Indian Health Service  
National Pharmacy and Therapeutics Committee  
Formulary Brief: Treatment of Tuberculosis  
-May 2019-

Background:
The IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed recent clinical data and guidelines for the treatment of tuberculosis (TB), specifically drug-susceptible active and latent TB infection. Ethambutol, isoniazid, pyrazinamide, rifampin and rifapentine are currently named on the IHS National Core Formulary. The NPTC strongly encourages the testing for and treatment of latent TB, specifically using the once weekly combination isoniazid/rifapentine for 12 weeks, to aide in the eradication of latent TB infection (LTBI). Following this review, no modifications were made to the NCF. The NPTC has endorsed a Strategic Initiative to systematize screening and treatment for LTBI in the IHS service population, with the goal of reducing TB-related morbidity and mortality and ultimately eradicating TB in Indian Country.

Tuberculosis is a preventable, treatable, and curable infectious disease, caused by Mycobacterium tuberculosis, which primarily infects the pulmonary system. The two main conditions are active TB and latent TB. Those infected with active TB are symptomatic, can spread disease, have a positive culture, and can die without treatment. Latent TB is asymptomatic, cannot be spread, has positive skin or blood tests, and can progress to active disease. Though anti-TB medications have been used for decades, resistance to TB is increasing and has been documented in every country. There are three types of drug-resistant TB forms, including rifampin-resistant (RR), multidrug-resistant (MDR), and extensively drug-resistant (XDR) TB. Treatment options exist for rifampin-resistant and multidrug-resistant types but require altered regimens or expensive, highly-toxic, second-line treatments for a duration of up to 24 months. Extensively drug-resistant TB does not respond to most effective therapies and often cannot be treated.

With one-quarter of the world population currently living with LTBI, a focus on prompt identification and effective treatment is at the forefront of global TB elimination efforts. The majority of active TB cases are a result of untreated LTBI. Testing for TB includes the tuberculin skin test (TST) and whole blood interferon gamma release assay (IGRA) tests. Prevention and treatment depends on clinical suspicion, proper diagnosis, use of personal protective equipment, isolation procedures, medication therapy, and medical follow up. Directly observed therapy (DOT) for both active and LTBI is advocated to improve adherence.

Discussion:
Clinical practice guidelines are similar, including those from the American Thoracic Society, U.S. Centers for Disease Control and Prevention, Infectious Diseases Society of America, World Health Organization (WHO), European Respiratory Society and the National Institute for Health and Care Excellence.

Active TB Disease, treatment:
Standard treatment of active, drug-susceptible TB includes up to 9 months of therapy with rifampin (RIF) or derivative, isoniazid (INH), pyrazinamide (PZA), and ethambutol (EMB). This core regimen ("RIPE") is effective but may be associated with severe adverse reactions or drug interactions and can also be toxic to those with liver impairment. Proper patient counseling regarding all anti-TB medications is very important. RIPE is used for the intensive phase of treatment for 8 weeks, followed by an 18-week continuation phase of INH/RIF. Frequency of treatment can vary from twice-weekly to daily administration. However, the greatest effectiveness has been shown with 5–7 days per week administration for both the intensive and continuation phases. Of note, patients at risk for neuropathy should also receive pyridoxine during INH therapy and those with HIV infection should continue antiretroviral therapy.

Treatment recommendations for active TB remain little changed. A 2007 Cochrane review examined ways to reduce treatment duration to less than six months using rifabutin or rifampin, with endpoints including cure, recurrence, and adverse effects. The review concluded no significant differences between rifabutin and rifampin treatment for curing TB [RR 1.00, 95% CI: 0.96 to 1.04], preventing relapse [RR 1.23, 95% CI: 0.45 to 3.35] or incidence of adverse effects [RR 1.42, 95% CI: 0.88 to 2.31]. A 2016 Cochrane review examined active TB treatment with fixed-dose combinations compared with single drug formulations for both efficacy and safety. The review concluded no significant differences between fixed-dosed combinations and single drug formulations for treatment failure [RR 1.28, 95% CI: 0.82 to 2.00], relapse [RR 1.28, 95% CI: 1.00 to 1.64], death [RR 0.96, 95% CI: 0.67 to 1.39], or adverse events [RR 1.45, 95% CI: 0.90 to 2.33].

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Treatment of drug-resistant TB should be managed by or in close consultation with an infectious disease expert and involves either a shorter standardized regimen consisting of seven drugs or a longer individualized regimen consisting of two phases of treatment. Those with MDR-TB (resistant to more than one anti-TB drug and at least INH and RIF) along with XDR-TB (resistant to INH and RIF, plus any fluoroquinolone and at least one injectable second-line medication) can have life-threatening side effects from inappropriate treatment.\(^5\)\(^6\) A substantial proportion of patients treated for these forms of drug-resistant TB experience serious side effects and can cost over $500,000 per treatment course. In March 2019, the WHO issued new guidance to improve the treatment of MDR-TB by recommending fully oral regimens to avoid adverse effects, along with appropriate counseling and support.\(^1\) Fluoroquinolone use is indicated for most patients who have drug-resistant TB or drug-resistant LTBI.

**Latent TB Infection, treatment:**

There are currently four recommended treatments for LTBI.\(^5\)\(^-\)\(^9\) All regimens are effective but providers are encouraged to prescribe the most convenient short-course regimen whenever possible. The combination of isoniazid and rifapentine given as 12 weekly doses (also known as 3HP) by directly-obtained therapy or self-administered therapy (SAT) is recommended in patients ages 2 years and older. This regimen may be used in patients with HIV infection, including those with AIDS and those taking antiretroviral medication.\(^5\)\(^-\)\(^9\) The combination of daily isoniazid and rifampin for three months offers another short-course option. Alternately, a four-month course of daily rifampin may be used. A 9-month course of daily INH may also be recommended for use in persons with LTBI, including those with HIV infection, pregnant women, and pediatric patients.

Recommended regimens for LTBI have not changed in recent years. However, treatment recommendations have been updated to reflect the favorability of the three-month, weekly 3HP combination regimen due to substantially higher treatment completion rates. A 2010 Cochrane review examined LTBI with INH in HIV patients to determine the risk of progressing to active TB disease.\(^13\) Prevention of progression to active TB disease was significant and favored treatment of LTBI when compared with placebo [RR 0.68, 95% CI: 0.54 to 0.85]. Efficacy was similar for all regimens. A 2017 meta-analysis further examined the treatment of LTBI for progression to active disease.\(^14\) The review found that all regimens examined were efficacious compared to placebo for the prevention of TB reactivation. Evidence supports the efficacy of the weekly rifapentine-INH (3HP) regimen compared with no treatment [OR 0.36; 95% CI: 0.18 to 0.73]. A 2018 meta-analysis examined rifapentine-INH use for treatment of LTBI in those ≥2 years of age, focusing on prevention of disease, treatment completion, adverse events and death.\(^15\) The review concluded that weekly rifapentine-INH was well-tolerated and as effective as 9 months of daily INH for preventing TB reactivation [OR 0.89, 95% CI: 0.46 to 1.70]. The review also reported that the combination was safe [RR 0.59, 95% CI: 0.23 to 1.52] and had higher treatment completion rates (87.5% vs. 65.9%) compared to daily INH therapy. Adverse events, including treatment discontinuation and death, were similar between regimens.

**Findings:**

Tuberculosis is a preventable, treatable, and curable disease affecting a substantial proportion of the worldwide population, remaining one of the top 10 global causes for death. American Indian/Alaska Native people suffer disproportionately, compared with non-Hispanic whites. Proactive screening for latent TB infection among high-risk persons as well as effective treatment of both LTBI and active TB are necessary to prevent the development and spread of illness. Fixed-dose combination therapy in a short course regimen with either directly-observed or self-administered therapy has been shown to increase adherence and completion of treatment. Enhanced recommendations favor weekly rifapentine-INH for 12 weeks (3HP) for LTBI treatment, including for children ≥2 years old and those with HIV infection.

*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:**


