



Drug-Susceptible TB: Standard & Shortened Regimens

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University of Nebraska Medical Center

Mayo TB Clinical Intensive · October 7, 2026

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Disclosure:

- No relevant financial relationships to disclose
- Volunteer faculty / medical consultant, Mayo Clinic Center for Tuberculosis.
- Nebraska DHHS TB medical consultant.

Guideline-supported regimens and a brief discussion of investigational treatment strategies

Learning frame

01

Select a standard or shortened regimen

02

Identify who should not receive 2HPZM/2HPM

03

Adapt duration to disease and response

04

Recognize and respond to key adverse reactions

Learning Objectives

📖 Updates on the Treatment of Drug-Susceptible and Drug-Resistant Tuberculosis: An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline

👤 Jussi J. Saukkonen *, 👤 Raquel Duarte *, 👤 Sonal S. Munsiff *, 👤 Carla A. Winston *, 👤 Manoj J. Mammen , 👤 Ibrahim Abubakar , 👤 Carlos Acuña-Villaorduña , 👤 Pennan M. Barry , 👤 Mayara L. Bastos , Wendy Carr , 👤 Hassan Chami , [Show All...](#)

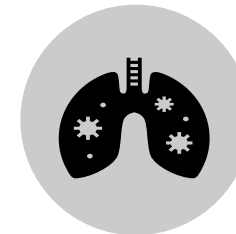
📈 147,811 🗨️ 28

Recall current treatment protocols for managing drug-susceptible TB



Analyze factors that determine length of therapy in drug-susceptible TB

Recall 2 TB patient populations eligible for shortened TB therapy



Recall key clinical and lab monitoring strategies to assess TB treatment success



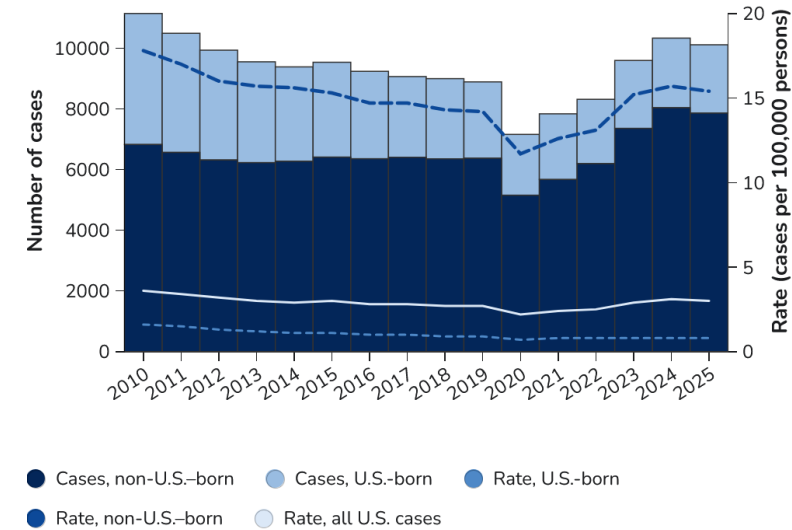
U.S. TB in 2025

10,260

reported TB cases

3.0

cases per 100,000



Cases decreased 1% from 2024

77% occurred among people born outside the U.S.

CDC provisional surveillance. All TB disease, not a drug-susceptible TB subset.

What is Drug-Susceptible TB?

Is *M. Bovis* drug-susceptible TB? (DS-TB)

“Tuberculosis caused by organisms that are not known or *suspected* to be drug resistant”- (ATS/CDC/IDSA Clinical Practice Guidelines: <https://doi.org/10.1093/cid/ciw376>)

“A bacteriologically confirmed or clinically diagnosed case of TB without evidence of infection with strains resistant to rifampicin and isoniazid” (WHO TB Consolidated Guidelines/ TB Sharing platform [Definitions | TB Knowledge Sharing](#))

DEFINITIONS: (WHO)

MDR-TB: form of disease caused by a strain of *M. tuberculosis* complex (MTB) that is resistant to rifampicin and isoniazid.

MDR/RR-TB: *Rifampicin resistant TB is essentially considered MDR TB.*

Pre-XDR TB: caused by *MTB* strains that fulfil the definition of multidrug resistant and rifampicin-resistant TB (MDR/RR-TB) and which are also resistant to any fluoroquinolone*

XDR TB: caused by *MTB* that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (levofloxacin or moxifloxacin) and to at least one other Group A drug (bedaquiline or linezolid)*

Mono-resistant TB disease is caused by TB bacteria that are resistant to one TB treatment drug.

Poly-resistant TB disease is caused by TB bacteria that are resistant to at least two TB drugs (but **not** both isoniazid and rifampin).

* (Or 2nd line injectables)

Appropriate Guidelines

Clinical Infectious Diseases

IDSA GUIDELINE



Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis

Payam Nahid,¹ Susan E. Dorman,² Narges Alipanah,³ Pennan M. Barry,⁴ Jan L. Brozek,⁵ Adithya Cattamanchi,¹ Lelia H. Chaisson,¹ Richard E. Chaisson,² Charles L. Daley,⁶ Malgosia Grzeska,⁷ Julie M. Higashi,⁸ Christine S. Ho,⁹ Philip C. Hopewell,¹ Salman A. Keshavjee,⁹ Christian Lienhardt,⁸ Richard Menzies,¹⁰ Cynthia Merrifield,¹¹ Masahiro Narita,¹² Rick O'Brien,¹³ Charles A. Peloquin,¹⁴ Ann Rahery,¹⁵ Jussi Saukkonen,¹⁶ H. Simon Schaaf,¹⁷ Giovanni Sotgiu,¹⁸ Jeffrey R. Starke,¹⁹ Giovanni Battista Migliori,²⁰ and Andrew Vernon²¹

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The American Thoracic Society, Centers for Disease Control and Prevention, and Infectious Diseases Society of America jointly sponsored the development of this guideline for the treatment of drug-susceptible tuberculosis, which is also endorsed by the European Respiratory Society and the US National Tuberculosis Controllers Association. Representatives from the American Academy of Pediatrics, the Canadian Thoracic Society, the International Union Against Tuberculosis and Lung Disease, and the World Health Organization also participated in the development of the guideline. This guideline provides recommendations on the clinical and public health management of tuberculosis in children and adults in settings in which mycobacterial cultures, molecular and phenotypic drug susceptibility tests, and radiographic studies, among other diagnostic tools, are available on a routine basis. For all recommendations, literature reviews were performed, followed by discussion by an expert committee according to the Grading of Recommendations, Assessment, Development and Evaluation methodology. Given the public health implications of prompt diagnosis and effective management of tuberculosis, empiric multidrug treatment is initiated in almost all situations in which active tuberculosis is suspected. Additional characteristics such as presence of comorbidities, severity of disease, and response to treatment influence management decisions. Specific recommendations on the use of case management strategies (including directly observed therapy), regimen and dosing selection in adults and children (daily vs intermittent), treatment of tuberculosis in the presence of HIV infection (duration of tuberculosis treatment and timing of initiation of antiretroviral therapy), as well as treatment of extrapulmonary disease (central nervous system, pericardial among other sites) are provided. The development of more potent and better-tolerated drug regimens, optimization of drug exposure for the component drugs, optimal management of tuberculosis in special populations, identification of accurate biomarkers of treatment effect, and the assessment of new strategies for implementing regimens in the field remain key priority areas for research. See the full-text online version of the document for detailed discussion of the management of tuberculosis and recommendations for practice.

Keywords. *Mycobacterium tuberculosis*; HIV infections; antitubercular agents; case management; public health.

<https://doi.org/10.1093/cid/ciw376>

Published: 10 August 2016

Check for updates

AMERICAN THORACIC SOCIETY DOCUMENTS

Updates on the Treatment of Drug-Susceptible and Drug-Resistant Tuberculosis

An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline

Jussi J. Saukkonen*, Raquel Duarte*, Sonal S. Munsiff*, Carla A. Winston*, Manoj J. Mammen, Ibrahim Abubakar, Carlos Acuña-Villaorduña, Pennan M. Barry, Mayara L. Bastos, Wendy Carr, Hassan Chami, Lisa L. Chen, Terence Chomba, Charles L. Daley, Anthony J. Garcia-Prats, Kelly Holland, Ioannis Konstantinidis, Marc Lipman, Giovanni Battista Migliori, Farah M. Parvez, Adrienne E. Shapiro, Giovanni Sotgiu, Jeffrey R. Starke, Angela M. Starks, Sanket Thakore, Shu-Hua Wang, Jonathan M. Wortham, and Payam Nahid; on behalf of the American Thoracic Society, U.S. Centers for Disease Control and Prevention, European Respiratory Society, and Infectious Diseases Society of America

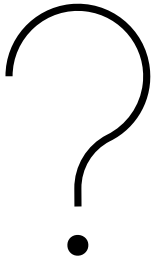
THIS OFFICIAL CLINICAL PRACTICE GUIDELINE WAS APPROVED BY THE AMERICAN THORACIC SOCIETY (ATS) AND THE INFECTIOUS DISEASES SOCIETY OF AMERICA (IDSA) SEPTEMBER 2024, WAS CLEARED BY THE U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC) SEPTEMBER 2024, AND WAS APPROVED BY THE EUROPEAN RESPIRATORY SOCIETY (ERS) OCTOBER 2024

<https://doi.org/10.1164/rccm.2024>

[10-2096ST](https://doi.org/10.1164/rccm.2024)

Published: January 2025

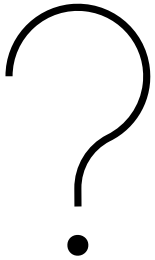
Polling Question



A patient on standard HRZE has baseline cavitation and a positive month-2 sputum smear. Susceptibility and adherence are confirmed. What treatment duration is appropriate?

- A. 4 months
- B. 6 months
- C. 9 months
- D. 6 months but add moxi in continuation phase

Polling Question



A patient on standard HRZE has baseline cavitation and a positive month-2 sputum smear. Susceptibility and adherence are confirmed. What treatment duration is appropriate?

A. 4 months

B. 6 months

C. 9 months

D. 6 months but add moxi to continuation phase

The current regimen choices

Patient / situation	Regimen	Total duration
Most drug-susceptible pulmonary TB	2HRZE / 4HR or 7 HR	6 months/9 months
Eligible age ≥ 12 years, weight ≥ 40 kg	HPZM then HPM	17 weeks
Child with nonsevere TB	2HRZ(E) / 2HR	4 months
Selected culture-negative adult TB	2HRZE / 2HR	4 months

H isoniazid · R rifampin · Z pyrazinamide · E ethambutol · P rifapentine · M moxifloxacin

The standard six-month regimen

Intensive phase	Continuation phase
8 weeks H + R + Z + E (RIPE)	18 weeks H + R

Ethambutol can stop when H and R susceptibility is established

Pyrazinamide in the initial phase enables the six-month course

Nahid et al. Clin Infect Dis 2016.

Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis (Drug-Susceptible)

Intensive Phase	Continuation Phase	Range of Total Doses	Comments
INH, RIF, PZA, EMB 7d/wk for 56 doses (8 wk) or 5d/wk for 40 doses (8 wk)	INH, RIF 7d/wk for 126 doses (18 wk) or 5d/wk for 90 doses (18 wk)	182–130	Preferred regimen for newly diagnosed pulmonary TB.
INH, RIF, PZA, EMB 7d/wk for 56 doses (8 wk) or 5d/wk for 40 doses (8 wk)	INH, RIF 3× weekly for 54 doses (18 wk)	110–94	Alternative when frequent DOT in continuation phase is difficult.
INH, RIF, PZA, EMB 3× weekly for 24 doses (8 wk)	INH, RIF 3× weekly for 54 doses (18 wk)	78	Use with caution in HIV/cavitary disease; missed doses risk relapse/drug resistance.
INH, RIF, PZA, EMB 7d/wk for 14 doses then 2× weekly for 12 doses (8 wk)	INH, RIF 2× weekly for 36 doses (18 wk)	62	Avoid in HIV or smear+/cavitary disease; missed doses equivalent to once weekly, which is inferior.

Effectiveness



ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clin Inf Dis 2016;63(7):e147–95

Recommended Drug Regimens – Updates 2025

Table 1. Recommended Drug Regimens

Q1: Treatment of Isoniazid-Susceptible, Rifampin-Susceptible TB in Adults		
Recommended 4-mo Rifapentine-Moxifloxacin-Containing Regimen*		
Isoniazid [†]		300 mg daily for 17 wk
Rifapentine		1,200 mg daily for 17 wk
Pyrazinamide	Weight-based dosing daily for 8 wk:	40 to <55 kg: 1,000 mg; ≥55–75 kg: 1,500 mg >75 kg: 2,000 mg
Moxifloxacin		400 mg daily for 17 wk

Q2: Treatment of Nonsevere, Presumed Isoniazid-Susceptible, Rifampin-Susceptible TB in Children		
Recommended Regimen	Intensive Phase (8 wk) [‡]	Continuation Phase (8 wk)
Isoniazid [†]	10–15 mg/kg	10–15 mg/kg
Rifampin	10–20 mg/kg	10–20 mg/kg
Pyrazinamide	35 (30–40) mg/kg	None
Ethambutol [§]	20 (15–25) mg/kg (included/excluded based on local guidelines)	None

Source: <https://doi.org/10.1164/rccm.202410-2096ST>

**Updates on the Treatment of Drug-Susceptible and Drug-Resistant Tuberculosis:
An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline**

The calendar does not cure TB.

CALENDAR

30	31	01	02	03
✓	✗	✓	✗	✓



DOSES

56 + 126

- Earlier and longer interruptions carry greater consequences.
- Reassess adherence, clinical response, bacteriology, and susceptibility.
- Engage the TB program early.

Longer standard therapy (9 months)

Cavitation AND a positive culture at completion of month 2

Pyrazinamide omitted, resistant, or lost early in treatment

HIV when ART cannot be given during TB treatment

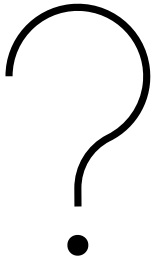
Standard pulmonary pathway: 2 months initial treatment + 7 months HR

Nine-month treatment applies to the standard pathway. Site-specific exceptions require consultation.

WHO Guidelines- “food for thought”

- 1.3 In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing is not recommended in both the intensive and continuation phases of therapy, and daily dosing remains the recommended dosing frequency (conditional recommendation, very low certainty of evidence).
- 1.4 The use of fixed-dose combination (FDC) tablets is recommended over separate drug formulations in treatment of patients with drug-susceptible TB (conditional recommendation, low certainty of evidence).

Polling Answer



A patient on standard HRZE has baseline cavitation and a positive month-2 sputum culture. Susceptibility and adherence are confirmed. What duration is appropriate?

A. 6 months total

B. 9 months total

C. 4 months total

D. 6 months with ethambutol throughout

B. Extend HR continuation to 7 months: 9 months total

Case Management in Tuberculosis

Priority to assure that the client receives:

- appropriate assessment, testing and diagnosis
- medication to assure cure is obtained
- supportive services to assist with participation to cure

Role of Public Health Nurse is essential in treatment success!

HRZE- Preferred Regimen (Pulmonary+ EP TB)

Intensive phase –8 weeks of INH, RIF, PZA, EMB

- EMB is included in original regimen due to INH resistance incidence worldwide. Can be discontinued once drug susceptibility results confirm susceptibility to INH and RIF

Continuation phase - 18 weeks of INH and RIF

- Extend continuation phase (7 instead of 4 months) if :
 - cavitary disease and culture positive at end of intensive phase
 - Loss of PZA in initial phase

Extensions

Proven increased risk of TB relapse : (extend to 9 months)

- Cavitory disease AND + sputum Cx for AFB at 2 months of therapy
- Loss of PZA

High risk situations (consider extension to 9 months HRZE):

- Heavy smoker, low BMI (<10 below IBW), Diabetes, HIV, immunosuppression, and whenever treatment doesn't feel like it's going smooth...

Management of Treatment Interruptions

Time Point of Interruption	Details of Interruption	Approach
During intensive phase	Lapse is <14 d in duration	Continue treatment to complete planned total number of doses (as long as all doses are completed within 3 mo)
	Lapse is ≥14 d in duration	Restart treatment from the beginning
During continuation phase	Received ≥80% of doses and sputum was AFB smear negative on initial testing	Further therapy may not be necessary
	Received ≥80% of doses and sputum was AFB smear positive on initial testing	Continue therapy until all doses are completed
	Received <80% of doses and accumulative lapse is <3 mo in duration	Continue therapy until all doses are completed (full course), unless consecutive lapse is >2 mo; If treatment cannot be completed within recommended time frame, restart therapy from the beginning (restart intensive phase, to be followed by continuation phase)
	Received <80% of doses and lapse is ≥3 mo in duration	Restart therapy from the beginning, new intensive and continuation phases (restart intensive phase, to be followed by continuation phase)

Interruptions

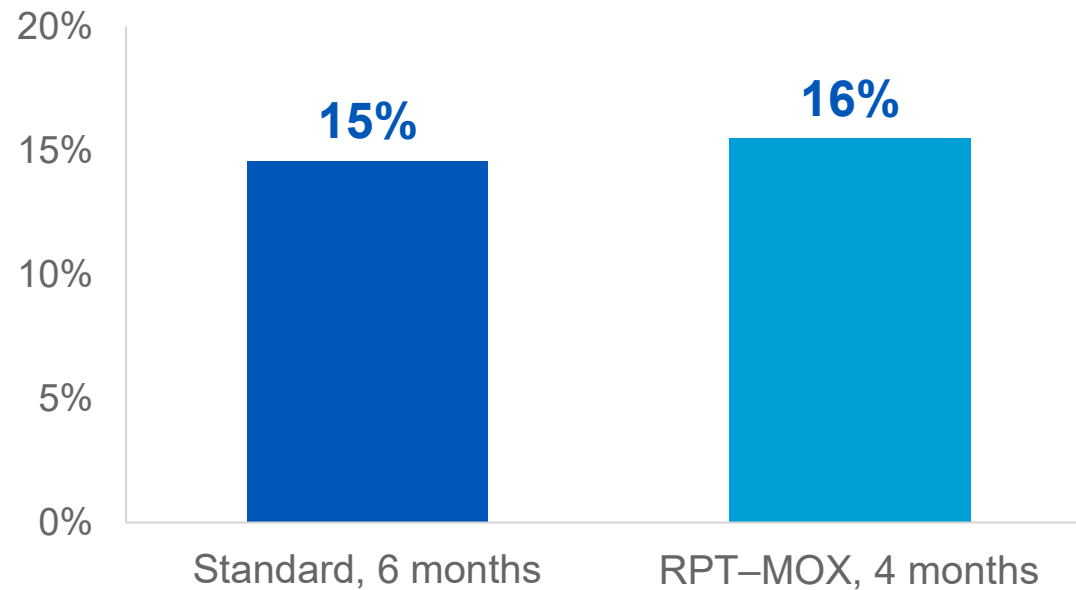
Intensive phase - 56 doses over minimum 8 weeks

Continuation phase - 126 doses over 18 weeks

- Intensive phase, RESTART therapy if > 2 weeks missed. Max allowed for 56 doses is 12 weeks.
- Completion phase allow 126 doses within 24 weeks. If Tx extended to 9 months – complete continuation phase within 36 weeks.

Study 31/A5349

Unfavorable outcome at 12 months



Noninferiority met

The rifapentine-only shortened arm did not meet noninferiority

Dorman et al. N Engl J Med 2021;384:1705–1718. Microbiologically eligible population.

Rifapentine–moxifloxacin: 17 weeks

8 weeks · 56 doses	9 weeks · 63 doses
H + P + Z + M	H + P + M

H 300 mg P 1,200 mg M 400 mg

Z: weight-based dosing during the first 8 weeks

119 total doses, taken 7 days each week

CDC MMWR 2022. ATS/CDC/ERS/IDSA 2025. All drugs once daily with food.

Important limits of the 17-week regimen

Pregnancy or breastfeeding, age <12 years, or weight <40 kg

Most extrapulmonary disease, especially CNS or bone/joint TB

Prolonged QT risk, interacting medications, or suspected resistance

HIV: CD4 $\geq$ 100 and an ART regimen compatible with daily rifapentine

CDC MMWR 2022. NIH HIV/TB guidance.

2HPZM/2HPM (RPT/MOX)

BENEFITS

- Shorter (4 months)
- Favorable sputum conversion timeline
- Different interaction profile
- Avoids EMB toxicity

PROBLEMS

- Cost
- RPT Availability
- Pill burden
- Long term profile- AE surveillance
- Requires food for absorption
- Fluoroquinolone use
- Uncertain efficacy for some extrapulmonary disease

2HPZM/2HPM (RPT/MOX)

WHO IS IT FOR

- Drug susceptible pulmonary tuberculosis
- Age 12 years or older
- Weight > 40 kg
- HIV with CD4 $\geq$ 100, on or starting ART without clinically significant drug-drug interactions with HPMZ
- Likely paucibacillary or low mycobacterial burden disease

WHO IS IT NOT FOR

- Body weight <40 kg
- Age <12 years
- Pregnant or breastfeeding •
- CNS/ osteo extrapulmonary TB infection
- • History of prolonged QT syndrome or concurrent use of $\geq$ 1 QT prolongator medications
- • Receiving medications with clinically relevant drug-drug interactions with RPT, MOX, INH, or PZA

Caution to use

- Received > 5 doses of treatment directed against active or latent TB in the preceding 6 months
- Received > 5 doses with 1 or more of these drugs (fluoroquinolone, INH, RIF, rifabutin, PZA) for any reason in the preceding 30 days
- ALT or AST > 3 x ULN, or total bilirubin > 2.5 x ULN
- Advanced liver or kidney disease

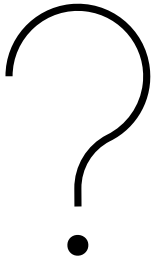
Pill Burden

	Standard Regimen (HRZE) >75Kg	Short course regimen (HPMZ) >75Kg	
Intensive Phase	8 weeks  Isoniazid Rifampin Pyrazinamide Ethambutol Vitamin B6	8 weeks  Isoniazid Rifapentine Moxifloxacin Pyrazinamide Vitamin B6	Treatment interruption: ▶ The 56 doses of initiation phase should be administered completely within 70 days. ▶ The 63 doses of the continuation phase should be administered within 84 days. ▶ If these targets are not met, the patient should be considered to have interrupted therapy and should be managed with clinical judgment and in consultation as described in TB treatment guidelines.
Continuation Phase	16-28 weeks  Isoniazid Rifampin Vitamin B6 Photos courtesy of George Lee, RN	9 weeks  Isoniazid Rifapentine Moxifloxacin Vitamin B6	

NTCA:

https://www.tbcontrollers.org/docs/resources/4-Month-HPMZ-TB-Regimen_NTCA-FAQ.pdf

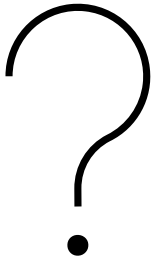
Polling Question



Assume drug susceptibility and adherence support are adequate. Which patient can receive the 17-week rifapentine–moxifloxacin regimen?

- A. Pregnant adult with pulmonary TB
- B. 14-year-old weighing 36 kg
- C. 72-kg adult with cavitary pulmonary TB
- D. Adult with TB meningitis

Polling Answer



Assume drug susceptibility and adherence support are adequate. Which patient can receive the 17-week rifapentine–moxifloxacin regimen?

A. Pregnant adult with pulmonary TB

B. 14-year-old weighing 36 kg

C. 72-kg adult with cavitary pulmonary TB

D. Adult with TB meningitis

C. Cavitation alone does not exclude this regimen

SHINE Trial:

- Completing 6 months of treatment for tuberculosis in children is a challenge.
- Open-label trial involving 1204 children in sub-Saharan Africa and India
- Four months of antituberculosis treatment was noninferior to 6 months of treatment in children with drug-susceptible, nonsevere, smear-negative tuberculosis.

RESEARCH SUMMARY

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

Turkova A et al. DOI: 10.1056/NEJMoa2104535

CLINICAL PROBLEM

Most children with tuberculosis (TB) have nonsevere disease, which probably could be treated with shorter regimens than the currently recommended 6 months. However, data from randomized trials of this approach in children are limited.

CLINICAL TRIAL

Design: An open-label, parallel-group, randomized, controlled trial examined whether 4 months of treatment would be noninferior to 6 months of treatment in children with nonsevere, symptomatic, presumably drug-susceptible, smear-negative TB in sub-Saharan Africa and India.

Intervention: 1204 children younger than 16 years of age were randomly assigned to 4 or 6 months of standard first-line anti-TB treatment with World Health Organization–recommended pediatric doses. The primary efficacy outcome was unfavorable status — defined as treatment failure or change, loss to follow-up during treatment, TB recurrence, or death — by 72 weeks.

RESULTS

Efficacy: The percentage of children with an unfavorable status by week 72 did not differ significantly between the groups, showing noninferiority of the shorter regimen.

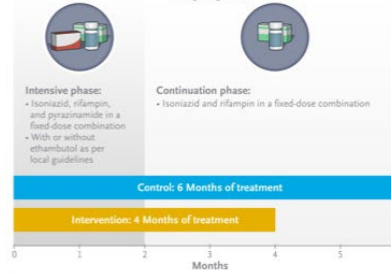
Safety: The percentage of children with an adverse event of grade 3 or higher during treatment or in the 30 days after treatment did not differ significantly between the groups. Pneumonia or other chest infections were the most common such events.

LIMITATIONS AND REMAINING QUESTIONS

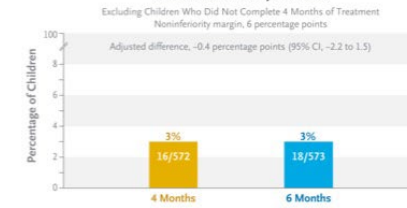
- The open-label design of the trial may have led to more treatment extensions with the 4-month regimen.
- It is unknown whether the results would apply to sites without radiographic capabilities to confirm nonsevere TB.

Links: Full Article | NEJM Quick Take | Editorial

Drug Regimen



Unfavorable Status by 72 Weeks



Grade ≥3 Adverse Events



CONCLUSIONS

Among children with nonsevere, drug-susceptible, smear-negative TB, a 4-month treatment regimen was noninferior to a 6-month regimen at 72 weeks of follow-up.

SHINE: nonsevere childhood TB

Ages 3 months–16 years

2HRZ(E) / 2HR

Primary-outcome events: **SAME**: 3% with 4 months and 3% with 6 months

Strong 2025 recommendation, moderate certainty of evidence

Turkova et al. N Engl J Med 2022;386:911–922. ATS/CDC/ERS/IDSA 2025.

Non-severe Childhood TB

Peripheral nodes, or intrathoracic nodes without airway obstruction

Uncomplicated pleural effusion

Paucibacillary, noncavitary pulmonary disease limited in extent

! Miliary, cavitary, CNS, or bone/joint disease requires another pathway !

2025 guideline. Source-case susceptibility helps establish presumed drug susceptibility.

Four months for adult culture-negative TB

Selected HIV-uninfected adults with smear- and culture-negative pulmonary TB

Adequate specimen collection and evaluation for alternative diagnoses

Clinical or radiographic improvement after 2 months of HRZE

2 months HR may successfully complete treatment. Uncertainty favors 6 months.

ATS/CDC/IDSA 2016. Conditional recommendation, very low certainty of evidence.

Monitoring / management

When	Essential assessment
Before treatment	Weight, medication review, HIV, labs Vision with E • QT/electrolytes with M as indicated
Monthly	Symptoms, toxicity, adherence, dose count, weight Sputum culture until 2 consecutive negatives
Month 2	Document culture response Reassess duration and diagnosis
Delayed response	Repeat DST and assess drug exposure Review adherence, interactions, and absorption

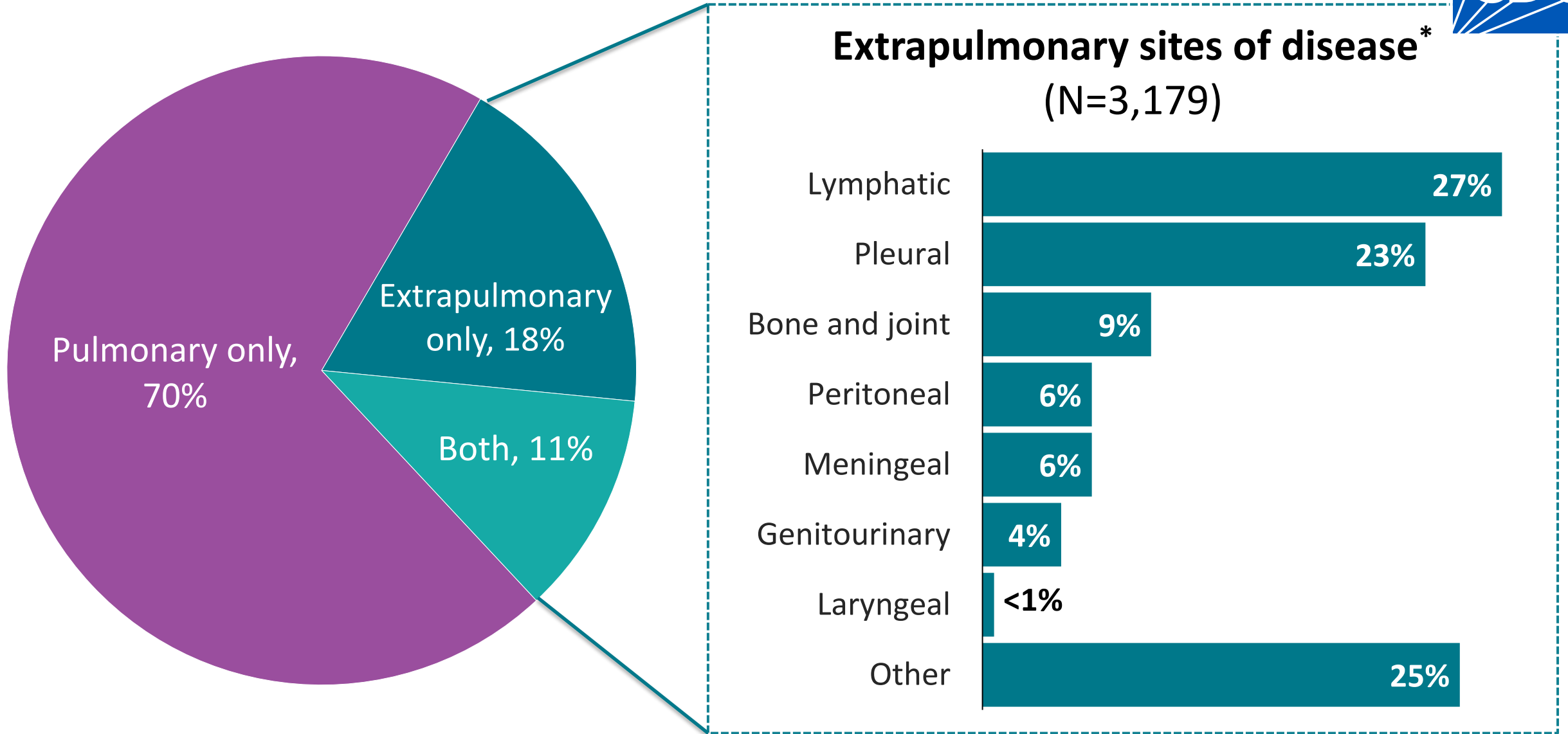
Clinical review at least monthly. Sputum culture, rather than smear alone, documents viable bacilli.

Sites and Special populations

Situation	Usual approach / caveat
Most extrapulmonary TB	Often 6 months with standard drugs HPMZ generally requires expert consideration
TB meningitis	Usually 9–12 months, adjunctive corticosteroids CNS-specific management
Bone / joint / spinal TB	Often 6–9 months; some experts use longer Individualize for extensive disease or hardware
Pregnancy, transplant, major organ disease	Expert selection and dosing Drug interactions can drive the regimen

Standard drugs remain the foundation. Duration depends on disease site and response.

Percentage of TB Cases by Site of Disease, United States, 2023



* Persons might have more than one extrapulmonary site of disease.

Extrapulmonary TB

Generally, HRZE regimen is more proven (avoid RPT/MOX regimen in severe CNS and osteoarticular cases)

ALWAYS obtain sputum samples and look to rule out pulmonary TB

Daily therapy is highly preferred. Penetration @ various body sites makes intermittent therapy problematic

Generally, 6-9 months of therapy (depending on location, disease burden) is enough. However, severe disseminated TB cases, CNS/ OSA TB may require 12 months

Adverse effects and urgent action

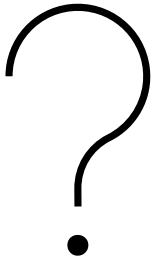
Signal	Immediate clinical response
Nausea, anorexia, dark urine, jaundice	Stop all drugs if severe; Check liver tests
Blurred or changed color vision on E	Stop E and arrange urgent eye assessment
Tendon pain or neuropathy on M	Stop M and assess a replacement regimen
Severe rash, mucosal lesions, bleeding, syncope	Urgent evaluation, hold culprit drugs Assess platelets and cardiac rhythm

All regimens need a clear patient plan for symptoms and whom to call.

Culture-Negative Suspected Pulmonary TB

- 10-15% of pulmonary cases
- Re-evaluation of patient after 2 months of treatment
- Repeat CXR (or CT chest if done)
- Clinical status
- Sputum cultures • If cultures remain neg (-), AND There is any clinical OR radiographic improvement while on treatment during the first 2 months, then → TB clinically diagnosed and continue treatment for active disease
- different mgmt options can apply
 - CDC/ATS/IDSA: 4 months total therapy • 2 mo (INH/RIF/PZA/EMB) • 2 mo (INH/RIF)
 - In some areas, 8%-18% of TB cases are INH-resistant and a very large percentage of these patients are from areas with INH R • Concern for INH-resistant culture-neg. TB and risk of MDR TB development
 - Mayo/Olmsted Co: Continue all 4-drug TB drugs for 4-6 months therapy

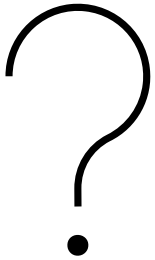
Polling Question



Week 3 of HRZE: nausea, anorexia, and ALT 4 times the upper limit of normal. What is the best immediate action?

- A. Stop H, R, Z, E and evaluate for liver injury
- B. Continue all drugs and repeat ALT in one month
- C. Stop only isoniazid
- D. Give an antiemetic and continue unchanged

Polling Answer



Week 3 of HRZE: nausea, anorexia, and ALT 4 times the upper limit of normal. What is the best immediate action?

A. Stop H, R, and Z and evaluate for liver injury

B. Continue all drugs and repeat ALT in one month

C. Stop only isoniazid

D. Give an antiemetic and continue unchanged

A. Symptoms + ALT $\geq 3 \times$ ULN meet the stopping threshold

Rifamycin drug interactions

Anticoagulants: review DOAC suitability or arrange INR-guided warfarin management

Hormonal contraception, methadone, and transplant drugs need a coordinated plan with care teams

ART compatibility can determine the TB regimen
Rifabutin may be substituted at times for Rifampin

Dose adjustments also need review when the rifamycin stops

Daily rifapentine is at least as potent an inducer as daily rifampin.

What may come next

TRUNCATE-TB

An 8-week initial regimen plus monitoring, extension, and retreatment

New combinations and risk-based duration

Promising research needs durable cure and implementation evidence

Investigational strategies. Not routine U.S. treatment pathways.

TRUNCATE-TB

Initial 8-week “boosted” regimen with high-dose rifampicin or rifapentine, plus novel drugs like linezolid, clofazimine, bedaquiline, or levofloxacin, combined with standard isoniazid, pyrazinamide, and ethambutol

The **bedaquiline + linezolid** 8-week regimen was **non-inferior** to standard 24-week treatment in preventing unfavourable outcomes (relapse, death, loss to follow-up) at 96 weeks

Rifampin/linezolid was inferior

RESEARCH SUMMARY

Treatment Strategy for Rifampin-Susceptible Tuberculosis

Paton NI et al. DOI: 10.1056/NEJMoa2212537

CLINICAL PROBLEM

The global standard treatment for drug-susceptible tuberculosis is a 24-week rifampin-based regimen, but adherence can be challenging. Clinical trials have shown a high probability of cure with shorter regimens, which suggests that a 24-week regimen may not be needed.

CLINICAL TRIAL

Design: A phase 2–3, international, adaptive, randomized, open-label, noninferiority trial assessed the efficacy and safety of a strategy involving shorter initial treatment for rifampin-susceptible tuberculosis.

Intervention: 674 participants 18 to 65 years of age were randomly assigned to undergo either standard treatment with a 24-week rifampin-based regimen or a strategy involving initial treatment with an 8-week regimen, extended treatment for persistent clinical disease, monitoring after treatment, and retreatment for relapse. There were four strategy groups with different initial regimens; noninferiority was assessed in the two strategy groups with complete enrollment, which had initial regimens of high-dose rifampin–linezolid and bedaquiline–linezolid (each with isoniazid, pyrazinamide, and ethambutol). The primary outcome was a composite of death, ongoing treatment, or active disease at week 96.

RESULTS

Efficacy: The strategy with an initial rifampin–linezolid regimen did not meet the noninferiority criterion, whereas the strategy with an initial bedaquiline–linezolid regimen was noninferior to standard treatment and was associated with a shorter total duration of treatment.

Safety: The incidence of grade 3 or 4 adverse events, serious adverse events, and respiratory disability did not differ significantly between the standard-treatment group and the two strategy groups.

LIMITATIONS AND REMAINING QUESTIONS

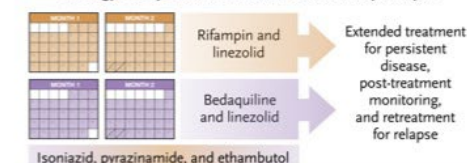
- Noninferiority of the treatment strategy was assessed with only two regimens, and the strategy could be refined with the use of alternative regimens.
- No HIV-positive persons were enrolled; further evaluation is warranted in this population.

Links: [Full Article](#) | [NEJM Quick Take](#) | [Editorial](#)

Standard Treatment (24 Wk)

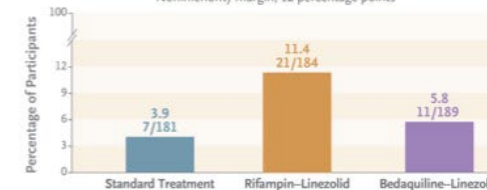


Strategy Groups Included in the Noninferiority Analysis

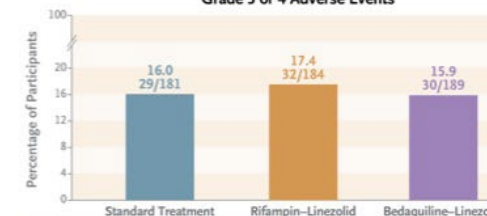


Death, Ongoing Treatment, or Active Disease

Noninferiority margin, 12 percentage points



Grade 3 or 4 Adverse Events



CONCLUSIONS

Among participants with rifampin-susceptible pulmonary tuberculosis, a strategy involving initial treatment with an 8-week bedaquiline–linezolid regimen was noninferior to standard treatment with respect to clinical outcomes, with no apparent safety concerns.

Table 2. Primary Efficacy Outcome.*

Outcome	Standard Treatment (N=181)	Strategy with Rifampin–Linezolid (N=184)	Strategy with Rifampin–Linezolid vs. Standard Treatment	Strategy with Bedaquiline–Linezolid (N=189)	Strategy with Bedaquiline–Linezolid vs. Standard Treatment
			Adjusted Difference (97.5% CI)†		Adjusted Difference (97.5% CI)†
Intention-to-treat population‡					
Primary outcome: composite of death, ongoing treatment, or active disease at wk 96 — no. (%)§	7 (3.9)	21 (11.4)	7.4 (1.7 to 13.2)	11 (5.8)	0.8 (–3.4 to 5.1)
Death before wk 96	2 (1.1)	5 (2.7)	—	1 (0.5)	—
Ongoing treatment at wk 96	2 (1.1)	8 (4.3)	—	5 (2.6)	—
Active disease at wk 96¶	1 (0.6)	4 (2.2)	—	3 (1.6)	—
Evaluation by telephone at wk 96 with no evidence of active disease but insufficient evidence of disease clearance when last seen	2 (1.1)	3 (1.6)	—	1 (0.5)	—
No evaluation at wk 96 and insufficient evidence of disease clearance when last seen	0	1 (0.5)	—	1 (0.5)	—
Outcomes classified as unassessable — no. (%)	1 (0.6)	1 (0.5)	—	2 (1.1)	—
Single positive culture at wk 96 but no other evidence of active disease	0	1 (0.5)	—	0	—
Death from a cause that was definitively unrelated to tuberculosis**	1 (0.6)	0	—	0	—
No evaluation at wk 96 and sufficient evidence of disease clearance when last seen	0	0	—	2 (1.1)	—
No primary outcome or outcome classified as unassessable — no. (%)	173 (95.6)	162 (88.0)	—	176 (93.1)	—
Assessable population††					
Primary outcome — no./total no. (%)	7/180 (3.9)	21/183 (11.5)	7.5 (1.7 to 13.2)	11/187 (5.9)	0.8 (–3.4 to 5.1)
Per-protocol population‡‡					
Primary outcome — no./total no. (%)	6/177 (3.4)	17/160 (10.6)	6.9 (0.9 to 12.8)	9/176 (5.1)	0.9 (–3.3 to 5.1)

* Results are shown for the standard-treatment group and the two strategy groups with complete enrollment; results for the two strategy groups with incomplete enrollment are shown in Tables S4 through S9.

† Differences were estimated with a generalized linear model with binomial distribution and adjustment for trial group, country, and relapse risk. Unadjusted results and results of Bayesian analysis are shown in Table S7. The 97.5% confidence intervals are shown to adjust for multiplicity. The differences are shown in percentage points.

‡ All 541 participants in the three groups with complete enrollment who were alive and undergoing follow-up were evaluated at week 96. Of these, 527 (97.4%) were evaluated in person and 14 (2.6%) by telephone. Of the participants who were evaluated in person, 522 (99.1%) underwent chest radiography, 505 (95.8%) produced at least one sputum sample that could be evaluated or were asymptomatic and unable to produce sputum (imputed negative), and 20 (3.8%) produced sputum samples that could not be evaluated.

§ The primary outcome was assessed with a prespecified algorithm (Section S10).

¶ All 8 participants had definitive active disease at week 96 with at least two positive sputum cultures. For each of these participants, whole-genome sequencing was performed on paired isolates obtained at week 96 and at baseline, and the week 96 strain was related to the baseline strain; this finding is consistent with relapse. There were no cases of presumptive or possible active disease at week 96.

|| Whole-genome sequencing showed that the strain from the single positive culture at week 96 was related to the baseline strain.

** The cause of death was cervical cancer.

†† The assessable population included all participants in the intention-to-treat population except those who had an outcome that was classified as unassessable.

‡‡ The per-protocol population included all participants in the intention-to-treat population except those who did not complete the protocol-specified initial treatment or had inadequate treatment during the first 56 days, unless the reason for inadequate treatment was death.

TRUNCATE-TB further analysis

- Even the best 8-week regimen (bedaquiline-linezolid) should only be used as part of a management strategy involving post-treatment monitoring and re-treatment if necessary
- In general, 8 week regimens fared worse



Efficacy and safety of 8-week regimens for the treatment of rifampicin-susceptible pulmonary tuberculosis (TRUNCATE-TB): a prespecified exploratory analysis of a multi-arm, multi-stage, open-label, randomised controlled trial



Nicholas I Paton, Christopher Cousins, Intan P Sari, Erlina Burhan, Nan-Kai Ng, Victoria B Dalay, Celina Suresh, Tutik Kusmiati, Ka Lip Chew, Vincent M Balanag, Qingshu Lu, Rovina Ruslami, Irawaty Djaharuddin, Jani J R Sugiri, Rholine S Veto, Christine Sekaggya-Wiltshire, Anchalee Avihingsanon, Jitendra Kumar Saini, Padmasayee Papineni, Andrew J Nunn, Angela M Crook, for the TRUNCATE-TB Trial Team*

Summary

Background WHO recommends a 2-month optimal duration for new drug regimens for rifampicin-susceptible tuberculosis. We aimed to investigate the efficacy and safety of the 8-week regimens that were assessed as part of the TRUNCATE management strategy of the TRUNCATE-TB trial.

Methods TRUNCATE-TB was a multi-arm, multi-stage, open-label, randomised controlled trial in which participants aged 18–65 years with rifampicin-susceptible pulmonary tuberculosis were randomly assigned via a web-based system, using permuted blocks, to 24-week standard treatment (rifampicin, isoniazid, pyrazinamide, and ethambutol) or the TRUNCATE management strategy comprising initial 8-week treatment, then post-treatment monitoring and re-treatment where needed. The four 8-week regimens comprised five drugs, modified from standard treatment: high-dose rifampicin and linezolid, or high-dose rifampicin and clofazimine, or bedaquiline and linezolid, all given with isoniazid, pyrazinamide, and ethambutol; and rifapentine, linezolid, and levofloxacin, given with isoniazid and pyrazinamide. Here, we report the efficacy (proportion with unfavourable outcome; and difference from standard treatment, assessed via Bayesian methods) and safety of the 8-week regimens, assessed in the intention-to-treat population. This prespecified exploratory analysis is distinct from the previously reported 96-week outcome of the strategy in which the regimens were deployed. This trial is registered with ClinicalTrials.gov (NCT03474198).

Findings Between March 21, 2018, and March 26, 2020, 675 participants (674 in the intention-to-treat population) were enrolled and randomly assigned to the standard treatment group or one of the four 8-week regimen groups. Two 8-week regimens progressed to full enrolment. An unfavourable outcome (mainly relapse) occurred in seven (4%) of 181 participants on standard treatment; 46 (25%) of 184 on the high-dose rifampicin and linezolid-containing regimen (adjusted difference 21·0%, 95% Bayesian credible interval [BCI] 14·3–28·1); and 26 (14%) of 189 on the bedaquiline and linezolid-containing regimen (adjusted difference 9·3% [4·3–14·9]). Grade 3–4 adverse events occurred in 24 (14%) of 181 participants on standard treatment, 20 (11%) of 184 on the rifampicin-linezolid regimen, and 22 (12%) of 189 on the bedaquiline-linezolid regimen.

Interpretation Efficacy was worse with 8-week regimens, although the difference from standard treatment varied between regimens. Even the best 8-week regimen (bedaquiline-linezolid) should only be used as part of a management strategy involving post-treatment monitoring and re-treatment if necessary.

Lancet Infect Dis 2025; 25: 1084–96

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This online publication has been corrected.

The corrected version first appeared at [thelancet.com/infection](https://www.thelancet.com/infection) on November 17, 2025

See [Comment](#) page 1056

*A complete list of members of the TRUNCATE-TB Trial Team is listed in the appendix

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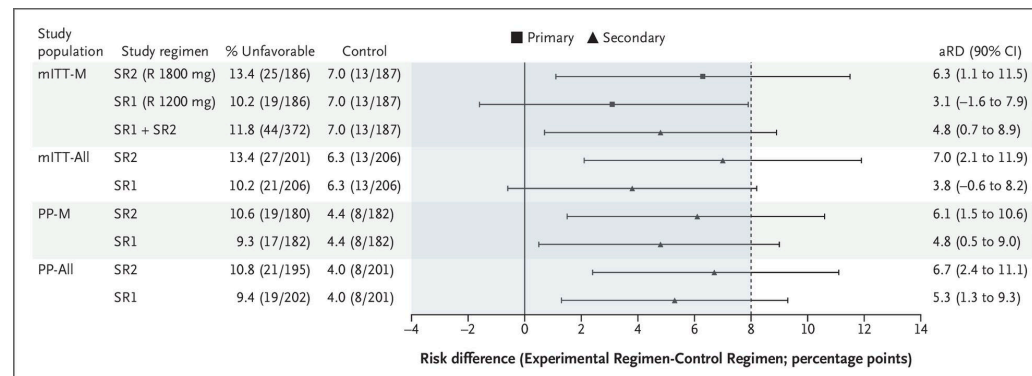
RIFASHORT TB-

- Phase 3 randomized 4-month high dose Rifampin regimens vs standard of care

Study Regimen 1 (SR1): 4-month daily high-dose rifampicin at **1200 mg**.

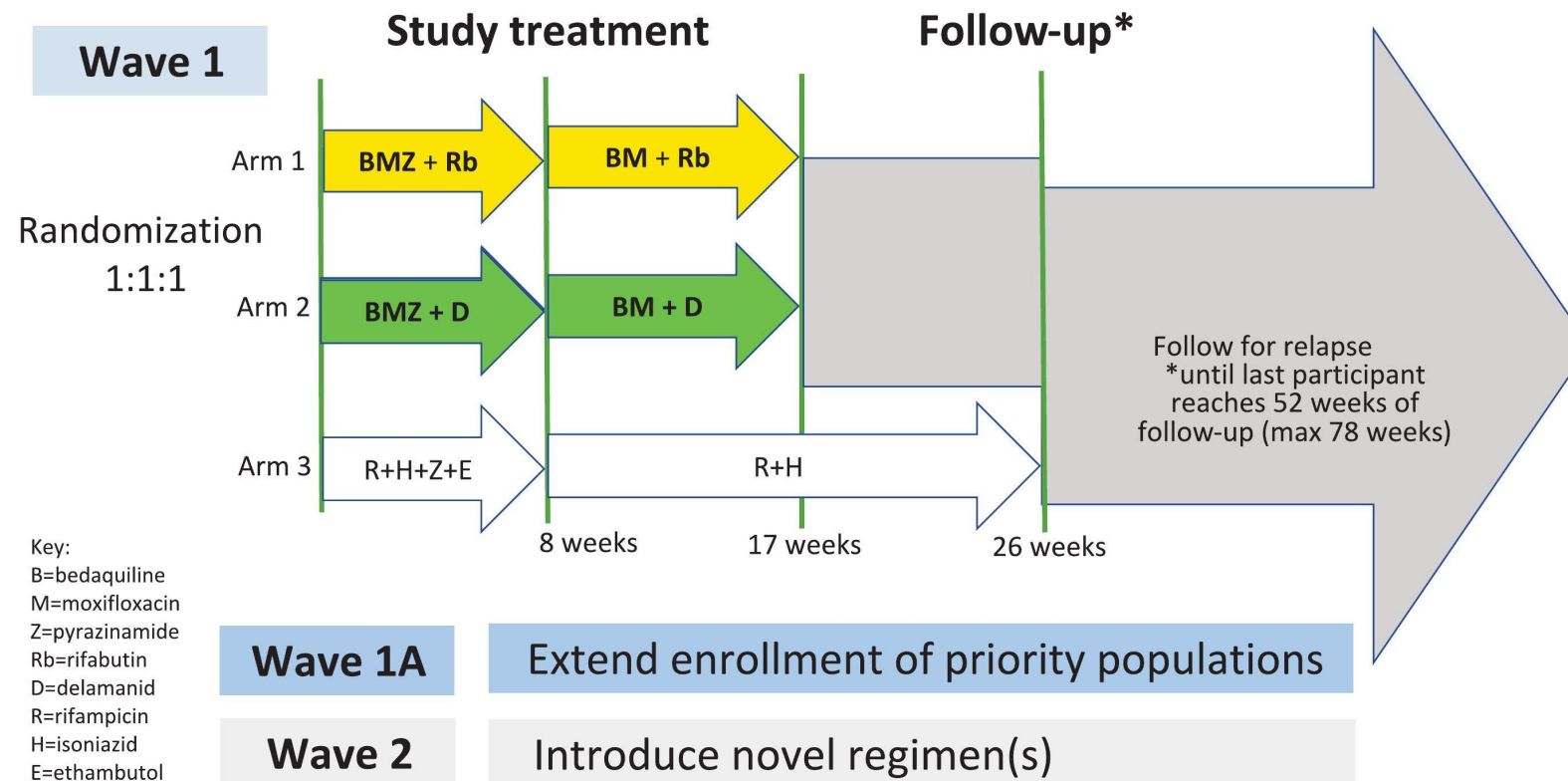
Study Regimen 2 (SR2): 4-month daily high-dose rifampicin at **1800 mg**

- Overall, the high dose Rif did not meet the noninferiority criteria



CRUSH-TB- Phase 2

Study 38 /CRUSH-TB Schema





Thank you