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Drug Class Review: Mycobacterium Drugs

Date of Review: June 2022 **Literature Search:** 01/01/2015-01/19/2022
Generic Name: See **Appendix 1**

Purpose for Class Review:
To review evidence related to agents targeting mycobacteria and identify appropriate utilization management strategies.

Research Questions:

1. What is the comparative efficacy and effectiveness of mycobacterial agents for the management of diseases caused by mycobacteria infections?
2. What are the comparative harms of antimicrobials used for the management of diseases caused by mycobacteria infections?
3. Are there subgroups of patients based on demographics (e.g., age, racial or ethnic groups, gender), other medications, prior anti-mycobacterial treatment experience, or co-morbidities for which one mycobacteria agent is more effective or associated with fewer adverse events?

Conclusions:

- Evidence was summarized from 3 systematic reviews, 10 high-quality guidelines, and 1 randomized controlled trial (RCT).
- For treatment of brucellosis infection, there was increased risk of treatment failure (relative risk [RR] 2.36; 95% confidence interval [CI] 1.72 to 3.23; P<0.001; I^2=0.0%) and higher risk of relapse (RR 2.74; 95% CI 1.80 to 4.19; I^2=0.0%) with rifampin compared to streptomycin, when given in conjunction with doxycycline background therapy. The subpopulation analysis when the mean population age was over 40 years did not show a difference in treatment failure between rifampin versus streptomycin (RR 1.92; 95% CI 0.93 to 3.97; P=0.078). Differences in safety between the two therapies were not assessed.[1]
- Treatment of non-tubercular pulmonary mycobacteria infections should include multi-drug therapy with the components and length of therapy tailored to the causative organism, susceptibility profile, and severity of illness. If susceptible, most commonly recommended agents are macrolides (clarithromycin, azithromycin), rifampin, isoniazid, ethambutol, fluoroquinolones (FQ) (levofloxacin, moxifloxacin), and aminoglycosides (amikacin, streptomycin).[2,3] Certainty of evidence is generally low.[2,3]
- For all patients with latent TB regardless of human immunodeficiency virus (HIV) status or tuberculosis (TB) prevalence, the World Health Organization (WHO) recommends 6 or 9 months of daily isoniazid, or 3 months of weekly rifapentine plus isoniazid, or 3 months of daily isoniazid plus rifampin as preferred regimens (strong recommendation, moderate to high certainty).[4,5]
- For latent TB, the Centers for Disease Control (CDC) recommend 3 months of weekly isoniazid plus rifapentine (strong recommendation; Adults and children aged >2 years, including HIV-positive persons [as drug interactions allow]), 4 months of daily rifampin (strong recommendation; HIV-negative adults and

children of all ages), and 3 months of daily isoniazid plus rifampin (conditional recommendation; Adults and children of all ages and for HIV-positive persons [as drug interactions allow]) as preferred regimens.[6]

- The preferred regimen for treatment of drug-susceptible TB is 8 weeks of daily isoniazid, rifampin, pyrazinamide, and ethambutol followed by 18 weeks of isoniazid plus rifampin.[7-9]
- Based on evidence from single, open-label RCT, a 4 month regimen consisting of 8 weeks of rifapentine, moxifloxacin, isoniazid, and pyrazinamide followed by 9 weeks of rifapentine, moxifloxacin, and isoniazid, is non-inferior compared to the standard 6 month treatment for the primary endpoint of TB free survival at 12 months for patients with pulmonary TB in those 12 years and older who met other specific inclusion criteria. There were no significant differences in grade 3 or higher adverse reactions.[10] This regimen may be considered as a possible alternative to the standard 6 month regimen in certain patients, particularly those who may be unlikely to complete the longer regimen.[11,12]
- For drug-resistant TB, the WHO recommends the shorter duration all-oral bedaquiline-containing regimen for eligible people who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to FQs has been excluded (conditional recommendation, very low certainly evidence). Bedaquiline, linezolid, and a FQ should be included in treatment of multi-drug resistant (MDR) or rifampin-resistant TB in patients on longer regimens (strong recommendation, moderate certainty evidence for bedaquiline 18 years and over, linezolid, and FQs; conditional recommendation with very low certainty evidence for bedaquiline in people aged 6 to 17 years).[13]
- For drug-resistant TB, the CDC recommends individualized therapy with at least 5 drugs during the intensive phase and 4 drugs during the continuation phase (conditional recommendation, very low certainty evidence). Bedaquiline, moxifloxacin, and levofloxacin all have strong recommendations for inclusion if microbe is susceptible (only one FQ agent in regimen) based on very low certainty evidence. [14]
- In children 3 months to 16 years with non-severe TB without drug resistance, a 4 month treatment regimen of 2 months isoniazid/rifampin/pyrazinamide +/- ethambutol, then 2 months isoniazid/rifampin is preferred (strong recommendation, moderate certainty of evidence).[15]
- Agents in this class have a variety of contraindications, adverse reactions, and drug interactions which are more likely to affect those with certain comorbidities, especially those with hepatic dysfunction and HIV patients taking certain medications. Treatment of mycobacterial infections should be individualized and monitored closely, particularly in at-risk subgroups.

Recommendations:

- Create New Preferred Drug List (PDL) class of oral drug therapies called Mycobacterium Agents as listed in **Appendix 1**
- After review of costs in executive session:
    - Remove bedaquiline non-preferred status and prior authorization requirement.
    - Make class open access with no utilization controls, including for new products and formulations as they come to market.

Background:

Mycobacteria are aerobic, non-motile bacteria which are identified in the laboratory by positive acid-fast alcohol stains.[16] Those responsible for human disease are generally categorized as tubercular (TB), caused by *Mycobacterium tuberculosis*, and nontuberculosis mycobacteria (NTM), such as *Mycobacterium avium* complex (MAC), *Mycobacterium abscessus*, and *Mycobacterium kansasii*.[16] Growth rates are further used to classify NTM as slowly growing (e.g. MAC) and rapidly growing (e.g. *M. abscessus*). Both *M. tuberculosis* and NTM are primarily associated with pulmonary infections, though both can affect other organ systems.[16]

M. tuberculosis exposure, via aerosol droplets, results in one of several outcomes. Exposed persons may immediately clear the organism, immediately develop active disease (primary disease), develop a latent infection, or experience active disease after latent infection (reactivation disease).[17] Reactivation occurs in 5 to 10% of healthy individuals. However, reactivation is markedly higher in those who are immunocompromised, especially those with uncontrolled HIV.[17] Young children are more likely to develop active TB disease, and severe forms of disease after exposure.[15] Most infections in low-burden countries like the United States are categorized as reactivation after exposure 2 years or earlier in foreign-born residents coming from countries with high endemic rates (subgroup case rate 11.5 per 100,000 in 2020).[18] In the United States in 2020, the total TB case rate was 2.2 per 100,000 persons with the highest rates (>2.8 per 100,000) in Hawaii, New York City, California, Washington DC, and Texas; Oregon TB case rates are estimated between 1.4 and 2.8 per 100,000 persons.[18] Testing for HIV should occur at TB diagnosis. Those at highest risk of new HIV diagnosis are people who inject drugs, persons experiencing homelessness, inmates, and those with alcohol use disorder.[18] The risk of TB acquisition after exposure or reactivation of latent disease is more likely with comorbid HIV, and simultaneously, the progression of HIV may be accelerated by concomitant TB.[18]

Public health reporting in Oregon is required for TB, *M. bovis*, and non-respiratory NTM infections.[19] Disease prevalence and laboratory isolation of NTM seem to be increasing with improved culture techniques.[16] Nontubercular mycobacteria are commonly found in the water and soil; water systems in hospitals, hemodialysis centers, and dental centers often have high rates of colonization, due to biofilm formation.[16] Most people have been exposed to NTM; however, disseminated disease is more common in those with significant immunosuppression, such as individuals with structural lung diseases and untreated HIV. Patients with cystic fibrosis (CF) or a history of lung transplantation are at particular risk of pulmonary NTM infections.[16] Patients with more common chronic lung conditions such as asthma or chronic obstructive pulmonary disease are also at higher risk, as the chronic epithelial cell inflammation and impaired mucociliary clearance may predispose patients to infection.[2] Nontubercular mycobacteria can reside in the lungs of exposed individuals transiently, intermittently, and permanently; differentiation of asymptomatic NTM pulmonary infection and active disease requiring treatment can be problematic.[2] Tuberculosis is the leading cause of death from infectious diseases worldwide, while NTM may also be fatal and is a common cause of lung disease.[16,20] Clinical trial outcomes vary based on organism (e.g. TB vs NTM, etc.), disease location, and active versus latent infection. Common outcomes of interest are cure, treatment completion, treatment failure, disease relapse, time to sputum culture or smear conversion (time to change from positive to negative status during treatment), clinical or radiological improvement at 8 weeks and at the end of treatment, mortality, and serious adverse events or adverse events requirement treatment alteration.[8]

The standard treatment for active pulmonary TB generally consists of an 8 week intensive phase followed by a continuation phase, usually for 18 additional weeks.[7-9] Fixed-dose combination products are sometimes available to simplify administration, though this is more common outside of the United States. First-line treatment includes isoniazid (with concomitant pyridoxine for individuals at higher risk peripheral neuropathy), rifampin (synonymous with official International and British nomenclature name of rifampicin), pyrazinamide, and ethambutol for the intensive phase and isoniazid plus rifampin for the continuation phase. Other medications can be considered based on resistance and drug intolerance for second-line therapy. If drug sensitivity is known and both isoniazid and rifampin are sensitive, then ethambutol can be omitted from the intensive phase.[9] Isoniazid causes a rapid drop in multiplying bacteria, ethambutol has early bactericidal activity, while both pyrazinamide and rifamycins have a sterilizing effect to prevent relapses. Rifamycin-type agents include rifampin,

rifabutin, and rifapentine, all used for mycobacteria, as well as rifamycin and rifaximin, which have non-mycobacterial indications. Rifabutin has a niche in first-line therapy to minimize drug interactions, as other rifamycins cause more pronounced hepatic enzyme induction which may result in problematic drug-drug interactions, particularly in certain antiretroviral (ART) regimens.[9] Rifapentine and rifampin are not interchangeable.[6] Rifamycins, specifically rifampin and rifapentine, have been plagued by drug shortages since at least 2020 when one manufacturer discontinued making rifampin and several rifampin-containing fixed-dose combination products, while simultaneously the FDA implemented new testing for nitrosamines, resulting some product shipments being held.[21-24]

Many different treatment dosing intervals have been studied for TB. For active disease, daily dosing remains preferred for the intensive phase and continuation phase, though in certain circumstances thrice-weekly regimens may also be preferred or a reasonable option in the continuation phase.[9] Recommendations can vary in certain clinical circumstances, such as latent infection, age, extrapulmonary or disseminated disease, previous treatment (1 month or more of anti-TB agents in past) and with comorbidities such as HIV.[9,13]

Concerns about drug resistance, specifically MDR-TB (resistant against at least rifampin and isoniazid) and extensively drug-resistant (XDR)-TB (resistant to rifampin, isoniazid, at least one injectable agent [amikacin, kanamycin, or capreomycin], and any of the FQs) are increasing.[14,25] The term “pre-XDR” TB is entering the lexicon as MDR-TB with FQ resistance.[13] Less than 5% of cases worldwide are considered MDR-TB, though this can be over 25% in some areas, specifically many former Soviet countries.[25] Resistance complicates treatment and often requires longer treatment durations.[25] Shorter MDR-TB regimens are defined as 9-12 months and is usually standardized, while longer MDR-TB regimens last 18 months or more and may be standardized or individualized.[13] Treatment of NTM disease includes multi-drug regimens with a duration of several months to greater than 1 year and varies widely by specific organism, site of infection, patient comorbidities, and susceptibility testing.[2,3] Other antimicrobial classes of medications, including FQs, aminoglycosides, and macrolides, can be used in the treatment of NTM and TB in specific treatment situations. Previous guidelines from WHO for treatment of MDR-TB have categorized medications in groups (e.g. group A/fluoroquinolones, group B/second-line injectable agents)[26], though classifications and nomenclature are being adjusted as recommendations change.[13] Rifampin and other rifamycins may also be used, usually in conjunction with other antimicrobials, to treat infections not caused by mycobacteria.

Table 1. World Health Organization Grouping of Medicines for longer MDR-TB regimens[27]

Medication Group	Medications*
Group A • Considered highly effective and strongly recommended for inclusion in all regimens unless contraindicated.	• Levofloxacin *or* Moxifloxacin • Bedaquiline • Linezolid
Group B • Conditionally recommended as agents of second choice.	• Clofazimine • Cycloserine *or* Terizidone
Group C • All other medicines that can be used when a regimen cannot be composed with Group A and B agents. • Ranked by the relative balance of benefit to harm usually expected of each agent.	• Ethambutol • Delamanid • Pyrazinamide • Imipenem-cilastatin *or* Meropenem • Amikacin *or* streptomycin (only if amikacin cannot be used because of availability or documented resistance) • Ethionamide *or* Prothionamide • *p*-aminosalicylic acid
Not included in Groups A through C: • Kanamycin and capreomycin are associated with poorer outcomes • Gatifloxacin and high-dose isoniazid were used in very few patients and thioacetazone was not used at all. Gatifloxacin and thioacetazone are not currently available in quality-assured formulations. High-dose isoniazid may have a role in patients with confirmed susceptibility to isoniazid. • Clavulanic acid should be included only as a companion agent to the carbapenems and should not be counted as an additional effective agent. *Not all agents currently marketed in the United States Note: Pretomanid is absent from table as current place in therapy is as a component of shorter MDR-TB regimens.[13]	

The medications specific to mycobacterial infections (**Appendix 1**) have not been previously reviewed for the Oregon Health Plan (OHP) Fee-for-Service (FFS) PDL, with the exception of bedaquiline, which was reviewed in 2014 after its Food and Drug Administration (FDA) approval using phase 2 studies. It was made non-preferred given insufficient evidence to support efficacy and a black box warning for increased risk of death. Pyridoxine, used as ancillary therapy to reduce the risk of peripheral neuropathy secondary to isoniazid, is a preferred agent on the OHP PDL. Other rifamycin type drugs (e.g. rifamycin, rifaximin) are FDA approved for *E. coli* related traveler's diarrhea and hepatic encephalopathy and are not part of the proposed Mycobacterium Drugs PDL class. Moxifloxacin was moved to preferred status on the PDL at the April 2022 Pharmacy and Therapeutics committee meeting, while levofloxacin was already a preferred agent. Linezolid, azithromycin, and immediate-release clarithromycin tablets are also preferred agents in the oxazolidinones and macrolide PDL classes. Based on 2019

medical claims, the Fee-For-Service (FFS) Medicaid population had fewer than 200 TB cases in adults and children (all anatomic locations). Only one TB patient was coded as having drug resistance and few individuals had concomitant HIV. There were fewer than 150 NTM cases with about 10% having HIV, while ~90 additional patients had ICD-10 codes consistent with latent TB infection. Given length of time in treatment, most patients with mycobacterial infections would be enrolled in a coordinated care organization (CCO) for the duration of therapy. Due to limitations of medical claims, this data may not accurately reflect all new or recent infections and numbers likely overestimate frequency of these infections in the FFS population.

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

Table 2. Indications and Dosing.[28]

Drug Name	Indication(s)*	Strength/Route	Dose and Frequency
Bedaquiline	• MDR TB, in combination with at least 3 other agents	Oral tablet: 20 mg, 100 mg	• 400 mg daily x2 weeks, then 200 mg 3 times weekly x 22 weeks
Aminosalicylic acid	• Active TB	Oral Powder for Suspension, Extended Release: 4 g/1 Packet	• 4 g orally 2 or 3 times/day
Cycloserine	• Active TB • Urinary tract infection (only when more conventional therapy has failed and organism has been demonstrated to be susceptible)	Oral Capsule: 250 mg	• Initial, 250 mg orally every 12 hours for 2 weeks • Then, 500 to 1000 mg/day given in divided doses • MAX dose, 1 g/day
Ethambutol	• Adjunct for pulmonary TB	Oral Tablet: 100 mg, 400 mg	• Varies by weight
Ethionamide	• Active TB	Oral Tablet: 250 mg	• Initial: 250 mg orally once daily for 1 or 2 days • Titration: increase to 250 mg twice daily for 1 or 2 days, then 1 g daily in 3 to 4 divided doses. • Usual dose is 15 to 20 mg/kg/day administered once daily if tolerated or in divided doses if necessary. A daily dosage of 0.5 g to 1 g may reduce resistance • MAX 1 g daily
Isoniazid	• Active TB (with and without concomitant HIV) • Latent TB (with and without concomitant HIV)	• Intramuscular Solution: 100 mg/1 mL • Oral Solution: 50 mg/5 mL • Oral Tablet: 100 mg, 300 mg	• Varies by indication
Pretomanid	• MDR TB, in combination bedaquiline and linezolid	Oral Tablet: 200 mg	• 200 mg once daily in combination with bedaquiline and linezolid for 26 weeks or longer if necessary
Pyrazinamide	• Active TB (with and without concomitant HIV)	Oral Tablet: 500 mg	• Varies, weight based
Rifabutin	• Disseminated infection due to MAC • Prophylaxis of MAC in patients with advanced HIV	Oral Capsule: 150 mg	• 300 mg once daily
Rifampin	• Active TB (with and without concomitant HIV) • Latent TB (with and without concomitant HIV) • Reactivation TB • Extrapulmonary TB • Asymptomatic carriers of *N. meningitidis*	IV Powder for Solution: 600 mg Oral Capsule: 150 mg, 300 mg	• Varies by indication
Rifapentine	• Active TB • Latent TB	Oral Tablet: 150 mg	• Varies by indication and weight

Abbreviations: g = gram; HIV = Human Immunodeficiency Virus; IV = intravenous; MAC = Mycobacterium avium complex; MAX = maximum; MDR = multidrug resistant; mg = milligram; mL = milliliter; TB = tuberculosis
*See current package inserts for age and weight restrictions

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Six-Month Therapy for Abdominal Tuberculosis[29]

A 2016 Cochrane review evaluated evidence related to 6-month therapy compared to longer courses for abdominal TB, defined as TB of the gastrointestinal tract or other organ of the abdominal cavity.[29] Three RCTs of children and adults (n=328) were included in this review comparing the standard 6-month regimen of isoniazid, rifampin, pyrazinamide, and ethambutol to longer regimens containing the same medications. Medications were given daily or thrice-weekly using a directly observed therapy (DOT) protocol.[29] All trials were done in Asia and excluded HIV positive individuals and those with anti-TB treatment in the previous 5 years.[29] Primary outcomes of interest were relapse occurring at least 6 months after therapy completion (median 12-39 months), and clinical cure at end of TB treatment.

Relapse was observed in 2 of 140 patients with 6 months of therapy and 0 of 129 who received 9 months of therapy.[29] Statistical comparison was unable to be performed due to low event rate, and there is likely no difference in relapse with the shorter therapy (very low quality evidence).[29] All deaths which occurred were during first 4 months of therapy, and therefore, unrelated to duration of treatment.[29] There is likely no difference in clinical cure between 6 months and 9 months of therapy (RR 1.02, 95% CI 0.97 to 1.08; 294 participants, moderate quality of evidence).[29]

Antibiotic Treatment for Nontuberculous Mycobacteria Lung Infection in People with Cystic Fibrosis[30]

A 2020 Cochrane review attempted to review antibiotic therapy for NTM in patients with CF to compare drug therapy to no treatment or combinations therapy.[30] However, only a single RCT meeting search criteria was identified, and it included individuals with and without CF. The trial sponsor did not provide the review authors with trial data which would allow for analysis of drug therapy in CF patients.[30]

Brucellosis Treatment in Humans[1]

A 2018 meta-analysis compared the use of rifampin versus streptomycin for brucellosis treatment in humans. Brucellosis is an infection caused by *Brucella*, and is endemic to many developing countries. However, it is also seen in developed countries, particularly related to contaminated food imports. Treatment usually involves doxycycline in combination with either rifampin or streptomycin. Fourteen RCTs (N=1383 patients) were included to compare risk of treatment failure; 11 trials were conducted in Europe and 3 were in Asia. The population had doxycycline background therapy included in all regimens, had a mean or median age ranging from 26.4 to 46.0 years, and had 37.0 to 82.0% of patients identified as male.[1] Pooled results showed an increased risk of treatment failure with rifampin

when compared with streptomycin (RR 2.36; 95% CI 1.72 to 3.23; P<0.001; I^2=0.0%) and higher risk of relapse (RR 2.74; 95% CI 1.80 to 4.19; I^2=0.0%).[1] Sensitivity analysis for both outcomes concluded no effect on the data by excluding each specific study.[1] The subpopulation analysis when the mean population age was over 40 years did not show a difference in treatment failure between rifampin versus streptomycin (RR 1.92; 95% CI 0.93 to 3.97; P=0.078).[1] Differences in safety between the two therapies were not assessed.[1]

After review, 93 systematic reviews were excluded due to poor quality (e.g., network meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), outcome studied (e.g., non-clinical), type of infection (e.g., rare infections non-endemic to the Pacific Northwest), or duplicate data (e.g., data assimilated into multiple high-quality guidelines reviewed below).

Guidelines:
High Quality Guidelines:

Management of Non-tuberculous Mycobacterial Pulmonary Disease (NTM-PD)[2]

The British Thoracic Society published a NICE-accredited, 2017 guideline related to clinical considerations for the care of patients with NTM-PD disease.[2] The scope of the document does not include extrapulmonary NTM, neonates and infants (up to 12 months of age), or patients with concomitant HIV infection. A high quality framework was used and recommendations were graded as A through D, with grade A being of high quality while grade D recommendations are based on non-analytic studies such as case reports, expert opinion, or extrapolation of evidence from well-done case-control or cohort studies. Additionally, the guideline committee included clinical practice points, in topic areas where no research evidence is available or likely to become available. Drug therapy recommendations were all grade D due to lack of high-quality data.[2] Treatment recommendations differentiated by organism are listed in **Table 3.**[2]

Table 3. Non-tubercular Pulmonary Mycobacteria Treatment Recommendation[2]

Recommendation
***Mycobacterium avium* complex (MAC)**
Clarithromycin-sensitive MAC-pulmonary disease should be treated with rifampicin, ethambutol and clarithromycin or azithromycin using an intermittent (three times per week) or daily oral regimen. The choice of regimen should be based on the severity of disease and treatment tolerance.
An intermittent (three times per week) oral antibiotic regimen should not be used in individuals with severe MAC-pulmonary disease or in individuals with a history of treatment failure.
An injectable aminoglycoside (amikacin or streptomycin) should be considered in individuals with severe MAC-pulmonary disease.
Clarithromycin-resistant MAC-pulmonary disease should be treated with rifampicin, ethambutol and isoniazid or a quinolone, and inclusion of an injectable aminoglycoside (amikacin or streptomycin) should be considered.
Nebulized amikacin may be considered in place of an injectable aminoglycoside when intravenous/intramuscular administration is impractical, contraindicated or when longer term treatment with an aminoglycoside is required for the treatment of MAC-pulmonary disease.
Macrolide monotherapy or macrolide/quinolone dual therapy regimens should not be used for the treatment of MAC-pulmonary disease.

Antibiotic treatment for MAC-pulmonary disease should continue for a minimum of 12 months after culture conversion.
Mycobacterium kansasii
Rifampicin-sensitive *M. kansasii*-pulmonary disease should be treated with rifampicin, ethambutol and isoniazid or a macrolide (clarithromycin or azithromycin) using a daily oral regimen.
Rifampicin-resistant *M. kansasii*-pulmonary disease should be treated with a three-drug regimen guided, but not dictated by, drug susceptibility test results using a daily oral regimen.
Antibiotic treatment for *M. kansasii*-pulmonary disease should continue for a minimum of 12 months after culture conversion.
Mycobacterium malmoense
M. malmoense-pulmonary disease should be treated with rifampicin, ethambutol and a macrolide (clarithromycin or azithromycin) using a daily oral regimen.
An injectable aminoglycoside (amikacin or streptomycin) should be considered in individuals with severe *M. malmoense*-pulmonary disease.
Nebulized amikacin may be considered in place of an injectable aminoglycoside when intravenous/intramuscular administration is impractical, contraindicated or when longer term treatment with an aminoglycoside is required in the treatment of *M. malmoense*-pulmonary disease.
Antibiotic treatment for *M. malmoense*-pulmonary disease should continue for a minimum of 12 months after culture conversion.
Mycobacterium xenopi
M. xenopi-pulmonary disease should be treated with a four-drug regimen (where tolerated) comprising rifampicin, ethambutol and a macrolide (clarithromycin or azithromycin), with either a quinolone (ciprofloxacin or moxifloxacin) or isoniazid.
An injectable aminoglycoside (amikacin or streptomycin) should be considered in individuals with severe *M. xenopi*-pulmonary disease.
Nebulized amikacin may be considered in place of an injectable aminoglycoside when intravenous/intramuscular administration is impractical, contraindicated or longer term treatment with an aminoglycoside is required in the treatment of *M. xenopi*-pulmonary disease.
Antibiotic treatment for *M. xenopi*-pulmonary disease should continue for a minimum of 12 months after culture conversion.
Mycobacterium abscessus-Initial Phase
M. abscessus-pulmonary disease treatment should comprise an initial phase antibiotic regimen (including intravenous and oral antibiotics) followed by a continuation phase antibiotic regimen (including inhaled and/or oral antibiotics).
For individuals with *M. abscessus* isolates that are clarithromycin sensitive or demonstrate inducible macrolide resistance, the initial phase antibiotic regimen should include at least a 4-week course of intravenous amikacin, intravenous tigecycline, and (where tolerated) intravenous imipenem, and (where tolerated) oral clarithromycin or oral azithromycin.
For individuals with *M. abscessus* complex isolates that demonstrate constitutive macrolide resistance, the initial phase antibiotic regimen should include a minimum 4-week course of intravenous amikacin, intravenous tigecycline and (where tolerated) intravenous imipenem.

The duration of intravenous treatment should be influenced by the severity of infection, treatment response and tolerance of the regimen.
To reduce the likelihood of treatment-related nausea and vomiting, antiemetic medication such as ondansetron (note potential for QT interval prolongation) and/or aprepitant should be prescribed to individuals receiving tigecycline and/ or imipenem.
Nebulized amikacin may be considered in place of intravenous amikacin when intravenous administration is impractical, contraindicated or longer term treatment with an aminoglycoside is required in individuals with *M. abscessus*-pulmonary disease.
In the context of amikacin-resistant *M. abscessus*, intravenous/nebulized amikacin should be substituted with an alternative intravenous/oral antibiotic.
Mycobacterium abscessus-Continuation Phase
For individuals with *M. abscessus* isolates that are clarithromycin-sensitive or demonstrate inducible macrolide resistance, the continuation phase antibiotic regimen should include nebulized amikacin and a macrolide (oral azithromycin or clarithromycin), in combination with one to three of the following oral antibiotics guided by drug susceptibility and patient tolerance: clofazimine, linezolid, minocycline or doxycycline, moxifloxacin or ciprofloxacin, and co-trimoxazole.
For individuals with *M. abscessus* complex isolates that demonstrate constitutive macrolide resistance, the continuation phase antibiotic regimen should include nebulized amikacin in combination with two to four of the following oral antibiotics guided by drug susceptibility and patient tolerance: clofazimine, linezolid, minocycline or doxycycline, moxifloxacin or ciprofloxacin, and co-trimoxazole.
In the context of amikacin-resistant *M. abscessus* nebulized amikacin should be substituted with an alternative oral antibiotic.
Antibiotic treatment for *M. abscessus*-pulmonary disease should continue for a minimum of 12 months after culture conversion. However, individuals who fail to culture-convert may benefit from a long-term suppressive antibiotic regimen.

Treatment of Nontuberculous Mycobacterial Pulmonary Disease[3]

A 2020 guideline jointly sponsored by the American Thoracic Society (ATS), European Respiratory Society (ERS), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Infectious Diseases Society of American (IDSA) updated treatment recommendations for NTM pulmonary diseases in adults without CF or HIV.[3] The task force conducted literature reviews around 22 different PICO (Population, Intervention, Comparator, and Outcome) questions and created 31 recommendations using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach. A selection relevant to this class review is included in **Table 4**.[3]

Drug resistance testing should routinely be conducted, particularly for bacteria and treatment combinations where *in vitro* activity is shown to correlate to *in vivo* treatment outcomes.[3] While additional testing can reveal other sensitivities and opportunities for synergy, key combinations to test are MAC to macrolides, *M. kansasii* to both rifampicin and clarithromycin, and *M. abscessus* to both macrolides and amikacin.[3]

Table 4. Non-tubercular Pulmonary Mycobacteria Treatment Recommendations[3]

Question	Clinical Recommendation	Recommendation/Evidence Rating
***Mycobacterium avium* complex**		
Should patients with macrolide-susceptible MAC pulmonary disease be treated with a three-drug regimen with a macrolide or without a macrolide?	Recommend a three-drug regimen that includes a macrolide over a three-drug regimen without a macrolide	Strong recommendation, very low certainty in estimates of effect.
In patients with newly diagnosed macrolide-susceptible MAC pulmonary disease, should an azithromycin-based regimen or a clarithromycin-based regimen be used?	Suggest azithromycin-based treatment regimens rather than clarithromycin-based regimens.	Conditional recommendation, very low certainty in estimates of effect.
Should patients with MAC pulmonary disease be treated with or without a parenteral amikacin or streptomycin-containing regimen?	Suggest that parenteral amikacin or streptomycin be included in the initial treatment regimen for patients with cavitary or advanced/severe bronchiectatic or macrolide-resistant MAC pulmonary disease.	Conditional recommendation, moderate certainty in estimates of effect.
In patients with macrolide-susceptible MAC pulmonary disease, should regimens include inhaled amikacin?	Suggest neither inhaled amikacin (parenteral formulation) nor amikacin liposome inhalation suspension be used as part of the initial treatment regimen in patients with newly diagnosed MAC pulmonary disease.	Conditional recommendation, very low certainty in estimates of effect.
	Recommend addition of amikacin liposome inhalation suspension (ALIS) to the treatment regimen rather than a standard oral regimen, only in patients with MAC pulmonary disease who have failed therapy after at least six months of guideline-based therapy.	Strong recommendation, moderate certainty in estimates of effect.
In patients with macrolide-susceptible MAC pulmonary disease, should a three-drug or a two-drug macrolide-containing regimen be used for treatment?	Suggest a treatment regimen with at least three drugs (including a macrolide and ethambutol) over a regimen with two drugs (a macrolide and ethambutol alone).	Conditional recommendation, very low certainty in estimates of effect.
In patients with macrolide susceptible MAC pulmonary disease, should a daily or a three-times weekly macrolide-based regimen be used for treatment?	Suggest a three times per week macrolide-based regimen rather than a daily macrolide-based regimen in patients with noncavitary nodular/bronchiectatic macrolide-susceptible MAC pulmonary disease.	Conditional recommendation, very low certainty in estimates of effect.

	Suggest a daily macrolide-based regimen rather than three times per week macrolide-based regimen in patients with cavitary or severe/advanced nodular bronchiectatic macrolide-susceptible MAC pulmonary disease.	Conditional recommendation, very low certainty in estimates of effect.
In patients with macrolide-susceptible MAC pulmonary disease, should patients be treated with less than 12 months of treatment after culture negativity or 12 or more months of treatment after culture negativity?	Suggest that patients with macrolide-susceptible MAC pulmonary disease receive treatment for at least 12 months after culture conversion.	Conditional recommendation, very low certainty in estimates of effect.
Mycobacterium kansasii		
In patients with rifampicin-susceptible *M. kansasii* pulmonary disease, should an isoniazid-containing regimen or a macrolide-containing regimen be used for treatment?	Suggest a regimen of rifampicin, ethambutol, and either isoniazid or macrolide.	Conditional recommendation, very low certainty in estimates of effect.
In patients with rifampicin-susceptible *M. kansasii* pulmonary disease, should parenteral amikacin or streptomycin be included in the treatment regimen?	Suggest that neither parenteral amikacin nor streptomycin be used routinely for treating patients with *M. kansasii* pulmonary disease.	Strong recommendation, very low certainty in estimates of effect.
In patients with rifampicin-susceptible *M. kansasii* pulmonary disease, should a treatment regimen that includes a fluoroquinolone or a regimen without a fluoroquinolone be used?	Suggest using a regimen of rifampicin, ethambutol, and either isoniazid or macrolide instead of a fluoroquinolone in patients with rifampin-susceptible *M. kansasii* pulmonary disease.	Conditional recommendation, very low certainty in estimates of effect.
	Suggest a fluoroquinolone (e.g., moxifloxacin) be used as part of a second-line regimen in patients with rifampicin-resistant *M. kansasii* or intolerance to one of the first line antibiotics.	Conditional recommendation, very low certainty in estimates of effect.
In patients with rifampicin-susceptible *M. kansasii* pulmonary disease, should a three times per week or daily treatment regimen be used?	Suggest either daily or three times weekly treatment in patients with noncavitary nodular/bronchiectatic *M. kansasii* pulmonary disease treated with a rifampicin, ethambutol and macrolide regimen.	Conditional recommendation, very low certainty in estimates of effect.
	Suggest daily treatment instead of three times weekly treatment in patients with cavitary *M. kansasii*	Conditional recommendation, very low certainty in estimates of effect.

	pulmonary disease treated with a rifampicin, ethambutol and macrolide-based regimen.	
In patients with rifampicin susceptible *M. kansasii* pulmonary disease, should treatment be continued for less than 12 months or 12 or more months?	Suggest that patients with rifampin susceptible *M. kansasii* pulmonary disease be treated for at least 12 months.	Conditional recommendation, very low certainty in estimates of effect.
Mycobacterium xenopi		
In patients with *M. xenopi* pulmonary disease, should a treatment regimen that includes a fluoroquinolone or a regimen without a fluoroquinolone be used?	Suggest using a multidrug treatment regimen that includes moxifloxacin or macrolide.	Conditional recommendation, low certainty in estimates of effect.
In patients with *M. xenopi* pulmonary disease, should a two, three or four-drug regimen be used for treatment?	Suggest a daily regimen that includes at least three drugs: rifampicin, ethambutol, and either a macrolide and/or a fluoroquinolone (e.g. moxifloxacin).	Conditional recommendation, very low certainty in estimates of effect.
In patients with *M. xenopi* pulmonary disease, should parenteral amikacin or streptomycin be included in the treatment regimen?	Suggest adding parenteral amikacin to the treatment regimen and obtaining expert consultation in patients with cavitary or advanced/severe bronchiectatic *M. xenopi* pulmonary disease.	Conditional recommendation, very low certainty in estimates of effect.
In patients with *M. xenopi* pulmonary disease, should treatment be continued for less than 12 months or 12 or more months after culture conversion?	Suggest that treatment be continued for at least 12 months beyond culture conversion.	Conditional recommendation, very low certainty in estimates of effect.

WHO Prevention of Tuberculosis[4]

In 2020, the Global TB Programme of the WHO began combining recommendations from various TB guidelines it had previously published into a consolidated guideline of current recommendations.[4] These consolidated guidelines are divided into modules, each to address a different area of programmatic management of TB. Module 1 is focused on prevention, including tuberculosis preventive treatment.[4] Latent TB is considered a persistent immune response to *M. tuberculosis* antigens with no evidence of clinically active TB. Most people exposed to TB have no signs or symptoms, but are at risk for active TB. Those who should be screened and treated for latent TB infection varies based on patient age, immune risk factors, exposure history, and a country's TB incidence.[5] This module builds on the 2018 guidelines to reflect newer evidence and simplify recommendations.[4,5] Based on 2018 recommendations, those requiring treatment as a high-risk contact of a patient with known MDR-TB, "preventative treatment may be considered based on individualized risk assessment and sound clinical judgement" (conditional recommendation, very low-quality evidence).[5] This area is identified as an area of opportunity for future research.[4] Updated recommended options for treatment of latent TB are[4]:

- Recommended regimens (strong recommendation; moderate to high certainty in the estimates of effect):
    - 6 or 9 months of daily isoniazid
    - 3 months of weekly rifapentine plus isoniazid
    - 3 months of daily isoniazid plus rifampicin
- Alternative regimens (conditional recommendation; low to moderate certainty in the estimates of effect):
    - 1 month of daily rifapentine plus isoniazid
    - 4 months of daily rifampicin

One additional recommendation, applicable only to settings with high TB transmission as defined by national authorities, is for adults and adolescents living with HIV who have latent TB, a positive skin test or status is unknown but are unlikely to have active TB, should receive at least 36 months of daily isoniazid preventive treatment (IPT). This recommendation applies regardless of ART use, immunosuppression, history of previous TB treatment, and pregnancy. (Conditional recommendation, low certainty in the estimates of effect)

Guidelines for the Treatment of Latent Tuberculosis Infection[6]

In 2020, the CDC and National Tuberculosis Controllers Association updated previous 2000 guidance for the treatment of latent TB in the US.[6] Recommended regimens are intended for persons who are presumed to be infected with TB that is susceptible to isoniazid or rifampin, but are not appropriate if exposure is likely from MDR-TB strains.[6] These recommendations are in **Table 5**. Preference was determined by balance of desirable and undesirable consequences of the intervention, quality of evidence, patient values, patient preferences, and regimen feasibility. Preference in priority rank for preferred versus alternative regimens was given for shorter duration given efficacy compared to 6 to 9 months of isoniazid, tolerability, and completion rates.[6] The authors note that 6 and 9 month treatment regimens of daily monotherapy isoniazid have not been directly compared. Additionally, 2 months of rifampin plus pyrazinamide are not recommended for treatment of latent TB due to hepatotoxicity, but in those treated for active disease with isoniazid, rifampin, and pyrazinamide for 2 months, who are later determined to have had latent disease, the regimen is considered an effective treatment.[6]

Table 5. Treatment Regimens for Latent TB Infection in the United States[6]

Treatment Recommendation	Population	Strength of Recommendation	Place in Therapy
3 months of once-weekly isoniazid plus rifapentine	Adults and children aged >2 years, including HIV-positive persons (as drug interactions allow)	Strong	Preferred
4 months of daily rifampin	HIV-negative adults and children of all ages	Strong	Preferred
3 months of daily isoniazid plus rifampin	Adults and children of all ages and for HIV-positive persons (as drug interactions allow)	Conditional	Preferred
6 months of daily isoniazid	HIV-negative adults and children of all ages	Strong	Alternative
6 months of daily isoniazid	HIV-positive adults and children of all ages	Conditional	Alternative
9 months of daily isoniazid	Adults and children of all ages, both HIV-negative and HIV-positive	Conditional	Alternative

Tuberculosis[7]

Guidelines on tuberculosis were published by NICE in 2016, with the last update in September of 2019.[7] This guidance focused on the prevention, identification, and management of both latent and active TB in children, young people, and adults and is created specifically for the United Kingdom and National Health Service.[7] Treatment related aspects of this guideline were reviewed.

Factors which increase risk for conversion of latent TB to active include: comorbid HIV, age less than 5 years, excessive alcohol intake, injection drug use, history of solid organ transplant, current hematological malignancy, concomitant chemotherapy, history of jejunal-ileal bypass, diabetes mellitus, chronic kidney disease (including dialysis), history of a gastrectomy, silicosis, or administration of anti-tumor necrosis factor-alpha or other therapeutic immune modulators.[7] Regimens recommended latent TB treatment in persons younger than 65 years, including those with HIV, who have evidence of latent TB or have been in close contact with a suspected or confirmed infectious contact are found in **Table 6**. Adults aged 35 to 65 years without other risk factors should be offered treatment only if hepatotoxicity is not a concern.[7] Testing for HIV, hepatitis B, and hepatitis C should be offered before starting latent TB treatment.[7]

Table 6. Latent Tuberculosis Treatment Regimens[7]

Agents	Duration	Preferred Circumstances
Isoniazid (with pyridoxine) plus rifampin	3 months	• Younger than 35 years • Concern for hepatotoxicity • Other risk factors
Isoniazid (with pyridoxine)	6 months	• Situations where drug-drug interactions from rifamycins are a concern (e.g. HIV, organ transplant)

The preferred regimen for active TB without suspected drug-resistance is isoniazid, rifampin, pyrazinamide, and ethambutol for a 2 month intensive phase followed by isoniazid plus rifampin for a 4 month continuation phase, with modifications as needed based on drug susceptibility testing.[7] People with active TB in the central nervous system should receive the standard intensive phase with a prolonged, 10 month, continuation phase.[7] Spinal TB without central nervous system involvement, as well as active TB of the lymph nodes should not be routinely extended beyond 6 months.[7] Dosing should be daily for extrapulmonary TB and is preferred for pulmonary TB.[7] Thrice-weekly may be considered if there is need for DOT and daily DOT is not possible.[7]

The use of rapid drug susceptibility testing for rifampin resistance should be performed in patients with the following risk factors: history of previous TB treatment, known contact with a case of MDR-TB, or birth/residence in a country identified by WHO with a high proportion (5% or greater) of new MDR-TB cases.[7] Identification of rifampin resistance should prompt additional drug-susceptibility testing and treatment with a regimen involving at least 6 active agents.[7] This guideline did not include specific treatments for MDR-TB.

Treatment of Drug-susceptible Tuberculosis[9]

A 2016 guideline, jointly sponsored by the ATS, CDC, and IDSA, provides recommendations for the treatment of drug-susceptible tuberculosis in children and adults in high-resource settings.[9] These are endorsed by ERS and the US National Tuberculosis Controllers Association. Additional American, Canadian, and International society representatives, including those from the WHO participated in guideline creation. The expert committee conducted literature reviews and created recommendations using the GRADE approach with the focus of cure for the individual patient while also preventing drug resistance and minimization of transmission to other exposed persons.

The PICO questions included in this guideline were primarily focused on treatment intervals and duration over specific medication choices, as the preferred regimen had not changed. Drug treatment can be done using DOT or self-administered therapy (SAT). Directly observed therapy has been associated with improved treatment success, and it is suggested over SAT for routine treatment of patients with all forms of tuberculosis (conditional recommendation; low certainty in the evidence).[9] The preferred regimen for microbiologically confirmed, drug-susceptible pulmonary TB is an intensive phase of isoniazid, rifampin, pyrazinamide, and ethambutol daily for 8 weeks followed by isoniazid plus rifampin daily for 18 weeks.[9] Alternatives for 5 days/week dosing are included, but only in the setting of DOT.[9] Use of daily dosing is preferred over intermittent dosing (thrice-weekly, twice-weekly, weekly) in the intensive phase (strong recommendation; moderate certainty in the evidence), while daily or thrice-weekly is preferred for the continuation phase over less frequent intermittent dosing (strong recommendation; moderate certainty in the evidence).[9] The 6-month preferred regimen is recommended in coinfected HIV patients who are receiving ART over treatment beyond 6 months (conditional recommendation; very low certainty in the evidence).[9] Pyridoxine should be included in all patients at risk of neuropathy while taking concomitant isoniazid.[9]

Treatment of Drug-susceptible Tuberculosis and Patient Care[8]

The World Health Organization published a 2017 update to previous 2010 guidelines focused on the treatment of drug-susceptible TB, with the aim to provide evidence across a variety of geographical, economic, and social settings.[8] Recommendations were created by the guideline development group (GDG) and received funding from the United States Agency for International Development (USAID). Members of the GDG followed the WHO policy on conflict of interest and used the GRADE approach. The ATS/CDC/IDSA guideline update on this topic was in process during preparation for the WHO update and information was shared between the two groups. The group provided recommendations in response to evidence for previously used and new PICO questions. Applicable treatment recommendations are located in **Table 7**.

Table 7. Treatment of Drug-susceptible Tuberculosis[8]

Clinical Recommendation	Recommendation/Evidence Rating
In patients with drug-susceptible pulmonary TB, 4-month fluoroquinolone containing regimens should not be used and the 6-month rifampicin-based 2HRZE/4H remains the recommended regimen. *Note: New evidence available for one specific regimen.*[10] *See June 2021 WHO rapid communication.*[11]	Strong recommendation Moderate certainty
The use of fixed-dose combination tablets is recommended over separate drug formulations in treatment of patients with drug-susceptible TB.	Conditional recommendation Low certainty
In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing is not recommended in both the intensive and continuation phases of therapy and daily dosing remains the recommended dosing frequency.	Conditional recommendation Very low certainty
ART should be started in all TB patients living with HIV regardless of their CD4 cell count.	Strong recommendation High certainty
TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment. HIV-positive patients with profound immunosuppression (e.g. CD4 cell counts less than 50 cells/mm^3) should receive ART within the first 2 weeks of initiating TB treatment.	Strong recommendation High certainty
In patients with drug-susceptible pulmonary TB who are living with HIV and receiving antiretroviral therapy during TB treatment, a 6-month standard treatment regimen is recommended over an extended treatment for 8 months or more.	Conditional recommendation Very low certainty
In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8 weeks should be used.	Strong recommendation Moderate certainty
In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used.	Conditional recommendation Very low certainty
In patients who require TB retreatment, the category II regimen should no longer be prescribed and drug susceptibility testing should be conducted to inform the choice of treatment regimen.	Good practice statement*
Abbreviations: ART = antiretroviral treatment; HIV = human immunodeficiency virus; TB = tuberculosis; 2HRZE/4HR = 2-month isoniazid/rifampin/pyrazinamide/ethambutol intensive phase then 4-month isoniazid/rifampin continuation phase * No randomized controlled trials or direct comparative evidence available for category II regimen vs. another regimen	

Treatment of Drug-Susceptible Tuberculosis: Rapid Communication[11]

The WHO issued a rapid communication for the treatment of drug-susceptible TB in June 2021.[11] The Global TB Programme received data from Study 31[10] and convened a guideline development group to review the results. This open-label, non-inferiority RCT included 2516 patients at 34 clinical sites in 13 countries.[10] Results indicate that a 4 month treatment regimen containing rifapentine, moxifloxacin, isoniazid, and pyrazinamide (intensive phase: daily dosing of all 4 agents for 8 weeks; continuation phase: discontinue pyrazinamide and continue remaining 3 agents daily for an additional 9 weeks) was as effective as the 6 month standard TB regimen at meeting the primary endpoint of tuberculosis disease-free survival at 12 months after randomization.[10] The other regimen studied, rifapentine, isoniazid, ethambutol, and pyrazinamide did not meet non-inferiority criteria.[10] The WHO guideline development group supports the 4 month rifapentine/moxifloxacin/isoniazid/pyrazinamide regimen as a possible alternative to the standard 6 months traditional regimen. Incorporation and grading of this data is planned for next drug-susceptible TB module update.[11]

Regimen for the Treatment of Drug-Susceptible Pulmonary Tuberculosis-Interim Guidance[12]

In 2022, the CDC issued interim guidance related to the results of a CDC and National Institutes of Health sponsored RCT (Study 31[10]/A5349).[12] The CDC recommends this regimen be considered a treatment option in patients 12 years and older, weighing 40 kg or more, with drug-susceptible TB and who are not pregnant or breastfeeding.[12] It can be used in those with concomitant HIV and CD4 counts ≥ 100 cells/mcg/L and who are on or plan to receive an efavirenz based ART regimen.[12] This regimen has not been compared in other studies. Given recent availability of the data, this guidance is not graded within the normal guideline creation process and is based on expert opinion with comments from external subject matter experts.[12]

Treatment of Drug-Resistant Tuberculosis[14]

In 2019 the ATS, CDC, ERS, and IDSA jointly sponsored a new practice guideline on the treatment of MDR-TB. Aspects of this document were previously reviewed by DURM in April 2022 in the fluoroquinolone class update. Methodology used matched the drug-sensitive TB guidelines previously described by these societies. The scope of this document included MDR-TB and isoniazid-resistant, rifampin-sensitive TB.[14]

Treatment of active MDR-TB is recommended to include at least 5 drugs during the intensive phase and 4 drugs during the continuation phase (conditional recommendation, very low certainty in the evidence).[14] The intensive phase is suggested to continue for 5 to 7 months beyond culture conversion (conditional recommendation, very low certainty in the evidence), with a total treatment duration of 15 to 21 months after culture conversion (conditional recommendation, very low certainty in the evidence).[14] Total duration is suggested as 15 to 24 months after culture conversion in pre-XDR TB and XDR-TB (conditional recommendation, very low certainty in the evidence).[14] Drug selection should be guided by susceptibility testing (*in-vitro* growth based or molecular resistance testing) and only include agents with documented or high likelihood of susceptibility (ungraded good practice statement).[14] Agent specific recommendations are included in **Table 8**, adjusted odds ratio and 95% confidence intervals for death or treatment success are included in full guideline.[14] For persons exposed to an MDR-TB contact, it is suggested to offer treatment for latent TB rather than observation (conditional recommendation, very low certainty of evidence).[14] For treatment of presumed MDR latent TB, it is suggested to treat with 6 to 12 months with a later generation FQ alone or with a second agent based on the susceptibility of the source-case of MDR-TB.[14] Pyrazinamide should not be generally used as the second agent due to increased toxicity, adverse events, and discontinuations.[14]

Table 8. Individual Drug Recommendations for Use in MDR-TB[14]

Drug or Drug Class	Recommendation		Certainty of the Evidence
	FOR	AGAINST	
Bedaquiline	Strong		Very Low
Fluoroquinolone: Moxifloxacin	Strong		Very Low
Fluoroquinolone: Levofloxacin	Strong		Very Low
Linezolid	Conditional		Very Low
Clofazimine	Conditional		Very Low
Cycloserine	Conditional		Very Low
Injectables: Amikacin	Conditional		Very Low
Injectables: Streptomycin	Conditional		Very Low
Ethambutol	Conditional		Very Low
Pyrazinamide Injectables:	Conditional		Very Low
Carbapenems w/ clavulanic acid	Conditional		Very Low
Delamanid	No recommendation for or against due to absence of data, committee concurs with 2019 WHO conditional recommendation that it may be included for treatment of MDR-TB or rifampin-resistant TB in longer regimens in individuals aged 3 years and older.		Very Low
Ethionamide		Conditional	Very Low
Prothionamide		Conditional	Very Low
Injectables: Kanamycin		Conditional	Very Low
P-Aminosalicylic Acid		Conditional	Very Low
Injectables: Capreomycin		Conditional	Very Low
Macrolides: Azithromycin		Strong	Very Low
Macrolides: Clarithromycin		Strong	Very Low
Amoxicillin-clavulanate		Strong	Very Low

Drug-resistant Tuberculosis Treatment[13]

The WHO published module 4 of its consolidated TB guidelines in 2020. Module 4 focuses on treatment of MDR-TB and rifampin-resistant TB, with a focus on providing evidence-based information to inform use of novel all-oral regimens and potential label expansion of new TB medications. The process and methods to develop recommendations complied with WHO standards for guideline development.[13] Drug therapy recommendations are included in **Table 9**.

Table 9. Drug Recommendations for Use in Drug-resistant TB[13]

Clinical Recommendation	Recommendation/Evidence Rating
In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months.	Conditional/very low certainty
In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen.	Conditional/very low certainty
A shorter all-oral bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed multidrug- or rifampicin-resistant tuberculosis who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded.	Conditional/very low certainty
In multidrug- or rifampicin-resistant tuberculosis patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it.	Conditional/very low certainty
Kanamycin and capreomycin are not to be included in the treatment of multidrug- or rifampicin-resistant tuberculosis patients on longer regimens.	Conditional/very low certainty
Levofloxacin or moxifloxacin should be included in the treatment of multidrug- or rifampicin-resistant tuberculosis patients on longer regimens.	Strong/moderate certainty
Bedaquiline should be included in longer MDR-TB regimens for patients aged 18 years or more.	Strong/moderate certainty
Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years.	Conditional/very low certainty
Linezolid should be included in the treatment of multidrug- or rifampicin-resistant tuberculosis patients on longer regimens.	Strong/moderate certainty
Clofazimine and cycloserine or terizidone may be included in the treatment of multidrug- or rifampicin-resistant tuberculosis patients on longer regimens.	Conditional/very low certainty
Ethambutol may be included in the treatment of multidrug- or rifampicin-resistant tuberculosis patients on longer regimens.	Conditional/very low certainty

Delamanid may be included in the treatment of multidrug- or rifampicin-resistant tuberculosis patients aged 3 years or more on longer regimens.	Conditional/moderate certainty
Pyrazinamide may be included in the treatment of multidrug- or rifampicin-resistant tuberculosis patients on longer regimens.	Conditional/very low certainty
Imipenem–cilastatin or meropenem may be included in the treatment of multidrug- or rifampicin-resistant tuberculosis patients on longer regimens.	Conditional/very low certainty
Amikacin may be included in the treatment of multidrug- or rifampicin-resistant tuberculosis patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions.	Conditional/very low certainty
Ethionamide or prothionamide may be included in the treatment of multidrug- or rifampicin-resistant tuberculosis patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible.	Conditional against use/very low certainty
P-aminosalicylic acid may be included in the treatment of multidrug- or rifampicin-resistant tuberculosis patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible.	Conditional against use/very low certainty
Clavulanic acid should not be included in the treatment of multidrug- or rifampicin-resistant tuberculosis patients on longer regimens.	Strong against use/low certainty
In multidrug- or rifampicin-resistant tuberculosis patients on longer regimens, a total treatment duration of 18–20 months is suggested for most patients; the duration may be modified according to the patient's response to therapy.	Conditional/very low certainty
In multidrug- or rifampicin-resistant tuberculosis patients on longer regimens, a treatment duration of 15–17 months after culture conversion is suggested for most patients; the duration may be modified according to the patient's response to therapy.	Conditional/very low certainty
In multidrug- or rifampicin-resistant tuberculosis patients on longer regimens containing amikacin or streptomycin, an intensive phase of 6–7 months is suggested for most patients; the duration may be modified according to the patient's response to therapy.	Conditional/very low certainty
A treatment regimen lasting 6–9 months, composed of bedaquiline, pretomanid and linezolid, may be used under operational research conditions in MDR-TB patients with TB that is resistant to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for no more than 2 weeks.	Conditional/very low certainty

Management of Tuberculosis in Children and Adolescents[15]

In 2022, the Global TB Programme of the WHO published Module 5 of consolidated guidelines on the management of tuberculosis in children and adolescents, which is primarily an update from previous 2014 guidelines.[15] These recommendations apply to children under 10 years of age and adolescents aged 10 through 19 years with various types of TB. Treatment recommendations for preventative treatment options mirror those described previously in Module 4, with the 3 month regimen of weekly rifapentine plus isoniazid restricted to those age 2 years and above, while the 1 month regimen of daily rifapentine plus isoniazid is reserved for the aged 13 years and older.[15] Additional treatment recommendations are contained in **Table 10**. Multiple recommendations were carried over from the 2014 guidelines for various extrapulmonary TB infections.[15] The treatment recommendations are all variations of the traditional 4-drug regimen with differences in duration and frequency of dosing during the intensive and continuation phase.[15] Other recommended regimens align with recommendations already described in the other WHO TB consolidated guideline modules.[15]

Table 10. Drug Recommendations for Children and Adolescents with Tuberculosis[15]

Clinical Recommendation	**Recommendation/Evidence Rating**
In children and adolescents between 3 months and 16 years of age with non-severe TB and without suspicion/evidence of MDR or rifampin-resistant TB, a 4-month treatment regimen (2 months isoniazid/rifampin/pyrazinamide +/- ethambutol, then 2 months isoniazid/rifampin) should be used. *Ethambutol should be included during intensive phase in settings with high HIV prevalence or of isoniazid resistance.*	Strong/moderate certainty
In children and adolescents with bacteriologically confirmed or clinically diagnosed TB meningitis without suspicion/evidence of MDR or rifampin-resistant TB, a 6-month intensive regimen (isoniazid/rifampin at higher doses with pyrazinamide and ethionamide) may be used as an alternative option to the 12-month regimen (2 months isoniazid/rifampin/pyrazinamide/ethambutol, 10 months isoniazid/rifampin).	Conditional/very low certainty
In children with MDR or rifampin-resistant TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used.	Conditional/very low certainty
Bedaquiline may be included in longer MDR-TB regimens for patients aged 6–17 years.	Conditional/very low certainty
In children with MDR or rifampin-resistant TB aged below 3 years, delamanid may be used as part of longer regimens.	Conditional/very low certainty
Patients aged 12 years and older with drug-susceptible pulmonary TB, may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide.	Conditional/moderate certainty

After review, 13 guidelines were excluded due to poor quality or obsolescence.

Randomized Controlled Trials:

A total of 18 citations were manually reviewed from the initial literature search. After further review, 17 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. Full abstract is included in **Appendix 4**.

Table 11. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Dorman et al.[10] Study 31	1. Study regimen 1 <u>8 week</u> rifapentine isoniazid moxifloxacin pyrazinamide <u>9 week</u> rifapentine isoniazid moxifloxacin 2. Study regimen 2 <u>8 week</u> rifapentine isoniazid pyrazinamide ethambutol <u>9 week</u> rifapentine isoniazid 3. Control <u>8 week</u> rifampin isoniazid pyrazinamide ethambutol <u>18 week</u> rifampin isoniazid 1:1:1 randomization	N=2343 71% male Median age (years) 31.0 (range 13.7-81.4) 3% 12-17 years 11% Asian 72% Black 2 % White 15% Multiracial 8% HIV+ Mean weight 53.1 kg 24% smoker 11% treatment-experienced Inclusion -12 years and older -Newly diagnosed pulmonary TB -susceptibility to isoniazid, rifampin, and fluoroquinolones confirmed by culture -If HIV+, CD4 count at least 100 cells/mcgL	Efficacy: Survival free of TB at 12 months after randomization as favorable, unfavorable, not-assessable Non-inferiority assessment, 6.6% or less in upper boundary of 95% confidence interval Total follow up 18 months-secondary endpoint of survival at 18 months not yet performed Safety: Adverse event grade 3 or higher with onset during treatment and up to 14 days after last dose	<u>Efficacy 12 months:</u> 1. 15.5% unfavorable 1.0% difference (95% CI -2.6% to 4.5%) Met non-inferiority criteria 2. 17.7% unfavorable 3.0% difference (95% CI -0.6% to 6.6%) Did NOT meet non-inferiority criteria 3. 14.6% unfavorable <u>Safety 12 months:</u> 1. 18.8% Adjusted difference -0.6% (95% CI -4.3% to 3.2%) 2. 14.3% Adjusted difference -5.1% (95% CI -8.7% to -1.5%) 3. 19.3%	Open-label Randomization stratified site, presence of baseline cavitation, and HIV status.

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Appendix 1: Specific Drug Information

Generic	Brand	Route	Form	PDL
bedaquiline fumarate	SIRTURO	ORAL	TABLET	N
aminosalicylic acid	PASER	ORAL	GRANPKT DR	
cycloserine	CYCLOSERINE	ORAL	CAPSULE	
ethambutol HCl	ETHAMBUTOL HCL	ORAL	TABLET	
ethambutol HCl	MYAMBUTOL	ORAL	TABLET	
ethionamide	TRECATOR	ORAL	TABLET	
isoniazid	ISONIAZID	ORAL	SOLUTION	
isoniazid	ISONIAZID	ORAL	TABLET	
pretomanid	PRETOMANID	ORAL	TABLET	
pyrazinamide	PYRAZINAMIDE	ORAL	TABLET	
rifabutin	MYCOBUTIN	ORAL	CAPSULE	
rifabutin	RIFABUTIN	ORAL	CAPSULE	
rifampin	RIFAMPIN	ORAL	CAPSULE	
rifapentine	PRIFTIN	ORAL	TABLET	

Table 12. Clinical Pharmacology and Pharmacokinetics [28]

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
bedaquiline	• Inhibits mycobacterial adenosine 5'-triphosphate (ATP) synthase	• Tmax, oral: 4 to 5 hours • Effects of food: Bioavailability increased by 2-fold	• Substrate of CYP3A4 • Renal excretion: 0.001% or less • Fecal excretion: Extensive • Dialyzable: No (hemodialysis); no (peritoneal dialysis)	• Half-life: 5.5 months (parent drug and M2 metabolite) • Vd: 164 L
aminosalicylic acid	• Inhibits folic acid and cell wall synthesis that leads to reduced iron uptake	• Oral: time to peak concentration, 5 h (1.5 to 24 h) • Effect of food: decreases time to peak to 2 h (45 min to 24 h)	• Acetylation • Renal (glomerular filtration): 80%, 50% or more as metabolites • Dialyzable: no	• Half-life: 26.4 min, Renal disease 30.8 min
cycloserine	• Inhibiting cell-wall synthesis	• Tmax: 3 to 4 hours Bioavailability: 70 to 90% • Effect of food: Reduced Cmax, Prolonged Tmax (high-fat meals)	• Hepatic: 35% • Fecal: minimal • Renal: 50% to 70% • Renal Clearance: 0.11 to 0.013 L/hour/kg • Dialyzable: yes (hemodialysis)	• Half-life: 10 to 25 hours • Vd: 0.11 to 0.26 L/kg
ethambutol	• Inhibits the synthesis of metabolites, subsequently impairing cell metabolism and cell multiplication eventually leading to cell death	• Tmax: 2 to 4 hours • Effect of food: not significant	• Liver: 10% to 20% via oxidation • Major metabolite: aldehydic intermediate, inactive • Dicarboxylic acid: inactive • Fecal: 20% to 22% unchanged • Renal: approximately 50% unchanged, 8% to 15% changed	• Half-life: 2.5 to 4 hours
ethionamide	• Unknown, appears to inhibit peptide synthesis	• Tmax, oral (film-coated tablet): 1.02 hours	• Hepatic: extensive • Ethionamide-sulphoxide: active against *M. tuberculosis*	• Half-life: 1.92 hours (film-coated tablet)

		• Bioavailability, oral: nearly 100%	• Renal: Less than 1% unchanged • Dialyzable: No; 2.1% removed	• Ethionamide-sulphoxide: 1.68 to 2.25 hours
isoniazid	• Unknown, may relate to inhibition of mycolic acid synthesis and disruption of the cell wall	• Systemic: Readily absorbed: food reduces bioavailability	• Systemic: Hepatic • Fecal: small amounts • Renal: 75–95%	• Half-life: Fast acetylators: 0.5 to 1.6 h Adults (including elderly patients) Slow acetylators: 2 to 5 h Adults (including elderly patients); 2.3 to 4.9 h Children (1.5 to 15 y); 7.8 to 19.8 h Neonates • Vd: 0.57 to 0.76 L/kg
pretomanid	Inhibits mycolic acid biosynthesis to block cell wall production	• Tmax, oral: 4 to 5 hours • Effects of food: Increased Cmax by 76%; increased AUC by 88%	• Metabolized via reduction and oxidation • Substrate of CYP3A4 • Inhibitor of OAT3 • Renal excretion: 53% as changed drug; 1% unchanged • Fecal excretion: 38% as changed drug • Total body clearance: 3.9 L/hr (fed); 7.6 L/hr (fasted)	• Half-time: 16 to 17.4 hrs • Vd: 97 L (fed), 180 L (fasted)
pyrazinamide	Unknown	• Tmax, Oral: 0.75 to 4 hours • Bioavailability, Oral: rapidly and almost completely absorbed • Effect of food: Cmax decreased by 17%, Tmax increased 80%	• Liver: primary site via hydrolysis • Pyrazinoic acid: active • Renal: approximately 70%, 1% to 14% unchanged • Dialyzable: yes (hemodialysis), 45% removed	• Half-life: adults 12.3 hours • Vd: 0.75 to 1.65 L/kg
rifabutin	Inhibition of DNA-dependent RNA polymerase resulting in the inhibition of protein synthesis	• Systemic: Readily absorbed; high fat food slows absorption	• Systemic: Hepatic • Systemic: 30% fecal; 5% unchanged in the urine; 5% unchanged in the bile; 53% in urine as metabolites	• 45 h (range 16 to 69) • Vd: 9.3 ± 1.5 L/kg

			• In dialysis—Hemodialysis is not expected to enhance elimination • Systemic: Fecal: 30%, 5% unchanged; Renal: 53% metabolites, 5% unchanged	
rifampin	Inhibition of DNA-dependent RNA polymerase resulting in the inhibition of protein synthesis	• Oral: Rapidly absorbed • Tmax, oral: 1 to 4 hours • Tmax, IV: 30 minutes • Effects of food: Absorption reduced by 30%, Cmax reduced by 36% ,Tmax increased by 103% • Effects of food (patients with tuberculosis): Tmax delayed by 2 hours; decreased Cmax	• 25-desacetyl-rifampin: Microbiologically active • Formylrifampin: Active • Renal excretion Up to 30% • Biliary excretion: Rapidly eliminated in the bile • Total body clearance: 0.19 L/hr/kg (300 mg); 0.14 L/hr/kg (600 mg)	• Half-life: Adults: 3.35 hours (600 mg); 5.08 hours (900 mg), reduced in pediatrics and prolonged in renal or hepatic impairment and biliary obstruction • Vd: 0.66 L/kg (300 mg); 0.64 L/kg (600 mg)
rifapentine	Inhibits bacterial RNA transcription by preventing initiation of RNA chain formation by forming a stable complex with bacterial DNA-dependent RNA polymerase	• Tmax, adult, oral: 4.83 to 6 hours • Tmax, pediatric, oral: 3.2 hours • Bioavailability (relative): 70% • Effects of food: Increases AUC and Cmax by 40% to 50%	• 25-desacetyl rifapentine (major): Active • Inducer of CYP3A4 and CYP2C8/9 • Renal excretion: 17% • Fecal excretion: 70%	• Half-life: Adult: 13.19 hours • Vd (adult): 70.2 L
Abbreviations: AUC=area under the curve; Cmax=maximum concentration; DNA=deoxyribonucleic acid; L=liter; RNA=ribonucleic acid; Tmax=time to maximum concentration; Vd=volume of distribution.				

Drug Safety:

Boxed Warnings:[28]

Bedaquiline: Increased risk of death; QT prolongation

Isoniazid: Severe and sometimes fatal hepatitis

Risk Evaluation Mitigation Strategy Programs:[28]

None

Contraindications:[28]

- General
  - Hypersensitivity: p-aminosalicylic acid, cycloserine, ethambutol, ethionamide, isoniazid, pyrazinamide, rifabutin, rifampin
  - History of severe adverse reactions to isoniazid (e.g. drug fever, chills, arthritis)
- Renal
  - End-Stage renal disease: p-aminosalicylic acid
  - Severe renal insufficiency: cycloserine
- Psychiatric
  - Depression, anxiety, psychosis: cycloserine
  - Alcohol use (excessive): cycloserine
- Neurologic
  - Epilepsy: cycloserine
  - Optic neuritis (clinical judgment of risk/benefit required): ethambutol
  - Inability to appreciate or report visual side effects/vision changes: ethambutol
- Hepatic
  - Severe hepatic impairment/damage: ethionamide, pyrazinamide
  - History of isoniazid associated or other drug induced liver injury: isoniazid
  - Acute liver injury: isoniazid
- Acute gout: pyrazinamide
- Drug Interactions/Place in therapy
  - Use when bedaquiline and/or linezolid are contraindicated: pretomanid (only approval is for use in combination with those agents)
  - Concomitant use of delavirdine, rilpivirine, voriconazole: rifabutin
  - Concomitant use with atazanavir, darunavir, fosamprenavir, saquinavir (unboosted or ritonavir boosted), tipranavir, rilpivirine, elvitegravir/cobicistat, or praziquantel (within 4 weeks prior to praziquantel use until 1 day after end of praziquantel treatment): rifampin
  - Concomitant rilpivirine: rifapentine

Table 13. Summary of Warnings and Precautions.[28]

Warnings and Precautions	bedaquiline	p-aminosalicylic acid	cycloserine	ethambutol	ethionamide	isoniazid	pretomanid	pyrazinamide	rifabutin	rifampin	rifapentine
Allergic dermatitis			X								
Anemia			X								
Central nervous system toxicity, increased risk with chronic alcoholism			X								
Clostridioides difficile-associated diarrhea									X		X
Drug Interactions	hepatotoxins (drug or alcohol); strong/ moderate CYP3A4 inducers			aluminum containing antacids		Avoid tyramine (e.g. wine, cheese) and histamine (e.g. tuna) containing foods.	strong/ moderate CYP3A4 inducers		Select HIV drugs	cefazolin/ rifampin or pre-existing vitamin K-dependent coagulation disorders in patients at increase bleeding risk; select HIV drugs	Select HIV drugs
Congestive heart failure		X									
Diabetes mellitus (preexisting)								X		X	
B vitamins		Vitamin B12 supplementation recommended	Folic acid and B12 deficiency			Vitamin B6 supplementation recommended					
Gout/hyperuricemia								X			
Hepatotoxicity	X	X		X			X	X		X (sometimes cholestatic or mixed pattern)	X
Hypersensitivity									X	X	X
Myelosuppression							X		X		
Ophthalmic				X		X	X		X		

				(including blindness)							
Paradoxical drug reaction										X	
Peptic ulcer disease		X									
Peripheral neuropathy						X	X				
Porphyria											X
Pulmonary toxicity										X	
QT prolongation	X						X				
Red-orange discoloration of body tissues/fluids.									X	X	X
Relapse, especially with poor adherence, cavitary pulmonary lesions, or bilateral pulmonary disease.											X
Resistance	X				X			X	X		
Severe cutaneous reactions/drug reaction with eosinophilia and systemic symptoms (DRESS)									X	X	X
Severe hepatic impairment (preexisting)	X	X						X			X
Severe Renal Impairment or end stage renal disease (preexisting)	X	X				X			X		

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2014, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 19, 2022

# ▲	Searches	Results
1	bedaquiline.mp.	987
2	Aminosalicylic Acid/ae, tu, th [Adverse Effects, Therapeutic Use, Therapy]	1306
3	Cycloserine/ae, tu, th [Adverse Effects, Therapeutic Use, Therapy]	721
4	Ethambutol/ae, tu [Adverse Effects, Therapeutic Use]	2538
5	Ethionamide/ae, tu [Adverse Effects, Therapeutic Use]	548
6	Isoniazid/ae, tu, th [Adverse Effects, Therapeutic Use, Therapy]	7801
7	pretomanid.mp.	253
8	Pyrazinamide/ae, tu, th [Adverse Effects, Therapeutic Use, Therapy]	1656
9	Rifabutin/ae, tu [Adverse Effects, Therapeutic Use]	521
10	Rifampin/ae, tu, th [Adverse Effects, Therapeutic Use, Therapy]	8472
11	Rifampin/ae, tu, th [Adverse Effects, Therapeutic Use, Therapy]	8472
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	17817
13	limit 12 to english language	12788
14	limit 13 to (clinical trial, phase iii or clinical trial, phase iv or guideline or meta analysis or practice guideline or "systematic review")	258
15	limit 14 to yr="2015 -Current"	136

Appendix 3: Key Inclusion Criteria

Population	Adults and children, including special populations such as immunocompromised individuals
Intervention	Medications in Appendix 1
Comparator	Active comparators
Outcomes	Cure, treatment completion, treatment failure, disease relapse, time to sputum culture or smear conversion, clinical or radiological improvement at 8 weeks and at the end of treatment, mortality, and serious adverse events or adverse events requirement treatment alteration
Timing	Treatment of active or latent mycobacterial infections (excluding diseases not generally prevalent in the United States, such as leprosy)
Setting	Outpatient

Appendix 4: Abstracts of Comparative Clinical Trials

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis[10]

BACKGROUND: Rifapentine-based regimens have potent antimycobacterial activity that may allow for a shorter course in patients with drug-susceptible pulmonary tuberculosis.

METHODS: In an open-label, phase 3, randomized, controlled trial involving persons with newly diagnosed pulmonary tuberculosis from 13 countries, we compared two 4-month rifapentine-based regimens with a standard 6-month regimen consisting of rifampin, isoniazid, pyrazinamide, and ethambutol (control) using a noninferiority margin of 6.6 percentage points. In one 4-month regimen, rifampin was replaced with rifapentine; in the other, rifampin was replaced with rifapentine and ethambutol with moxifloxacin. The primary efficacy outcome was survival free of tuberculosis at 12 months.

RESULTS: Among 2516 participants who had undergone randomization, 2343 had a culture positive for Mycobacterium tuberculosis that was not resistant to isoniazid, rifampin, or fluoroquinolones (microbiologically eligible population; 768 in the control group, 791 in the rifapentine-moxifloxacin group, and 784 in the rifapentine group), of whom 194 were coinfected with human immunodeficiency virus and 1703 had cavitation on chest radiography. A total of 2234 participants could be assessed for the primary outcome (assessable population; 726 in the control group, 756 in the rifapentine-moxifloxacin group, and 752 in the rifapentine group). Rifapentine with moxifloxacin was noninferior to the control in the microbiologically eligible population (15.5% vs. 14.6% had an unfavorable outcome; difference, 1.0 percentage point; 95% confidence interval [CI], -2.6 to 4.5) and in the assessable population (11.6% vs. 9.6%; difference, 2.0 percentage points; 95% CI, -1.1 to 5.1). Noninferiority was shown in the secondary and sensitivity analyses. Rifapentine without moxifloxacin was not shown to be noninferior to the control in either population (17.7% vs. 14.6% with an unfavorable outcome in the microbiologically eligible population; difference, 3.0 percentage points [95% CI, -0.6 to 6.6]; and 14.2% vs. 9.6% in the assessable population; difference, 4.4 percentage points [95% CI, 1.2 to 7.7]). Adverse events of grade 3 or higher occurred during the on-treatment period in 19.3% of participants in the control group, 18.8% in the rifapentine-moxifloxacin group, and 14.3% in the rifapentine group.

CONCLUSIONS: The efficacy of a 4-month rifapentine-based regimen containing moxifloxacin was noninferior to the standard 6-month regimen in the treatment of tuberculosis. (Funded by the Centers for Disease Control and Prevention and others; Study 31/A5349 ClinicalTrials.gov number, NCT02410772.).