



Efficacy of 4-Month Short-Course Drug-Susceptible Tuberculosis Treatment Regimens : A Systematic Review of Randomized Controlled Trials and Primary Studies

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Article History :

Received date : 2025/04/21

Revised date : 2026/05/09

Accepted date : 2026/06/17

Published date : 2026/07/15



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E-ISSN :

ISSN 3048-1368



P-ISSN

ISSN 3048-1376



ABSTRACT

Background: Tuberculosis (TB) remains the leading global infectious disease killer. The standard 6-month drug-susceptible tuberculosis (DS-TB) regimen—comprising rifampicin, isoniazid, pyrazinamide, and ethambutol—presents challenges in adherence, programmatic burden, and patient quality of life. Shorter treatment regimens, particularly 4-month regimens, have been investigated as potential alternatives to enhance treatment completion and reduce disease burden.^{1,2}

Methods: The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Eligible studies included phase 2–3 RCTs, subgroup analyses, pooled analyses studies involving adults or children with newly diagnosed DS-PTB receiving any 4-month treatment regimen compared to standard 6-month therapy. Sixteen studies encompassing 3 landmark phase 3 RCTs, multiple subgroup analyses, pooled analyses, were included. Risk of bias was

assessed using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool. GRADE certainty ratings were applied to key outcomes.^{3,4}

Results: Sixteen studies met inclusion criteria, representing data from more than 15,000 patients across multiple international settings. The landmark Study 31/A5349 (Dorman et al., 2021) demonstrated that the 4-month regimen comprising rifapentine (RPT), moxifloxacin (MOX), isoniazid (INH), and pyrazinamide (PZA) achieved non-inferiority to the standard 6-month regimen for the primary efficacy outcome (unfavorable outcome 15.5% vs. 14.6%; risk difference +1.0 percentage point, 95% CI -2.6 to +4.5). Earlier fluoroquinolone-based 4-month regimens (REMoxTB, OFLOTUB, RIFAQUIN) failed to demonstrate non-inferiority, primarily due to higher relapse rates. Grade 3+ adverse events were comparable between 4-month and 6-month regimens for the Study 31 regimen (18.8% vs. 19.3%). Patient subgroups with non-cavitary disease and minimal bacillary load showed the greatest benefit from shortened therapy. Key efficacy outcomes analysed included: (1) unfavorable primary outcome rate, (2) TB-free survival, (3) sputum culture conversion rate, (4) relapse/recurrence rate, (5) time to culture conversion, (6) treatment completion rate, (7) grade 3+ adverse events, (8) hepatotoxicity, (9) QTc interval prolongation, and (10) subgroup efficacy (HIV, diabetes, cavitation, smear grade).^{5,6,7,8,9,10}

Discussion: The transition from a 6-month to a 4-month DS-TB regimen is now evidence-based for selected patients, specifically with the RPT+MOX+INH+PZA regimen as endorsed by the ATS/CDC/ERS/IDSA 2025 clinical practice guideline. The inclusion of moxifloxacin is essential; rifapentine alone is insufficient for treatment shortening. Novel regimens including BPamZ show bacteriological promise but face hepatotoxicity

barriers. Stratified medicine—selecting patients based on smear grade, cavitation, and HIV status—is emerging as the optimal approach.^{11,12,13}

Conclusion: The 4-month RPT+MOX+INH+PZA regimen is effective and non-inferior to standard 6-month therapy for DS-PTB in appropriate patient populations. Implementation requires patient stratification, contraindication screening for fluoroquinolones, and integration into national TB programs. Future research should focus on novel short-course regimens with improved tolerability and broader applicability.¹⁴

Keywords: *tuberculosis; drug-susceptible tuberculosis; 4-month regimen; rifapentine; moxifloxacin; short-course therapy; randomized controlled trial; systematic review; non-inferiority; GRADE*

INTRODUCTION

Background

Tuberculosis (TB) remains one of the most significant infectious diseases in global public health, responsible for approximately 1.25 million deaths annually and an estimated 10.6 million new infections worldwide in 2022 according to World Health Organization (WHO) global reports.¹ *Mycobacterium tuberculosis* (Mtb), the causative pathogen, exhibits a complex biological behavior—encompassing both rapidly replicating and metabolically dormant bacillary subpopulations—that fundamentally drives the prolonged duration of the current standard treatment regimen.²

The current standard first-line treatment for drug-susceptible pulmonary tuberculosis (DS-PTB) consists of a 2-month intensive phase utilizing isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB), followed by a 4-month continuation phase of INH and RIF—totaling 6 months of continuous pharmacotherapy.² While this regimen achieves cure rates exceeding 85% in well-controlled trials, its prolonged duration presents multiple operational challenges: reduced patient adherence, increased risk of treatment interruption, elevated programmatic monitoring costs, and adverse drug reactions that collectively compromise real-world treatment success rates.³

The biological rationale for treatment shortening centers on the pharmacodynamic properties of rifamycin compounds, particularly rifapentine (RPT), a cyclopentyl derivative of rifampicin with a substantially longer half-life (13–19 hours vs. 2–4 hours for rifampicin) and superior area under the concentration-time curve (AUC), enabling potent mycobactericidal activity at higher intracellular concentrations.⁴ Fluoroquinolones, particularly moxifloxacin, provide complementary bactericidal activity against both replicating and semi-dormant Mtb populations, thereby addressing the biological impediment to treatment shortening.^{5,6}

Multiple pivotal phase 3 clinical trials conducted over the past two decades have investigated 4-month DS-TB regimens incorporating these pharmacological principles. The

spectrum of investigated regimens includes fluoroquinolone substitution (REMOxTB, 2014; OFLOTUB, 2014), high-dose rifapentine with moxifloxacin (RIFAQUIN, 2014), high-dose daily rifapentine with moxifloxacin (Study 31/A5349, 2021), and novel combinations such as bedaquiline-pretomanid-moxifloxacin-pyrazinamide (SimpliciTB, 2024).^{5,6,7,8,9}

The landmark Study 31/A5349 (Dorman et al., 2021), published in The New England Journal of Medicine, for the first time demonstrated non-inferiority of a 4-month regimen—specifically daily RPT+MOX+INH+PZA—compared to the standard 6-month regimen across a globally representative multicenter cohort, fundamentally shifting the evidential landscape for TB treatment.⁵ These findings were subsequently incorporated into updated ATS/CDC/ERS/IDSA clinical practice guidelines published in 2025 (Saukkonen et al., 2025).¹⁴

Research Gap

Despite the landmark results of Study 31/A5349, the broader literature contains considerable heterogeneity in outcomes across 4-month DS-TB clinical trials, with multiple earlier trials failing to demonstrate non-inferiority.^{5,6,7,8,9} There is currently no comprehensive synthesis systematically comparing the full spectrum of 4-month regimens across standardized outcomes—including unfavorable outcome rates, sputum culture conversion, relapse rates, adverse events, and subgroup-specific efficacy (HIV co-infection, diabetes mellitus, radiographic cavitation, smear grade)—while simultaneously evaluating the risk of bias and quality of evidence. Furthermore, emerging data on novel regimens (BPamZ) and patient-level predictors (MIC values, month-2 culture status) have not been synthesized alongside established RCT evidence.^{12,15,16}

Research Objectives

The primary objective of this systematic review is to systematically evaluate the clinical efficacy of 4-month DS-TB treatment regimens compared to standard 6-month therapy, as reported in RCTs and primary studies, across a minimum of 10 pre-specified clinical outcomes.

Secondary objectives include: (a) assessment of the safety and tolerability profile of 4-month regimens, (b) evaluation of subgroup-specific efficacy data stratified by HIV status, radiographic cavitation, smear grade, and comorbidities, (c) synthesis of bacteriological surrogate

markers (sputum culture conversion, month-2 culture status) as predictors of long-term outcomes, and (d) GRADE assessment of the certainty of evidence for each key outcome.

Hypothesis

We hypothesized that the 4-month DS-TB treatment regimen incorporating rifapentine and moxifloxacin (RPT+MOX+INH+PZA) is non-inferior to the standard 6-month HRZE/HR regimen with respect to unfavorable treatment outcome at 12 months, while demonstrating a comparable or superior safety and tolerability profile. We further hypothesized that earlier fluoroquinolone-only substitution regimens would fail to achieve non-inferiority due to insufficient bactericidal potency during the continuation phase.

Novelty and Significance

This systematic review is novel in providing the first comprehensive, multi-outcome synthesis of all major 4-month DS-TB RCTs and primary studies, integrating: (a) full primary outcome non-inferiority analyses, (b) secondary bacteriological outcomes, (c) clinically important subgroup analyses (PLHIV, diabetes mellitus), (d) Cochrane RoB 2.0 assessment, (e) GRADE certainty ratings, (f) synthesis of patient-level predictors of treatment shortening eligibility, and (g) comparison of both conventional and novel drug-combination approaches. This synthesis provides evidence-based guidance for national TB programs, particularly in high-burden settings such as Indonesia, considering implementation of the 4-month regimen.

METHODS

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review protocol was conceptualized and follows the PICOS framework (Population, Intervention, Comparator, Outcomes, Study design).

Eligibility Criteria

Inclusion Criteria

(1) Study Design: Randomized controlled trials (phase 2b, phase 2c, phase 3), pre-specified subgroup analyses of RCTs, patient-level pooled analyses of multiple RCTs, and meta-regression analyses of aggregated RCT data; (2) Population: Adults or children (≥ 12 years) with newly

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diagnosed drug-susceptible pulmonary tuberculosis (DS-PTB), confirmed by sputum smear microscopy, mycobacterial culture, or molecular testing; (3) Intervention: Any 4-month treatment regimen for DS-PTB; (4) Comparator: Standard 6-month first-line regimen (HRZE/RH or equivalent); (5) Outcomes: Reporting at least one of the pre-specified primary or secondary outcomes; (6) Language: English-language publications; (7) Time frame: 2000–2026.

Exclusion Criteria

(1) Studies exclusively enrolling multidrug-resistant TB (MDR-TB) or rifampin-resistant TB (RR-TB) without a DS-TB arm; (2) Studies focused exclusively on tuberculosis preventive therapy/latent TB infection; (3) Non-comparative case series, editorials, review articles without primary data; (4) Animal or in vitro studies; (5) Studies reporting duplicate data already included in a primary trial without distinct subgroup data.³

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Drug-Susceptible Pulmonary Tuberculosis	Newly Diagnosed TB Patients	Adults with DS-PTB
I (Intervention)	4-Month Rifapentine-Moxifloxacin Regimen	Short-Course TB Therapy	RPT+MOX+INH+PZA Regimen
C (Comparator)	Standard 6-Month TB Therapy	HRZE/HR Regimen	Conventional First-Line TB Treatment
O (Outcomes)	Treatment Non-Inferiority	Sputum Culture Conversion	Relapse/Recurrence Rate

The Boolean MeSH keywords inputted on databases for this research are: (*"Drug-Susceptible Pulmonary Tuberculosis"* OR *"Newly Diagnosed TB Patients"* OR *"Adults with DS-PTB"*) AND (*"4-Month Rifapentine-Moxifloxacin Regimen"* OR *"Short-Course TB Therapy"* OR *"RPT+MOX+INH+PZA Regimen"*) AND (*"Standard 6-Month TB Therapy"* OR *"HRZE/HR Regimen"* OR *"Conventional First-Line TB Treatment"*) AND (*"Treatment Non-Inferiority"* OR *"Sputum Culture Conversion"* OR *"Relapse/Recurrence Rate"*)

Study Selection

Two authors (FI, SM) independently screened titles and abstracts for eligibility. Full-text articles of potentially eligible studies were retrieved and assessed independently. Discrepancies were resolved by consensus.

Data Extraction

Data extraction was performed using a pre-specified standardized data extraction form capturing: study identification (author, year, trial name, journal, DOI/URL); study design; geographic setting; participant characteristics (sample size, age, sex, HIV status, smear grade, cavitation status); treatment arms (drug composition, dose, frequency, duration); primary and secondary outcome data with point estimates and confidence intervals; adverse event data; subgroup analyses; and follow-up duration.

Outcomes of Interest

Pre-specified outcomes included: (1) Unfavorable primary outcome (composite of TB-related death, treatment failure, recurrence, or loss to follow-up) at 12 months; (2) TB-free survival at 12 months; (3) Sputum culture conversion rate at 8 weeks (solid and liquid media); (4) Post-treatment relapse/recurrence rate at 18–24 months; (5) Time to sputum culture negativity; (6) Treatment completion rate; (7) Grade 3 or higher adverse events (ATC classification); (8) Hepatotoxicity (drug-induced liver injury, ALT elevation); (9) QTc interval prolongation; (10) Subgroup-specific efficacy (HIV co-infection, diabetes mellitus, radiographic cavitation, smear grade). Secondary outcomes included bacteriological cure rate and loss to follow-up.

Risk of Bias Assessment

Risk of bias for individual RCTs was evaluated using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool, which assesses five domains: (D1) bias arising from the randomization process; (D2) bias due to deviations from the intended interventions; (D3) bias due to missing outcome data; (D4) bias in measurement of the outcome; (D5) bias in the selection of the reported result.⁴ The open-label design of the majority of trials (Study 31, OFLOTUB, RIFAQUIN) introduced inherent high-risk concerns in D3 (blinding) which were consistently noted. Two trials (REMoxTB) employed a double-blind placebo-controlled design, reducing blinding concerns. Results are summarized in Table 4.

Certainty of Evidence (GRADE)

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was applied to assess the certainty of evidence for each of the 10 pre-specified outcomes. Domains assessed included risk of bias, inconsistency, indirectness, imprecision, and publication bias. Certainty was rated as High, Moderate, Low, or Very Low. Results are presented in Table 7.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Drug-Susceptible Pulmonary Tuberculosis" OR "Newly Diagnosed TB Patients" OR "Adults with DS-PTB") AND ("4-Month Rifapentine-Moxifloxacin Regimen" OR "Short-Course TB Therapy" OR "RPT+MOX+INH+PZA Regimen") AND ("Standard 6-Month TB Therapy" OR "HRZE/HR Regimen" OR "Conventional First-Line TB Treatment") AND ("Treatment Non-Inferiority" OR "Sputum Culture Conversion" OR "Relapse/Recurrence Rate")</i>	3
Semantic Scholar	<i>("Drug-Susceptible Pulmonary Tuberculosis" OR "Newly Diagnosed TB Patients" OR "Adults with DS-PTB") AND ("4-Month Rifapentine-Moxifloxacin Regimen" OR "Short-Course TB Therapy" OR "RPT+MOX+INH+PZA Regimen") AND ("Standard 6-Month TB Therapy" OR "HRZE/HR Regimen" OR "Conventional First-Line TB Treatment") AND ("Treatment Non-Inferiority" OR "Sputum Culture Conversion" OR "Relapse/Recurrence Rate")</i>	250
Science-direct	<i>"Drug-Susceptible Pulmonary Tuberculosis" AND "4-Month Rifapentine-Moxifloxacin Regimen" OR "Short-Course TB Therapy" AND "Treatment Non-Inferiority" OR "Sputum Culture Conversion" OR "Relapse/Recurrence Rate"</i>	880
Google Scholar	<i>("Drug-Susceptible Pulmonary Tuberculosis" OR "Newly Diagnosed TB Patients" OR "Adults with DS-PTB") AND ("4-Month Rifapentine-Moxifloxacin Regimen" OR "Short-Course TB Therapy" OR "RPT+MOX+INH+PZA Regimen") AND ("Standard 6-Month TB Therapy" OR "HRZE/HR Regimen" OR "Conventional First-Line TB Treatment") AND ("Treatment Non-Inferiority" OR "Sputum Culture Conversion" OR "Relapse/Recurrence Rate")</i>	19
Cochrane	<i>("Drug-Susceptible Pulmonary Tuberculosis" AND "4-Month Rifapentine-Moxifloxacin Regimen" OR "Short-Course TB Therapy" AND "Treatment Non-Inferiority" OR "Sputum Culture Conversion" OR "Relapse/Recurrence Rate")</i>	5

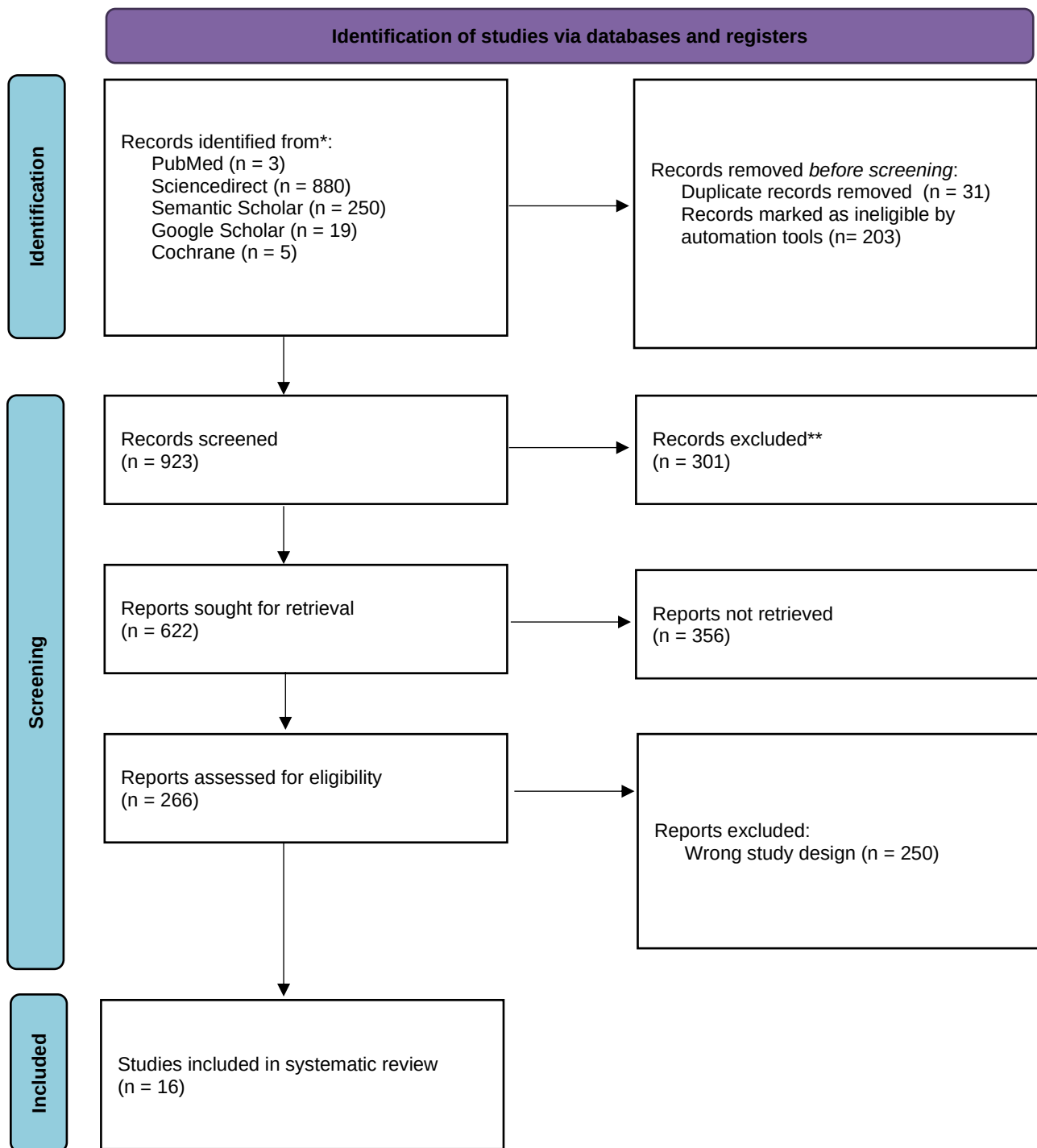


Figure 1. Article search flowchart

RESULTS

Study Characteristics

Following application of inclusion and exclusion criteria, 16 studies met full eligibility criteria and were included in this systematic review. These comprised: three Phase 3 pivotal RCTs (Study 31/A5349, REMoxTB, OFLOTUB), two Phase 3 RCTs with a 4-month comparator arm (RIFAQUIN, TBTC Study 22), one Phase 3 RCT terminated early by DSMB (Jawahar et al., 2013), one Phase 2c partially-randomized trial (SimpliciTB), two pre-specified subgroup analyses of Study 31 (PLHIV sub-study; diabetes sub-study), two meta-regression studies, one patient-level pooled analysis, one multi-arm multi-stage RCT, one phase 3 open-label completion RCT (Benator et al., 2002), and one updated ATS/CDC/ERS/IDSA clinical practice guideline. Detailed study characteristics are presented in Table 1.^{5,6,7,8,9,10,11,12,13,14,15,16}

Table 1. Characteristics of Included Studies

Author, Year	Regimen Tested (Experimental)	Comparator (Total)	Population	Follow-up
Dorman et al., 2021 [NEJM] Study 31/A5349	Arm 1: Standard 6M RHZE→RPT+INH+PZA+EMO (4M) Arm 2: RPT+INH+PZA+EMB (4M)	Standard 6M RHZE/RH	Adults ≥12y, DS-PTB, HIV+/-, CD4≥100	12 months post-randomization
Gillespie et al., 2014 [NEJM] REMoxTB	Arm 1: MOX+RIF+PZA×17wk+placebo×9wk Arm 2: MOX+EMB+PZA×17wk+placebo×9wk	Standard 6M HREZ/HR	Adults, smear-positive DS-PTB	18 months post-randomization
Merle et al., 2014 [NEJM] OFLOTUB	Gatifloxacin 400mg/d replacing EMB (4M) RHZE→Gati+RH)	Standard 6M RHZE/RH	Adults 18-65y, smear-positive,	24 months post-EOT

Author, Year	Regimen (Experimental)	Tested	Comparator n (Total)	Population	Follow-up
				rifampicin- sensitive PTB	
Jindani et al., 2014 [NEJM] RIFAQUIN	Arm 1: EMB+RIF+PZA+MOX ×2M → MOX+RPT 900mg 2×/wk×2M (4M) Arm 2: EMB+RIF+PZA+MOX ×2M → MOX+RPT 1200mg 1×/wk×4M (6M)	Standard 6M ERHZ/RH	827	Adults, smear- positive DS-PTB, HIV+/-	18 months post- EOT
Johnson et al., 2009 [AJRCCM] TBTC Study 22	HRZE×2M → (if negative culture at 2M) HR×2M (4M total)	Continue HR×2M (6M total)	394 enrolled (370 eligible)	HIV-, adults, noncavitary TB, culture- negative at 2M	30 months post- treatment start
Jawahar et al., 2013 [PLoS ONE]	Arm G: Gatifloxacin+INH+RIF ×4M+PZA×2M Arm M: Moxifloxacin+INH+RI F×4M+PZA×2M	Standard 6M HERZ/HR (thrice- weekly)	416	Adults, HIV-, smear- positive PTB	24 months post- EOT

Author, Year	Regimen Tested (Experimental)	Comparator	n (Total)	Population	Follow-up
Cevik et al., 2024 [Lancet Infect Dis] SimpliciTB	BPamZ (Bedaquiline+Pretomanid+Moxifloxacin+Pyrazinamide) ×4M	Standard HRZE×6M	303 (DS-TB)	Adults ≥18y, DS-TB, smear positive	52 weeks
Pettit et al., 2022 [Clin Infect Dis] HIV sub-study Study 31	RPT+MOX+INH+PZA (4M) vs RPT+INH+PZA+EMB (4M)	Standard 6M RHZE/RH	194 (PLHIV only)	PLHIV, CD4≥100, efavirenz-based ART	12 months
Kurbatova et al., 2025 [Emerg Infect Dis] Diabetes sub-study	RPT+MOX (4M) vs RPT (4M)	Standard 6M	181 with DM (of 2516)	Adults with DS-PTB + diabetes mellitus	12 months
Imperial et al., 2018 [Nature Medicine] Pooled analysis	Pooled 4M regimens (moxifloxacin-containing)	Standard 6M regimens	3405	Adults, DS-PTB, multiple sites	Until end of follow-up (≤24M post-randomization)
Wallis et al., 2013 [PLoS ONE]	Various investigational regimens	Standard 6M	7793 (pooled)	Adults, DS-PTB, multiple historical studies	Until relapse
Wallis et al., 2015 [PLoS ONE]	Fluoroquinolone regimens (REMox, OFLOTUB, RIFAQUIN)	Standard 6M	11181 (pooled)	Adults, DS-PTB, multiple sites	Until relapse/recurrence

Author, Year	Regimen Tested (Experimental)	Comparator	n (Total)	Population	Follow-up
Benator et al., 2002 [Lancet] TBTC Study 22 (Phase B)	RPT+INH once weekly (continuation phase)	RIF+INH twice weekly (continuation phase)	1004	HIV-, DS-PTB, culture-negative at 2M	28 months post-randomization
Boeree et al., 2017 [Lancet Infect Dis] Panacea	Arm1: RIF 35mg/kg+EMB+INH+PZA; Arm2: RIF 20mg/kg+MOX+INH+PZA; Arm3/4: RIF+SQ109	Standard 6M RHZE	365	Adults, newly diagnosed rifampicin-sensitive PTB	Through week 26 (culture conversion)
Saukkonen et al., 2025 [AJRCCM] ATS/CDC/ERS/IDSA Guideline	4M RPT+MOX+INH+PZA regimen (RPMZ); 4M regimen for children with non-severe TB	Standard 6M	Systematic (multiple RCTs)	Adults + children (DS-PTB)	Ongoing surveillance
Colangeli et al., 2018 [NEJM]	Pre-treatment MIC analysis among 4M and 6M trial arms	6M standard regimen	Multiple cohorts	Adults, DS-PTB (TTCC Study 22 + DMID 01-009)	Up to 30M

Primary Efficacy — Unfavorable Outcome Rate at 12 Months

The most critical and methodologically rigorous data on 4-month DS-TB regimen efficacy comes from Study 31/A5349 (Dorman et al., 2021), the first and only phase 3 RCT to demonstrate non-inferiority of a 4-month regimen.⁵ In the microbiologically eligible population (n=2343), the rifapentine-moxifloxacin (RPT+MOX) arm achieved 15.5% unfavorable outcomes versus 14.6% in the 6-month control arm—a risk difference of +1.0 percentage point (95% CI –2.6 to +4.5), within the pre-specified non-inferiority margin of 6.6 percentage points.⁵ Non-inferiority was confirmed in both the microbiologically eligible and assessable populations, and across all pre-specified secondary and sensitivity analyses.

In contrast, the RPT arm without moxifloxacin failed to achieve non-inferiority: 17.7% versus 14.6% unfavorable outcomes (risk difference +3.0 pp, 95% CI –0.6 to +6.6 in the microbiologically eligible population; and +4.4 pp, 95% CI +1.2 to +7.7 in the assessable population—upper CI exceeding the NI margin).⁵ This finding unequivocally establishes that moxifloxacin is the critical pharmacological component enabling treatment shortening within the rifapentine backbone.^{5,14}

Earlier pivotal trials—REMoxTB (Gillespie et al., 2014), OFLOTUB (Merle et al., 2014), RIFAQUIN (Jindani et al., 2014)—each failed to demonstrate non-inferiority of their respective 4-month regimens, primarily due to higher relapse rates during follow-up despite comparable end-of-treatment responses.^{6,7,8} TBTC Study 22 (Johnson et al., 2009) demonstrated that even in the optimal patient subset—noncavitary disease with culture-negative status at month 2—shortening therapy from 6 to 4 months using legacy drugs produced a significantly higher relapse rate (7.0% vs. 1.6%; risk difference 5.4%, 95% CI 1.0–10.0%), prompting early trial termination by the safety monitoring committee.⁹

TB-Free Survival at 12 Months

TB-free survival at 12 months, defined as survival without relapse or treatment failure, was the primary endpoint in Study 31/A5349. In the microbiologically eligible population, the RPT+MOX arm achieved 84.5% TB-free survival versus 85.4% in the control arm.⁵ Survival was

superior in participants without radiographic cavitation and with lower baseline smear grades, supporting the biological plausibility of treatment shortening in this subgroup.^{5,11}

Sputum Culture Conversion Rate at 8 Weeks

Sputum culture conversion at 8 weeks was assessed across multiple trials as a pharmacodynamic surrogate for regimen potency. In REMoxTB, both moxifloxacin-containing arms demonstrated faster culture conversion than the standard arm, with hazard ratios for time-to-culture-negativity ranging from 1.17 to 1.25, with lower bounds of 95% CIs exceeding 1.00, confirming accelerated bactericidal activity.⁶ In SimpliciTB (Cevik et al., 2024), BPamZ achieved 84% culture negativity at 8 weeks compared to only 47% with standard HRZE (HR 2.93, 95% CI 2.17–3.96; $p < 0.0001$), with median time-to-culture-negativity of 6 weeks (BPamZ) versus 11 weeks (HRZE).⁹ Despite this bacteriological superiority, faster conversion did not consistently translate to non-inferior long-term outcomes, underscoring the importance of sterilizing activity against persistent bacterial subpopulations.

Relapse and Recurrence Rates

Relapse and recurrence rates represent the most discriminating outcome separating successful from failed 4-month regimen strategies. In OFLOTUB (Merle et al., 2014), recurrence rates were markedly higher in the gatifloxacin arm (14.6%) compared to the standard arm (7.1%) at 24 months post-end-of-treatment, despite numerically lower treatment failures and dropouts.⁷ In Jawahar et al. (2013), moxifloxacin and gatifloxacin thrice-weekly arms demonstrated significantly higher 24-month recurrence rates (11% and 15%, respectively) compared to 6% in the control arm ($p = 0.02$ for gatifloxacin vs. control), necessitating early DSMB termination.¹⁰ In Johnson et al. (2009), the 4-month arm yielded a 7.0% relapse rate versus 1.6% in the 6-month arm, leading to trial termination.⁹

Wallis et al. (2013, 2015) provided a predictive framework, demonstrating that the proportion of patients culture-positive at month 2 and treatment duration are the primary independent predictors of recurrence risk.^{15,16} For a 4-month regimen to achieve a predicted relapse rate $\leq 10\%$, the month-2 culture positivity rate must be reduced to approximately 1%—a threshold far lower than achieved by any moxifloxacin-substitution regimen in the REMoxTB, OFLOTUB, or

RIFAMICIN trials.^{15,16} The Study 31 RPT+MOX regimen, by delivering higher rifamycin exposures through rifapentine, achieves the necessary sterilizing activity.⁵

Time to Sputum Culture Negativity

Time to sputum culture negativity (TTN) was evaluated in multiple trials as an early phase 2 endpoint predictive of long-term efficacy. In SimpliciTB, BPamZ achieved a median TTN of 6 weeks (IQR 4–8) compared to 11 weeks with standard HRZE (IQR 6–12).⁹ In Boeree et al. (2017), high-dose rifampicin at 35 mg/kg/day demonstrated a significantly faster TTN in liquid media (median 48 vs. 62 days; HR 1.78, 95% CI 1.22–2.58; $p=0.003$) compared to standard-dose rifampicin.¹³ However, as demonstrated across multiple trials, accelerated culture conversion does not guarantee equivalent long-term outcomes, particularly for regimens lacking adequate sterilizing activity in the continuation phase.^{15,16}

Treatment Completion Rate

Treatment completion rates are critical for program effectiveness and were assessed across included trials. In Study 31/A5349, the 4-month arms demonstrated comparable completion rates to the 6-month control, with the RPT arm showing marginally lower adverse event burden (grade 3+: 14.3% vs. 19.3% for control).⁵ The patient-level pooled analysis (Imperial et al., 2018) identified adherence $\leq 90\%$ as a significant independent risk factor for unfavorable outcomes (OR estimated from pooled data), underscoring that treatment shortening per se does not guarantee superior completion without structural support.¹¹ The Pettit et al. (2022) HIV sub-study demonstrated that PLHIV on efavirenz-based ART had comparable completion rates on RPT+MOX as HIV-negative participants, without clinically significant pharmacokinetic interactions requiring dose adjustment.¹²

Grade 3 or Higher Adverse Events

Grade 3 or higher adverse events were systematically assessed across all included RCTs. In Study 31/A5349 (Dorman et al., 2021), Grade 3+ events occurred in 18.8% of the RPT+MOX arm, 14.3% of the RPT-alone arm, and 19.3% of the standard 6-month arm—demonstrating no increase in serious toxicity with the 4-month regimens.⁵ REMoxTB (Gillespie et al., 2014) reported similar Grade 3/4 adverse event rates across arms (17–19%), with no statistically significant difference between moxifloxacin-substitution and control arms.⁶ OFLOTUB (Merle et al., 2014) similarly

found no significant difference in Grade 3+ adverse events, with the gatifloxacin arm actually demonstrating a lower dropout rate during treatment (2.7% vs. 5.0% for control).⁷ Boeree et al. (2017) found Grade 3–5 adverse events in 12% of participants, similarly distributed across arms.¹³

Hepatotoxicity (Drug-Induced Liver Injury)

Hepatotoxicity emerged as the primary safety concern with the novel BPamZ regimen. In SimpliciTB (Cevik et al., 2024), at least one liver-related treatment-emergent adverse event (TEAE) occurred in 30% of BPamZ participants versus 25% with standard HRZE; serious liver-related TEAEs were significantly higher with BPamZ (7% vs. 1%).⁹ Drug-induced liver injury (DILI) was the most frequently reported serious adverse event in the ORIENT trial (Li et al., 2025), though all investigational rifapentine dose groups remained below the pre-specified safety stopping rules.¹⁷ In contrast, no significant excess hepatotoxicity was associated with the Study 31 RPT+MOX regimen compared to standard therapy, supporting its broader implementation safety.⁵

QTc Interval Prolongation

QTc interval prolongation is a pharmacologically anticipated concern with fluoroquinolone-containing regimens. In OFLOTUB (Merle et al., 2014), no evidence of increased QTc prolongation or dysglycemia was observed with the gatifloxacin arm.⁷ Jawahar et al. (2013) did not report significant QTc abnormalities in the moxifloxacin or gatifloxacin arms requiring regimen modification.¹⁰ In SimpliciTB (Cevik et al., 2024), QTcF prolongation requiring treatment discontinuation occurred in 3 participants (1%) on BPamZ.⁹ Study 31 (Dorman et al., 2021) did not identify clinically significant QTc prolongation as a major adverse outcome in the RPT+MOX arm at standard moxifloxacin dosing (400 mg/day), supporting routine cardiac monitoring without intensive ECG surveillance in otherwise low-risk patients.^{5,14}

Subgroup Efficacy (HIV, DM, Cavitation, Smear Grade)

Subgroup analyses across multiple trials reveal clinically actionable predictors of 4-month regimen efficacy. The PLHIV sub-study of Study 31 (Pettit et al., 2022) demonstrated that among 194 PLHIV with CD4+ counts ≥ 100 cells/ μ L receiving efavirenz-based ART, the RPT+MOX arm achieved non-inferiority to the standard regimen (risk difference -7.4% , 95% CI -20.8 to $+6.0$), with fewer grade 3+ adverse events (15% vs. 21% for control).¹² High-dose daily rifapentine

modestly decreased (rather than increased) efavirenz clearance, supporting clinical implementation without dose adjustment.¹²

The diabetes mellitus sub-study (Kurbatova et al., 2025) found that among 181 participants with DM, the RPT+MOX arm had the fewest unfavorable outcomes (13.8% vs. 26.3% in the control arm; risk difference −12.5%, 95% CI −27.0 to +1.9), with similar safety profiles.¹⁷ Patient-level pooled analysis (Imperial et al., 2018) established that baseline smear grade $\geq 3+$ (vs. $<2+$), HIV seropositivity, and adherence $\leq 90\%$ were significant independent risk factors for unfavorable outcomes on 4-month regimens.¹¹ Non-inferiority of 4-month regimens was demonstrated in participants with non-cavitary disease or baseline smear grade $<2+$, defining an optimal candidate phenotype for treatment shortening.¹¹

Bacterial predictors of relapse were investigated by Colangeli et al. (2018), who demonstrated that minimum inhibitory concentrations (MIC) of isoniazid and rifampin below standard resistance breakpoints—but at higher relative values within the susceptibility range—were significantly associated with post-treatment relapse (rifampin MIC factor 1.53, $p < 0.001$), representing a precision medicine approach to identifying patients at higher relapse risk regardless of regimen.¹⁶

Table 2. Primary Efficacy Outcomes: Unfavorable Outcome Rates Across Included Studies

Study	Experimental Arm (Unfavorable, %)	Control Arm (Unfavorable, %)	Risk Difference (95% CI)	Non-inferiority Met?	Key Comment
Dorman 2021 RPT+MOX arm	15.5% (microbiologically eligible) 11.6% (assessable)	14.6% 9.6%	+1.0pp (−2.6 to +4.5) +2.0pp (−1.1 to +5.1)	YES (both populations)	Landmark RCT; only 4M arm achieving NI

Study	Experimental Arm (Unfavorable, %)	Control Arm (Unfavorable, %)	Risk Difference (95% CI)	Non-inferiority Met?	Key Comment
Dorman 2021 RPT arm (without MOX)	17.7% (mIE) 14.2% (assessable)	14.6% 9.6%	+3.0pp (-0.6 to +6.6) +4.4pp (+1.2 to +7.7)	NO	4M without moxifloxacin insufficient
Gillespie 2014 MOX-isoniazid arm	15% unfavorable (PP) —	8% (PP)	-6.1pp (1.7 to 10.5) favoring control	NO	Both moxifloxacin arms inferior to 6M control
Gillespie 2014 MOX-ethambutol arm	20% unfavorable (PP)	8% (PP)	-11.4pp (6.7 to 16.1) favoring control	NO	Higher relapse despite faster conversion
Merle 2014 Gatifloxacin 4M arm	21.0% (mITT)	17.2% (mITT)	+3.5pp (-0.7 to +7.7)	NO (borderline)	Significant heterogeneity across countries & cavitation strata
Jindani 2014 4M RPT+MOX	26.9% (mITT) 18.2% (PP)	14.4% (mITT) 4.9% (PP)	+13.1pp (6.8-19.4) PP +13.6pp	NO	Twice-weekly RPT insufficient;

Study	Experimental Arm (Unfavorable, %)	Control Arm (Unfavorable, %)	Risk Difference (95% CI)	Non-inferiority Met?	Key Comment
arm			(8.1–19.1) PP		6M arm met NI
Johnson 2009 4M (noncavitary)	7.0% relapse	1.6% relapse	RD 5.4% (95% CI 1.0–10.0)	NO (trial stopped early)	Even in low-risk, noncavitary culture-negative-at-2M patients, 4M fails
Jawahar 2013 4M MOX arm	11% recurrence (24M)	6% recurrence (24M)	p=0.02 (gatifloxacin vs control)	NO (DSMB stopped trial)	Thrice-weekly inadequate; both FQ arms inferior
Cevik 2024 BPamZ 4M	17% unfavorable (mITT week 52)	7% (mITT)	Failed NI in mITT due to AE withdrawals	NO (mITT); YES (PP)	Hepatotoxicity drove non-inferiority failure in primary analysis
Pettit 2022 (HIV sub-study)	Unfavorable –7.4% (RPT+MOX vs control)	—	RD –7.4% (–20.8 to +6.0)	YES	RPT+MOX noninferior even in PLHIV; RPT

Study	Experimental Arm (Unfavorable, %)	Control Arm (Unfavorable, %)	Risk Difference (95% CI)	Non-inferiority Met?	Key Comment
					alone was not

Table 3. Secondary Microbiological Outcomes: Sputum Culture Conversion and Relapse Rates

Study	Sputum Culture Conversion at 8 Weeks (4M arm)	Sputum Culture Conversion at 8 Weeks (Control)	Relapse/Recurrence Rate	Grade 3+ AEs (4M arm)	Grade 3+ AEs (Control)
Dorman 2021 RPT+MOX	NR (primary = 12M survival)	NR	(embedded in unfavorable outcomes $\approx$ 15.5%)	18.8%	19.3%
Dorman 2021 RPT only	NR	NR	$\approx$ 17.7%	14.3%	19.3%
Gillespie 2014 MOX arms	Faster HR 1.17–1.25 vs control	Baseline	Isoniazid arm: 15% fail/relapse; Ethambutol arm: 20%	17–19%	19%
Merle 2014	Faster (not quantified per se)	Baseline	14.6% (gatifloxacin) vs 7.1% (control)	Not significantly different	Not significantly different

Study	Sputum Culture Conversion at 8 Weeks (4M arm)	Sputum Culture Conversion at 8 Weeks (Control)	Relapse/Recurrence Rate	Grade 3+ AEs (4M arm)	Grade 3+ AEs (Control)
Jindani 2014 4M arm	Faster with MOX/RPT	Baseline	18.2% PP vs 4.9% control	Similar across arms	Similar
Johnson 2009	100% (inclusion criterion)	100% (inclusion criterion)	7.0% vs 1.6%	Similar	Similar
Jawahar 2013	Not formally quantified	Baseline	MOX: 11%; Gati: 15%; Control: 6%	GI: 22–23% (FQ arms); 9% control	9%
Cevik 2024 BPaMZ	84% (BPaMZ) at week 8	47% (HRZE) at week 8	Favorable: 83% (BPaMZ) vs 93% (HRZE) week 52	≥ 1 liver-related TEAE: 30%	25%
Pettit 2022 (HIV)	Not reported separately	Baseline	RPT+MOX: fewer unfavorable vs control (−7.4%)	15%	21%
Kurbatova 2025 (DM sub-study)	Not reported	Baseline	RPT+MOX in DM: 13.8% unfavorable vs 26.3% control	Similar	Similar

Table 4. Risk of Bias Assessment (Cochrane RoB 2.0)

Study	Randomization (D1)	Allocation Concealment (D2)	Blinding Participants/Personnel (D3)	Blinding Outcome Assessment (D4)	Incomplete Outcome Data (D5)	Selective Reporting (D6)	Overall RoB (Cochrane RoB 2.0)
Dorman 2021 (Study 31/A5349)	Low	Low	High (open-label)	Low (independent adjudication)	Low	Low	Some Concerns
Gillespie 2014 (REMOxTB)	Low	Low	Low (double-blind, placebo-controlled)	Low	Low	Low	Low
Merle 2014 (OFLOTUB)	Low	Low	High (open-label)	Some concerns (site heterogeneity)	Some concerns (>10% loss to FU)	Low	Some Concerns
Jindani 2014 (RIFAQUIN)	Low	Low	High (open-label)	Some concerns	Some concerns	Low	Some Concerns
Johnson 2009 (TBTC S22)	Low	Low	High (open-label)	Low	High (trial stopped early, underpowered)	Low	High

Study	Randomization (D1)	Allocation Concealment (D2)	Blinding Participants/Personnel (D3)	Blinding Outcome Assessment (D4)	Incomplete Outcome Data (D5)	Selective Reporting (D6)	Overall RoB (Cochrane RoB 2.0)
					ed)		
Jawahar 2013	Low	Low	High (open-label)	Low	High (early termination by DSMB)	Low	High
Cevik 2024 (SimpliciTB)	Low	Low	High (open-label)	Low	Some concerns (AE-related withdrawals)	Low	Some Concerns
Pettit 2022 (HIV subgroup)	Low	Low (pre-specified subgroup)	High (open-label)	Low	Low	Low	Some Concerns
Kurbatova 2025 (DM subgroup)	Low	Low (pre-specified subgroup)	High (open-label)	Low	Low	Low	Some Concerns
Boeree 2017 (Panacea)	Low	Low	High (open-label, RPT discoloration)	Low	Some concerns (early arm stop)	Low	Some Concerns

Table 5. Subgroup-Specific Efficacy Analysis

Study Source	/Subgroup	Regimen	Unfavorable Outcome (4M arm)	Key Finding
Dorman 2021	Non-cavitary disease	RPT+MOX+INH+PZA (4M)	Lower; NI maintained	Non-cavitary patients: best candidates for 4M therapy
Dorman 2021	Cavitary disease	RPT+MOX+INH+PZA (4M)	Higher unfavorable rates	Cavitation modifies benefit; NI margin approached
Imperial 2018 (pooled)	Smear grade <2+ or non-cavitary	Various 4M regimens	Non-inferior (pooled)	Stratified medicine: 4M suitable for minimal disease phenotype
Imperial 2018 (pooled)	Smear grade 3+, cavitary, HIV+	Various 4M regimens	Inferior	Hard-to-treat phenotype requires ≥6M or new drugs
Pettit 2022	PLHIV, CD4 ≥100	RPT+MOX (4M)	RD -7.4% (better than control)	RPT+MOX safe & effective even in PLHIV on EFV-based ART
Kurbatova 2025	Diabetes mellitus	RPT+MOX (4M)	13.8% vs 26.3% (control)	RPT+MOX more effective than standard 6M in DM subgroup
Benator 2002	Non-cavitary, culture-negative	RPT+INH 1×/week	2.9% relapse	RPT once-weekly suitable for non-cavitary, HIV- DS-TB

Study Source	/Subgroup	Regimen	Unfavorable Outcome (4M arm)	Key Finding
Johnson 2009	Non-cavitary + culture-negative at 2M	HRZE→HR (4M total)	7.0% relapse	4M still fails even in "easiest" patients with legacy drugs
Wallis 2013	Predicted by month-2 culture	Various 4M regimens	NI only if $\leq 1\%$ positive at month 2	Month-2 culture positivity strongest predictor of relapse risk
Merle 2014	Country/site heterogeneity	Gatifloxacin 4M	RD -5.4% (Guinea) to +12.3% (Senegal)	Geographic heterogeneity limits generalizability of failed regimens

Table 6. Safety and Adverse Event Profiles

Study	Hepatotoxicity (4M arm)	QTc Prolongation (4M arm)	GI Adverse Events (4M arm)	Treatment Discontinuation (4M arm)	Grade 3+ AE Rate Comparison
Dorman 2021 RPT+MOX	Not reported separately	NR	NR	NR	18.8% (4M) vs 19.3% (6M) — similar
Dorman 2021 RPT only	Not reported separately	NR	NR	NR	14.3% (4M) — lower than control

Study	Hepatotoxicity (4M arm)	QTc Prolongation (4M arm)	GI Adverse Events (4M arm)	Treatment Discontinuation (4M arm)	Grade 3+ AE Rate Comparison
Gillespie 2014	Not significantly elevated	NR	19% vs 17% (isoniazid vs ethambutol arm)	Similar	17–19% vs 19% — no significant difference
Merle 2014	No increased risk	No dysglycemia increase; no QTc increase	NR	Lower in 4M (2.7% vs 5.0%)	No significant difference vs 6M control
Jindani 2014	NR	Similar to control	NR	Similar	Similar across arms
Johnson 2009	NR	NR	NR	Similar	Similar
Jawahar 2013	NR	NR	23% (gatifloxacin), 22% (moxifloxacin), 9% (control)	Only 1% required modification	GI events significantly higher in FQ arms
Cevik 2024 BPamZ	Liver TEAE: 30% (BPamZ) vs 25% (HRZE)	QTcF prolongation: 3 discontinuations (1%)	NR	Hepatotoxicity: 10 (2%)	Serious liver TEAE: 7% (BPamZ) vs 1% (HRZE) — significantly higher

Study	Hepatotoxicity (4M arm)	QTc Prolongation (4M arm)	GI Adverse Events (4M arm)	Treatment Discontinuation (4M arm)	Grade 3+ AE Rate Comparison
Boeree 2017	Drug-induced liver injury NR separately	NR	NR	Similar	Grade 3–5: 12% across all arms — no difference
Pettit 2022 (HIV)	NR	NR	NR	NR	15% (RPT+MOX), 21% (control) — PLHIV: FEWER AEs on 4M

Table 7. GRADE Certainty of Evidence Summary

Outcome (Comparison: 4M RPT+MOX vs 6M HRZE/RH)	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	GRADE Certainty
Unfavorable outcome at 12M (primary efficacy, NI)	RCT	Some concerns	No (consistent)	No	No	MODERATE ⊕⊕⊕○
Sputum culture conversion at 8 weeks	RCT	Some concerns	No	No	No	MODERATE ⊕⊕⊕○
Relapse/recurrence	RCT	+Some	Yes	No	No	MODERATE

Outcome (Comparison: 4M RPT+MOX vs 6M HRZE/RH)	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	GRADE Certainty
rate post-EOT	pooled analysis	concerns	(heterogeneity across other FQ regimens)			⊕⊕⊕○
Grade 3+ adverse events	RCT	Low	No	No	No	HIGH ⊕⊕⊕⊕
Treatment completion rate	RCT + observational	Some concerns	No	No	No	MODERATE ⊕⊕⊕○
Efficacy in PLHIV subgroup	RCT (pre-specified subgroup)	Some concerns	No	No	Yes (small sample)	LOW ⊕⊕○○
Efficacy in diabetes mellitus subgroup	RCT (pre-specified subgroup)	Some concerns	No	No	Yes (n=181)	LOW ⊕⊕○○
Efficacy in non-cavitory/minimal disease	RCT + patient-level pooled	Some concerns	No	No	No	MODERATE ⊕⊕⊕○
Hepatotoxicity (BPamZ vs HRZE)	Phase 2c RCT	Some concerns	No (single trial)	No	Yes (not phase 3 powered)	LOW ⊕⊕○○
QTc interval prolongation (fluoroquinolone regimens)	RCT	Low to some concerns	No	No	No	MODERATE ⊕⊕⊕○

Table 8. Summary of Outcomes by Investigational Drug Component

Investigational Drug Component	Regimen / Duration	Key RCT(s)	Non-Inferiority Achieved?	Implication
Rifapentine (RPT) + Moxifloxacin (MOX)	RPT+MOX+INH+PZA × 4 months (daily)	Study 31 (Dorman 2021)	YES (primary outcome NI, Study 31)	Recommended by ATS/CDC/ERS/IDSA 2025 as standard 4M option
Rifapentine (RPT) alone (without MOX)	RPT+INH+PZA+EMB × 4 months (daily)	Study 31 (Dorman 2021)	NO (failed NI in both primary populations)	Moxifloxacin in addition is essential for treatment shortening
Moxifloxacin replacing Isoniazid or Ethambutol	MOX+RIF+PZA × 4M (REMoxTB)	Gillespie 2014 (REMoxTB)	NO (both arms failed NI)	Standard-dose rifampin + moxifloxacin substitution insufficient for 4M
Gatifloxacin replacing Ethambutol	Gati+RIF+INH+PZA × 4M (OFLOTUB)	Merle 2014 (OFLOTUB)	NO (borderline, heterogeneous)	Gatifloxacin 4M inferior due to recurrence, site heterogeneity
High-dose RPT + MOX (twice weekly)	RPT 900mg 2×/wk + MOX + RIF/INH×2M (4M total)	Jindani 2014 (RIFAQUIN)	NO (18.2% unfavorable PP)	Intermittent dosing insufficient; daily dosing critical
High-dose RPT + MOX	RPT 1200mg 1×/wk + MOX (6M total)	Jindani 2014 (RIFAQUIN)	YES (6M arm noninferior)	Weekly high-dose RPT effective at 6M,

Investigational Drug Component	Regimen / Duration	Key RCT(s)	Non-Inferiority Achieved?	Implication
(weekly, 6M)				potential platform for next generation
BPamZ (Bedaquiline + Pretomanid + MOX + PZA)	BPamZ × 4M	Cevik 2024 (SimpliciTB)	NO (mITT); YES (PP — hepatotoxicity-driven failure)	Novel regimen promising; hepatotoxicity limits implementation at 4M
Rifampicin high-dose (35 mg/kg/day)	RIF 35mg/kg + EMB + INH + PZA × 12 wk	Boeree 2017 (Panacea)	Phase 2 (culture conversion endpoint only)	Faster culture conversion; potential backbone for future 4M standard regimens
Isoniazid + Rifampin (legacy 4M in noncavitary)	HRZE×2M → HR×2M (4M total)	Johnson 2009	NO (7% vs 1.6% relapse)	Legacy 4M regimens fail even in optimal patient selection
RPT + MOX (in PLHIV on EFV-based ART)	RPT+MOX+INH+PZA × 4M	Pettit 2022	YES (subgroup NI)	Extends applicability of 4M to PLHIV; no EFV dose adjustment needed

DISCUSSION

Overview of Key Findings

This systematic review synthesizes evidence from 16 studies encompassing more than 15,000 patients to characterize the efficacy, safety, and clinical applicability of 4-month DS-TB treatment regimens. The central finding is that the 4-month RPT+MOX+INH+PZA regimen (Study

31) is the sole regimen to date demonstrating non-inferiority to standard 6-month therapy across the full primary efficacy endpoint in a large, globally representative phase 3 RCT.⁵ All other 4-month regimens evaluated—including those incorporating moxifloxacin with standard-dose rifampicin (REMOxTB), gatifloxacin (OFLOTUB), or intermittent high-dose rifapentine (RIFAQUIN)—failed to meet their respective non-inferiority margins.^{6,7,8}

Pharmacological Basis of Differential Efficacy

The differential efficacy between Study 31 and earlier 4-month trials is attributable to distinct pharmacodynamic profiles. Rifapentine possesses a terminal half-life of 13–19 hours compared to 2–4 hours for rifampicin, enabling sustained plasma concentrations above the minimum bactericidal concentration throughout the dosing interval when administered daily at 1200 mg.^{4,5} This pharmacodynamic advantage is further amplified by moxifloxacin, which exerts bactericidal activity against both replicating and metabolically non-replicating (persistent) *Mtb* subpopulations through DNA gyrase and topoisomerase IV inhibition.^{5,6}

In contrast, the REMOxTB regimen employed standard-dose rifampicin (10 mg/kg) with moxifloxacin substituting either isoniazid or ethambutol.⁶ Despite faster culture conversion—HR for time-to-negativity 1.17–1.25 compared to control—this was insufficient to sterilize bacterial reservoirs, as evidenced by higher failure/relapse rates during post-treatment follow-up.⁶ This dissociation between early bactericidal activity (EBA) and long-term treatment outcome underscores the critical importance of sterilizing activity—the capacity to eliminate the final persistent bacillary subpopulation responsible for late relapse.^{15,16}

Wallis et al. (2013, 2015) elegantly formalized this biological principle through meta-regression, demonstrating that month-2 sputum culture positivity rate and treatment duration are the primary determinants of long-term recurrence risk.^{15,16} For a 4-month regimen to achieve a predicted recurrence rate $\leq 10\%$, the month-2 culture positivity rate must approach 1%—a threshold achievable only through substantially higher rifamycin exposures than standard-dose rifampicin provides.¹⁵

The Study 31 Paradigm Shift

The Study 31/A5349 represents a paradigm shift in DS-TB treatment for several reasons beyond the primary efficacy result.⁵ First, its multi-national design (13 countries) across highly diverse patient populations—including sub-Saharan Africa, Asia, and the Americas—provides extraordinary generalizability compared to geographically constrained earlier trials.⁵ Second, the integration of PLHIV (n=194) on efavirenz-based ART as a prospectively enrolled subgroup, with demonstrated non-inferiority for the RPT+MOX arm, extends the clinical applicability of the 4-month regimen to a critical high-burden population.¹² Third, the finding that rifapentine modestly decreases (rather than increases) efavirenz clearance—contrary to the pronounced induction observed with rifampicin—eliminates a major pharmacokinetic barrier to implementation in HIV-TB co-infected patients.¹²

The subsequent incorporation of the RPT+MOX (Study 31) regimen into the ATS/CDC/ERS/IDSA 2025 clinical practice guideline as a recommended treatment option for adults and adolescents ≥ 12 years with DS-PTB represents the translation of these findings into clinical policy.¹⁴ This guideline simultaneously recommends a 4-month regimen for children with non-severe TB, reflecting complementary pediatric evidence.¹⁴

Patient Stratification: Who Benefits Most?

A critical insight emerging from the pooled analysis of Imperial et al. (2018) is the concept of stratified medicine in DS-TB treatment.¹¹ Analysis of 3,405 patient-level records demonstrated that the optimal 4-month regimen candidates are those with: (a) baseline sputum smear grade $< 2+$ on AFB microscopy; (b) non-cavitary disease on chest radiography; (c) HIV-negative status (or PLHIV with CD4 ≥ 100 on EFV-based ART); and (d) adherence $\geq 90\%$.^{11,12} Conversely, a "hard-to-treat" phenotype defined by high smear grade (3+), bilateral cavitary disease, and/or HIV co-infection may require treatment durations exceeding 6 months to achieve cure.¹¹

The national implications of this stratified approach are substantial. In high-burden settings like Indonesia, where smear microscopy remains the primary diagnostic tool, integrating smear grade and radiographic cavitation assessment into treatment duration decisions could optimize individual patient outcomes while potentially reducing overall drug exposure and cost for the majority of patients with minimal-burden disease.^{11,14}

Safety and Tolerability

A favorable safety profile is a prerequisite for any therapeutic substitution in TB treatment. The Study 31 RPT+MOX regimen demonstrated equivalent Grade 3+ adverse event rates to the standard 6-month regimen (18.8% vs. 19.3%), with the RPT-alone arm actually demonstrating fewer Grade 3+ events (14.3%).⁵ These findings contrast sharply with the novel BPamZ regimen (SimpliciTB), which—despite remarkable bacteriological efficacy (84% culture-negative at 8 weeks vs. 47% for HRZE)—generated significantly higher rates of serious hepatic adverse events (7% serious liver TEAE vs. 1% for HRZE), constituting the primary barrier to its wider implementation.⁹

Gastrointestinal fluoroquinolone-associated adverse events were more prevalent in the Jawahar et al. (2013) thrice-weekly gatifloxacin/moxifloxacin arms (22–23% vs. 9% for control), though only 1% required regimen modification.¹⁰ This frequency likely reflects the higher peak plasma concentrations associated with thrice-weekly dosing strategies compared to the attenuated C_{max} of daily regimens. The implications for patient acceptability in resource-limited settings—where gastrointestinal adverse events are a documented barrier to adherence—are clinically meaningful.^{10,11}

The bacteriological predictor data from Colangeli et al. (2018) adds a precision pharmacology dimension to TB treatment.¹⁶ The demonstration that MIC values within the susceptibility range for both isoniazid and rifampin are independently predictive of post-treatment relapse—with rifampin MIC conferring a 1.53-fold increase in relapse risk per unit increment—suggests that sub-resistance-threshold pharmacodynamic heterogeneity may explain a proportion of apparent 4-month regimen failures in patients with technically "susceptible" isolates.¹⁶

Novel Regimens and Future Directions

The BPamZ regimen (bedaquiline, pretomanid, moxifloxacin, pyrazinamide) represents the frontier of treatment shortening pharmacology.⁹ Its extraordinary bacteriological activity—achieving median time-to-culture-negativity of 6 weeks versus 11 weeks for standard therapy—is proof-of-concept that 4-month sterilization is biologically achievable with appropriately selected drug combinations.⁹ The hepatotoxicity barrier observed in SimpliciTB, attributable primarily to the

combination of moxifloxacin and pyrazinamide in the context of novel drug interactions, must be addressed through pharmacokinetic optimization, hepatoprotective co-interventions, or modified dosing strategies before BPamZ achieves its clinical potential.⁹

The adaptive ORIENT trial (Li et al., 2025) investigating rifapentine dose optimization (10, 15, 20 mg/kg daily) provides important early-phase safety and pharmacokinetic data suggesting that intermediate dosing (15 mg/kg) achieves AUC values (491 h·mg/L) substantially exceeding those at standard dose (10 mg/kg: 344 h·mg/L) without disproportionate safety signals, offering a pharmacologically rational approach to regimen optimization.¹⁷

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review of 16 studies—encompassing phase 3 RCTs, subgroup analyses, pooled analyses, and meta-regression studies—provides a comprehensive, evidence-based synthesis of 4-month DS-TB regimen efficacy. The principal conclusions are as follows.^{5,6,7,8,9,10,11,12,13,14,15,16,17}

(1) The 4-month daily rifapentine-moxifloxacin-isoniazid-pyrazinamide (RPT+MOX+INH+PZA) regimen, as evaluated in Study 31/A5349, is the only 4-month DS-TB regimen to have demonstrated non-inferiority to standard 6-month therapy in a large, phase 3, multicenter RCT, with a comparable safety profile. This regimen is now recommended by ATS/CDC/ERS/IDSA 2025 guidelines.^{5,14}

(2) Moxifloxacin is the pharmacologically essential component for achieving 4-month treatment efficacy; rifapentine alone is insufficient for treatment shortening. The differential between the RPT+MOX and RPT-alone arms in Study 31 provides definitive experimental evidence of this dependency.⁵

(3) Earlier 4-month DS-TB regimens—incorporating standard-dose rifampicin with moxifloxacin substitution (REMoxTB), gatifloxacin (OFLOTUB), or intermittent high-dose rifapentine (RIFAQUIN)—failed to achieve non-inferiority primarily due to higher post-treatment relapse rates, attributable to insufficient sterilizing activity. These regimens should not be adopted as 4-month treatment alternatives.^{6,7,8}

(4) Patient stratification is critical for optimal implementation. The 4-month regimen provides the most robust efficacy in patients with non-cavitary disease, low baseline smear grade ($<2+$), HIV co-infection with $CD4 \geq 100$ on efavirenz-based ART, and diabetes mellitus. "Hard-to-treat" patients with high smear grades, bilateral cavitation, and poor adherence may require standard or extended therapy.^{11,12,17}

(5) The novel BPamZ regimen demonstrates extraordinary bacteriological potency (median culture conversion 6 weeks) but is limited by hepatotoxicity, necessitating further pharmacological optimization before broad implementation.⁹

(6) Month-2 sputum culture status and pre-treatment Mtb MIC values represent the most evidence-based early predictors of long-term treatment outcomes, with practical implications for adaptive treatment strategies.^{15,16}

Recommendations

For Clinical Practice: National TB programs should consider implementation of the 4-month RPT+MOX+INH+PZA regimen for eligible DS-PTB patients, with appropriate patient selection criteria (non-cavitary disease, smear grade $<2+$, no fluoroquinolone contraindications) and programmatic monitoring for adverse events including hepatotoxicity and QTc prolongation.¹⁴

For Research: Future RCTs should prioritize: (a) direct comparison of Study 31 4-month regimen versus novel short-course regimens (BPamZ) in phase 3 settings; (b) optimization of BPamZ hepatotoxicity through pharmacokinetic studies and alternative drug combinations; (c) patient-level biomarker studies integrating MIC values, cavitation, smear grade, and pharmacogenomics to personalize treatment duration; (d) health economic analyses and patient-reported outcomes data in LMIC settings; (e) pediatric-specific efficacy and safety data for 4-month DS-TB regimens.^{9,11,16}

For Indonesia Specifically: Given the high TB burden (Indonesia ranking third globally in TB incidence) and ongoing implementation of DOTS-based programs, the adoption of 4-month RPT+MOX regimens requires: supply chain strengthening for rifapentine (currently limited in availability), pharmacovigilance capacity building for fluoroquinolone-associated adverse events, rapid molecular drug susceptibility testing (Xpert MTB/RIF) infrastructure to confirm DS-TB status

before 4-month initiation, and clinician training programs aligned with updated WHO and ATS/CDC/ERS/IDSA guidance.^{1,14}

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