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Treatment of latent tuberculosis infection – An Update

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Abstract

Treatment of latent tuberculosis infection (LTBI) is an important component of TB control and elimination. LTBI treatment regimens include once-weekly isoniazid plus rifapentine for 3 months, daily rifampin for 4 months, daily isoniazid plus rifampin for 3–4 months, and daily isoniazid for 6–9 months. Isoniazid monotherapy is efficacious in preventing TB disease, but the rifampin- and rifapentine-containing regimens are shorter and have similar efficacy, adequate safety, and higher treatment completion rates. Novel vaccine strategies, host immunity directed therapies and ultra-short antimicrobial regimens for TB prevention, such as daily isoniazid plus rifapentine for 1 month, are under evaluation.

Keywords

latent tuberculosis infection; treatment; tuberculosis; prevention and control; isoniazid; rifampin; rifapentine; review

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INTRODUCTION

Latent tuberculosis infection (LTBI) is defined by the presence of detectable immune responses to *Mycobacterium tuberculosis* antigens with no clinical evidence of active TB disease.[1] It has been estimated that one-quarter of the world population has LTBI; however, there are wide variations in the rates of LTBI across regions.[2] In high-income countries, the incidence of active TB disease has continued to decline over the recent decades,[3,4] but the prevalence of LTBI has remained stable. For example, in the U.S., 4 to 5% of the population was estimated to have LTBI in 2011–2012,[5] similar to prevalence rates reported in 1999–2000.[6] This indicates a persistent reservoir of *M. tuberculosis* infection even in countries where active disease is less frequent. Since the majority of new TB cases in these settings are a result of reactivation of remote LTBI rather than recent infection,[7-9] intensification of LTBI screening and treatment strategies is recognized as a crucial component of TB elimination in low TB prevalence settings.[3,10,11] Modeling studies also show the significant contribution of LTBI treatment in controlling the TB epidemic in high burden settings.[4,12] Ongoing efforts to target LTBI are challenged by limitations of current diagnostic tests to identify LTBI and persons at highest risk for progression to TB disease, potential toxicities of available LTBI therapies, suboptimal treatment adherence rates, and limited resources of TB control programs.[13-15]

In this article, we review current LTBI treatment regimens. Our primary focus is on LTBI treatment in low TB prevalence settings such as the U.S. and Canada. We include sections of LTBI management in special populations (i.e., HIV-positive individuals, transplant patients, pregnant women, children, and contacts of multidrug-resistant TB) and considerations for LTBI treatment in high TB prevalence settings.

Indications for LTBI screening and treatment

LTBI screening is indicated in populations with a high risk of progression to TB disease and populations with increased risk for LTBI (Box 1).[1,16,17] Persons at increased risk of progression to TB disease include household contacts of confirmed pulmonary TB cases (particularly children < 5 years of age), persons living with HIV/AIDS (PLWHA), patients initiating antitumor necrosis factor-alpha (TNF) therapy, candidates for hematologic or solid organ transplant, patients receiving dialysis, and patients with silicosis.[1] In low TB prevalence settings, populations at increased risk for LTBI may include immigrants from countries with high TB prevalence, health care workers, persons who live in high-risk congregate settings such as homeless shelters or correctional facilities, and users of illicit drugs.[1,16,17] Recently, diabetes mellitus has been identified as a risk factor for LTBI and progression to TB disease;[18,19] however, routine LTBI screening in diabetic patients is not recommended by current World Health Organization (WHO) guidelines.[1]

Screening tests for LTBI include the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs).[20] Readers can refer to Michelle K. Haas and Robert W. Belknap's article, "Diagnostic Tests for Latent Tuberculosis Infection," in this issue for a discussion on LTBI diagnosis and testing modalities.

LTBI treatment regimens

Four main antimicrobial regimens are currently available for LTBI treatment: isoniazid monotherapy, rifampin monotherapy, isoniazid plus rifampin in combination, and isoniazid plus rifapentine in combination (Table 1). Isoniazid monotherapy for 6–12 months has been used for decades, and its efficacy in preventing progression to TB disease is ~ 90%.[21] However, its overall effectiveness has been hindered by low adherence and completion rates due to its prolonged duration and hepatotoxicity risk.[22,23] Shorter rifamycin-based regimens have similar efficacy and are being increasingly used. These regimens are associated with improved completion rates as well as reduced risk of hepatotoxicity compared to isoniazid monotherapy.[24] Importantly, studies have not shown an increased risk of developing isoniazid- or rifamycin-resistant TB disease after receiving LTBI treatment regimens that contain these drugs.[25,26]

Isoniazid daily for six to twelve months.—Isoniazid inhibits the synthesis of mycolic acids, which are essential components of the mycobacterial cell wall.[27] Isoniazid monotherapy has been considered standard of care for LTBI treatment for several decades.[28,29] Multiple studies have demonstrated the TB preventive efficacy of this drug. Isoniazid is administered at a dose of 5 mg/kg/day (conventional adult dose, 300 mg daily).[30] A meta-analysis of randomized controlled trials showed that the odds ratios of TB disease in persons with LTBI treated with 6 and ≥12 months of isoniazid were 0.65 (95% credible interval, 0.50–0.83) and 0.50 (95%, credible interval, 0.41–0.62) respectively, compared to placebo.[31] In a trial of 28,000 HIV-negative persons with fibrotic pulmonary lesions, 12 months of isoniazid achieved a 75% reduction on the incidence of TB disease, compared to a 65% reduction in the group receiving 6 months of isoniazid.[32] However, a re-analysis of U.S. Public Health Service (USPHS) trials data suggested that the maximal benefit from isoniazid monotherapy was achieved by 9 months.[33] Therefore, the recommended duration of isoniazid monotherapy for LTBI has been 6 to 9 months.[1,34] Isoniazid has been used as the main standard of care comparator regimen in recent clinical trials of LTBI. Pyridoxine should be administered concomitantly with isoniazid.

Side effects from isoniazid may include hepatitis (fatigue, decreased appetite, abdominal discomfort, nausea, jaundice) and peripheral neuropathy (Table 2).[34] A survey of 13,838 persons who received isoniazid found a rate of probable and possible isoniazid-related hepatitis of 1.3%.[23] The risk of hepatitis increases with age and alcohol consumption. Pre-existing liver conditions such as chronic hepatitis C infection are also associated with higher risk of hepatotoxicity, and therefore closer follow-up is advised in these patients.[34,35] Isoniazid may interact with some drugs such as phenytoin, carbamazepine, valproate, acetaminophen, warfarin, and monoamine oxidase inhibitors.[36]

Rifampin daily for three to four months.—Rifampin inhibits RNA synthesis by binding to the mycobacterial RNA polymerase.[37] Rifampin monotherapy for LTBI has been associated with similar efficacy and lower hepatotoxicity rates compared to isoniazid.[1,38,39] Rifampin is administered at a dose of 10 mg/kg/day (conventional adult dose, 600 mg daily) for 3–4 months. In a recent multicenter trial, 6,063 adults with LTBI were randomized to receive 4 months of daily rifampin or 9 months of daily isoniazid.[38] Participants were

followed up to 28 months for the development of active TB. The rates of confirmed and clinically diagnosed TB disease were similar between the study groups and thus rifampin was determined to be non-inferior to isoniazid for TB prevention. Rifampin was associated with higher treatment completion rates than isoniazid (78.8% vs. 63.2%). As shown in a prior smaller trial,[40] rifampin had a more favorable safety profile including lower frequency of grade 3 to 4 hepatotoxicity events that required permanent drug discontinuation compared to isoniazid (0.3% vs. 1.8%).[38]

Rifampin may cause gastrointestinal symptoms (i.e., abdominal pain, nausea), dermatologic reactions, hypersensitivity reactions, hematological side effects, and hepatotoxicity. Urine and other body fluids may develop an orange discoloration, which can lead to staining of soft contact lenses and dentures.[34] Rifampin is a potent CYP3A inducer and may affect the metabolism of several drugs including antiretrovirals, anticonvulsants, warfarin, azole antifungals, methadone, cyclosporine and other immunosuppressants.[21,36] Therefore, checking for potential drug-drug interactions is advised when considering rifampin for LTBI.

Isoniazid and rifampin daily for three to four months.—A meta-analysis showed that the odds ratio of TB disease in persons with LTBI treated with daily isoniazid plus rifampin for 3–4 months was 0.53 (95% credible interval, 0.36–0.78), compared to placebo.[31] Randomized trials have compared 3–4 months of daily isoniazid plus rifampin to 6–12 months of daily isoniazid monotherapy in HIV-positive and HIV-negative persons.[41-45] Overall, similar TB prevention efficacy rates and safety profiles have been reported for the isoniazid plus rifampin combination regimen compared to standard isoniazid monotherapy.[46]

Isoniazid and rifapentine once-weekly for 3 months.—Rifapentine is a rifamycin derivative with a longer half-life and increased potency compared to rifampin.[47,48] In the PREVENT TB trial (Tuberculosis Trials Consortium Study 26 / AIDS Clinical Trials Group 5259), 7,731 high-risk individuals with positive TST (contacts of pulmonary TB cases, recent TST convertors, PLWHA, presence of fibrosis on chest radiograph) were randomized to receive 3 months of directly observed isoniazid 900 mg and rifapentine 900 mg once weekly, or 9 months of isoniazid 300 mg daily monotherapy.[49] Participants were followed for 33 months. The isoniazid-rifapentine combination regimen was non-inferior to isoniazid in preventing TB disease. The risk of hepatotoxicity was lower in the isoniazid-rifapentine combination group as compared to isoniazid (0.4% vs. 2.7%). Notably, treatment completion rates were higher with the isoniazid-rifapentine combination than isoniazid (82.1% vs. 69%). Similar completion rates have been reported among patients receiving the 3-month isoniazid-rifapentine regimen for LTBI in U.S. TB Control Programs after its implementation in routine practice.[50] Based on the PREVENT TB trial design, the isoniazid-rifapentine regimen was initially administered only by directly observed therapy (DOT). However, a recent study compared the isoniazid-rifapentine regimen given by DOT versus self-administered therapy (SAT).[51] Among U.S. sites, once-weekly isoniazid-rifapentine given as SAT achieved similar treatment completion rates and safety outcomes as DOT, and therefore this regimen is now recommended as SAT by Centers for Disease Control and Prevention (CDC) guidelines.[52] Rifapentine is a potent CYP3A inducer (~85% as potent as

rifampin). Rifapentine and rifampin share similar drug-drug interaction and toxicity profiles.[53]

Initial assessment

Patients found to have LTBI should be evaluated by health care provider teams with experience in managing LTBI to rule out active TB, discuss implications of the diagnosis, risk of TB reactivation, and available treatment options. A detailed history of TB risk factors, presence of comorbidities, and current medications should be obtained. Electronic decision support tools that provide personalized estimates of annual and cumulative risks of progression to TB disease, such as the Online TST/IGRA Interpreter (www.tstin3d.com), are available to assist patients and providers.[54,55] HIV testing is advised in all patients with LTBI. Baseline liver function tests should be considered in patients with baseline liver disease and/or risk factors for hepatotoxicity. Women of childbearing potential should be screened for pregnancy. Patients in whom rifamycin-containing regimens are considered should have their current list of medications analyzed for potential drug-drug interactions. Providers should discuss potential side effects of LTBI therapy, and inform patients of signs and symptoms that require medical attention. Resources for educating patients on LTBI and available therapies can be found at the CDC website (www.cdc.gov/tb/topic/treatment/ltbi.htm). For the 3-month isoniazid plus rifapentine regimen, the decision on SAT versus DOT should be based on patient's age, medical history, social circumstances, risk factors for TB disease progression, and program resources.[52]

LTBI treatment monitoring

Patients who initiate LTBI treatment should be routinely monitored for medication adherence and tolerability. The CDC recommends monthly visits to assess medication adherence and signs or symptoms of drug toxicity.[34] No laboratory tests are routinely ordered at follow-up visits, unless there is a clinical indication and/or concern for drug toxicity. In patients with abnormal baseline liver enzymes and/or at risk for hepatotoxicity, periodic laboratory monitoring is recommended.[34] LTBI drugs should be held if the patient is symptomatic and transaminase levels exceed 3 times the upper limit of normal, or if asymptomatic and transaminase levels are ≥ 5 times the upper limit of normal. Patients who develop signs or symptoms of active TB disease should be screened with a chest radiograph even if they are receiving LTBI treatment.

Special populations

Persons living with HIV/AIDS (PLWHA).—HIV/AIDS carries a significant risk of progression to TB disease. It is estimated that in the absence of antiretroviral therapy (ART) as many as 10% of PLWHA with LTBI co-infection may develop TB disease each year.[56,57] The risk of progression to active TB among PLWHA on ART and optimal virologic response remains higher than the general population.[58] ART and treatment of LTBI both decrease the risk of TB among PLWHA;[59-62] thus, both are indicated.[63] Isoniazid monotherapy has been the preferred LTBI treatment regimen for PLWHA given its proven efficacy.[34,63] A meta-analysis showed that isoniazid decreased the incidence of TB disease in 64% among PLWHA with a positive TST.[64] The 3-month once-weekly isoniazid plus

rifapentine regimen is non-inferior to isoniazid monotherapy in PLWHA who have not yet started ART,[65] and can be used in PLWHA taking compatible ART such as efavirenz- or raltegravir-containing regimens.[66,67] Additional investigation is needed to determine the safety of once-weekly isoniazid plus rifapentine in PLWHA receiving dolutegravir-containing ART, as a severe flu-like syndrome occurred in 2 of 4 healthy volunteers.[68] A recent trial (AIDS Clinical Trials Group 5279) showed that an ultrashort course of 1 month of daily isoniazid 300 mg and rifapentine 300–600 mg was non-inferior to 9 months of isoniazid for TB prevention in PLWHA (most of the study participants were living in high TB burden settings and were TST-negative).[69] The 1-month daily isoniazid-rifapentine regimen had fewer adverse events and higher treatment completion rates than 9 months of isoniazid.

In PLWHA in settings with high TB prevalence, 36 months of isoniazid has been associated with a greater reduction in the risk of incident TB disease than 6 months of isoniazid;[70] however, the potential toxicities and adherence difficulties of such prolonged TB preventive therapy have made its implementation challenging.

Transplant candidates and persons receiving TNF-alpha inhibitors.

Transplant candidates found to have LTBI should receive one of the recommended LTBI treatment regimens, ideally prior to transplantation.[71] If transplantation occurs prior to LTBI treatment completion, treatment should be resumed after transplant as soon as medically feasible to complete the originally planned duration. Most of the clinical experience in transplant candidates with LTBI has been with isoniazid monotherapy. However, case series of kidney, liver, and heart transplant candidates receiving the 3-month isoniazid-rifapentine regimen suggest adequate completion rates and tolerability in selected patients.[72-74] Close follow-up is required in transplant candidates who initiate LTBI treatment to monitor for side effects and treatment adherence.

Persons initiating TNF-alpha inhibitors should be systematically tested and treated for LTBI.[1] The American College of Rheumatology recommends completing at least one month of LTBI treatment prior to starting or resuming TNF-alpha inhibitors and other biologic agents in patients with rheumatoid arthritis.[75]

Pregnant women.

Current CDC guidelines recommend considering LTBI treatment in pregnant women who are HIV-positive or recent TB contacts.[34] In pregnant women not at high risk of progression to TB, LTBI treatment may be delayed until 2–3 months post-partum. Isoniazid has been the preferred regimen for LTBI treatment during pregnancy.[1,34] Rifampin is an alternative option. Both isoniazid and rifampin are considered category C drugs during pregnancy. Whether to initiate or delay LTBI treatment during pregnancy should be a joint decision with each individual patient, considering the patient's risks factors for TB reactivation and potential side effects from LTBI treatment. A recent randomized trial showed that HIV-positive pregnant women living in high TB burden settings (most of whom did not have evidence of LTBI) who initiated isoniazid therapy during pregnancy had higher rates of adverse pregnancy outcomes compared to women who deferred LTBI treatment until 12

weeks post-partum.[76] Therefore, the recommendation for LTBI treatment during pregnancy in HIV-positive pregnant women is being re-evaluated. A sub-analysis of the PREVENT TB and iAdhere trials assessed the outcomes of 125 pregnant women who received some isoniazid-rifapentine or isoniazid monotherapy.[77] No unexpected fetal loss or congenital abnormalities were reported in these women, providing some reassurance that these drugs may be used in pregnancy or women of childbearing potential when deemed clinically necessary.

Children.—Children with LTBI are at increased risk for progression to TB disease, particularly in the setting of HIV co-infection.[78] In the U.S., isoniazid monotherapy for 9 months remains the preferred recommended regimen for children and adolescents.[34] Daily rifampin for 6 months is recommended by the American Academy of Pediatrics when the case source is known to be isoniazid resistant and rifampin susceptible.[79] Four months of rifampin is safe and effective in children.[80] Isoniazid plus rifampin for 3–4 months appears to be safe and effective in the pediatric population.[81,82] The CDC now recommends the use of the 3-month isoniazid-rifapentine regimen in adolescents and children aged 2 or older.[52]

Multidrug-resistant (MDR) TB contacts.

Studies have confirmed that contacts of MDR TB patients are at increased risk of developing MDR TB disease.[83] There are no standardized recommendations for MDR TB contacts due to lack of randomized clinical trials of TB preventive therapy in this population. Consultation with an expert in MDR TB is generally advised to assist with monitoring and therapy decisions.[34] If preventive treatment is considered, the drug(s) should be selected based on the drug susceptibility profile of the source patient.[1] Although there is no consensus on whether periodic screening versus preventive therapy is better for LTBI management in MDR TB contacts, observational studies suggest a benefit of preventive therapy. A study showed that none of 104 MDR TB contacts who started a fluoroquinolone-based LTBI regimen developed MDR TB after 36 months of follow-up, whereas 3 of 15 (20%) contacts who refused LTBI treatment developed MDR TB.[84] A recent meta-analysis of 21 observational studies found that LTBI treatment reduced MDR TB incidence by 90% (9–99%), with greatest cost-effectiveness using fluoroquinolone plus ethambutol in combination.[85] Thus, many programs have adopted the use of fluoroquinolone-based regimens for MDR TB contacts with LTBI based on growing clinical experience and expert opinion.[24,86,87]

However, randomized trials are urgently needed in this population. In the ongoing V-QUIN trial, household contacts of MDR TB cases are randomized to 6 months of levofloxacin or placebo. The PHOENIx MDR TB trial () will randomize household contacts of MDR TB cases to 6 months of delamanid or isoniazid therapy.

Treatment of LTBI in high TB prevalence settings

LTBI screening and preventive therapy in high TB prevalence settings prioritizes groups with the highest risk for TB reactivation, such as PLWHA and contacts of pulmonary TB cases, especially children < 5 years of age.[1] Unfortunately, implementation of LTBI programs has been difficult, as most available resources are utilized to manage active TB

cases. Isoniazid given for 6–9 months has been the preferred treatment regimen due to its low cost, availability and proven efficacy. However, studies indicate that the 3-month isoniazid-rifapentine regimen is likely to be cost-effective relative to isoniazid in high TB burden settings.[88]

Future approaches

Shorter and better-tolerated LTBI regimens are under development. The 3-month isoniazid-rifapentine combination regimen represent an important step forward in reducing LTBI treatment duration and improving adherence, thus facilitating large-scale implementation. In an effort to overcome challenges posed by poor treatment adherence and low completion rates of current LTBI therapies, there is ongoing work to develop long-acting formulations suitable for LTBI.[89] For PLWHA in high TB prevalence settings, cyclic administration of LTBI treatment may be an alternative to single rounds of prolonged, continuous TB preventive therapy. Such strategy is being investigated in the WHIP3TB trial (), which is comparing the 3-month isoniazid-rifapentine regimen given in annual cycles for 2 consecutive years with standard 3-month isoniazid-rifapentine or 6 months of isoniazid given as single cycles. Novel vaccination strategies are under development, as the only licensed TB vaccine available (Bacillus Calmette– Guérin; BCG) does not provide substantial protection against pulmonary TB disease.[90] A phase 2b trial of an adjuvant subunit vaccine containing two *M. tuberculosis* antigens showed 54% efficacy in preventing TB disease development among HIV-negative adults with LTBI from endemic areas.[91] Readers can refer to Lisa Stockdale and Helen Fletcher's article, "The Future of Vaccines for Tuberculosis," in this issue for further discussion on the future of vaccines in TB prevention. Targeted host-directed therapies that enhance immune responses to *M. tuberculosis* may offer opportunities as future adjuvant and/or primary TB preventive strategies.[92,93]

SUMMARY

Regimens of isoniazid, rifampin, or combinations of isoniazid plus rifampin or rifapentine are available for treating LTBI. Rifamycin-based therapies are shorter and better tolerated than isoniazid monotherapy, and thus are important tools to prevent TB disease and contribute to end the TB epidemic. Novel vaccine strategies, host immunity directed therapies and ultra-short antimicrobial regimens for TB prevention are under evaluation.

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Key Points

- Treatment of latent tuberculosis infection is an important component of tuberculosis control and elimination.
- Treatment regimens for latent tuberculosis infection include once-weekly isoniazid plus rifapentine for 3 months, daily rifampin for 4 months, daily isoniazid plus rifampin for 3–4 months, and daily isoniazid for 6–9 months.
- Isoniazid monotherapy is efficacious in preventing tuberculosis, but the rifampin- and rifapentine-containing regimens are shorter, have similar efficacy, adequate safety, and higher treatment completion rates.

Box 1.

Populations at risk of latent tuberculosis infection (LTBI) and tuberculosis disease (TB)

- Contact of pulmonary TB cases
- Immigrants from high-burden TB areas
- Persons with HIV infection
- Transplant candidates
- Patients receiving hemodialysis
- Patients starting tumor necrosis factor-alpha (TNF) inhibitors
- Patients with silicosis
- Homeless individuals
- Correctional facilities
- Health care workers
- Injection drug users

Data from World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva, Switzerland. 2018.

Other agencies include additional populations at risk such as persons receiving immunosuppression other than anti-TNF treatment.[17,34] Recent LTBI test convertors are at highest risk of TB progression within the first 2 years after infection.

Table 1.

Latent tuberculosis infection (LTBI) treatment regimens.

Regimen	Duration	Dose	Frequency	Total doses
Isoniazid plus rifapentine	3 months	Isoniazid 900 mg (15 mg/kg) Rifapentine: 750 mg if 32-50kg; 900 mg if > 50 kg	Once weekly [a]	12
Rifampin	4 months	600 mg (10 mg/kg)	Daily	120
Isoniazid plus rifampin	3–4 months	Isoniazid 300 mg (5mg/kg) Rifampin 600 mg (10 mg/kg)	Daily	90–120
Isoniazid	6–9 months	300 mg (5mg/kg) 900 mg (15 mg/kg)	Daily Twice-weekly [b]	180–270 52–76

[a] Isoniazid and rifapentine weekly can be given as self-administered therapy (SAT) or direct observed therapy (DOT).[52]

[b] Isoniazid twice-weekly regimens must be provided by DOT.[34]

Table 2.

Potential adverse events of drugs used for latent tuberculosis infection (LTBI) treatment

Drug	Potential adverse effects	Comments
Isoniazid	Elevation of aminotransferases Symptomatic hepatitis Peripheral neuropathy	Close follow-up and caution in patients with baseline liver disease
Rifamycins (includes rifampin,rifapentine, and rifabutin)	Cutaneous rash Hematologic abnormalities Flu-like illness Elevation of aminotransferases Symptomatic hepatitis Orange discoloration of body fluids	Consider multiple potential drug-drug interactions (i.e., warfarin, anticonvulsants, opioids, antiretrovirals) Isoniazid-rifapentine not recommended in pregnant women or women expecting to be pregnant during treatment Isoniazid-rifapentine not recommended for children < 2 years of age