



INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: Treatment of Tuberculosis
-October 2021-



Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) reviewed recent clinical data on a 4-month treatment for drug susceptible pulmonary tuberculosis (TB) and the 2020 National Society of Tuberculosis Clinicians recommendations for the testing and treatment of Latent Tuberculosis Infection (LTBI) in the United States. Ethambutol, isoniazid, pyrazinamide, rifampin and rifapentine are currently on the IHS National Core Formulary. Following this review, **no modifications were made to the NCF.**

Discussion:

Each day, nearly 4,000 people die worldwide and close to 28,000 fall ill to TB, a preventable and curable disease. It is estimated that 25% of the world's population is infected¹. While the United States has a low infection rate compared to most other countries, the American Indian/Alaska Native (AI/AN) population suffers from an almost 5-fold higher rate of TB infections per 100,000 people compared to the national average for all citizens born in the United States². The Centers for Disease Control and Prevention (CDC) reported that 79 AI/AN patients were diagnosed with active pulmonary TB in 2020³. TB should be considered with symptoms such as a bad cough for 3 or more weeks which is often productive of sputum or blood, weight loss or poor appetite, night sweats or fevers. These patients should be screened for TB with either a skin test or a blood test. If positive, an exam and chest x-ray should be obtained along with sputum looking for acid-fast bacilli and a sputum culture. Thirteen million people were estimated to be living with LTBI in the United States in 2015 and 5-10% of those people living with LTBI will reactivate their disease during their lifetime³. Most reactivations occur within 5 years. People living with HIV have a 10% annual risk of reactivation. Screening for LTBI requires risk stratification of the individual patient. People who live with a person diagnosed with active TB or a close contact to that person, people who live or work in high-risk settings such as correctional facilities, nursing homes or shelters, healthcare workers involved in caring for people with TB, and children exposed to adults at increased risk for LTBI or active TB should all be screened. Numerous health conditions also warrant screening including immunosuppression such as HIV infection, organ transplantation, treatment with TNF-alpha antagonists, high dose steroids and certain medical conditions including diabetes. People with birth or residency in a country with high or medium incidence rates of TB should also be screened. Treatment is based on a diagnosis of active pulmonary TB, extrapulmonary TB, or a diagnosis of LTBI.

Current [United States guidelines for the treatment of pulmonary drug-susceptible TB](#) recommend a 4-drug regimen which consists of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA) and ethambutol (EMB), commonly known by the acronym RIPE⁴. These four medications are given during the intensive phase of treatment for 2 months, followed by INH and RIF for an additional 4 months during the continuation phase. Certain conditions require extension of the continuation phase from 4 months to 7 months, such as sputum cultures positive at the 2-month end of the intensive phase with risk factors, and for extrapulmonary TB based on site location. Treatment is most effective given daily by directly observed therapy (DOT), and 5 times weekly with DOT is considered clinically equivalent to 7 days. In cases of treatment interruption, the earlier the break and the longer the duration of the break, the more serious the effect is on the treatment which may require retreating entirely. A [new 4-month treatment regimen](#) for drug susceptible pulmonary TB published in May 2021 substituting rifapentine (RPT) for RIF and moxifloxacin (MOX) for ethambutol appears to be non-inferior to RIPE therapy in the study's assessable population (11.6 vs. 9.6%; 95% CI: -1.1 to 5.1)⁵. Four drugs are used for the 2-month intensive phase and the following 2-month continuation phase consists of INH, RPT and MOX. At this time, most TB experts in the United States **do not recommend** using this regimen due to lack of long-term data and the medication risks posed by use of MOX. Treatment guidelines for drug resistant TB were last published in 2019. They recommend a minimum 5-drug treatment based on drug sensitivities and should be developed in consultation with an expert in the treatment of TB⁶.

[Guidelines for treating LTBI in the United States](#) were updated in 2020⁷. These guidelines favor the use of rifamycin-containing regimens (i.e., rifampin, rifapentine) over INH monotherapy. The two preferred and recommended regimens include once weekly INH with RPT for 12 weeks ("3HP"), and daily RIF for 4 months ("4R"). There is another rifamycin regimen which includes daily INH and RIF for 3 months ("3HR") but has a conditional recommendation due to a lack of well-designed clinical trials supporting its use (other than one study of HIV-positive patients which demonstrated a 60% protective effect in that high-risk population)⁸. RPT is not approved for children under 2 years of age and is generally not used during pregnancy due to a lack of safety data from clinical studies. INH for 6 months ("6H") or 9 months ("9H") are alternative treatments for patients who

are unable to take rifampin or rifapentine, which generally include patients with a hypersensitivity to or drug-drug interactions (e.g., direct oral anticoagulants and warfarin) with rifamycins. Reviewing patient's medications for interactions with the rifamycin medication is very important before starting a rifamycin-based treatment. When using INH, "6H" is recommended over the "9H" regimen due to improved adherence and completion rates. Both "6H" and "9H" can be self-administered therapy (SAT) daily or given by DOT on a twice weekly basis. The "4R" regimen is generally SAT. Patients on any of these regimens need monthly visits to monitor for compliance and adverse drug events. Adults on INH need baseline labs including liver function tests. Continued monitoring of these labs is indicated for patients with risks for developing hepatitis, such as taking other hepatotoxic drugs, pregnancy, alcohol use and HIV infection. Patients should be advised of possible adverse drug events and instructed to contact their provider and discontinue their medication until a medical evaluation is made. This is especially important for patients on SAT. Common side effects of rifamycins can include "flu-like" symptoms, which tends to occur with intermittent use of high doses, and orange discoloration of urine and body fluids, which is normal.

In August 2020, the Food and Drug Administration (FDA) announced detection of increased levels of nitrosamine impurities in samples of RIF and RPT⁹. Nitrosamines are frequently found in processed foods and beverages as well as some other medications. They have been implicated in long-term animal studies as a possible human carcinogen. The risk of cancer from treatment for TB with these drugs is unknown, but the risks of TB infection and increased risks for serious toxicity from INH-induced hepatitis may be substantial with alternative regimens. The CDC and FDA both recommend continued use of RIF and RPT for the treatment of LTBI and TB disease. Informed verbal consent with documentation in the chart by the provider should be obtained.

Findings:

- Treat drug susceptible pulmonary TB using a 4-drug regimen including INH, RIF, PZA and EMB for 2 months during the intensive phase of treatment, and INH and RIF for an additional 4 months. Any drug resistant pulmonary TB infection should be managed in consultation with an expert in treating TB and will generally require five or more drugs.
- Patients with LTBI should be encouraged to pursue treatment whenever possible to minimize development of active TB later in life using a rifamycin-based regimen of either "3HP" or "4R". In cases where a rifamycin cannot be used, "6H" by DOT at least twice weekly can be considered as an alternative regimen.
- An excellent LTBI resource for providers is the National Society of Tuberculosis Clinicians guidelines, available at https://cdn.indiancountryecho.org/wp-content/uploads/2021/10/LTBI_Clinical_Recommendations.pdf
- In addition, the NPTC has a Strategic Initiative to systematize screening and treatment for LTBI in the IHS patient population, which can be found at: <https://www.ihs.gov/nptc/strategic-initiatives/latent-tb-infection/>
- The NPTC strongly encourages testing for and treatment of LTBI, specifically using the once weekly combination of INH and RPT for 12 weeks, or daily RIF for 4 months, for LTBI eradication.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the [NPTC website](#).

References:

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