from a 2020 RCT that used an equivalence design suggest that a shortened 4-month, once-daily moxifloxacin-containing regimen was considered equivalent to the 6-month thrice-weekly control regimen with regard to the recurrence of TB.[6] The patients treated with this 4-month once-daily moxifloxacin-containing regimen experienced a higher incidence of mild arthralgia but no difference in any other adverse event.[6] In addition, with regard to recurrence of TB, equivalence was not shown for the 4-month moxifloxacin-containing regimens that had thrice-weekly continuation phases compared to the 6-month thrice-weekly control regimen.[6] The 4-month moxifloxacin-containing regimen with the thrice-weekly ethambutol-containing continuation phase was associated with a higher risk of mild gastrointestinal symptoms compared to the control; both regimens were associated with a higher incidence of mild arthralgia relative to the control, but neither was associated with a higher incidence of moderate to severe adverse events.[6] However, this equivalence trial[6] is associated with some reporting and methodological limitations that may affect the certainty of these findings.

The shortened 3-month regimen that contained moxifloxacin was considered inferior to the 6-month thrice-weekly control regimen with regard to the recurrence of TB and was suspended early by the data safety and monitoring board due to a high rate of TB recurrence.[6] This 3-month regimen was also associated with a higher incidence of mild arthralgia compared to the control but no other differences in the incidence of adverse events.[6]

For the shortened 4-month regimens that contained gatifloxacin, the findings from a 2019 SR with meta-analysis that combined evidence from 2 RCTs suggest that the risk of TB

recurrence with 2 years of completing treatment was higher compared to a 6-month control regimen. However, there was no difference in the risk of treatment failure, of discontinuing treatment, of acquired drug resistance, of all-cause mortality, or of serious adverse events between the shortened and control regimens.[5]

The shortened 4-month once-daily regimen that contained rifapentine with moxifloxacin was considered no worse than the 6-month once-daily control regimen in the proportion of patients with an "unfavourable" outcome at 12 months (i.e., absence of a cure).[9] The patients treated with the 4-month rifapentine-moxifloxacin–containing once-daily regimen also had no difference in premature discontinuation of treatment, all-cause mortality, or the incidence of Grade 3 or higher adverse events compared to the control.[9]

The shortened 4-month once-daily regimen that contained rifapentine without moxifloxacin was not shown to be noninferior than the 6-month, once-daily control regimen with regard to treatment failure (i.e., absence of a cure).[9] However, the incidence of Grade 3 or higher adverse events was 5% lower and the incidence of premature treatment discontinuation was 3% lower in those treated with a 4-month rifapentine-containing regimen compared to the 6-month control regimen, with no difference in all-cause mortality.[9]

Overall, a shortened 3-month moxifloxacin-containing regimen was considered inferior to a standard 6-month regimen,[6] and 4-month gatifloxacin-containing regimens were associated with a higher risk of TB recurrence compared to standard 6-month regimens.[5] Shortened 4-month regimens that contain moxifloxacin and/or rifapentine were not associated with an increased risk of serious adverse events, but the clinical benefit of these shortened regimens may depend on the specific combination of drugs and dose schedule.[5,6,9] The equivalence of the 4-month, once-daily moxifloxacin-containing regimen to a 6-month thrice-weekly regimen with regard to recurrence of TB,[6] and the noninferiority of the 4-month, once-daily rifapentine-moxifloxacin–containing treatment relative to the 6-month control, with regard to treatment failure,[9] may be relevant to clinical practice given that neither shortened treatment regimen was associated with an increase in serious adverse effects. As well, these shorter and simpler treatment regimens may be easier for patients to tolerate.

References

1. Menzies D, Elwood K. Canadian Tuberculosis Standards, Chapter 5 - Treatment of Tuberculosis Disease. Ottawa: Public Health Agency of Canada. 2014: https://www.canada.ca/en/public-health/services/infectious-diseases/canadian-tuberculosis-standards-7th-edition/edition-17.html.. Accessed 2021 Aug 17.
2. Reichman LB. Adherence to tuberculosis treatment Waltham (MA): UpToDate; 2019 Sep 26.
3. Organization. WH. Guidelines for treatment of drug-susceptible tuberculosis and patient care (2017 update). Geneva: World Health Organization; 2017: https://www.who.int/tb/publications/2017/dstb_guidance_2017/en/.. Accessed April 22 2021.
4. Shortened Drug Regimens for the Treatment of Active Tuberculosis. Ottawa: CADTH; 2020 Aug. (CADTH rapid response report: summary of abstracts). https://cadth.ca/sites/default/files/pdf/htis/2020/RB1515%20Short%20vs%20Long%20Tx%20TB%20Final.pdf. Accessed 2021 Aug 17.
5. Grace AG, Mittal A, Jain S, et al. Shortened treatment regimens versus the standard regimen for drug-sensitive pulmonary tuberculosis. *Cochrane Database of Systematic Reviews.* 2019(12).
6. Velayutham B, Jawahar MS, Nair D, et al. 4-month moxifloxacin containing regimens in the treatment of patients with sputum-positive pulmonary tuberculosis in South India–a randomised clinical trial. *Tropical Medicine & International Health.* 2020;25(4):483-495. PubMed
7. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *bmj.* 2017;358.
8. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-384. PubMed
9. Dorman SE, Nahid P, Kurbatova EV, et al. Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis. *New England Journal of Medicine.* 2021;384(18):1705-1718. PubMed
10. EMA. Points to consider on switching between superiority and non-inferiority. 2000: https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-switching-between-superiority-non-inferiority_en.pdf. Accessed June 4, 2021.

Appendix 1: Characteristics of Included Publications

Note that this appendix has not been copy-edited.

Table 2: Characteristics of Included Systematic Review and Meta-Analysis

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Grace et al. (2019)[5] India Funding: Department for International Development, UK	5 RCTs included in SR and MA	Individuals with newly diagnosed pulmonary TB, with presumed or confirmed drug-sensitive TB, irrespective of HIV status	Interventions: Any anti-TB drug(s) or combination of anti-TB drugs, with a regimen that is less than 6 months Comparators: standard first-line therapy for pulmonary TB (i.e., a regimen of 2 months of HRZE and 4 months of HR or HRE)	Primary: relapse of TB within 2 years of completion of anti-TB therapy Secondary: death, treatment discontinuation or failure, positive TB culture at 8 weeks, acquired drug resistance, serious adverse events

HR = isoniazid and rifampin; HRE = isoniazid and rifampin with ethambutol; HRZE = isoniazid, rifampin, pyrazinamide, and ethambutol; MA = meta-analysis; SR = systematic review; TB = tuberculosis.

Table 3: Characteristics of Included Primary Clinical Study

Study citation, country, funding	Study design	Population characteristics	Interventions and comparator	Clinical outcomes, length of follow-up
Dorman et al. (2021)[9] US Funding: the Centers for Disease Control and Prevention, the National Institutes of Health, and Sanofi.	RCT, 3 arm trial, open label Noninferiority design Randomization was stratified by site, HIV status, and presence of cavitation on chest X-ray International, multicenter (34 sites) conducted between January 2016 and October 30, 2018	Individuals ≥ 12 years with newly diagnosed pulmonary TB with confirmed susceptibility to isoniazid, rifampin, and fluoroquinolones. Excludes: those with more than 5 days of treatment for active TB within previous 6 months; suspected non-pulmonary TB, those with known resistance to rifampin, isoniazid, pyrazinamide, ethambutol, or fluoroquinolones Number of patients randomized: 2,516 Numbers in modified intention-to-treat analysis: • 2PHZE-2PH: 784 • 2PHZM-2PHM: 791 • Control: 768 Numbers in the 95% per-protocol analysis: • 2PHZE-2PH: 650 • 2PHZM-2PHM: 641 • Control: 563	2PHZE/2PH: 4-month therapy (8 weeks of once-daily PHZE followed by 9 weeks of once-daily PH) 2PHZM/2PHM: 4-month therapy (8 weeks of once-daily PHZM, followed by 9 weeks of once-daily PHM) Control: standard 6 months therapy (8 weeks of once-daily HRZE followed by 18 weeks of once-daily rifampin and isoniazid) Daily doses: • Rifapentine = 1,200 mg • Moxifloxacin = 400 mg • Rifampin = 600 mg • Isoniazid = 300 mg • Pyrazinamide = 1,000 to 2000 mg (varies by body weight) • E = 800 to 1,600 mg (varies by body weight) • For all groups: Medications administered 7 days a week, with ≥ 5 days of in-person directly observed therapy	Outcomes: • TB disease-free survival • adverse events of Grade 3 or higher • treatment discontinuation Follow-up: 12 months

Study citation, country, funding	Study design	Population characteristics	Interventions and comparator	Clinical outcomes, length of follow-up
Velayutham et al. (2020)[6] India Funding: Indian Council of Medical Research of the Government of India	RCT, open label, 5-arm trial. Equivalence design. Randomization was stratified by sputum smear grading, results of chest X-ray, and duration of previous TB treatment. Setting: 3 sites in South India	Inclusion criteria: adults with newly diagnosed pulmonary TB Excludes: those with previous TB treatment exceeding 30 days, or more than 1 week in the month before enrolment, those with extra-pulmonary TB, those with HIV, hepatitis or renal disease Number of patients randomized: 1,371 Number of patients included in the per-protocol analysis (i.e., received ≥ 80% of allocated treatment) (N = 1,223): • M3 = 99 • M4 = 299 • M4-I = 308 • M4-EI = 305 • Control = 212	Interventions: M3: 3-month moxifloxacin (M) regimen (i.e., MHRZE daily) [This arm was suspended due to safety partway through the study] M4: 4-month M regimen (i.e., MHRZE daily for 2 months then MHR daily for 2 months) M4-I: 4-month M regimen with intermittent continuation phase (i.e., MHRZE daily for 2 months then MHR 3 times a week for 2 months) M4-IE: 4-month M regimen with intermittent continuation phase plus E (i.e., MHRZE daily for 2 months then MHRE 3 times a week for 2 months) Control: standard 6-month therapy for TB (i.e., a regimen of 2 months of HRZE 3 times a week, followed by 4 months of isoniazid and rifampin 3 times a week For all groups: • During the daily phase, treatments were directly observed 5 days of the week, and self-administered on the weekend. • During the 3 times a week phase, all treatments were directly observed.	Outcomes: • Recurrence of TB among those with a 'favourable' response at the end of treatment • status at end of treatment [i.e., favourable (3 negative sputum cultures after 2 months of treatment) or unfavourable (positive sputum culture, clinical deterioration, or death)] • adverse reactions to drugs Follow-up: 24 months post-treatment.

E = ethambutol; I = intermittent; HRZE = isoniazid, rifampin, pyrazinamide, and ethambutol; M = moxifloxacin; MHR = moxifloxacin. isoniazid and rifampin; MHRE = moxifloxacin. isoniazid. rifampin, and ethambutol; MHRZE = moxifloxacin, isoniazid. rifampin, pyrazinamide, and ethambutol; PH = rifapentine and isoniazid; PHM = rifapentine, isoniazid, and moxifloxacin; PHZE = rifapentine, isoniazid, pyrazinamide, and ethambutol; PHZM = rifapentine, isoniazid, pyrazinamide, and moxifloxacin; RCT = randomized controlled trial; TB = tuberculosis.

Appendix 2: Main Study Findings and Authors' Conclusions

Note that this appendix has not been copy-edited.

Summary of Findings Included Systematic Review and Meta-Analysis

Grace et al. (2019)[5]

Main Study Findings

Moxifloxacin-containing 4-month anti-TB regimen versus (vs.) standard 6-month anti-TB regimen

Treatment failure:

- Relative risk (RR) = 0.71; 95% confidence interval (CI), 0.33 to 1.52
- Fixed effects, 3 RCTs, I^2 = 0%
- Moderate certainty in the evidence

Relapse:

- RR = 3.56; 95% CI, 2.37 to 5.37
- Fixed effects, 3 RCTs, I^2 = 54.1%
- Moderate certainty in the evidence

Treatment discontinuation:

- RR = 1.12; 95% CI, 0.78 to 1.61
- Fixed effects, 3 RCTs, I^2 = 0%
- Certainty in the evidence not reported

Acquired drug resistance:

- RR = 0.33; 95% CI, 0.08 to 1.31
- Fixed effects, 3 RCTs, I^2 = 0%
- Low certainty in the evidence

All-cause mortality:

- RR = 1.06; 95% CI, 0.65 to 1.75
- Fixed effects, 3 RCTs, I^2 = 19.5%
- Moderate certainty in the evidence

Serious adverse events:

- RR = 0.97; 95% CI, 0.74 to 1.27
- Fixed effects, 4 RCTs, I^2 = 0%
- Moderate certainty in the evidence

Gatifloxacin-containing 4-month anti-TB regimen vs. standard 6-month anti-TB regimen

Treatment failure:

- RR = 0.93; 95% CI, 0.51 to 1.70
- Fixed effects, 2 RCTs, I^2 = 36.8%

- Moderate certainty in the evidence

Relapse:

- RR = 2.11; 95% CI, 1.56 to 2.84
- Fixed effects, 2 RCTs, I^2 = 0%
- Moderate certainty in the evidence

Treatment discontinuation:

- RR = 0.70; 95% CI, 0.46 to 1.08
- Fixed effects, 2 RCTs, I^2 = 23.6%
- Certainty in the evidence not reported

Acquired drug resistance:

- RR = 0.24; 95% CI, 0.01 to 5.01
- Fixed effects, 1 RCT, I^2 = not applicable
- Very low certainty in the evidence

All-cause mortality:

- RR = 0.90; 95% CI, 0.53 to 1.53
- Fixed effects, 2 RCTs, I^2 = 0%
- Moderate certainty in the evidence

Serious adverse events:

- RR = 1.02; 95% CI, 0.58 to 1.77
- Fixed effects, 2 RCTs, I^2 = 55.7%
- Moderate certainty in the evidence

Authors' Conclusions

"Evidence to date does not support the use of fluoroquinolone containing shortened ATT [anti-tuberculosis treatment] regimens for adults with newly diagnosed drug-sensitive pulmonary tuberculosis. Although there is probably little or no difference in cure or serious adverse events with four-month ATT regimens that replace ethambutol with moxifloxacin or gatifloxacin, or isoniazid with moxifloxacin, compared to standard six-month ATT regimens, the shortened regimens will probably increase relapse substantially." (p. 24)

"The 4-month [moxifloxacin-containing] regimen probably results in little or no difference in treatment failure compared to the 6-month regimen." (p. 4)

"The 4-month [moxifloxacin-containing] regimen probably increases relapse compared to the 6-month regimen." (p. 4)

"The 4-month [moxifloxacin-containing] regimen may be little or no different than the 6-month regimen in the incidence of acquired drug resistance." (p. 4)

"The 4-month [moxifloxacin-containing] regimen probably makes little or no difference in death from any cause compared to the 6-month regimen." (p. 4)

"The 4-month [moxifloxacin-containing] regimen probably results in little or no difference in serious adverse events compared to the 6-month regimen." (p. 5)

"The 4-month [gatifloxacin-containing] regimen probably makes little or no difference in treatment failure compared to the 6-month regimen." (p. 6)

"The 4-month [gatifloxacin-containing] regimen probably increases relapse compared to the 6-month regimen." (p. 6)

"We do not know if acquired drug resistance is any different in the 4-month [gatifloxacin-containing] and the 6-month regimens." (p. 6)

"The 4-month [gatifloxacin-containing] regimen probably makes little or no difference in death compared to the 6-month regimen." (p. 6)

"The 4-month [gatifloxacin-containing] regimen probably results in little or no difference in serious adverse events compared to the 6-month regimen." (p. 6)

Summary of Findings of the Included Primary Clinical Study

Dorman et al. (2021)[9]

Main Study Findings

The modified intention-to-treat (MITT) analysis was based on populations that were microbiologically eligible (i.e., culture confirmed TB). Individuals where primary outcome was classified as "not assessable" were considered to have an unfavourable outcome.

The 95% per-protocol analysis was based on populations where participants completed at least 95% of their treatment doses

Noninferiority margin = 6.6%, based on the difference between the control and the intervention in the proportion of patients classified as having unfavourable outcome (where lower absolute values are better)

"Unfavourable" status at 12 months, MITT analysis, n (%):

- 2PHZM-2PHM: 123 (15.5)
- 2PHZE-2PH: 139 (17.7)
- Control: 112 (14.6)

Difference between the test and control regimen, MITT analysis, % (95% CI):

- 2PHZM-2PHM vs control: 1.0 (– 2.5 to 4.5)
- 2PHZE-2PH vs. control: 3.0 (– 0.6 to 6.6)

"Unfavourable" status at 12 months, 95% per-protocol analysis, n (%):

- 2PHZM-2PHM: 37 (5.8)
- 2PHZE-2PH: 71 (10.9)
- Control: 15 (2.7)

Difference between the test and control regimen, 95% per-protocol analysis, % (95% CI):

- 2PHZM-2PHM vs control: 3.1 (0.9 to 5.3)
- 2PHZE-2PH vs. control: 8.2 (5.5 to 11.0)

For 2PHZM-2PHM, the upper limit of the 95% CI was smaller than the noninferiority margin (i.e., + 6.6%) in both the MITT and 95% per-protocol analyses, and it is considered noninferior to the control

For 2PHZE-2PH, the upper limit of the 95% CI was equal to and greater than the noninferiority margin (i.e., + 6.6%) in the MITT and 95% per-protocol analyses, respectively, and noninferiority was not shown relative to the control

Participants experiencing any Grade 3 or higher adverse event, n (%):

- 2PHZM-2PHM: 159 (18.8)
- 2PHZE-2PH: 119 (14.3)
- Control: 159 (19.3)

Difference between the test and control regimen, % (95% CI):

- 2PHZM-2PHM vs control: −0.6 (−4.3 to 3.2)
- 2PHZE/2PH vs. control: −5.1 (− 8.7 to −1.5)

All-cause mortality, n (%):

- 2PHZM-2PHM: 3 (0.4)
- 2PHZE-2PH: 4 (0.5)
- Control: 7 (0.8)

Treatment discontinuation, MITT analysis, n (%):

- 2PHZM-2PHM: 55 (7.0)
- 2PHZE-2PH: 37 (4.7)
- Control: 61 (7.9)

Difference between the test and control regimen, % (95% CI):

- 2PHZM-2PHM vs control: −1.0 (−3.6 to 1.6)
- 2PHZE-2PH vs. control: −3.3 (− 5.7 to −0.9)

Authors' Conclusions

"In this phase 3 trial, the efficacy of the 4-month regimen containing rifapentine and moxifloxacin was noninferior to that of the standard 6-month regimen. Noninferiority of the rifapentine–moxifloxacin regimen to the control regimen was confirmed across analysis populations as well as in sensitivity and pre-specified subgroup analyses. The efficacy of the 4-month regimen containing rifapentine without moxifloxacin did not meet the criteria for noninferiority." (p. 1713)

"The incidence of grade 3 or higher adverse events during the on-treatment period was similar in the rifapentine–moxifloxacin group and the control group and was slightly lower in the rifapentine group." (p. 1713 to 1715)

"No evidence was found of a difference in premature discontinuation between the rifapentine–moxifloxacin group and the control group (risk difference, −1.0 percentage points; 95% CI, −3.6 to 1.6). Premature discontinuation occurred less frequently with the rifapentine regimen than with the control regimen (−3.3 percentage points; 95% CI, −5.7 to −0.9)." (p. 1713)

Velayutham et al. (2020)[6]

Main Study Findings

"Favourable" status at end of treatment, per-protocol analysis, n (%):

- Moxifloxacin (M)3 = 99 (100)
- M4 = 292 (98)
- M4-intermittent (I) = 297 (96)
- M4-ethambutol (E)I = 294 (96)
- Control = 198 (93)

"Favourable" status at end of treatment, MITT analysis, n (%):

- M3 = 103 (92)

- M4 = 296 (92)
- M4-I = 298 (91)
- M4-EI = 295 (90)
- Control = 201 (83)

Recurrence of TB among those with a "favourable" response at the end of treatment —

- TB recurrence, per-protocol analysis, n (%):
  - M3 = 19 (19.2)
  - M4 = 12 (4.1)
  - M4-I = 25 (8.4)
  - M4-EI = 19 (6.5)
  - Control = 9 (4.5)
- TB recurrence, MITT analysis, n (%):
  - M3 = 20 (19.4)
  - M4 = 12 (4.1)
  - M4-I = 26 (8.7)
  - M4-EI = 19 (6.4)
  - Control = 9 (4.5)
- Difference between the test and control regimen, per-protocol analysis, %, 95% CI:
  - M3 vs. control = 14.6, 95% CI, 5.61 to 23.69
  - M4 vs. control = 0.4, 95% CI, −3.68 to 4.55
  - M4-I vs. control = 3.9, 95% CI, −0.84 to 8.58
  - M4-EI vs. control = 1.9, 95% CI, −2.54 to 6.38
- Difference between the test and control regimen, MITT analysis, %, 95% CI:
  - M3 vs. control = 14.9, 95% CI, 6.05 to 23.83
  - M4 vs. control = 0.4, 95% CI, −3.63 to 4.48
  - M4-I vs. control = 4.3, 95% CI, −0.46 to 8.96
  - M4-EI vs. control = 1.9, 95% CI, −2.46 to 6.38

For M3, the upper and lower limits of the 95% CI are greater than the positive margin of equivalence (i.e., + 5%), and it is considered inferior to the control.

For M4, the limits of the 95% CI fell within the equivalence range of −5% to 5%, in both the per-protocol and the MITT analyses, and it is considered equivalent to the control.

For M4-I and M4-EI, the upper limit of the 95% CI crosses the upper boundary for equivalence (i.e., + 5%) and equivalence was not shown relative to the control (i.e., inconclusive).

Adverse reactions to drugs, MITT analysis —

Arthralgia, mild, n (%):

- M3 = 36 (32), P < 0.001 compared to control
- M4 = 83 (26), P < 0.001 compared to control
- M4-I = 70 (21), P < 0.001 compared to control

- M4-EI = 67 (20), P < 0.001 compared to control
- Control = 12 (5)

Gastrointestinal, mild, n (%):

- M3 = 9 (8)
- M4 = 19 (6)
- M4-I = 16 (5)
- M4-EI = 26 (8), P = 0.03 compared to control
- Control = 10 (4)

No significant differences compared to control for moderate to severe arthralgia, gastrointestinal symptoms, cutaneous symptoms, giddiness, hepatic symptoms, cardia symptoms, seizures, peripheral neuropathy, renal symptoms, or thrombocytopenia.

Authors' Conclusions

"In per-protocol analysis, of 292 patients treated with the M4 regimen who had a 'Favourable' response at the end of treatment, 12 (4.1%) had recurrence of TB during 24 months of follow-up, vs. 9 (4.5%) of 198 patients treated with the control regimen. The difference in TB recurrence rate was 0.44% and 95%CI of the difference was – 3.68, 4.55, thus demonstrating equivalence with the margin of indifferency being within 5%. Similar findings were observed in the modified intention-to-treat analysis favouring theM4 regimen (difference 0.42%; 95%CI – 3.63, 4.48)." (p. 486)

"The M3, M4-I and M4-IE regimens did not show equivalence with the control regimen with TB recurrence rates of 19.2%, 8.4% and 6.5%, respectively." (p. 486)

"The commonest adverse events were arthralgia (21– 32% in the moxifloxacin regimens compared to 5% in the control regimen, P < 0.001). Gastrointestinal symptoms occurred in 6–8% of patients in the moxifloxacin regimens and 4% in the control regimen." (p. 488)

"This study shows that a daily 4-month moxifloxacin regimen (M4) is equivalent to a 6-month thrice-weekly regimen in new sputum-positive pulmonary TB patients with advanced disease (95% with sputum culture grading of ≥2+ and 79% with involvement of >2 zones in chest radiograph) without HIV infection, diabetes mellitus or other comorbidities." (p. 490)