

AMERICAN THORACIC SOCIETY DOCUMENTS

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

6 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 Chorbha, 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

Abstract

Background: On the basis of recent clinical trial data for the treatment of drug-susceptible and drug-resistant tuberculosis (TB), the American Thoracic Society, U.S. Centers for Disease Control and Prevention, European Respiratory Society, and Infectious Diseases Society of America have updated clinical practice guidelines for TB treatment 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.

Methods: A Joint Panel representing multiple interdisciplinary perspectives convened with American Thoracic Society methodologists to review evidence and make recommendations using the GRADE (Grading of Recommendations Assessment,

Development and Evaluation) and GRADE-ADOLOPMENT (adoption, adaptation, and, as needed, *de novo* development of recommendations) methodology.

Results: New drug-susceptible TB recommendations include the use of a novel 4-month regimen for people with pulmonary TB and a shortened 4-month regimen for children with nonsevere TB. Drug-resistant TB recommendation updates include the use of novel regimens containing bedaquiline, pretomanid, and linezolid with or without moxifloxacin.

Conclusions: All-oral, shorter treatment regimens for TB are now recommended for use in eligible individuals.

Keywords: tuberculosis; drug-resistant; drug-susceptible; children; adults

6 You may print one copy of this document at no charge. However, if you require more than one copy, you must place a reprint order. Domestic reprint orders: amy.schrivver@sheridan.com; international reprint orders: louisa.mott@springer.com.

ORCID IDs: 0009-0001-4200-315X (J.J.S.); 0000-0003-2257-3099 (R.D.); 0000-0002-7493-9163 (S.S.M.); 0000-0002-2591-1439 (C.A.W.); 0000-0003-0343-3234 (M.J.M.); 0000-0002-0370-1430 (I.A.); 0000-0001-6966-5682 (C.A.-V.); 0000-0003-2962-1890 (P.M.B.); 0000-0003-0582-8870 (M.L.B.); 0000-0002-9239-2528 (H.C.); 0000-0001-6804-0111 (L.L.C.); 0000-0001-7722-0958 (T.C.); 0000-0003-3324-926X (C.L.D.); 0000-0002-9610-1134 (K.H.); 0000-0001-6785-1318 (I.K.); 0000-0001-7501-4448 (M.L.); 0000-0002-2597-574X (G.B.M.); 0000-0002-3106-1258 (A.E.S.); 0000-0002-1600-4474 (G.S.); 0000-0001-6218-6697 (J.R.S.); 0000-0001-9606-5623 (A.M.S.); 0000-0001-8006-2401 (S.-H.W.); 0000-0003-0355-5290 (J.M.W.); 0000-0003-2811-1311 (P.N.).

*Joint first authors.

The American Thoracic Society provided methodological and administrative support.

Correspondence and requests for reprints should be addressed to Jussi J. Saukkonen, M.D., A.T.S.F., Division of Pulmonary and Critical Care Medicine, Department of Medicine, Boston Veterans' Administration Health Care System, 1400 VFW Parkway, GB-138, West Roxbury, MA 02132. E-mail: jussi.saukkonen@va.gov.

A data supplement for this article is available via the Supplements tab at the top of the online article.

Am J Respir Crit Care Med Vol 211, Iss 1, pp 15–33, Jan 2025

Copyright © 2025 by the American Thoracic Society

DOI: 10.1164/rccm.202410-2096ST

Internet address: www.atsjournals.org

Contents

Summary of Recommendations
Introduction
Methods
Panel Composition

Conflict-of-Interest Management

Guideline Development
Methodology
Literature Search
Evidence-to-Decision Tables

Independent Review

Funding and Updating
Recommendations
Discussion

Summary of Recommendations

Treatment of isoniazid-susceptible, rifampin-susceptible TB in adults with a 4-month rifapentine-moxifloxacin versus 6-month regimen

Question: In adolescents and adults with drug-susceptible pulmonary tuberculosis (TB), is a 4-month regimen composed of 2 months of isoniazid, rifapentine, pyrazinamide, and moxifloxacin followed by 2 months of isoniazid, rifapentine, and moxifloxacin (2HPZM/2HPM) as efficacious and safe as the standard 6-month drug-susceptible TB regimen of 2 months of isoniazid, rifampin, pyrazinamide, and ethambutol (2HRZE) followed by 4 months of isoniazid, and rifampin (4HR) endorsed by the American Thoracic Society (ATS)/U.S. Centers for Disease Control and Prevention (CDC)/European Respiratory Society (ERS)/Infectious Diseases Society (IDSA) guidelines?

Recommendation: In people aged 12 years or older with drug-susceptible pulmonary tuberculosis, we conditionally recommend the use of a 4-month regimen of isoniazid, rifapentine, moxifloxacin, and pyrazinamide (conditional recommendation, moderate certainty of evidence). See Table 1 for dosing details.

Treatment of nonsevere, presumed isoniazid- and rifampin-susceptible TB in children with 4 months versus 6 months of standard therapy

Question: In children and adolescents with nonsevere, drug-susceptible pulmonary TB, is a 4-month regimen composed of standard-dose 2 months of isoniazid, rifampin, pyrazinamide, and ethambutol followed by 2 months of isoniazid and rifampin (2HRZE/2HR) as efficacious and safe as the standard 6-month drug-susceptible TB regimen of 2 months of isoniazid, rifampin, pyrazinamide, and ethambutol followed by 4 months of isoniazid and rifampin (2HRZE/4HR) endorsed by the ATS/CDC/ERS/IDSA guidelines?

Recommendation: In children and adolescents between 3 months and 16 years of age with nonsevere TB (without suspicion or evidence of multidrug-resistant [MDR]/rifampin-resistant [RR]-TB), we recommend the use of a 4-month treatment regimen of 2HRZ(E)/2HR rather than the 6-month drug-susceptible TB regimen of 2HRZ(E)/4HR (strong recommendation, moderate certainty of evidence).

Remarks: Nonsevere TB is defined as peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion; or paucibacillary and noncavitary disease confined to one lobe of the lungs or without a miliary pattern. Children and adolescents who do not meet the criteria for nonsevere TB should receive the standard 6-month treatment regimen (2HRZE/4HR) or recommended treatment regimens for severe forms of extrapulmonary TB. Some children may be eligible for the 4-month rifapentine-moxifloxacin regimen. Dosing is found in Table 1.

Treatment of rifampin-resistant, fluoroquinolone-resistant TB with a 6-month bedaquiline, pretomanid, and linezolid (BPaL) regimen versus 15-month or longer regimens in adolescents aged 14 and older and adults with rifampin-resistant pulmonary TB

Question: In adolescents aged 14 and older and adults with rifampin-resistant pulmonary TB, is a 6-month BPaL regimen as efficacious and safe as the current 15-month or longer drug-resistant TB regimens composed according to current ATS/CDC/ERS/IDSA drug-resistant (DR)-TB treatment guidelines?

Recommendation: In adolescents aged 14 and older and adults with rifampin-resistant pulmonary TB with resistance or patient intolerance to fluoroquinolones, who either have had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month, we recommend the use of the 6-month treatment BPaL regimen, rather than more than 15-month regimens (strong

recommendation, very low certainty of evidence). See Table 1 for dosing details.

Treatment of rifampin-resistant, fluoroquinolone-susceptible TB with a 6-month bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) regimen versus 15-month or longer regimens in adolescents aged 14 and older and adults with rifampin-resistant pulmonary TB

Question: In adolescents aged 14 and older and adults with rifampin-resistant, fluoroquinolone-susceptible pulmonary TB, is a 6-month BPaLM regimen as effective and safe as the 15-month or longer drug-resistant TB regimens composed according to current ATS/CDC/ERS/IDSA DR-TB treatment guidelines?

Recommendation: In adolescents aged 14 and older and adults with rifampin-resistant, fluoroquinolone-susceptible pulmonary TB, we recommend the use of a 6-month BPaLM treatment regimen, rather than the 15-month or longer regimens in patients with MDR/RR-TB (strong recommendation, very low certainty of evidence). See Table 1 for dosing details.

Introduction

Successful treatment and cure of tuberculosis (TB) improves individual health and reduces *Mycobacterium tuberculosis* transmission. Historically, treatment of TB, particularly of drug-resistant TB (DR-TB), has involved prolonged courses of multiple medications and frequent adverse reactions. Patients and clinicians prefer shorter, safer, and more effective regimens with fewer pills and injections for drug-susceptible (DS)-TB and DR-TB (Table 2). Recent clinical treatment trials of both DS- and DR-TB provided new evidence toward these objectives. On the basis of favorable study outcomes, the U.S. Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) updated DS- and DR-TB treatment recommendations in 2022 (1–4).

This guideline update, written by a panel of American Thoracic Society (ATS),

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
Q3: Treatment of Rifampin-Resistant, Fluoroquinolone Resistant TB		
Recommended BPaL Regimen		
Bedaquiline	400 mg daily for 2 wk, then 200 mg three times/wk for subsequent 24 wk	
Pretomanid	200 mg daily for 26 wk	
Linezolid	600 mg daily for 26 wk	
Q4: Treatment of Rifampin-Resistant, Fluoroquinolone-Susceptible TB		
Recommended BPaLM Regimen		
Bedaquiline	400 mg daily for 2 wk, then 200 mg three times/wk for subsequent 24 wk	
Pretomanid	200 mg daily for 26 wk	
Linezolid	600 mg daily for 26 wk	
Moxifloxacin	400 mg daily for 26 wk	

*Using actual body weight. Medications should be administered 7 d/wk with food, avoiding milk, antacids, or other cationic items, with DOT 5 of 7 days per week.

[†]Pyridoxine (vitamin B₆), 25–50 mg/d, should be given with isoniazid to all patients.

[‡]Using actual body weight and DOT 5 of 7 days per week.

[§]To avoid potential ocular toxicity, some clinicians exclude ethambutol for children who are HIV-uninfected, have no prior TB treatment history, live in an area of low prevalence of DR-TB, and have no exposure to an individual from an area of high prevalence of DR-TB. Prevalence and risk factors can be difficult to ascertain; therefore, the American Academy of Pediatrics and most experts include ethambutol as part of the intensive phase regimen for children with TB.

^{||}Medications should be administered 7 d/wk with food, with DOT 5 of 7 days per week.

[¶]Medications should be administered 7 d/wk with food, avoiding milk, antacids, or other cationic items with DOT 5 of 7 days per week.

d = day; kg = kilograms; mg = milligrams; wk = week.

Table 2. Patient Perspective

“For individuals living with tuberculosis, the path from diagnosis to recovery is full of many challenges. Delay in diagnosis and prolonged symptoms can be common. Long periods of isolation carry both economic and emotional costs. The difficulty of high pill burden, medication side effects and long treatment regimens is frequently discussed by TB survivors in We Are TB support meetings. During my own treatment I felt the weight of 16 pills in my hand every morning, and of stigma, financial cost and isolation. I felt the added burden on my family, the medication side effects, and the physical manifestations of the disease. Progress to shorten this journey and to ease these burdens is valued by patients.”

Kelly Holland, We Are TB patient advocate

CDC, European Respiratory Society (ERS), and Infectious Diseases Society of America (IDSA) specialists, relied on recent reviews of clinical data conducted by the WHO Guideline Development Group (GDG). This Joint Panel guideline focuses on TB in low-incidence settings without significant resource limitations.

Methods

Panel Composition

The Joint Panel was composed of 25 international specialists in pulmonary medicine, infectious diseases, pediatrics, epidemiology, and public health. A member of *We Are TB*, a patient advocacy organization, was included for patient perspective. All members helped to review and rate evidence with guidance from the methodology team. The co-sponsoring organizations each provided a co-chair and representatives responsible for the content of the manuscript.

Conflict-of-Interest Management

Guideline panel members disclosed all potential conflicts of interest (CoIs) according to the ATS policies (*see* author disclosures). The chairs and ATS reviewed and managed potential CoIs. Panel members with potential CoIs abstained from decisions about specific questions and recommendations related to their potential CoIs. Most panelists had no substantial CoIs and were approved to participate without limitation. One protocol chair panelist (P.N.) participated in the discussions but was recused from formulating, grading, writing, or editing the recommendation related to the treatment of DS-TB in adults. Another panelist (A.J.G.-P.) had a manageable conflict requiring recusal from the formulation of antibiotic-related recommendations pertaining to DR-TB.

Guideline Development Methodology

This guideline is a targeted update to the treatment of TB and specifically as an adaptation (5) of the WHO 2022 guidelines (1, 2) relevant to the prior Joint Panel's guideline recommendations (6, 7). Four methodologists followed the GRADE-ADOLOPMENT (Grading of Recommendations Assessment, Development and Evaluation – adoption, adaptation, and, as needed, *de novo*

development of recommendations) (5) process and used the evidence-to-decision (EtD) frameworks in the adaptation of published WHO guidelines (1, 2). ADOLOPMENT is a GRADE framework that involves either adoption of recommendations from existing guidelines, adaptation of recommendations from existing guidelines, or, if needed, *de novo* development of recommendations (5).

The methodologists administered online surveys to confirm the panelists' selection of PICO (population, intervention, comparison, outcome) questions for ADOLOPMENT and prioritization of critical outcomes on the basis of recently published treatment trials and recent CDC and WHO guidelines (1–4) through a modified Delphi process. The Joint Panel arrived at consensus to use the WHO prioritization of critical outcomes. Specifically, the Joint Panel consensus was to adapt specific questions on DS- and DR-TB as worded in the WHO guidelines pertaining to TB treatment (1, 2) provided in an update to the 2016 and 2019 Joint Panel's guidelines on TB treatment (6, 7). Subsequently, the Joint Panel used the same wording of questions as noted in WHO guidelines, except to refer to the standard of care (SoC) noted in the prior Joint Panel's guidelines as active comparators as opposed to active comparators from the SoC from prior WHO guidelines (1, 2).

The Joint Panel chose through consensus to adapt the 2022 WHO guidelines on TB treatment (1, 2) on the basis of the relevance, rigor, quality of evidence, and GRADE methodology used in their development. In addition, the methodology team conducted a targeted literature search in three databases (Medline, Embase, Cochrane Central Register of Clinical Trials), using “tuberculosis” and “randomized clinical trial” as filters to confirm the absence of new clinical trial data pertinent to selected PICO questions since the publication of the WHO Guidelines in 2022 (1, 2).

Literature Search

The following steps were conducted after the literature search: 1) title and abstract screening (a preliminary screen review of all titles and abstracts to determine which studies are potentially eligible) and 2) full-text screening (a more in-depth review of the full text for all included studies from the title/abstract phase to establish final eligibility

for the review). For steps 1 and 2, the methodology team screened the titles and abstracts (TAs) of the uncovered citations and excluded studies on the basis of the predefined study selection criteria that were specific to each of the four study PICO. Only studies that were deemed eligible (or were judged “unsure” by screeners) went on to the full-text (FT) phase. At the TA and FT phases of screening, screening was performed in duplicate and independently by pairs of screeners with consensus debate to settle disagreements and third-party adjudication when and if needed. At the FT phase, the full studies were retrieved so that the screeners could read the study in its entirety to make a definitive decision on whether a study would be retained to inform the respective PICO. Panel members were asked to be alert to any recently published trials or any studies that they thought were relevant to a particular PICO and that may have been missed in the electronic database search or TA and FT screening steps.

Evidence-to-Decision Tables

The methodology team provided transcribed versions of the EtDs of the selected WHO guidelines (1, 2) in GDT (<http://www.gradepro.org/>) (8). The terms, definitions of data, and evidence tables included in each EtD framework are derived from the published WHO consolidated guidelines on TB (1, 2) with the addition of data for the percentages of participants for each outcome and the treatment effect estimates derived from the evidence tables and EtD tables, respectively. The analyses documented in the published WHO guidelines' EtD tables were used for the GRADE-ADOLOPMENT process with inclusion of intervention and control population numbers from corresponding evidence tables. Joint Panel members without a CoI reviewed the EtD tables derived from WHO (1, 2) EtD tables from corresponding PICO questions and recommendations and voted on the recommendations. As part of the ADOLOPMENT process, the Joint Panel critically appraised and evaluated the WHO guidelines on TB treatment, particularly focusing on the relevance of the EtD judgments in the context of low TB burden, high-resource settings, in contrast to the WHO's focus on higher TB burden, low-resource settings (reassessed EtDs are provided in Tables E1–E4 in the data supplement). The Joint Panel and methodology team revised the EtD tables

transcribed from the WHO EtDs (1, 2) to reflect the Joint Panel reassessments of the judgments for each PICO. Recommendations were formulated and rated as either “strong” or “conditional” as explicit statements of recommendation strength as per GRADE guidance (Table 3) (9, 10). The term “we recommend” is used for a “strong” recommendation; “we conditionally recommend” is used for a “conditional” recommendation, analogous to “we suggest” used in the Joint Panel’s 2016 and 2019 guidelines (6, 7). The Joint Panel’s recommendations are based on the quality of evidence, the balance between benefits and harms, the certainty of the evidence, and other factors. Sequential observational evidence was considered when published randomized controlled trial evidence was not available. All panel members without a declared CoI reviewed the EtD tables and recommendations and voted on the Joint Panel’s recommendations. The Joint Panel and methodology team drafted the adapted guidelines EtDs and the document manuscript.

Independent Review

The resulting final guideline was reviewed by the ATS documents editor, by anonymous peer reviewers, ERS, IDSA, and CDC and approved for publication by the ATS Executive Committee.

Funding and Updating

The ATS provided logistical and methodological support and was responsible for CoI disclosures, vetting, and management. The guideline will be reevaluated for updating by the sponsoring ATS Assembly 3 years after publication or sooner.

Recommendations

Drug-susceptible TB

PICO Question 1: In adolescents and adults with DS pulmonary TB, is a 4-month regimen composed of 2 months of isoniazid, rifapentine, pyrazinamide, and moxifloxacin followed by 2 months of isoniazid, rifapentine, and moxifloxacin (2HPZM/2HPM) as efficacious and safe as the standard 6-month DS-TB regimen of 2 months of isoniazid, rifampin, pyrazinamide, and ethambutol (2HRZE) followed by 4 months of isoniazid and rifampin (4HR) endorsed by the ATS/CDC/ERS/IDSA guidelines?

1. Topic/overview/background

Standard treatment for culture-positive DS-TB has required ≥6 months of antibiotics (6). Shorter, effective regimens enable patients to be cured faster and can potentially reduce treatment costs,

improve patient quality of life, and increase completion of therapy. The Joint Panel reviewed evidence from Study 31/A5349, a randomized, open-label, phase III trial comparing two 4-month rifapentine-containing regimens with the standard 6-month control regimen (11). Participants aged 12 years and older with newly diagnosed pulmonary TB were enrolled at 34 trial sites worldwide (Table 4).

2. Summary of evidence for benefits and harms

For the 4-month rifapentine and moxifloxacin (RPT-MOX)-based regimen compared with the standard 6-month regimen (consisting of 2 mo of isoniazid, rifampin, pyrazinamide, and ethambutol followed by 4 mo of isoniazid and rifampin [2HRZE/4HR]), the Joint Panel assessed equivalent outcomes of TB disease-free survival at 12 months postrandomization (cure/favorable outcome), treatment retention, acquired drug resistance, adverse events (grade 3 or higher), and all-cause mortality within 14 days after the last dose of study medication (Tables 4 and E1). The microbiologically eligible population for analysis had 791 participants in the 4-month RPT-MOX arm and 768 participants in the 6-month control

Table 3. Implications of Strong and Conditional Recommendations

	Strong Recommendation ("We recommend ...")*	Conditional Recommendation ("We conditionally recommend ...")†
For patients	The overwhelming majority of individuals in this situation would want the recommended course of action, and only a small minority would not	The majority of individuals in this situation would want the suggested course of action, but a sizable minority would not
For clinicians	The overwhelming majority of individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences	Different choices will be appropriate for different patients, and you must help each patient arrive at a management decision consistent with her or his values and preferences Decision aids may be useful to help individuals make decisions consistent with their values and preferences Clinicians should expect to spend more time with patients when working toward a decision
For policy makers	The recommendation can be adapted as policy in most situations, including for use as performance indicators	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place

*Strong recommendations will apply to most patients for whom these recommendations are made, but they may not apply to all patients in all conditions; no recommendation can take into account all of the unique features of individual patients and clinical circumstances.
†“We conditionally recommend” is analogous to the phrase “we suggest” in the 2016 and 2019 joint panel TB guidelines.

Table 4. Study 31/A5349 Evidence: Drug Regimens and World Health Organization Critical Outcomes in Treatment of Isoniazid-Susceptible, Rifampin-Susceptible Tuberculosis in Adults*

Study 31/A5349*					
Design	Randomized, open-label, phase III, noninferiority trial				
Setting	Compared a 4-mo regimen (including moxifloxacin and rifapentine) with standard 6-mo regimen International, multicenter (34 sites): Brazil, China, Haiti, India, Kenya, Malawi, Peru, South Africa, Thailand, Uganda, United States of America, Vietnam, Zimbabwe				
Inclusion criteria	Participants ≥12 yr old with TB (sputum acid-fast bacilli smear or rapid nucleic acid amplification test positive) susceptible to isoniazid, rifampin, and fluoroquinolones				
Exclusion criteria	If HIV positive, CD4 T cell count ≥100 cells/mm ³ , on (or planned) efavirenz-based antiretroviral therapy Pregnant and breastfeeding women Receiving >5 d of treatment directed against TB or latent TB infection within prior 6 mo or >5 d latent TB infection treatment with isoniazid, rifamycins, pyrazinamide, or any fluoroquinolone within prior 30 d Known history of prolonged QT syndrome Extrapulmonary TB (central nervous system, bones or joints, miliary) Weight <40 kg Known drug resistance				
Regimen and duration	Intervention: 4-mo regimen 2HPZM/2HPM [†]		Comparator: 6-mo regimen 2HRZE/4HR [‡]		
WHO Outcomes	Intervention Percentage	Comparator Percentage	Relative Effect (95% CI) Anticipated Absolute Difference (95% CI)	Certainty of the Evidence (GRADE)	
Cure (<i>n</i> = 1,559)	84.6%	85.4%	RR 0.99 (0.95 to 1.03) 9 fewer per 1,000 (from 43 fewer to 26 more)	⊕⊕⊕⊕ High	
Retention in treatment (<i>n</i> = 1,559)	99.9%	99.0%	RR 1.01 (1.00 to 1.02) 10 more per 1,000 (from 0 fewer to 20 more)	⊕⊕⊕⊕ High	
Amplified drug resistance (<i>n</i> = 1,559)	0.0%	0.0%	RR 3.13 (0.13 to 76.69) 0 fewer per 1,000 (from 0 fewer to 0 more)	⊕⊕○○ Low	
Adverse events during treatment (grade 3 or higher; <i>n</i> = 1,671)	18.7%	19.3%	RR 0.97 (0.76 to 1.24) 6 fewer per 1,000 (from 46 fewer to 46 more)	⊕⊕○○ Moderate	
All-cause mortality (within 14 d after end of treatment; <i>n</i> = 1,671)	0.4%	0.8%	RR 0.42 (0.11 to 1.61) 5 fewer per 1,000 (from 8 fewer to 5 more)	⊕⊕○○ Low	

*Adapted from WHO DS 2022 TB treatment guidelines evidence-to-decision tables (from Module 4 treatment, Web annex EtD corresponding to question "In patients aged ≥12 yr with drug-susceptible pulmonary TB, is a 4-mo regimen composed of rifapentine, isoniazid, pyrazinamide and moxifloxacin as effective and safe as the standard drug-susceptible TB regimen composed according to WHO guidelines?," pages 20–41).

[†]Four months total with 2 months of isoniazid, rifapentine, pyrazinamide, moxifloxacin (2HPZM) followed by 2 months of isoniazid, rifapentine, moxifloxacin (2HPM).

[‡]Six months total with 2 months of isoniazid, rifampin, pyrazinamide, ethambutol (2HRZE) followed by 4 months of isoniazid, rifampin (4HR).
d = day; RR = risk ratio.

arm, all with culture-confirmed susceptibility to isoniazid, rifampin, and fluoroquinolones. RPT-MOX was noninferior to control (84.6% vs. 85.4% cure, respectively). No significant differences in outcomes were identified for RPT-MOX and 6-month standard regimens on the basis of smear grade, cavitation, radiologic extent, age, diabetes, body weight, or HIV status. However, the number of participants living with HIV infection, diabetes, or extreme weight or age was small (e.g., ~9% of trial participants were people living with HIV infection with CD4 count ≥100 cells/μL, and most participants were aged under 35 years) (11, 12) (Table E1). As part of the ADOLOPMENT process, we adapted the WHO guideline question,

evidence table, EtD framework, and recommendation to the scope and audience of this guideline. We performed a literature search to update the evidence base. The literature search revealed no other clinical trials to include in this question, and only one study and corresponding analysis from the WHO guideline was used. Although other clinical trials included shorter regimens for the treatment of DS-TB, they did not address the specific PICO question regarding a rifapentine-moxifloxacin regimen.

3. Monitoring and additional considerations

Individuals with TB affecting the central nervous system, bones, or joints, miliary TB, and/or pericardial TB were not included in the above study and would

not usually be treated with a 6- or 4-month regimen. In low-incidence settings, more people with TB may be older than in the clinical trial and may receive concurrent medications or have underlying comorbidities with a higher risk for adverse events. Specifically, this may include fluoroquinolone-related adverse events, including neuropathology, tendinitis, QT prolongation, and dysglycemia (13). There was no evidence in the trial to suggest that routine baseline or subsequent electrocardiographic (ECG) monitoring is required. The panel did not recommend baseline ECG monitoring for those receiving the shorter regimen (unless clinically indicated, such as by older age, presence of cardiac conditions, history of

prolonged QT interval, or use of additional QT prolonging medication). The Joint Panel noted that the RPT-MOX regimen avoids the potential ocular toxicity of ethambutol and decreases the time to culture conversion. Implementation of the RPT-MOX regimen may face challenges related to feasibility and cost. Although the shorter treatment duration may benefit patients and healthcare systems, the RPT-MOX regimen increases daily pill burden, especially compared with fixed-dose combinations (FDCs) that might be used in some European locations for the 6-month regimen. The trial used directly observed therapy (DOT) for at least 5 of 7 treatment days per week as recommended (6), which may have improved adherence. DOT may not be feasible in settings that rely on unsupervised self-administered therapy. Although the likelihood of fluoroquinolone resistance was considered small (<5%) in otherwise DS-TB, there is widespread community use of fluoroquinolones. Therefore, obtaining samples to send for molecular and possibly phenotypic fluoroquinolone DST is advisable before starting the RPT-MOX regimen. The availability and affordability of rifapentine and other medications pose significant challenges in some settings. Nitrosamine impurities in rifampin and rifapentine may also impact availability, although joint panel opinion agreed with the U.S. Food and Drug Administration (FDA) assessment that the benefit of treating TB with rifamycins likely exceeds the risk (<https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-nitrosamines-rifampin-and-rifapentine>). ECG monitoring might be used in some patients at risk for cardiac events and could increase costs. In terms of health equity, no information was available regarding the use of RPT-MOX for extrapulmonary TB (EPTB) or during pregnancy or in young children. Rifapentine with isoniazid was not associated with unfavorable pregnancy outcomes in trials including weekly therapy for latent TB infection treatment (14). Pediatric studies are enrolling for pharmacokinetics

underlying the 4-month RPT-MOX regimen (ClinicalTrials.gov identifier NCT03730181), and weekly rifapentine with isoniazid is recommended therapy for latent TB infection for persons aged 2 years and older (15).

4. **Certainty of evidence**

The Joint Panel concurred with the WHO GDG that the overall certainty of evidence for benefits of cure and retention in treatment is high, moderate for adverse events, and low for acquisition of drug resistance and for all-cause mortality, based on the low frequency of harmful events. Although typically overall certainty is based on the lowest certainty for the agreed critical outcomes, the panel agreed with WHO in using GRADE guidance (10) that drug resistance and all-cause mortality would no longer rate as critical outcomes, because the range of effect would not impact the strength or direction of recommendations. Thus, the panel concurred with WHO that the overall certainty of evidence is moderate.

5. **Panel recommendation**

In people aged 12 years or older with DS pulmonary tuberculosis, we conditionally recommend the use of a 4-month regimen of isoniazid, rifapentine, moxifloxacin, and pyrazinamide (conditional recommendation, moderate certainty of evidence; Table E1). See Table 1 for dosing details.

PICO Question 2: In children and adolescents with nonsevere DS pulmonary TB, is a 4-month regimen composed of standard-dose 2 months of isoniazid, rifampin, pyrazinamide, and ethambutol followed by 2 months of isoniazid and rifampin (2HRZE/2HR) as efficacious and safe as the standard 6-month DS-TB regimen of 2 months of isoniazid, rifampin, pyrazinamide, and ethambutol followed by 4 months of isoniazid and rifampin (2HRZE/4HR) endorsed by the ATS/CDC/ERS/IDSA guidelines?

1. **Topic/overview/background**

Currently recommended treatment regimens are ≥ 6 months in duration, regardless of disease severity (6). The SHINE (Shorter Treatment for Minimal TB in Children) trial (16) was a multicenter, randomized, controlled,

two-arm noninferiority trial comparing 4 months with 6 months of standard treatment for nonsevere TB. This was defined as intrathoracic lymph node TB without airway obstruction, uncomplicated TB pleural effusion, or paucibacillary and noncavitary disease confined to one lobe of the lungs, or without a miliary pattern. Data from this clinical trial informed these recommendations (16). As part of the ADOLOPMENT process, we adapted the WHO guideline question, evidence table, EtD framework, and recommendation to the scope and audience of this guideline. We performed a literature search to update the evidence base. The literature search revealed no other clinical trials to include in this question, and only the one study and corresponding analysis from the WHO guideline were used.

2. **Summary of evidence, benefits, and harms**

SHINE enrolled 1,204 children and adolescents <16 years old weighing ≥ 3 kg with nonsevere TB disease (Table 5). Exclusion criteria included known drug resistance, contact to persons with DR-TB, pregnancy, and more severe TB disease (e.g., miliary TB, TB meningitis).

The SHINE trial demonstrated a success rate of 97.1% for participants receiving the 4-month regimen (2 mo of isoniazid, rifampin, and pyrazinamide, with or without ethambutol, followed by 2 mo of isoniazid and rifampin [2HRZ(E)/2HR]) compared with 96.9% among those receiving the 6-month regimen (2HRZ(E)/4HR; Table 5). Noninferiority of the 4-month regimen compared with the 6-month regimen was consistent across the intention-to-treat, per-protocol, and key secondary analyses, including the analyses restricted to patients independently adjudicated to have TB disease. Adverse event incidence was similar between the 4-month (7.8%) and 6-month regimens (8.0%) (Table 5).

The SHINE trial documented similar treatment success rates and adverse events between the 4-month and 6-month regimens, supporting a recommendation for the 4-month regimen. The shortened treatment duration is a significant benefit and

Table 5. SHINE Trial Evidence: Drug Regimens and World Health Organization Analyzed Critical Outcomes in Treatment of Nonsevere Presumed Isoniazid-Susceptible, Rifampin-Susceptible Tuberculosis in Children*

Study	SHINE Trial*				
Design	Open-label, parallel-group, noninferiority, randomized, controlled, two-arm trial Compared 4-mo (16 wk) versus standard 6-mo (24 wk) treatment using WHO-recommended anti-TB drug dosing in children <16 yr with symptomatic nonsevere TB Sample size: 1,121 (per-protocol; PP), 1,145 (modified intention-to-treat; mITT), 1,204 (intention-to-treat; ITT)				
Setting	Uganda, Zambia, South Africa, India				
Inclusion criteria	Age 0–16 yr Weight ≥3 kg Symptomatic, nonsevere TB Clinician decision to treat with standard first-line regimen				
Exclusion criteria	Smear-positive respiratory sample Cavitation on chest radiograph Premature (<37 wk) and aged under 3 mo Miliary TB, spinal TB, TB meningitis, osteoarticular TB, abdominal TB, congenital TB Preexisting nontuberculous disease likely to prejudice the response to, or assessment of, treatment, e.g., liver or kidney disease, peripheral neuropathy Any known contraindication to taking anti-TB drugs Known contact with drug-resistant TB adult source case (including mono-resistant TB) or known TB drug resistance in the child Severely ill Pregnancy				
Symptomatic, nonsevere TB defined	Disease confined to one lobe on chest radiograph No cavities or complex pleural effusion, or significant airway obstruction Extrathoracic lymph node (LN) TB Intrathoracic uncomplicated (hilar) LN TB Smear-negative on gastric aspirate/other respiratory sample				
Participant characteristics	Median age 3.5 yr (range, 2 mo–15 yr), 52% male	HIV seropositive Respiratory TB Peripheral LN TB Mixed respiratory and peripheral LN TB Bacteriologically confirmed TB Culture-positive Xpert MTB/RIF-positive Culture-Xpert MTB/RIF-positive	11% 67% 3% 29% 14% 7% 2% 5%	Adherence to assigned treatment: 94%	
Drug regimen and duration	Intervention: 4 mo of isoniazid, rifampin, pyrazinamide with or without ethambutol [†]	Comparator: 6 mo of isoniazid, rifampin, pyrazinamide with or without ethambutol [‡]			
WHO Outcomes	Intervention Percentage	Comparator Percentage	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI) Difference	Certainty of the Evidence (GRADE)
Death (all-cause; <i>n</i> = 1,145)	1.2%	2.3%	RR 0.54 (0.22 to 1.34)	10 fewer per 1,000 (from 18 fewer to 8 more)	⊕⊕⊕○ Moderate
Treatment success (<i>n</i> = 1,145)	96.9%	96.9%	RR 1.00 (0.98 to 1.02)	0 fewer per 1,000 (from 19 fewer to 19 more)	⊕⊕⊕⊕ High
Treatment failure (<i>n</i> = 1,145)	0.50%	0.20%	RR 3.01 (0.31 to 28.81)	4 more per 1,000 (from 1 fewer to 49 more)	⊕⊕⊕⊕ High
Relapse (<i>n</i> = 1,145)	1.0%	0.7%	RR 1.50 (0.43 to 5.30)	3 more per 1,000 (from 4 fewer to 30 more)	⊕⊕⊕○ Moderate
Treatment adherence (<i>n</i> = 1,204)	95.1%	93.2%	RR 1.02 (0.99 to 1.05)	19 more per 1,000 (from 9 fewer to 47 more)	⊕⊕⊕○ Moderate
Adverse events during treatment (grade 3 or higher; <i>n</i> = 1,204)	7.8%	8.0%	RR 0.98 (0.67 to 1.44)	2 fewer per 1,000 (from 26 fewer to 35 more)	⊕⊕⊕○ Moderate
Loss to follow up (<i>n</i> = 1,204)	1.8%	1.8%	RR 1.00 (0.44 to 2.29)	0 fewer per 1,000 (from 10 fewer to 24 more)	⊕⊕⊕○ Moderate

*Adapted from WHO DS 2022 TB treatment guidelines evidence-to-decision tables (from EtD corresponding to question "A 4-month treatment regimen compared with currently recommended 6-month treatment regimen in children and adolescents with non-severe drug-susceptible tuberculosis," pages 45–58. These numbers and terms may differ from other publications of the underlying studies due to differences from specific WHO-related definitions, assessment, and analysis methodology of the primary data.

†Interventional regimen of 8-week intensive phase of daily fixed-dose combination of isoniazid, rifampin, pyrazinamide with inclusion/exclusion of ethambutol per local guidelines, followed by 8-week continuation phase of daily isoniazid and rifampin.

‡Control regimen of 8-week intensive phase of daily fixed-dose combination of isoniazid, rifampin, pyrazinamide with inclusion/exclusion of ethambutol per local guidelines, followed by 16-week continuation phase of daily isoniazid and rifampin.

kg = kilograms; mo = months; MTB/RIF+ = Mycobacterium tuberculosis detected, rifampin resistant; RR = risk ratio; wk = week; yr = year.

could reduce the use of healthcare services and potentially improve adherence.

Relying on the noninferior outcome between the 4-month regimen and the current standard, the Panel judged both desirable and undesirable effects to be trivial in difference (2). The Joint Panel agreed that implementing the regimen would be cost saving for programs, although the size of this effect is uncertain.

3. Monitoring and additional considerations

Although the SHINE trial enrolled children and adolescents with symptomatic TB disease, many children are diagnosed during contact investigations with TB disease while asymptomatic. The Joint Panel agreed that, provided patients meet the demographic, radiographic, epidemiologic, and clinical criteria for nonsevere TB, without suspicion of RR/MDR-TB, these patients should also be eligible for the 4-month regimen. Recommendations for other specific subgroups are provided in Table 6.

Because there is an age overlap between the RPT/MOX regimen and this 4-month regimen, some children may be eligible for either regimen. Figure 1 provides information on how to identify children eligible for the 4-month regimens, based on the data on children in the SHINE trial (16) and Study 31/A5349 (11).

Children and adolescents who do not meet the criteria for nonsevere TB should receive the standard 6-month treatment regimen (2HRZ(E)/4HR) or other recommended regimens for which they are eligible or for severe forms of EPTB (6).

The clinical monitoring requirements for the shorter regimen remain the same as for the 6-month regimen (6). Monitoring for potential recurrence is a priority for shorter regimens, and programs should have plans to monitor children after treatment. TB programs should also assess for barriers to offering this regimen.

4. Certainty of evidence

The Joint Panel concurred with the WHO GDG that certainty in the

estimated effect was judged to be high for treatment success. Specifically, the Joint Panel judged the certainty of the evidence to be high for treatment success and moderate for both all-cause death and adverse events. This was due to imprecision for estimates of treatment failure, relapse, adherence, and loss to follow-up. The Joint Panel agreed with the WHO that overall certainty of the evidence is moderate (2). This was not downgraded for indirectness, because the trial population may be representative of patients with TB treated in the countries represented by the Joint Panel. The Joint Panel concurred with the WHO GDG that the certainty in the estimated effects was judged to be moderate for all-cause death and adverse events. The Joint Panel agreed with the WHO that the overall certainty of evidence is moderate (2).

5. Panel Recommendation

In children and adolescents between 3 months and 16 years of age with nonsevere TB (without suspicion or evidence of MDR/RR-TB), we recommend

Table 6. Subgroup Considerations for 4-Month 2HRZE/2HR Regimen for Children with Nonsevere DS-TB

Subgroup	SHINE Study Eligibility and Outcomes	Management Considerations/Recommendations
Children with asymptomatic disease	Not study eligible	Asymptomatic children with nonsevere TB disease should receive the 4-mo recommended regimen even without microbiologic results
Children with peripheral lymph node TB	Included in study Despite small numbers, the 4-mo regimen was noninferior for peripheral lymph node disease across all subgroups, including those with concomitant pulmonary disease	Peripheral and intrathoracic lymph nodes may remain enlarged and regress over several months We recommend the 4-mo regimen
Children living with HIV	Included in study The 4-mo regimen was noninferior regardless of antiretroviral treatment and CD4 count, including those with severe HIV infection (per WHO immunological classification)	Monitor children with HIV on this regimen closely, especially with severe HIV disease or opportunistic infections, and extend to 6 mo if insufficient clinical progress at 4 mo We recommend the 4-mo regimen
Children with severe acute malnutrition (SAM)	Included in study, but no separate subgroup analysis In SHINE trial, SAM was defined as weight-for-height z-score ≤ 3 or mid-upper arm circumference of < 115 mm	Because no separate subgroup analysis was conducted, children with SAM and nonsevere disease should preferably receive 6-mo regimen
Premature infants < 37 wk gestation and aged < 3 mo or infants weighing < 3 kg but ≥ 37 wk gestation	Not study eligible	These children should be treated with a 6-mo regimen
Children treated for TB in the past 2 yr	Not study eligible	Generally not eligible for this regimen, but consider individual circumstances and assess if appropriate for the 4-mo regimen
Children exposed to drug-resistant TB (DR-TB)	Not study eligible	These children should be treated with a regimen appropriate for the DR-TB exposure

SAM = severe acute malnutrition.

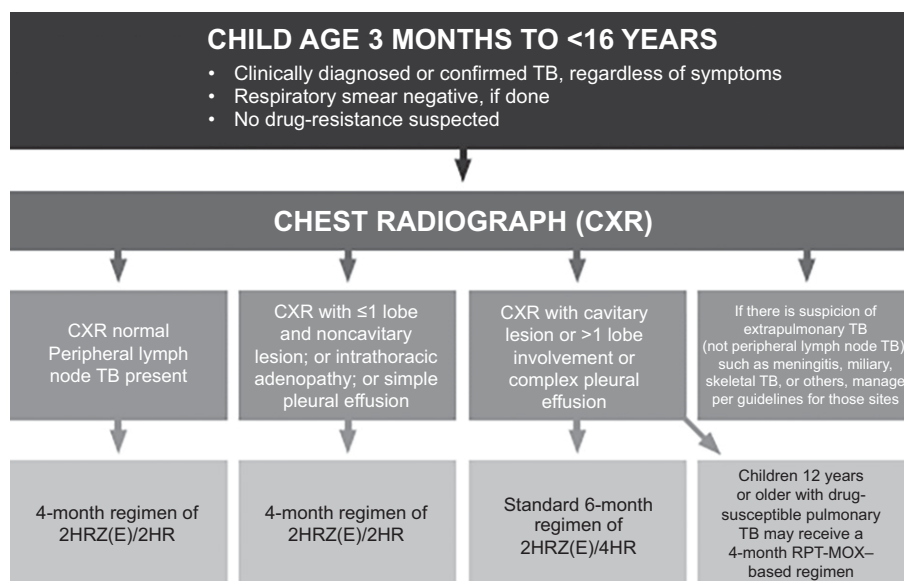


Figure 1. Identifying children eligible for 4-month regimens. Figure developed by the Joint Panel on the basis of data in the SHINE trial and Study 31/A5349 to address eligibility of some children for either the RPT/MOX regimen or the 4-month standard drug regimen. CXR = chest x-ray; HRZE = isoniazid, rifampin, pyrazinamide, ethambutol; RPT-MOX = rifapentine-moxifloxacin.

the use of a 4-month treatment regimen of 2HRZ(E)/2HR rather than the 6-month DS-TB regimen of 2HRZ(E)/4HR (strong recommendation, moderate certainty of evidence; Table E2). See Table 1 for dosing details.

Drug-resistant TB

PICO Question 3: In adolescents aged 14 and older and adults with rifampin-resistant pulmonary TB, is a 6-month regimen composed of bedaquiline, pretomanid, and linezolid as efficacious and safe as the current 15-month or longer drug-resistant TB regimens composed according to current ATS/CDC/ERS/IDSA DR-TB treatment guidelines?

1. Topic/overview/background

MDR-TB (resistant to at least isoniazid and rifampin), RR-TB, and TB in people intolerant of rifampin (due to severity of adverse effects) are associated with significant morbidity and mortality. These conditions have required substantially different medications and extended treatment durations compared with DS-TB. Before 2019, global treatment success rates for MDR-TB ranged from 50% to 88% (1, 17), often accompanied by significant adverse events. However, the Nix-TB study demonstrated a 90% treatment success

rate for treatment of extensively drug-resistant (XDR) or MDR-TB using a regimen of bedaquiline, pretomanid, and linezolid (BPAL) over a 6-month period. Adverse events associated with this regimen were primarily attributed to a daily dose of 1,200 mg of linezolid. In the ZeNix trial (18), lower linezolid dosing and shorter treatment durations were evaluated. The WHO compared ZeNix trial data with programmatic individual patient data (IPD) of SoC regimens (Table E3).

The WHO also analyzed data from TB-PRACTECAL (Pragmatic Clinical Trial for More Effective Concise and Less Toxic MDR-TB Treatment Regimens) (19), a randomized controlled trial comparing programmatic SoC regimens with 6-month BPAL-based regimens (Table 7) for MDR-/RR- or pre-XDR-TB. Data from these analyses were considered in this guideline. As part of the ADOLOPMENT process, we adapted the WHO guideline question, evidence table, evidence-to-decision framework, and recommendation to the scope and audience of this guideline. We performed a literature search to update the evidence base. The literature search revealed no other clinical trials to include in this question in addition to the clinical trials and corresponding

evidence analysis noted in the WHO guideline.

2. Summary of evidence, benefits, and harms

In the ZeNix trial, 181 participants with MDR-/RR- or pre-XDR-TB received 26 weeks of BPAL (Table 7). They were randomized to receive 1,200 or 600 mg of linezolid daily for 9 or 26 weeks. Treatment with 600 mg of linezolid in the regimen for 26 weeks demonstrated similar favorable outcomes with a reduced incidence of peripheral neuropathy compared with the regimen with 1,200 mg dosing. Comparing ZeNix data (linezolid 600 mg for 26 wk; $n = 43$) with longer observational SoC IPD ($n = 850$), BPAL had higher treatment success (100% vs. 74%), with lower mortality (0% vs. 11%) and loss to follow-up (0% vs. 12%) (Table 7). Grade 3 or higher adverse events were observed more frequently with BPAL (14% vs. 5%). Potential reporting bias in observational data might have led to underestimating adverse events in IPD. In TB-PRACTECAL (19), people receiving BPAL ($n = 60$) for 24 weeks, including linezolid initiated at 600 mg for MDR-/RR- or pre-XDR-TB, had a higher success rate than persons receiving SoC ($n = 66$) regimens (77% vs. 52%) and fewer grades 3 to 5 adverse events (20% vs. 51%) (Tables 7 and E3).

Table 7. TB-PRACTECAL, ZeNIX Trial Evidence: Drug Regimens and World Health Organization–analyzed Critical Outcomes in Treatment of Rifampin-Resistant, Fluoroquinolone-Resistant/Susceptible Tuberculosis*

Study	TB-PRACTECAL ^{*,†,§,}		ZeNix ^{*,†,§, ,¶}	WHO Long SoC Regimens Registries: Individual Patient Dataset (IPD) 2021*	
Design	Phase 2/3 open-label RCT, two stages with randomization to: I. BPaL or WHO long standard of care II. BPaLM or WHO long standard of care		Open-label RCT: BPaL 600 for 9 or 26 wk, or BPaL 1,200 for 9 or 26 wk	Program registry observational data	
Setting	Belarus, South Africa, Uzbekistan		South Africa, Georgia, Moldova, Russia	Belarus, Georgia, Moldova, Somalia, India, Mozambique, Belgium, Armenia, South Africa, and multiple sites from Einstein, End TB, CDC, Harvard, and France datasets	
Inclusion criteria	MDR/RR-TB or Pre-XDR-TB Above regardless of quinolone resistance or HIV status Aged 15 yr or more		XDR TB, Pre-XDR, RR TB Aged 14 yr or more	For long comparator regimen (target 18–24 mo), patients had each of the following: Regimen classified as long regimen in dataset Treatment duration ≤24 mo Received ≥4 drugs (regardless of DST or effectiveness) Bedaquiline allowed in regimen If cure or completion, treatment duration of 17.5 mo or more Patients receiving injectable antibiotics excluded	
Exclusion criteria	Pregnancy, Hepatic or heart disease Suspected resistance to bedaquiline, pretomanid, or linezolid Prior use of bedaquiline and/or pretomanid and/or linezolid for 1 or more months		HIV+ and CD4 <100, ALT and AST >3× ULN, grade >3 peripheral neuropathy, prior treatment with any of 3 trial drugs or delamanid for 2+ wk		

Regimen (see footnotes)	TB-PRACTECAL BPaL ^{*,†,§} (n = 126)		TB-PRACTECAL BPaLM ^{*,†,} (n = 128)		WHO Long SoC, with Injectables*		ZeNix BPaL (600 mg) ^{*,†,¶}		WHO Long SoC, Individual Patient Data Registry	
Duration	24 wk		24 wk		9–20 mo		26 wk		Variable	
WHO Outcomes*	%	RR** (95% CI)	%	RR** (95% CI)	%	%	RD†† (95% CI)	%	RD†† (95% CI)	%
Success rate	76.7	1.47 (1.09 to 1.99)	88.7	1.73 (1.31 to 2.27)	51.5	97.7	1.32 (1.19 to 1.39)	73.9		
Failure and recurrence	13.3	0.52 (0.22 to 1.18)	8.1	0.26 (0.10 to 0.71)	25.8	2.3	0.71 (0.12 to 3.80)	3.3		
Loss to follow-up	10.0	0.60 (0.24 to 1.56)	3.2	0.16 (0.04 to 0.61)	19.7	0.0	RD†† −0.11 (−0.13 to −0.03)	11.8		
Adverse events	19.6	0.38 (0.24 to 0.60)	21.0	0.41 (0.26 to 0.63)	50.9	14.0	RD†† −0.12 (−0.14 to −0.04)	4.7		
Death	0.0	RD†† 0.03 (−0.1 to 0.03)	0.0	RD†† −0.03 (−0.1 to 0.03)	3.0	0.0	3.99 (1.67 to 9.57)	11.0		
Amplified resistance	2.9	1.59 (0.32 to 7.84)	0.0	RD†† −0.02 (−0.07 to 0.02)	1.9	0.0	RD†† −0.02 (−0.04 to 0.06)	2.4		

*Adapted from WHO DS 2022 TB treatment guidelines evidence tables and evidence-to-decision tables, specifically corresponding to WHO questions “Should BPaL (Lzd 600 mg/300 mg) vs. local SoC regimens (TB-PRACTECAL comparator) be used for pulmonary MDR/RR-TB and pre-XDR-TB?” and question “Should BPaL vs. WHO long be used for pulmonary MDR/RR-TB?”, the data for the percentages of participant for each outcome and the treatment effect estimates were derived from the evidence tables and EtD, respectively (Module 4 Treatment, Web annex under PICO 6.6 pages 47–48 [evidence table] and 294–309 [EtD] and PICO 5.2 pages 33–34 [evidence table] and 196–212 [EtD]). In addition, for question “BPaLM compared with TB-PRACTECAL comparator in pulmonary MDR/RR-TB and pre-XDR-TB.” The data for the percentages of participant for each outcome and the treatment effect estimates were derived from the evidence tables and EtD, respectively (Module 4 Treatment, Web annex under PICO 6.1 pages 37–38 [evidence table] and 226–241 [EtD]). These numbers and terms may differ from other publications of the underlying studies due to differences from specific WHO-related definitions, assessment and analysis methodology of the primary data.

†Compared with WHO Long Standard of Care (SoC).

‡Compared with WHO Long Individual Patient Data registry.

§TB-PRACTECAL BPaL: bedaquiline 400 mg daily for 2 weeks then 200 mg 3 times a week for 22 weeks; pretomanid 200 mg daily for 24 weeks; linezolid 600 mg daily for 16 weeks, then 300 mg daily for 8 weeks.

||TB-PRACTECAL BPaLM: bedaquiline 400 mg daily for 2 weeks then 200 mg 3 times a week for 22 weeks; pretomanid 200 mg daily for 24 weeks; linezolid 600 mg daily for 16 weeks, then 300 mg daily for 8 weeks; moxifloxacin 400 mg daily for 24 weeks.

¶ZeNix BPaL (600 mg): ZeNix (BPaL with 600 mg linezolid daily for 26 wk).

**Risk ratio.

††Real difference (RD) is used for comparison instead of RR because the numerator for a risk requires a nonzero number.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; DST = drug susceptibility test; MDR/RR-TB = multi-drug resistant/rifampin-resistant tuberculosis; mo = month; RCT = randomized controlled trial; RR = risk ratio; ULN = upper limit of normal; wk = week; XDR = extensively drug resistant.

3. Certainty of evidence

Certainty in estimated effects was very low because of multiple factors: bias risk from imbalance of comorbidities, high risk of unmeasured confounding, small event numbers, lack of blinding, early trial termination, population differences, varied comparator regimens (inclusion of 9- to 20-mo regimens), inconsistent treatment outcomes, and imprecision from small participant and outcome numbers (Table E4). The ZeNix versus IPD-2021 analysis lacked adjustment because of few events, potential misclassification bias in the comparator group under programmatic conditions, and indirectness from assessment and procedural differences between intervention and programmatic comparators (1).

4. Monitoring and additional considerations

a. Patient selection

Patients should have MDR-/RR-TB confirmed by genotypic (e.g., Xpert MTB/Rif [original or Ultra], DNA sequencing, or line probe assay) or phenotypic methods. For patients with conditions excluded from the above trials (Table 7), the risks, limited safety data, and benefits of BPpL or a more extended regimen should be carefully weighed and discussed with the patient before initiating therapy.

Individuals who have experienced rifampin intolerance would also potentially be eligible for BPpL, according to Joint Panel opinion and the FDA. Although the minimum age for eligibility was 15 years in TB-PRACTECAL and 14 years in ZeNix, the Joint Panel opinion was that BPpL could be used in individuals aged 14 years and older. Patients initiating treatment for MDR/RR-TB but ineligible for BPpL (e.g., resistance or intolerance to bedaquiline, pretomanid, or linezolid; severe extrapulmonary TB; pregnant; lactating; or aged <14 yr) can receive an individualized regimen based on the Joint Panel's 2019 DR-TB guidelines (7). For individuals treated with BPpL who have received more than 9 weeks of linezolid but are unable to tolerate it, expert opinion suggests that some individuals, after

careful review, may continue the remaining medications without it (20). Prior recommendations discuss the role of surgery for DR-TB (7).

b. Subgroup considerations

Age

In low-incidence settings a greater proportion of people with TB may be older than in the ZeNix and TB PRACTECAL trials. Older individuals may receive more concurrent medications or have comorbidities with a higher risk for adverse events.

Children and Pregnant and Lactating Individuals

Trials included participants ≥ 14 years old, excluding pregnant or lactating individuals, with median participant age between 35 and 37 years old. Bedaquiline has a favorable pediatric adverse effect profile (21), whereas linezolid (22) and pretomanid data are limited or absent. At this time, longer regimens are recommended (7) for children under 14 years old and for lactating and pregnant individuals until safety and efficacy data become available.

People Living with HIV Infection

People living with HIV infection comprised 20–33% of the ZeNix and TB-PRACTECAL trial populations, with median CD4 counts of 326 and 330 cells/ μ L. However, subgroup outcome analyses were not offered in these trials. In the Nix-TB study, in which 51% of participants were living with HIV, unfavorable outcomes were not influenced by HIV status (23). Treatment recommendations for BPpL, based on Joint Panel opinion, may be applied to all patients with RR/MDR-TB, regardless of HIV infection and CD4 count. The risks and benefits of 6-month or longer regimens should be discussed with the patient. Close monitoring is advised with low CD4 counts because of higher rates of disseminated disease and potential immune reconstitution syndrome. The potential for drug–drug interactions should be considered, in particular avoiding efavirenz in a BPpL-based regimen, because it

can significantly decrease bedaquiline levels.

Extrapulmonary TB

Trials included patients with nonsevere forms of EPTB, making such patients eligible for BPpL. Severe forms, such as disseminated central nervous system or bone/joint TB, were excluded. No clinical trial evidence supports their treatment with BPpL, although limited programmatic experience has been published (24).

c. Clinical monitoring

According to the Joint Panel opinion (Table 8), patients should be monitored during treatment for response to treatment and for adverse events, with clinical, radiologic, and laboratory assessments, including baseline, monthly, and as needed. Monitoring frequency should be increased for those of older age; people living with HIV; diabetes; baseline anemia; visual impairment; renal or liver disease; or if significant clinical, ECG, or laboratory abnormalities are found. Post-treatment monitoring for at least 1–2 years is recommended to identify recurrence.

Baseline and follow-up ECGs with QTc measurement are necessary during bedaquiline treatment. For BPpL without additional QT-prolonging agents, ECG should be conducted at 2, 12, and 24 weeks after initiation (25, 26). With a concomitant QT-prolonging agent, including moxifloxacin, as below, monthly ECGs are recommended (3).

d. Bacteriologic and drug susceptibility testing

Sputum should be obtained before treatment for drug susceptibility testing (DST) and monitored weekly until smear conversion, every other week until culture conversion, and then monthly until the end of treatment. Isolates should be evaluated for susceptibility changes. Molecular methods, available through some state and national laboratories, such as the CDC (3), can detect moxifloxacin resistance and should be followed, when possible, by phenotypic testing

Table 8. Monitoring Plan for Patients Treated with BPaL or BPaLM*

Activity	Month of Treatment										Post-Treatment [†]				
	0 (Baseline)	1 [‡]	2	3	4	5	6	7	8	9	3	6	12	18	24
Sputum smear and culture [§]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Imaging (CXR, CT, other)	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Weight [¶]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Symptom review ^{**}	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
DST ^{††}	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
CBC ^{‡‡}	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Creatinine ^{§§}	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
ALT/AST, alkaline phosphatase, bilirubin	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
K ⁺ , Ca ²⁺ , Mg ²⁺ , bicarbonate ^{¶¶}	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Serum drug concentration ^{***}	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
HIV ^{†††}	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Pregnancy ^{‡‡‡}	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
EKG ^{§§§}	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Vision exam	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Peripheral neuropathy ^{¶¶¶}	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Arthralgias ^{****}	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Amylase, lipase, TSH ^{††††}	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

• Indicates activity is recommended by joint panel opinion.

○ Indicates activity that is optional or contingent on other information.

Monitoring recommendations may change if treatment regimen or patient status changes.

When treatment extended to 9 months, monitoring for Months 7–9 (Weeks 27–39) would be “as needed.”

*Joint panel opinion, adapted by permission from Reference 29.

†Recommend clinical assessment (including physical examination and symptom review), sputum collection (two or three specimens), and chest imaging at 3, 6, 12, 18, and 24 months after treatment completion.

‡Split column indicates weekly or biweekly testing.

§Obtain three sputa at the start of treatment and every 1–2 weeks until smear conversion, followed by one or two sputa every 2 weeks until culture conversion and then one sputum monthly throughout treatment.

||Obtain baseline imaging and monitor approximately every 3 months until end of treatment.

¶Monitor weight monthly and adjust medications as needed.

**Monitor for TB symptoms monthly.

††Obtain first and second-line DSTs at baseline. Repeat if culture remains positive after 2–3 months of treatment.

‡‡Obtain CBC every 1–2 weeks for the first 6–8 weeks, then monthly while on LZD. A decrease of hemoglobin of greater than 10% or more at 4 weeks of treatment may identify those at high risk for severe anemia.

§§Obtain serum creatinine at baseline and monthly while on BPaL or BPaLM.

||||Obtain ALT, AST, alkaline phosphatase, and bilirubin at baseline and then monthly while on BDQ and Pa.

¶¶Obtain K⁺, Ca²⁺, Mg²⁺, and bicarbonate at baseline and monthly while on BDQ.

***Obtain therapeutic drug monitoring (TDM), if possible, of LZD after 1–2 weeks on therapy and if signs of toxicity develop. Recommend collecting an LZD trough concentration if resources allow. TDM may be obtained for other drugs as clinically indicated.

†††Obtain baseline HIV test.

‡‡‡Consider baseline and monthly pregnancy test for patients capable of becoming pregnant who decline long-acting forms of birth control (e.g., intrauterine devices or implantable contraception).

§§§Obtain EKG (check QTcF) at baseline, 2, 12, and 24 weeks while on BDQ. Consider checking monthly if taking additional QT-prolonging agents (e.g., MFX, CFZ, other).

|||||Perform visual acuity (e.g., Snellen) + color discrimination (i.e., Ishihara) examinations at baseline and monthly while on LZD.

¶¶¶Monitor for peripheral neuropathy at baseline and monthly while on LZD.

****Monitor for arthralgias at baseline and monthly while patient on an FQ.

††††Note that CDC provisional guidance (3) for use of BPaL recommends amylase, lipase, and TSH at baseline. These may not be necessary for all patients, according to joint panel opinion. Consider checking amylase and lipase if underlying concerns for pancreatitis or if symptoms develop. Consider checking TSH if there are concerns for prolonged QT interval on baseline EKG.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; EKG = electrocardiogram or ECG; CBC = complete blood count; CXR = chest x-ray; CT = computed tomography; DST = drug susceptibility testing; TSH = thyroid stimulating hormone.

because some molecular methods may miss heteroresistant populations (27, 28). DST is limited for bedaquiline, linezolid, and pretomanid but may become more available. DNA sequencing can detect mutations in genetic loci associated with resistance to BPaL

drugs (30–32). If resistance to a drug in BPaL is detected by a molecular method or DST, an alternate regimen should be considered in consultation with laboratory and clinical experts, tailored to susceptibility results (7).

e. Drug–drug interactions

Drug–drug interactions should always be considered. Classes of drugs and specific medications to avoid or that require additional precautions include, but are not limited to, efavirenz, QTc-prolonging medications, strong

CYP3A4 inducers (including rifamycins), strong CYP3A4 inhibitors, monoamine oxidase inhibitors, many antidepressants, and drugs known to induce myelosuppression (Tables E3 and E4).

f. Regimen administration,

composition, dosing, frequency, duration, and changes

DOT and integrated case management remain the standard of care, as noted in the Joint Panel's prior guidance (6, 7). The dosing of BPAL-based regimens is shown in Table 1. The Joint Panel acknowledges the 2-week difference in treatment duration between ZeNix and TB-PRACTECAL and recommends a treatment duration of 26 weeks, considering expert opinion and CDC guidance (3). Early discontinuation or replacement of BPAL components may lead to worse treatment outcomes. In the Nix-TB and ZeNix trials, treatment was extended for a few patients to 39 weeks if sputum remained culture-positive or reverted to positive between months 4 and 6 or if clinical condition suggested progressive TB. For such patients or suspected failure, we recommend a complete reevaluation, including both molecular and phenotypic DST for resistance to components of BPAL, and weighing the individualized risks and benefits of extending BPAL to 39 weeks. Although at this time there is insufficient clinical trial evidence for or against such prolongation, expert opinion suggests consideration of treatment extension to 39 weeks if there is delayed treatment response (e.g., culture conversion >8 wk with clinical condition slow to improve) (3).

g. Linezolid dosing

The preferred dose of linezolid is 600 mg daily throughout the regimen. Therapeutic drug monitoring may help guide linezolid dosing with a goal trough of less than 2 µg/ml to minimize adverse reactions (33). This may be available through some public health or academic TB laboratories. If the

trough level is elevated, the Joint Panel suggests the dosing interval should be increased or the dose lowered.

5. Panel recommendation

In adolescents aged 14 years and older and adults with rifampin-resistant pulmonary TB who have resistance or patient intolerance to fluoroquinolones and either have had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month, we recommend the use of the 6-month treatment regimen, composed of bedaquiline, pretomanid, and linezolid (BPAL), rather than more than 15-month regimens (strong recommendation, very low certainty of evidence; Table E3). See Table 1 for dosing details.

PICO Question 4: In adolescents aged 14 and older and adults with rifampin-resistant, fluoroquinolone-susceptible pulmonary TB, is a 6-month regimen composed of bedaquiline, pretomanid, linezolid, and moxifloxacin as effective and safe as the 15-month or longer DR-TB regimens composed according to current ATS/CDC/ERS/IDSA DR-TB treatment guidelines?

1. Topic/overview/background

As discussed above, MDR-TB, RR-TB, and TB in individuals intolerant of rifampin have been associated with extended treatment duration and major morbidity and mortality. In the TB-PRACTECAL trial (19), which included study participants with MDR/RR- or pre-XDR-TB with or without fluoroquinolone resistance, WHO SoC regimens were compared with three all-oral 24-week investigative regimens, including a BPAL plus moxifloxacin (BPALM) arm. The SoC regimens included 9–12-month injectable-containing regimens; 18–24-month-long pre-2019 WHO regimens; a 9–12-month all-oral regimen; and an 18–20-month all-oral regimen. The study was an all open-label, multicenter, randomized noninferiority trial with a primary outcome of unfavorable status, which was a composite of death, treatment failure, treatment discontinuation, loss to follow-up, or recurrence of tuberculosis, at 72 weeks after randomization (19).

TB-PRACTECAL provided evidence for an assessment by WHO in 2022 (1). For individuals treated with BPALM who have received more than 9 weeks of linezolid but are unable to tolerate it, expert opinion suggests that some individuals, after careful review, may continue the remaining medications without linezolid (20). Prior recommendations discuss the role of surgery for DR-TB (6).

2. Summary of evidence, benefits, and harms

Participants receiving the BPALM regimen ($n = 62$) compared with those treated with SoC regimens ($n = 66$) experienced higher levels of treatment success (89% vs. 52%), lower levels of failure and recurrence (8% vs. 26%), lower levels of loss to follow-up (3% vs. 20%), and lower levels of grades 3 to 5 adverse events (21% vs. 51%). See Table 7.

3. Certainty of evidence

Certainty in estimated effects was very low because of multiple factors: bias risk from imbalance of comorbidities, high risk of unmeasured confounding, small event numbers, lack of blinding, early trial termination, population differences, varied comparator regimens (inclusion of 9- to 20-mo regimens), inconsistent treatment outcomes, and imprecision from small participant and outcome numbers (Table E4).

4. Monitoring and other considerations

a. Patient selection

The same selection considerations as in PICO 3 apply, but with the absence of known fluoroquinolone resistance here.

b. Subgroup considerations

Age

In low-incidence settings, a greater proportion of people with TB may be older than in the TB-PRACTECAL trial. Older individuals may receive more concurrent medications or have comorbidities with a higher risk for adverse events, including fluoroquinolone-related adverse events, such as neuropathy, tendinitis, QT prolongation, and dysglycemia (13).

Children and Pregnant and Lactating Individuals

Trials included participants ≥ 14 years old, excluding pregnant or lactating individuals, with

median participant age between 35 and 37 years old. Bedaquiline has a favorable pediatric adverse effect profile (21), whereas linezolid (22) and pretomanid data are limited or absent. At this time, longer regimens are recommended (6) for children under 14 years old and for lactating and pregnant individuals until safety and efficacy data become available. Moxifloxacin in the BPALM regimen was well tolerated in the age groups enrolled in TB-PRACTECAL (19).

People Living with HIV Infection

People living with HIV infection comprised 33% of the TB-PRACTECAL trial population, with median CD4 counts 330 cells/ μ l, although subgroup outcome analyses were not offered in these trials. In the Nix-TB study, in which 51% of participants were living with HIV, unfavorable outcomes were not influenced by HIV status (23). Treatment recommendations for BPALM, based on expert opinion, may be applied to all patients with RR/MDR-TB, regardless of HIV infection and CD4 count. The risks and benefits of 6-month or longer regimens should be discussed with the patient. Close monitoring is advised with low CD4 counts because of higher rates of disseminated disease and potential immune reconstitution syndrome. The potential for drug–drug interactions should be considered, in particular avoiding efavirenz in a BPAL-based regimen, because it can significantly decrease bedaquiline levels.

Extrapulmonary TB

Trials included patients with nonsevere forms of EPTB, making such patients eligible for BPALM. Severe forms, such as disseminated central nervous system or bone/joint TB, were excluded. No clinical trial evidence supports their treatment with BPALM, although limited programmatic experience has been published (24).

c. Clinical evaluation, monitoring, and evaluation

During treatment, patients should be monitored for treatment response and adverse events, with clinical, radiologic, and laboratory

assessments, including baseline, monthly, and as needed, according to Joint Panel opinion (Table 8). Monitoring frequency should be increased for those of older age, people living with HIV, diabetes, baseline anemia, visual impairment, renal or liver disease, or if significant clinical or laboratory abnormalities are found. Post-treatment monitoring for at least 1–2 years is recommended to identify recurrence. During BPALM treatment, baseline and follow-up monthly ECGs with QTc measurement are necessary (3, 25, 26).

d. Bacteriologic testing and DST

Sputum cultures should be obtained before treatment for DST and monitored weekly until smear conversion, every other week until culture conversion, and then monthly until the end of treatment. Isolates should be evaluated for susceptibility changes. Molecular methods, available through some state and national laboratories, such as the CDC (3), can detect moxifloxacin resistance and should be followed, when possible, by phenotypic testing because some molecular methods may miss heteroresistant populations (27, 28). DST is limited for bedaquiline, linezolid, and pretomanid but may become more available. DNA sequencing can detect mutations in genetic loci associated with resistance to BPALM drugs (29–31). If resistance to a drug in BPALM is detected by a molecular method or DST, an alternate regimen should be considered in consultation with laboratory and clinical experts tailored to susceptibility results (7).

e. Drug–drug interactions

Drug–drug interactions should always be considered. Classes and specific medications to avoid or that require additional precautions include but are not limited to efavirenz, QTc-prolonging medications, strong CYP3A4 inducers (including rifamycins), strong CYP3A4 inhibitors, monoamine oxidase inhibitors, many antidepressants, and drugs known to induce myelosuppression (Tables E3 and E4).

f. Regimen administration, composition, dosing, frequency, duration, and changes

DOT and integrated case management remain standard of care, as noted in the Joint Panel's 2019 guidance (6). The dosing of BPAL-based regimens is shown in Table 1. The Joint Panel acknowledges the 2-week difference in treatment duration between ZeNix and TB-PRACTECAL and recommends a treatment duration of 26 weeks, considering expert opinion and CDC guidance (3). Early discontinuation or replacement of BPALM components may lead to worse treatment outcomes. In the Nix-TB and ZeNix trials, treatment was extended for a few patients to 39 weeks if sputum remained culture-positive or reverted to positive between months 4 and 6 or if clinical condition suggested progressive TB. For such patients or suspected treatment failure, we recommend a complete reevaluation, including both molecular and phenotypic DST for resistance to components of BPALM, and weighing the individualized risks and benefits of extending BPALM to 39 weeks. Although at this time there is insufficient clinical trial evidence for or against such prolongation, expert opinion suggests consideration of treatment extension to 39 weeks if there is delayed treatment response (e.g., culture conversion >8 wk with clinical condition slow to improve) (3).

g. Linezolid dosing

The preferred dose of linezolid is 600 mg daily throughout the regimen. Therapeutic drug monitoring may help guide linezolid dosing with a goal trough of less than 2 μ g/ml to minimize adverse reactions (32). If the trough level is elevated, Joint Panel opinion suggests the dosing interval should be increased or the dose lowered.

5. Panel recommendation

In adolescents aged 14 years and older and adults with rifampin-resistant, fluoroquinolone-susceptible pulmonary TB, we recommend the use of a 6-month treatment regimen, composed of bedaquiline, pretomanid, linezolid, and moxifloxacin (BPALM), rather than the 15-month or longer regimens in patients with MDR/RR-TB (strong

recommendation, very low certainty of evidence; Table E4).

Discussion

Shorter treatment duration, oral regimens, reduced number of medications, reduced pill burden, and less adverse drug effects are valued by patients and providers (34–36). Individuals with DS-TB may be eligible for effective regimens that reduce treatment duration by one-third. Previously, only patients with smear- and culture-negative “nonsevere” pulmonary TB were recommended to receive 4 months of treatment (6). Adults and adolescents with DS-TB may now be offered 4 months of an RPT-MOX-based regimen. Most children with nonsevere TB can now be treated with 4 months of standard medications. For DR-TB, new all-oral 6-month regimens are more effective and safer than SoC regimens used for decades and may reduce morbidity and mortality. The BPAL-based regimens can be considered applicable also to those with intolerance of rifampin.

The regimens and staff training can be implemented within existing programmatic efforts. Access to regimens, monitoring tests, and DST may vary and should be assured. These regimens may allow redirection of resources for other programmatic needs. Patient-centered support, case management, education, and, in some cases, incentives may improve adherence and treatment success (6, 7).

The new shorter regimens are probably acceptable to clinicians and people with TB. The SHINE acceptability substudy (16) indicated that treatment administration was more difficult for younger than older children but may be offset by an 8-week shorter regimen. In the United States, BPAL regimen uptake within 2 years of FDA approval has been reported with good clinical outcomes (24).

Access to medications is variable, notably FDCs, rifapentine, bedaquiline, and pretomanid, which may improve. Child-friendly FDCs, which reduce pill burden, are available from the Stop TB Partnership’s Global Drug Facility, but not in the United States or many places in Europe. Increased availability would promote uptake of these recommended regimens. Net costs of implementing new regimens may improve with fewer patient visits, potentially offsetting higher costs of medications and

DST. Studies assessing the cost-effectiveness, impact on health equity, acceptability, and feasibility of these newest regimens are needed.

Evidence supports higher treatment success rates for MDR/RR-TB with BPAL/BALM treatment, with fewer adverse events and shorter duration than with longer SoC regimens. The 600-mg linezolid dose is preferred. A study in a country with high TB burden (37) found that BPAL-based regimens are cost-saving and more effective than WHO SoC regimens. In low TB incidence countries, bedaquiline is currently expensive and can be difficult to access. The all-oral, shorter-duration regimen with a reduced pill burden offered by BPAL/BPaLM is likely to confer substantial benefits, although these advantages were not directly quantified in clinical trials.

On the basis of the evidence available, the critical outcomes supported the benefits of BPAL/BPaLM. Although the certainty of evidence for adverse events was low, the likelihood of severe adverse events or amplification of resistance occurring was low.

A strong recommendation based on very low-quality evidence is justified because the evidence that the recommended regimen causes less overall harm is of high quality (38) despite the low certainty of evidence for desirable outcomes. Specifically, the Joint Panel had decided that the lone critical outcome for harms would be *on-treatment* adverse effects. This outcome was not measured in the published evidence, which had included follow-up beyond treatment completion. Therefore, the Joint Panel considered unpublished observational evidence as sequential evidence (39). The Joint Panel considered unpublished observational data from Panel members’ clinical experience in the use of both BPAL and BPaLM. The unpublished observational evidence indicated that standard therapy was associated with a very large increase in on-treatment adverse effects, which constitutes high-quality evidence. Although observationally based outcomes would, at first consideration, be rated as low certainty of evidence, with large treatment effect, the rating of the on-treatment adverse events as a critical outcome elevates by two levels the evidence to high quality of evidence.

The Joint Panel judged the 6-month BPAL/BPaLM regimens to be safer and easier for patient tolerance and adherence relative to prior longer SoC regimens. As the Joint Panel discussed while preparing this

guideline, the *de facto* situation is that the 6-month all-oral BPAL regimens are the accepted treatment of choice in TB treatment centers in higher-resourced countries that have access to BPAL. Other outcomes considered important to decision making include the potential for medication adverse effects to be drawn out over long periods of time with the SoC regimens, which is not captured by the adverse event incidence data; the high value placed on the all-oral, shorter BPAL and BPaLM regimens exemplified by their widespread adoption; and the potential for more rapid reintegration of treated patients into society, which may be related to more rapid destigmatization and improved health. The Joint Panel believes that there are significant harms associated with longer SoC regimens that are improved upon by the 6-month BPAL-based regimens. Thus, the strong recommendation in favor of the 6-month regimens is warranted.

We recommend BPaLM as the first line for MDR/RR-TB without fluoroquinolone resistance or intolerance. Although BPAL is an alternative, the Joint Panel believed that BPaLM, with DOT and close monitoring, might safely add protection against the emergence of drug resistance and increase culture conversion at 2 months. The BPAL-based regimens can be considered to apply to those with intolerance of rifampin. Monitoring DST for the emergence of resistance during treatment is very important.

The main limitations of this guideline update are methodological, using ADOLPMENT, and the level of certainty of evidence. We did not review raw data available to WHO. For all of our PICO questions, we specifically focused on WHO recommendations that updated prior joint panel guidance, and several newer regimens were out of scope of the selected PICO questions. Our PICO questions 3 and 4 were focused on 15-month or greater comparator regimens, although the WHO data available included 9-month treatment regimens. The certainty of the evidence for some outcomes was very low. Nevertheless, the beneficial treatment effects, all-oral regimen, and relatively few adverse events favored the shorter intervention regimens.

These recommendations are based on single or small studies, which may not reflect TB populations in the United States and Europe. TB clinical trial participants are younger than TB patients in the United States and Europe (40, 41). Adverse events may be more common in older individuals and may

Table 9. Research Needs

Diagnostic and translational studies

- Expansion of methods and use of culture-free rapid DST for moxifloxacin
- Description of the mechanism and molecular markers of pretomanid resistance, allowing development of DST methods
- Analyses of cross-resistance between drugs in current regimens with delamanid and surveillance for the development of resistance
- Analyses of cross-resistance between bedaquiline and clofazimine and surveillance for the development of resistance
- Assessment of the feasibility and accuracy of applying definitions for non-severe TB in routine clinical practice with particular emphasis on the radiographic components of the definition for children and adolescents <16 yr old

Treatment and outcomes

- Evaluation of longer-term outcomes for newly recommended regimens
- Reports of efficacy, safety, and tolerability of newly recommended regimens for subpopulations for whom current data are limited or missing (pregnant and lactating people, young children, older adults, people with significant renal or hepatic disease)
- Evaluation of these regimens for treatment of extrapulmonary and disseminated forms of tuberculosis
- Evaluation of treatment data from other regions and countries using these regimens
- Assessment of barriers to implementation of shorter regimens
- Evaluation of the uptake of shortened treatment regimens
- Evaluation of the acceptability of shorter treatment regimens from patient, medical provider, and other perspectives
- Evaluation of efficacy and added value in multidrug regimens of pretomanid and delamanid
- Determination of efficacy of other and even shorter regimens
- Evaluation of outcomes for which current evidence is scarce (e.g., acquisition of drug resistance and quality of life)
- Examination of the geographical differences in the frequency and severity of linezolid-related adverse events and the underlying cause
- Testing replacement of moxifloxacin with levofloxacin in newly recommended regimens
- Defining the role of and methods for ECG monitoring with newly recommended regimens, particularly for older adults
- Implementation of antibiotic stewardship measures for TB and community use of fluoroquinolones
- Use of pharmacokinetic data to refine dosing or for use in treatment monitoring
- Identification of strategies to ensure treatment adherence and completion to cure
- Data collection for cost-effectiveness and feasibility of newly recommended regimens
- Impact on health equity and acceptability of newly recommended regimens
- Ascertainment of efficacy of regimens by TB lineage
- Evaluating efficacy of adding clofazimine to BPaL in fluoroquinolone-resistant TB
- Analyses of pharmacokinetic data for crushed tablets used in treating children with TB
- Developing child friendly formulations for TB medications in high income countries
- Economic analyses of shorter regimen costs, DST, and monitoring

Definition of abbreviations: BPaL = bedaquiline, pretomanid, and linezolid; DST = drug susceptibility testing; TB = tuberculosis.

differ between trial and TB programmatic settings. These studies also excluded children with severe TB or DR-TB, pregnant individuals, and patients with severe forms of EPTB. Studies of treatment of individuals excluded from these trials, new regimens, emergence of drug resistance, and other issues will inform future guidelines (Table 9).

This Joint Panel guideline updates the 2016 and 2019 TB treatment guidelines (6, 7) in specific types of DS- and DR-TB. For patients who do not fit these categories, the

Joint Panel's prior guidelines should be consulted (6, 7). This document's focus is TB low-incidence high-resource contexts, in contrast to WHO's TB high-burden, lower-resource settings. DOT and integrated case management remain standard of care, as noted in the Joint Panel's prior guidance (6, 7). The Joint Panel offered a strong recommendation for BPaL/BPaLM for MDR-/RR-TB, whereas the WHO GDG provided a conditional recommendation. We continue to recommend DST to

guide therapy and DOT as standard of care for TB treatment. ■

Acknowledgment: The Joint Panel is very grateful to and thanks Drs. Dennis Falzon, Fuad Mirzayev, and Matteo Zignol and the WHO Global Tuberculosis Programme for sharing relevant materials for this guideline update. The authors thank John Harmon and Rachel Kaye of the American Thoracic Society for their tremendous support during the preparation and submission of this guideline. The authors also thank Dr. Beverly Sweeney and Dr. Ekaterina Kurbatova for their presentations to the Joint Panel.

This clinical practice guideline was prepared by an *ad hoc* joint panel of the ATS, CDC, ERS, and IDSA.

Members of the joint panel are as follows:

RAQUEL DUARTE, M.D., Ms.P.H., Ph.D. (Co-Chair)^{1,2,3*}
 SONAL S. MUNIFF, M.D., F.I.D.S.A. (Co-Chair)^{4†}
 PAYAM NAHID, M.D., M.P.H. (Co-Chair)^{6§}
 JUSSI J. SAUKKONEN, M.D., A.T.S.F. (Co-Chair)^{8,10§}
 CARLA A. WINSTON, Ph.D., M.A. (Co-Chair)^{11||}
 IBRAHIM ABUBAKAR, Ph.D.^{12*}
 CARLOS ACUÑA-VILLAORDUÑA, M.D.^{9,14‡}
 PENNAN M. BARRY, M.D., M.P.H.^{15§}
 MAYARA L. BASTOS, M.D., Ph.D.^{16,17‡}
 WENDY CARR, Ph.D.^{11||}
 HASSAN CHAMI, M.D., M.Sc.^{18¶}

LISA L. CHEN, M.D.^{7§}
 TERENCE CHORBA, M.D., D.Sc.^{11||}
 CHARLES L. DALEY, M.D.^{19§}
 ANTHONY J. GARCIA-PRATS, M.D., M.Sc., Ph.D.^{20,21§,**}
 KELLY HOLLAND, M.D.^{22‡‡}
 IOANNIS KONSTANTINIDIS, M.D., M.S.^{23¶||}
 MARC LIPMAN, M.D., F.R.C.P.^{13,24*}
 MANOJ J. MAMMEN, M.D., M.S.^{5§§}
 GIOVANNI BATTISTA MIGLIORI, M.D.^{25*}
 FARAH M. PARVEZ, M.D., M.P.H.^{11||}
 ADRIENNE E. SHAPIRO, M.D., Ph.D.^{26‡}
 GIOVANNI SOTGIU, Ph.D., M.D.^{27*}
 JEFFREY R. STARKE, M.D.^{28‡,**}

ANGELA M. STARKS, Ph.D.^{11||}
 SANKET THAKORE, M.D.^{29¶}
 SHU-HUA WANG, M.D., PHARM.D., M.P.H.^{30‡}
 JONATHAN M. WORTHAM, M.D.^{11||}

*ERS representative.

‡IDSA-selected representative.

§ATS representative.

||CDC representative.

¶Methodology scholar.

**Pediatric specialist.

‡‡Patient representative.

§§Lead methodologist.

¹EPIUnit – Instituto de Saúde Pública, Universidade do Porto, Laboratório para a Investigação Integrativa e Translacional em Saúde Populacional, Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Porto, Portugal; ²Unidade de Investigação Clínica da ARS Norte, Porto, Portugal; ³Serviço de Pneumologia, Centro Hospitalar de Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal; ⁴Division of Infectious Diseases and ⁵Division of Pulmonary & Critical Care, Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, New York; ⁶UCSF Office of Research and ⁷Curry International Tuberculosis Center, UCSF Center for Tuberculosis, UCSF Institute for Global Health Sciences, Division of Pulmonary & Critical Care Medicine, University of California, San Francisco, Zuckerberg San Francisco General Hospital and Trauma Center, San Francisco, California; ⁸Division of Pulmonary and Critical Care Medicine and ⁹Section of Infectious Diseases, Department of Medicine, Boston University Chobanian & Avedisian School of Medicine, Boston, Massachusetts; ¹⁰Boston Veterans Administration Health Care System, West Roxbury, Massachusetts; ¹¹Division of Tuberculosis Elimination, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, U.S. Centers for Disease Control and Prevention, Atlanta, Georgia; ¹²Faculty of Population Health Sciences and ¹³UCL Respiratory Medicine, Faculty of Medicine, University College London, London, United Kingdom; ¹⁴Lemuel Shattuck Hospital, Massachusetts Department of Public Health, Boston, Massachusetts; ¹⁵Tuberculosis Control Branch, Division of Communicable Disease Control, Center for Infectious Diseases, California Department of Public Health, Richmond, California; ¹⁶McGill International TB Center, Faculty of Medicine, McGill University, Montreal, Quebec, Canada; ¹⁷Department of Family Medicine, Max Rady College of Medicine, University of Manitoba,

Winnipeg, Manitoba, Canada; ¹⁸Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland; ¹⁹Division of Mycobacterial and Respiratory Infections, Department of Medicine, National Jewish Health and University of Colorado School of Medicine, Denver, Colorado; ²⁰Department of Pediatrics, School of Medicine and Public Health, University of Wisconsin–Madison, Madison, Wisconsin; ²¹Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa; ²²We Are TB; ²³Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, Department of Medicine, Veterans Affairs Pittsburgh Health Care System and University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; ²⁴Respiratory Medicine, Royal Free Hospital, London, United Kingdom; ²⁵Servizio di Epidemiologia Clinica delle Malattie Respiratorie, Istituti Clinici Scientifici Maugeri, Istituto di Ricovero e Cura a Carattere Scientifico, Tradate, Italy; ²⁶Department of Global Health and Division of Allergy and Infectious Diseases, Department of Medicine, University of Washington, Seattle, Washington; ²⁷Clinical Epidemiology and Medical Statistics Unit, Department of Medicine, Surgery and Pharmacy, University of Sassari, Sassari, Italy; ²⁸Department of Pediatrics, Baylor College of Medicine, Houston, Texas; ²⁹Section of Pulmonary Critical Care and Sleep Medicine, Department of Internal Medicine, Yale School of Medicine, Yale University, New Haven, Connecticut; and ³⁰Division of Infectious Diseases, Department of Internal Medicine, College of Medicine, The Ohio State University, Columbus, Ohio

Joint Panel Disclosures: R.D. received research support from Unite4TB. M.M. served as a consultant for the American College of Chest Physicians; served as president-elect for the New York State Thoracic Society; and received research support from the University

of Rochester. L.C. received honoraria from the Federal Advisory Council for the Elimination of Tuberculosis/DHHS; served in a leadership role for the International Union Against TB and Lung Disease North American Region and Stop-TB USA; and received research support from the CDC and USAID. C.L.D. served as a consultant for AN2, AstraZeneca, Galapagos, Genentech, Hyfe, Insmmed, Juvabis, MannKind Corporation, Matinas Biopharma, Paratek Pharmaceuticals, Pfizer, Spero, and Zambon; served on a data and safety monitoring board for AN2, AstraZeneca, the Bill and Melinda Gates Foundation, Cepheid, Eli Lilly, Galapagos, Hyfe, Insmmed, MannKind, Matinas, Nob Hill, Otsuka American Pharmaceuticals, Paratek, Spero, and Zambon; served as a scientific advisor and investigator for the Cystic Fibrosis Foundation; received research support from AN2, Bugworks, COPD Foundation, Cystic Fibrosis Foundation, FDA, Insmmed, Juvabis, NIH, Paratek, PCORI, and Renovion; served as a speaker for Med Learning Group, NACE, RMEI, and Rockpointe; and holds stock with Nob Hill. A.J.G.P. received research support from NIH and UnitaId. K.H. received travel support from the National Tuberculosis Coalition of America. M.L. served in a leadership role for NTM Network UK and NTM Patient Care UK. A.E.S. served on a data and safety monitoring board for the Datura clinical trial; and received research support from the NIH/NIAID and Vir Biotechnology. S.H.W. served on an advisory board for the Texas Biomedical Research Institute; served in a leadership role for the National Tuberculosis Coalition of America; received research support from Oxford Immunotec and Revvity; and served as a reviewer and received royalties from UpToDate. P.N. served as an expert witness for Bowman Brooke. J.S., S.S.M., C.A.W., I.A., C.A.V., P.B., M.L.B., W.C., H.C., T.C., I.K., G.B.M., F.P., G.S., J.S., A.S., S.T., and J.M.W. reported no commercial or relevant non-commercial interests from ineligible companies.

References

- World Health Organization (WHO). WHO consolidated guidelines on tuberculosis. Module 4: treatment—drug-resistant tuberculosis treatment, 2022 update. Geneva, Switzerland: WHO; 2022.
- World Health Organization (WHO). WHO consolidated guidelines on tuberculosis. Module 4: treatment: drug-susceptible tuberculosis treatment. Geneva, Switzerland: WHO; 2022.
- Centers for Disease Control and Prevention (CDC). Provisional CDC guidance for the use of Pretomanid as component by a regimen [Bedaquiline, Pretomanid, the Linezolid (BPAL)] to treatments drug-resistant tuberculosis condition. Atlanta, GA: CDC; 2023.
- Carr W, Kurbatova E, Starks A, Goswami N, Allen L, Winston C. Interim guidance: 4-month rifampentine-moxifloxacin regimen for the treatment of drug-susceptible pulmonary tuberculosis—United States, 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:285–289.
- Schünemann HJ, Wiercioch W, Brozek J, Etzeandia-Ikobaltzeta I, Mustafa RA, Manja V, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. *J Clin Epidemiol* 2017;81:101–110.
- Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis* 2016;63:e147–e195.
- Nahid P, Mase SR, Migliori GB, Sotgiu G, Bothamley GH, Brozek JL, et al. Treatment of drug-resistant tuberculosis. An official ATS/CDC/ERS/IDSA clinical practice guideline. *Am J Respir Crit Care Med* 2019;200:e93–e142.
- Evidence Prime. GRADEpro Guideline Development Tool. Hamilton, ON, Canada: McMaster University and Evidence Prime; 2024.
- Akl EA, Guyatt GH, Irani J, Feldstein D, Wasi P, Shaw E, et al. “Might” or “suggest”? No wording approach was clearly superior in conveying the strength of recommendation. *J Clin Epidemiol* 2012;65:268–275.
- Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. *J Clin Epidemiol* 2013;66:151–157.
- Dorman SE, Nahid P, Kurbatova EV, Phillips PP, Bryant K, Dooley KE, et al. Tuberculosis Trials Consortium. Four-month rifampentine regimens with or without moxifloxacin for tuberculosis. *N Engl J Med* 2021;384:1705–1718.

12. Pettit AC, Phillips PP, Kurbatova E, Vernon A, Nahid P, Dawson R, *et al.*; Tuberculosis Trials Consortium (TBTC) Study 31/AIDS Clinical Trials Group (ACTG) A5349 study team. Rifapentine with and without moxifloxacin for pulmonary tuberculosis in people with human immunodeficiency virus (S31/A5349). *Clin Infect Dis* 2023;76: e580–e589.
13. Stahlmann R, Lode H. Safety considerations of fluoroquinolones in the elderly: an update. *Drugs Aging* 2010;27:193–209.
14. Moro RN, Scott NA, Vernon A, Tepper NK, Goldberg SV, Schwartzman K, *et al.* Exposure to latent tuberculosis treatment during pregnancy. The PREVENT TB and the iAdhere trials. *Ann Am Thorac Soc* 2018; 15:570–580.
15. Sterling TR, Njie G, Zenner D, Cohn DL, Reves R, Ahmed A, *et al.* Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. Philadelphia, PA: Elsevier; 2020. p. 1196–1206.
16. Turkova A, Wills GH, Wobudeya E, Chabala C, Palmer M, Kinikar A, *et al.*; SHINE Trial Team. Shorter treatment for nonsevere tuberculosis in African and Indian children. *N Engl J Med* 2022;386: 911–922.
17. Shah N, Westenhouse J, Lowenthal P, Schechter G, True L, Mase S, *et al.* The California multidrug-resistant tuberculosis consult service: a partnership of state and local programs. *Public Health Action* 2018;8: 7–13.
18. Conradie F, Bagdasaryan TR, Borisov S, Howell P, Mikiashvili L, Ngubane N, *et al.*; ZeNix Trial Team. Bedaquiline–pretomanid–linezolid regimens for drug-resistant tuberculosis. *N Engl J Med* 2022;387: 810–823.
19. Nyang'wa B-T, Berry C, Kazounis E, Motta I, Parpieva N, Tigay Z, *et al.* A 24-week, all-oral regimen for rifampin-resistant tuberculosis. *N Engl J Med* 2022;387:2331–2343.
20. World Health Organization (WHO). WHO operational handbook on tuberculosis. Module 4: treatment—drug-resistant tuberculosis treatment, 2022 update. Geneva, Switzerland: WHO; 2022.
21. Moodliar R, Aksenova V, Frias M, Van de Logt J, Rossenu S, Birmingham E, *et al.* Bedaquiline for multidrug-resistant TB in paediatric patients. *Int J Tuberc Lung Dis* 2021;25:716–724.
22. Garcia-Prats AJ, Schaaf HS, Draper HR, Garcia-Cremades M, Winckler J, Wiesner L, *et al.* Pharmacokinetics, optimal dosing, and safety of linezolid in children with multidrug-resistant tuberculosis: combined data from two prospective observational studies. *PLoS Med* 2019;16:e1002789.
23. Solans BP, Imperial MZ, Olugbosi M, Savic RM. Analysis of dynamic efficacy endpoints of the Nix-TB Trial. *Clin Infect Dis* 2023;76:1903–1910.
24. Haley CA, Schechter MC, Ashkin D, Peloquin CA, Cegielski JP, Andriano BB, *et al.*; BPaL Implementation Group. Implementation of bedaquiline, pretomanid, and linezolid in the United States: experience using a novel all-oral treatment regimen for treatment of rifampin-resistant or rifampin-intolerant tuberculosis disease. *Clin Infect Dis* 2023;77:1053–1062.
25. U.S. Food and Drug Administration (FDA). Sirturo [prescribing information]. Silver Spring, MD: FDA; 2023 [accessed 2024 Nov 19]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/204384s017bl.pdf.
26. Janssen Science. Sirturo (bedaquiline). Beerse, Belgium: Janssen Pharmaceuticals; 2024 [accessed 2024 Nov 19]. Available from: <https://www.janssenscience.com/products/sirturo>.
27. Rigouts L, Miotto P, Schats M, Lempens P, Cabibbe A, Galbiati S, *et al.* Fluoroquinolone heteroresistance in *Mycobacterium tuberculosis*: detection by genotypic and phenotypic assays in experimentally mixed populations. *Sci Rep* 2019;9:11760.
28. Ye M, Yuan W, Molaeipour L, Azizian K, Ahmadi A, Kouhsari E. Antibiotic heteroresistance in *Mycobacterium tuberculosis* isolates: a systematic review and meta-analysis. *Ann Clin Microbiol Antimicrob* 2021;20: 73–79.
29. UCSF. Drug Resistant TB: a Survival Guide for Clinicians, 3rd edition, 2022 [accessed 2024 Nov 11]. Available from: https://www.currytbcenter.ucsf.edu/sites/default/files/2023-06/SG3_2022_Chapter8_MonitoringCaseManagement.pdf#monitorchklist.
30. World Health Organization (WHO). Catalogue of mutations in *Mycobacterium tuberculosis* complex and their association with drug resistance. Geneva, Switzerland: WHO; 2021.
31. World Health Organization (WHO). Technical guide on next-generation sequencing technologies for the detection of mutations associated with drug resistance in *Mycobacterium tuberculosis* complex. Geneva, Switzerland: WHO; 2018.
32. Kadura S, King N, Nakhoul M, Zhu H, Theron G, Köser CU, *et al.* Systematic review of mutations associated with resistance to the new and repurposed *Mycobacterium tuberculosis* drugs bedaquiline, clofazimine, linezolid, delamanid and pretomanid. *J Antimicrob Chemother* 2020;75:2031–2043.
33. Song T, Lee M, Jeon H-S, Park Y, Dodd LE, Dartois V, *et al.* Linezolid trough concentrations correlate with mitochondrial toxicity-related adverse events in the treatment of chronic extensively drug-resistant tuberculosis. *EBioMedicine* 2015;2:1627–1633.
34. Nagarajan K, Kumarsamy K, Begum R, Panibatl V, Reddy R, Adepu R, *et al.* A dual perspective of psycho-social barriers and challenges experienced by drug-resistant TB patients and their caregivers through the course of diagnosis and treatment: findings from a qualitative study in Bengaluru and Hyderabad Districts of South India. *Antibiotics* 2022; 11:1586.
35. Baral SC, Aryal Y, Bhatrai R, King R, Newell JN. The importance of providing counselling and financial support to patients receiving treatment for multi-drug resistant TB: mixed method qualitative and pilot intervention studies. *BMC Public Health* 2014;14:46–47.
36. Thomas BE, Shanmugam P, Malaisamy M, Ovung S, Suresh C, Subbaraman R, *et al.* Psycho-socio-economic issues challenging multidrug resistant tuberculosis patients: a systematic review. *PLoS One* 2016;11:e0147397.
37. Sweeney S, Berry C, Kazounis E, Motta I, Vassall A, Dodd M, *et al.* Cost-effectiveness of short, oral treatment regimens for rifampicin resistant tuberculosis. *PLoS Glob Public Health* 2022;2:e0001337.
38. Andrews JC, Schünemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, *et al.* GRADE guidelines: 15. Going from evidence to recommendation—determinants of a recommendation's direction and strength. *J Clin Epidemiol* 2013;66:726–735.
39. Gershon AS, Lindenauer PK, Wilson KC, Rose L, Walkey AJ, Sadatsafavi M, *et al.* Informing healthcare decisions with observational research assessing causal effect. An official American Thoracic Society research statement. *Am J Respir Crit Care Med* 2021;203: 14–23.
40. Centers for Disease Control and Prevention (CDC). Reported tuberculosis in the United States, 2023 [accessed 2024 Nov 19]. Available from: <https://www.cdc.gov/mmwr/volumes/73/wr/mm7312a4.htm>.
41. European Centre for Disease Prevention and Control and World Health Organization. Tuberculosis surveillance and monitoring in Europe 2022–2020 data. European Centre for Disease Prevention and Control; 2022 [accessed 2024 Nov 19]. Available from: <https://www.ecdc.europa.eu/en/publications-data/tuberculosis-surveillance-and-monitoring-europe-2022-2020-data>.