



Treatment of Latent Tuberculosis Infection and Its Clinical Efficacy

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The role of the treatment for latent tuberculosis infection (LTBI) has been underscored in the intermediate tuberculosis (TB) burden countries like South Korea. LTBI treatment is recommended only for patients at risk for progression to active TB—those with frequent exposure to active TB cases, and those with clinical risk factors (e.g., immunocompromised patients). Recently revised National Institute for Health and Care Excellence (NICE) guideline recommended that close contacts of individuals with active pulmonary or laryngeal TB, aged between 18 and 65 years, should undergo LTBI treatment. Various regimens for LTBI treatment were recommended in NICE, World Health Organization (WHO), and Centers for Disease Control and Prevention guidelines, and superiority of one recommended regimen over another was not yet established. Traditional 6 to 9 months of isoniazid (6H or 9H) regimen has an advantage of the most abundant evidence for clinical efficacy—60%–90% of estimated protective effect. However, 6H or 9H regimen is related with hepatotoxicity and low compliance. Four months of rifampin regimen is characterized by less hepatotoxicity and better compliance than 9H, but has few evidence of clinical efficacy. Three months of isoniazid plus rifampin was proved equivalence with 6H or 9H regimen in terms of efficacy and safety, which was recommended in NICE and WHO guidelines. The clinical efficacy of isoniazid plus rifampentine once-weekly regimen for 3 months was demonstrated recently, which is not yet introduced into South Korea.

Keywords: Latent Tuberculosis; Antitubercular Agents; Treatment Outcome; Interferon-Gamma Release Tests; Tuberculin Test; Epidemiology

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What is Latent Tuberculosis Infection?

Mycobacterium tuberculosis is carried in airborne droplet nuclei coughed into the atmosphere by patients with active tuberculosis (TB). The infected droplet nuclei remain suspended in the air and can be transmitted when inhaled¹. About 90% of infected patients can normally respond to *M. tuberculosis* infection by granuloma formation, without manifesting clinical symptoms of active TB disease, in a condition known as latent tuberculosis infection (LTBI). However, in 10% of infected patients with various immunological conditions, dormant mycobacterium begins to grow and LTBI develops into active TB². Transmission of TB to the community occurs in the endless repetitive cycle of contact, infection, and development of active disease. World Health Organization (WHO) guidelines define LTBI as state of persistent immune response to stimulation by *M. tuberculosis* antigens without evidence of clinically manifested active TB³. Current diagnostic tests for *M. tuberculosis* infection cannot distinguish between completely

cured TB infections, active and latent TB. Therefore, in addition to positive testing for *M. tuberculosis* infection, proper diagnosis of LTBI requires that the presence of active TB disease must be excluded.

Why Treatment of LTBI Is Important Worldwide?

To eliminate TB worldwide by 2050, which means annual incidence of TB less than one case per million people, the incidence of TB must decrease at 20% per year on average from 2015 to 2050⁴. That target can only be achieved with effective treatment of active TB combined with treatment of LTBI that can progress to active TB. In most high TB burden countries, where the majority of cases result from recent infection, earlier detection, accurate diagnosis and achieving high cure rates is the pillar of their anti-tuberculosis strategy. Where the prevalence of human immunodeficiency virus (HIV) infection is high, as in South Africa, preventive therapy with isoniazid or other anti-tuberculosis drug among people infected with HIV is vital in addition to case finding and case management strategy. Where the prevalence of HIV infection is low (<1%), as in China, mass preventive therapy for LTBI plays an important role in TB elimination. In low TB burden countries, maintaining low transmission rate, preventing TB cases which result from remote infection among native born population, especially for the elderly is important. Because the majority of TB cases occur among the immigrants, screening of immigrants is another important anti-tuberculosis strategy in low TB burden countries. Under these circumstances, WHO recommended treatment of patients with LTBI at high risk of progressing to active TB, in high- and middle-income countries with annual TB incidence below 100 cases per 100,000 persons³.

Why Treatment of LTBI Is Important in South Korea?

South Korea has the disproportionately high TB burden among the member countries of the Organization for Economic Co-operation and Development (OECD)⁵. One of the reasons for the relatively high burden of TB in South Korea is high prevalence of LTBI in the elderly population⁶. The number and proportion of notified TB patients over 65 years of age is increasing despite the decrease in total incidence of TB, rising from 6,547 new TB cases out of 34,123 total new TB cases (19.2%) in 2001 to 12,328 new TB cases out of 30,892 total new TB cases (39.9%) in 2016⁷. Increasing TB burden in elderly is related with aging society⁸. LTBI prevalence among the elderly population in South Korea is estimated to be high. In one study, among the participants >60 years of age without radiographic evidence of prior TB, 67.2% were diagnosed as

LTBI, based on interferon- γ release assay result⁹. TB in elderly population in low burden countries is associated with endogenous reactivation rather than recent transmission¹⁰. This phenomenon is also observed in many other intermediate burden countries, where the risk of transmission tends to decrease¹¹.

In South Korea, TB incidence decreased from 100.8 cases per 100,000 people in 2011 to 76.8 cases per 100,000 people in 2016⁷. Until recently, LTBI treatment was not a possible option in South Korea for controlling active TB. However, the 2011 Korean guidelines on TB recommended treatment of LTBI in patients with close contacts of active TB below the age of 35 years, and non-contacts with risk factor of development to active TB. The revised 2014 guidelines recommended treatment of LTBI in more specific clinical situations, especially in immunocompromised patients.

How Was the Treatment of LTBI Introduced?

After confirming isoniazid's clinical efficacy in TB treatment in the 1950s, isoniazid has been essential for TB therapy. In 1954, Dr. Lincoln at Bellevue Hospital in New York City found that children with primary tuberculosis who had undergone isoniazid treatment had no complication like meningitis, and suggested that children with recent conversion of tuberculin skin test (TST), so called asymptomatic primary tuberculosis should be treated with isoniazid for a year—a period in which meningitis most likely to develop¹². In a multi-clinic placebo controlled clinical trial organized by U.S. Public Health Service in which 2,750 asymptomatic children with recent TST conversion were enrolled, 1-year isoniazid preventive therapy made 94% reduction in the incidence of TB during a year of treatment, and 70% reduction over following 8-year period¹³. In 1965, American Thoracic Society adopted preventive chemotherapy for LTBI¹⁴.

Whom to Treat?

Considering that only 10% of LTBI proceeds to active TB, LTBI treatment is recommended only for LTBI patients at risk of progressing to active TB. In other words, diagnostic test for LTBI is recommended only for those who need treatment when LTBI is confirmed¹⁵. Patients at risk for progression to active TB can be classified into two groups: those with frequent exposure to active TB cases and those with clinical risk of developing active TB. The former includes persons in close contact to active cases, for example, family contacts or employees in correctional and nursing facilities. A typical example of the latter is people with HIV. Recommended indications for diagnosis and treatment of LTBI according to the current guidelines of National Institute for Health and Care Excellence

Table 1. Recommended indications for diagnosis and treatment of LTBI according to the current guidelines of NICE, WHO, CDC

	NICE	WHO	CDC
Contacts of pulmonary TB cases	O	O	O
People with HIV	O	O	O
Patients initiating anti-TNF treatment	O	O	O
Patients with radiograph consistent with old TB	-	-	O
Patients with prolonged use of corticosteroid	-	-	O
Patients with chronic kidney disease	O	-	O
Patients receiving dialysis	O	O	O
Patients preparing for organ transplantation	O	O	O
Patients with hematologic malignancy	O	-	-
Patients with head and neck cancer	-	-	O
Patients having chemotherapy	O	-	
Patients who have had a jejunioileal bypass	O	-	O
Patients who have had a gastrectomy	O	-	O
Patients with silicosis	O	O	O
Patients with diabetes	O	Not recommended	O
Healthcare workers	O	O	O
Residents and employees of high-risk congregate settings (correctional facilities, nursing homes, homeless shelters)	O	O	O
Immigrants from high TB burden countries	O	O	O
Illicit drug users	O	O	O
Excessive alcohol use	O	Not recommended	-
Underweight (10% below ideal)	-	Not recommended	O

LTBI: latent tuberculosis infection; NICE: National Institute for Health and Care Excellence; WHO: World Health Organization; CDC: Centers for Disease Control and Prevention; TB: tuberculosis; HIV: human immunodeficiency virus; TNF: tumor necrosis factor.

(NICE, UK), WHO, and Centers for Disease Control and Prevention (CDC, USA) are listed in Table 1.

1. Non-close contacts

In United Kingdom, TB cases amongst immigrants comprise over two-thirds of total TB cases¹⁶. Reactivation of TB at least 6 years after immigration to United Kingdom is increasing, and accounts for 60% of total TB cases amongst immigrants. It is recommended that immigrants from high TB burden countries (prevalence higher than 150 patients per 100,000 people) below the age of 65 years should be tested and treated for LTBI, according to the revised NICE guidelines¹⁷.

Also in United States, active TB among foreign-born persons accounted for two-thirds of total TB cases in 2015¹⁸. CDC guideline classified persons who have immigrated from TB-endemic regions of the world as persons at risk for developing TB disease, and recommended test and treatment for LTBI¹⁹.

In contrast to NICE guidelines, WHO guidelines recom-

mended against patients with diabetes mellitus and alcoholics undergoing test and treatment for LTBI. Whereas CDC guidelines recommended test and treatment for LTBI of those who are underweight, WHO guidelines opposed that.

2. Close contacts

Guidelines published by NICE, WHO, and CDC suggested treatment for LTBI in close contacts of persons with TB disease (Table 1). Close contacts of persons with TB disease in all age groups were required to undergo diagnostic tests for active TB; however, additional diagnostic testing and treatment for LTBI were recommended only for those below the age of 35 years, according to the previous version of NICE guideline (2006). However, according to CDC guideline, diagnosis and treatment of LTBI was not limited to specific age groups; additionally, targeted and personalized treatment was recommended, after estimating the patients' lifelong benefit and risk of LTBI treatment¹⁹. Recently, revised NICE guideline (2016) recommended that close contacts of active pulmonary or

laryngeal TB, 18–65 years old, should undergo diagnosis and treatment of LTBI, after excluding active TB¹⁷. Revised NICE guideline, taking into account an economic model analysis on the risk and benefit of LTBI treatment, amended the age limit of LTBI treatment indication from 35 years old to 65 years old and recommended LTBI treatment for persons over 35 years old only when there is low risk for hepatotoxicity.

How to Treat?

Chest radiography should be performed before LTBI treatment to exclude active TB disease³. LTBI patients, recently exposed to active cases, were advised to refer to the drug susceptibility test results of the index case. Baseline blood test should be performed before treatment, and regular blood chemistry follow-up is needed in case of hepatotoxicity risk. NICE guidelines recommended baseline blood test for hepatitis B and C. If active TB is diagnosed during LTBI treatment, the LTBI regimen should be amended to standard treatment regimen for active TB, including the drug used in LTBI treatment¹⁷. Recommended regimens according to the current guidelines of NICE (UK), WHO, and CDC (USA) are listed in Table 2.

1. Isoniazid monotherapy

Isoniazid treatment is advantageous due to the considerable clinical experience and low cost. In several placebo-controlled trials, 12 months isoniazid monotherapy (12H)'s average protective effect for TB was approximately 60% during the observation period^{20,21}. When analysis was limited to participants with good compliance, the efficacy increased to 93%. In one report, the protective effect of 12H regimen lasted 19 years²². Optimal duration of taking isoniazid remains controversial. In International Union Against Tuberculosis (IUAT) trial published in 1982, 27,830 participants with fibrotic pulmonary lesions but not active TB were randomized to each group taking isoniazid for 3 months, 6 months, 12 months, and placebo²¹. After 5 years of follow-up, the risk for developing active TB compared with placebo was reduced by 21%, 65%, and 75%, respectively. Additional cost-effect analysis of IUAT trial had concluded that 6 months of isoniazid (6H) regimen is more cost effective than 3 months of isoniazid regimen or 12H regimen²³. According to these results, American Thoracic Society guideline published in 1994 recommended that 6H regimen is nearly as good as 12H regimen²⁴.

The evidence of 9 months of isoniazid (9H) regimen was derived from retrospective re-analysis of Bethel Isoniazid Studies²². In this study, participants were randomized to either placebo or 12H group, and after a year, all participants in both

Table 2. Recommended regimens for treatment of LTBI according to the current guidelines of NICE¹⁷, WHO³, and CDC¹⁹

NICE	WHO	CDC
6H Preferred: when interactions with rifamycins are a concern	6H	6H
		6H Twice weekly with DOT
	9H	9H Preferred: pregnant women; persons living with HIV; children aged 2–11 yr
		9H Twice weekly with DOT Preferred: pregnant women
	3–4R*	4R
3HR Preferred: people younger than 35 yr if hepatotoxicity is a concern	3–4HR*	-
	3HP with DOT*	3HP with DOT Preferred: persons 12 years or older Not recommended: younger than 2 years old; living with HIV/AIDS taking antiretroviral treatment; presumed infected with INH or RIF-resistant <i>Mycobacterium tuberculosis</i> ; women who are pregnant or expect to become pregnant within the 12-week regimen

*Should be prescribed with caution to people with HIV who are on antiretroviral treatment.

LTBI: latent tuberculosis infection; NICE: National Institute for Health and Care Excellence; WHO: World Health Organization; CDC: Centers for Disease Control and Prevention; 6H: 6 months of isoniazid; DOT: directly observed treatment; 9H: 9 months of isoniazid; HIV: human immunodeficiency; 3–4R: 3–4 months of rifampin; 3HR: 3 months of isoniazid plus rifampin; 3HP: isoniazid plus rifapentine once-weekly regimen for 3 months; AIDS: acquired immunodeficiency syndrome; INH: isoniazid; RIF: rifampin.

groups were supplemented with isoniazid. According to the patients' various compliance, total duration of actually taking isoniazid ranged from 0 to 24 months. In a plot of TB cases per 100 persons against the total duration of taking isoniazid, steep slope of the decline curve became flattened after 9–10 months suggesting that there is little additional protective effect after 9–10 months of taking isoniazid²⁵. Both WHO and CDC guidelines recommended 6H or 9H regimens for LTBI treatment, in the absence of a direct comparison between 6H and 9H regimens^{3,19}. 9H regimen is superior to 6H regimen, in terms of clinical efficacy, but 6H regimen is more cost-effective with better compliance. Based on the equivalence between 6H and 9H, revised NICE guideline recommended 6H regimen, because it is shorter¹⁷. NICE guideline also recommended pyridoxine supplementation with all isoniazid regimens. 6H regimen was also recommended in case of potential adverse effects due to drug interactions with rifamycins, for example, in HIV patients taking antiretroviral treatment.

A major adverse effect of isoniazid is hepatotoxicity that increases with older age—the estimated incidence of hepatotoxicity is 0.1%–0.2% in those who under 20 years of age, 0.3% in 20–34 years of age, 0.5% in 35–49 years of age, 1%–3% in 50–64 years of age, and 2%–5% in over 65 years of age²⁶. Other risk factors for hepatotoxicity include preexisting liver disease, concomitant use of other hepatotoxic medications, prior isoniazid-related hepatotoxicity, and regular alcohol consumption²⁷.

2. Rifampin monotherapy

As the isoniazid regimen had shortcomings of suboptimal compliance and hepatotoxicity, rifampin was proposed as an alternative agent for treatment of LTBI which can shorten the treatment duration²⁸. In one experimental study with LTBI mouse model, the proportions of mice with positive spleen culture which was done at 6 months after treatment with each regimen (6H, 3 months of rifampin [3R], 2 months of rifampin plus pyrazinamide [2RZ], or 2 months of isoniazid plus rifampin plus pyrazinamide) were 100%, 60%, 56%, and 95%, respectively, suggesting that 3R or 2RZ regimen were more effective than 6H regimen²⁹. There is no large scaled randomized controlled trial (RCT) on comparing the long term protective effect of rifampin with that of isoniazid among the general LTBI patients, not in a specific disease group. The only RCT which can be a clue for estimation of efficacy is that performed among silicosis patients in Hong Kong. In this study, the protective effects of 3R, 3 months of isoniazid plus rifampin (3HR), and 6H regimens were 63%, 48%, and 41%, respectively³⁰. When it comes to compliance and hepatotoxicity, 4 months of rifampin (4R) regimen showed better compliance with less hepatotoxicity, and was more cost-effective when compared with 9H regimen in a meta-analysis that included two RCTs and two retrospective studies³¹. 4R regimen is pre-

ferred in United States when the index case is isoniazid-resistant¹⁹. Currently, large scaled RCT is under way that compares long term protective efficacy of 4R with 9H regimen (<https://clinicaltrials.gov/ct2/show/NCT00931736>).

3. Isoniazid plus rifampin

The regimen of isoniazid plus rifampin was introduced to United Kingdom in 1981 for the prophylaxis of children with exposure history and immigrants with LTBI, especially from India. The reason for adding rifampin was high (6%) incidence of isoniazid resistance in index cases from India. The original treatment duration was 9 months (9 months of isoniazid plus rifampin) in 1981, and was gradually shortened to 3 months (3HR) in 1989. Though there was no comparison with isoniazid monotherapy, regimen of isoniazid plus rifampin was successful in reducing TB burden of community, with only a few cases of adverse effect³². With this evidence, British Thoracic Society recommended a 3-month regimen of rifampin plus isoniazid as an alternative short-course therapy for LTBI in 1998³³. In a meta-analysis study of five RCTs comparing 3HR regimen with isoniazid monotherapy for 6 to 12 months, both regimens were equivalent in terms of efficacy and safety³⁴. In a network meta-analysis study of RCTs comparing each regimen, 3HR was an effective regimen along with 3R or 4R regimen³⁵. Consistent with the results of this study, NICE guidelines recommended 3HR regimen as a standard regimen¹⁷, and WHO guidelines published in 2015 also recommended 3HR regimen³. In a retrospective study conducted in South Korea which compared 9H, 4R, and 3HR regimens among the patients receiving anti-tumour necrosis factor therapy, completion rates were 73.8%, 87.1%, and 94.2%, respectively, with no difference in adverse drug reaction³⁶.

4. Isoniazid plus rifapentine

Rifapentine is a rifamycin derivative with a long half-life and greater potency against *M. tuberculosis* than rifampin. Since pharmacokinetic study of rifapentine with murine LTBI model had proved efficacy of regimen of once weekly, once weekly isoniazid plus rifapentine regimen was tested in several studies with murine LTBI model, and showed superior or at least equivalent efficacy when compared with isoniazid monotherapy^{37,38}. The most important RCT which compared directly observed once-weekly isoniazid plus rifapentine for 3 months (3HP) with conventional daily self-administered 9H regimen was PREVENT TB trial conducted by the Tuberculosis Trials Consortium in Brazil, Canada, Spain, and the United States³⁹. In this study, 3HP regimen was noninferior to 9H in preventing active TB in 33 months of follow-up period. Treatment completion rates were higher with 3HP regimen compared to 9H regimen (82% vs. 69%, respectively), and the rate of treatment discontinuation due to hepatotoxicity was low (0.3% vs.

2.0%). But the rate of permanently stopping treatment due to serious adverse effect was higher with 3HP regimen (4.9% vs. 3.7%). Hypersensitivity reaction was common serious adverse effect that caused permanent stop of the treatment, which was higher with 3HP regimen (2.9% vs. 0.4%). The rate of hepatotoxicity was lower with 3HP regimen (0.4% vs. 1.9%). After the end of PREVENT TB trial, significant systemic drug reactions (SDR) that occurred during the treatment period were reviewed⁴⁰. Of the 138 patients in 3HP arm who reported SDRs, 87 (63%) had flu-like syndrome and 23 (17%) had cutaneous reactions. Symptoms occurred after a median of three doses, and 4 hours after administration of the dose. Median time to resolution was 24 hours.

3HP regimen under directly observed treatment is now recommended by CDC and WHO^{3,19}. The regimen containing rifapentine is currently not available in South Korea.

Conclusion

Treatment of LTBI is important for the elimination of TB, especially in intermediate burden countries like South Korea. Although the incidence of TB is decreasing after launching National Tuberculosis Control Programs, South Korea is still the highest burden TB country among the OECD countries. South Korea has unique epidemiologic features of TB due to rapid economic growth, rapid population aging, and rapid urbanization. The burden of TB among the elderly population is increasing, which indicates the preventive strategies for reactivation from remote TB infection is needed. To reduce TB burden, more accurate active diagnosis and better treatment of LTBI are needed in addition to increasing early detection and treatment completion rate for active TB.

After the efficacy of isoniazid had been proved in treatment of LTBI, various regimens were tested for their efficacy and safety. RCTs comparing each regimen are in progress. Guidelines published by NICE, WHO, and CDC were based on their own evidences. Before government's extension of LTBI treatment policy, various prospective and retrospective studies are needed to tailor the national strategy for TB elimination in South Korea. Those studies will serve as the basis for the development of National Tuberculosis Control Programs.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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