

Isoniazid Prophylaxis of Latent Tuberculous Infection among Healthcare Workers in Bamrasnaradura Infectious Diseases Institute

Patama Suttha, M.D.* , Pranom Noppakun, M.NS.* , Patchara Tanthirapat, R.N.* , Boonchai Kowadisaiburana, M.D.†

*Bamrasnaradura Infectious Diseases Institute, Nonthaburi 11000. †Bangkok Hospital, Bangkok, 10310 Thailand.

ABSTRACT

Background: Treatment of latent tuberculosis infection (LTBI) is one of the essential measures for tuberculosis (TB) control. The tuberculin skin test (TST) is an important tool for the detection of LTBI and the identification of healthcare workers (HCWs) who require chemoprophylaxis. Also, the rate of active TB should be evaluated among HCWs with and without isoniazid (INH) prophylactic treatment for LTBI.

Objective: To evaluate the rate of active TB disease among HCWs with or without INH prophylaxis for LTBI.

Methods: We retrospectively studied the clinical records of HCWs with LTBI at the employee TB screening clinic in Bamrasnaradura Infectious Diseases Institute from January 2008 to December 2010. Voluntary INH prophylaxis was recommended by physicians and nurses at the TB clinic in case of recent positive 2-step TST. The rate of active TB disease in HCWs with and without INH prophylaxis for LTBI was evaluated and followed during a period of 5 years. As well, the compliance and adverse effects of INH prophylaxis were identified by history taking.

Results: There were 29 from 113 HCWS (25.7%) receiving INH prophylaxis for 6 months (23 HCWs) and 9 months (6 HCWs). 2 HCWs in each 6- and 9-month group did not complete INH prophylaxis for LTBI. After 5 years of TST, no case of active TB disease was found in HCWS with or without INH prophylaxis. Moreover, no adverse drug reactions were reported.

Conclusion: No active tuberculosis disease was noted between the INH treatment and the control groups.

Keywords: INH prophylaxis, healthcare workers, Thailand

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INTRODUCTION

Tuberculosis (TB) remains a major global problem despite widespread awareness as well as effective prevention and treatment. It follows an airborne route of transmitted diseases and has become an occupational threat to healthcare workers (HCW) who inevitably work in settings with congregated TB patients.

Latent tuberculosis infection (LTBI) is defined as infection with *M. tuberculosis* and manifested by the positive tuberculin skin test (TST) or the interferon-gamma release assay (IGRA) result, but without any evidence of active TB disease including symptoms, progressive radiographic changes, or microbiological replicating organisms. Approximately 5% of those with the multiplication of bacilli become ill due to primary infection. Meanwhile, another 5% are later affected by bacilli reactivation or exposure to a new source of infection despite blocking the infection at their early stage of infection. In

Correspondence to: Patama Suttha

E-mail: mueyeing64@gmail.com

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addition, the annual rates of TB reactivation are about 3% and 0.1% during the first year and after 10 years of acquiring TB infection, respectively.¹ To mitigate the adverse effects of TB among HCWs, the World Health Organization (WHO) has proposed a TB control program be established in all healthcare settings.²

Besides, a 2-step tuberculin skin test (TST) is recommended for use as part of administrative TB control and a TB screening tool by the Center for Disease Control and Prevention.³ Chemoprophylaxis with isoniazid (INH) is also generally suggested after a reactive TST, and its use was expanded successfully to prevent active tuberculous disease. Several randomized controlled trials have demonstrated that treatment of LTBI can decrease the risk of progression by 90%.⁴⁻⁷ INH prophylaxis reduces the incidence of active TB by 60-93% in developed countries, and especially 85-93% in those with completion of a full 6-month course.⁸⁻¹⁰

Hence, this study aimed to analyze the progression of tuberculosis among HCWs with or without INH prophylaxis for LTBI during 5-year observation period.

MATERIALS AND METHODS

Bamrasnaradura Infectious Diseases Institute (BIDI) annually has provided the voluntary 2-step TST for all employees who worked in the institute both old and new hires since 2007. To avoid misinterpretation between a boosted response and a new infection, the institute employ the 2-step testing procedure. In this procedure a HCW is given a baseline PPD test. If the test is negative, a second test is administered 2-3 weeks later. If the second test is negative, the person is considered uninfected. If the second test is positive, then the person is considered to have a "boosted" reaction to an infection that occurred a long time ago. Those with positive 2-step TST results (positive TST: TST indurations of ≥ 10 mm) were examined and evaluated for active tuberculosis by a physician. However, INH for LTBI treatment, laboratory testing, and medical evaluation were only given to persons who had recent conversion of 2 step TST in 2 years of

follow up, because TB reactivation usually occurs in the first few years after TB infection.

A retrospective cohort study was performed in all employees with positive 2-step TST results between January 2008 and December 2010. All of them were evaluated by occupational health nurses and physicians. Data on their current and prior 2-step TST results, medication(s), history of active tuberculosis, previous chest radiograph, liver function test, and compliance rate were obtained from the BIDI's employee records. When a true conversion was determined to have occurred, the HCW was considered to have LTBI and should undergo a symptom review and chest radiograph as soon as possible to exclude active disease.

HCWs who had positive 2-step TST at the first time of testing were excluded from the study. Voluntary INH prophylactic treatment would be discussed and recommended to HCWs who had recent conversion of 2-step TST. Physicians would weigh all available clinical evidence in the management of LTBI. Normal chest X-ray (CXR) and liver function test results were also considered for those who desired to receive INH treatment. The 6-month and 9-month INH treatment regimens were recommended. However, BIDI has started the 9-month INH prophylaxis for LTBI in HCWs since 2010 as a standard therapy to maximize efficacy. INH side effects and compliance were assessed monthly by nursing staff and a physician at the clinic. An occupational health database was maintained including date of testing, date of given INH, and number of months for INH. The adverse effects and compliance of treatment were only assessed by taking history. INH prophylaxis was not prescribed in HCWs who had abnormal liver function test from initial screening. (Fig 1) HCWs with remote LTBI or recent infection, but declined INH prophylaxis would be observed for symptoms of active TB and scheduled for annual CXR screening.

The primary outcome was the incidence of active TB disease in recent latent tuberculosis infected HCWs with or without INH treatment during the 5 years of performed TST. The secondary outcomes were the rate of compliance and adverse effects of INH prophylaxis among HCWs

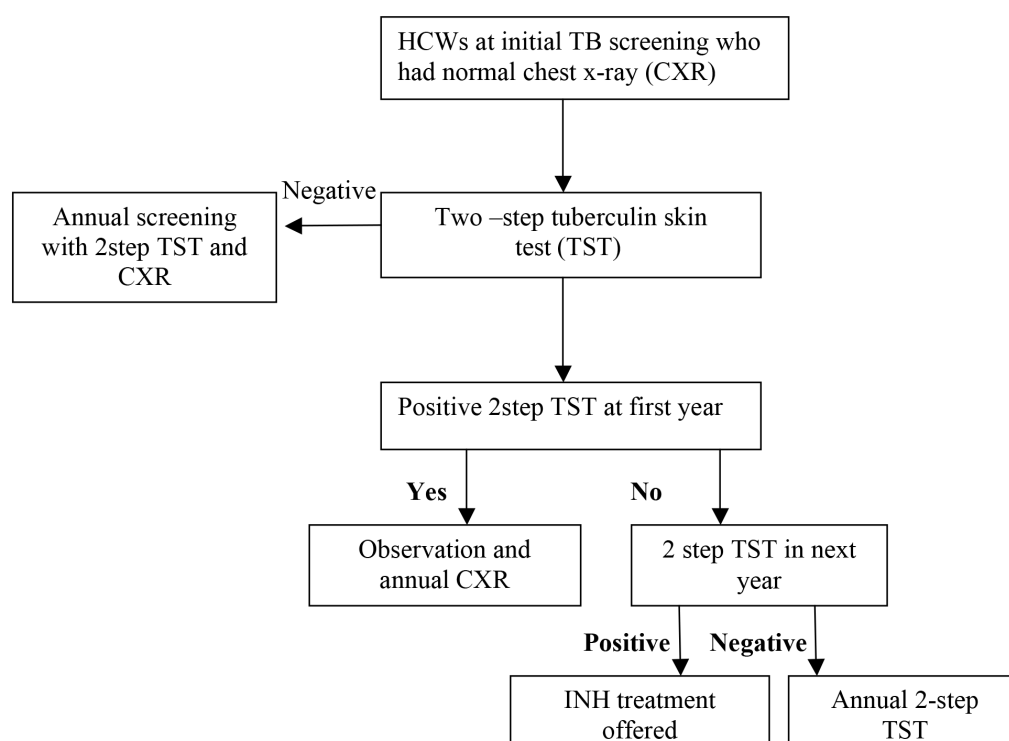


Fig 1. Algorithm of TB screening and INH prophylaxis for HCWs in Bamrasnaradura Infectious Diseases Institute
 TB= Tuberculosis, INH = Isoniazid, HCW= Health care worker
 CXR= Chest X-ray, TST= Tuberculin skin test

advised by infectious disease physicians for voluntary INH prophylaxis.

Data were analyzed by Wilcoxon rank-sum tests for continuous variables with non-normal distribution and the Fisher's exact test or Chi-square test (χ^2) for categorical variables. The p-value <0.05 was considered as statistically significant.

This study was approved by the Research Ethics Committee of Bamrasnaradura Infectious Diseases Institute, Nonthaburi, Thailand.

RESULTS

Acceptance of INH treatment

Out of the 113 HCWs who received reactive 2-step TST from January 2008 to December 2010, only 29 (25.7%) accepted for voluntary INH prophylaxis. Most of the HCWs were female without direct contact to TB patients. The mean age of treatment group was older than in control group. (41.33 years: $p=0.033$) (Table 1)

In the treatment group, HCWs who initiated treatment for LTBI were slightly older and

more likely to be female. Our retrospective study also demonstrated that the clinical HCWs at risk for acquiring tuberculosis were less likely than the nonclinical HCWs for initiating for LTBI treatment. (Table 1)

Adherence to INH prophylaxis and adverse reactions

Starting the implementation in 2011, there were 23 HCWs with the 6-month INH treatment for LTBI. Only 6 cases received the 9-month INH treatment. Those who completed the 6-month and the 9-month INH therapy were 21 (91.3%) and 4 (66.7%), respectively. Adherence to the 6 months was better than the 9 months. (Table 2) The major causes of deferring INH prophylaxis in other INH treatments were not identified at the clinic and also without any complications such as peripheral neuropathy, nausea or rash.

Incidence of active TB in 5 years of observation

During the 5 years of follow-up, there was no active TB disease in HCWs with and without INH prophylaxis.

TABLE 1. Demographics of healthcare workers receiving positive Tuberculin Skin Test (TST) with or without treatment for latent tuberculosis infection.

Characteristics	IINH Treatment (N=29)	Without Treatment (N=84)	
Sex			
Female	23	62	0.554
Male	6	22	
Age (years); Median (IQR)	41 (11)	33 (13.5)	0.033
Workplace			0.075
Nonclinical*	21	45	
Clinical**	8	39	
Underlying diseases	0	0	0.074
Duration of work (years)			
< 2	7	19	
> 2-5	2	6	
> 5- 10	1	21	
>10	19	38	
Previous TST mean (IQR)	5 (5)	5 (3)	0.254
Induration of TST (mm) (Median : IQR)	15 (5.75)	14.5 (6.00)	0.59
Previous history of tuberculosis	0	0	N/A
Number of active TB cases in 5 years	0	0	N/A

*Clinical healthcare workers included those with direct patient contact, such as physicians and nurses at TB clinic, TB ward nurses, patient-care HCWs, respiratory therapists, and microbiologists dealing with TB specimens.

** Nonclinical healthcare workers included those who did not have direct patient contact, such as clerical, administrative or non-microbiological laboratory staffs.

INH = Isoniazid, mm = millimeter, IINH = As above

TABLE 2. Adherence to INH chemoprophylaxis in treatment group.

Regimen of LTBI treatment	Completed (n=25)	Not completed (n=4)
INH prophylaxis 6 months (n=23)	21 (91.3%)	2 (8.7%)
INH prophylaxis 9 months (n=6)	4 (66.7%)	2 (33.3%)

LTBI = Latent tuberculous infection

INH = Isoniazid

DISCUSSION

The prevalence of LTBI in BIDI was approximately 30%.¹⁴ This study demonstrated that HCWs in our TB clinic were at the low rate to initiate treatment for LTBI (25.7%), especially in clinical HCWs who had higher risk of acquiring LTBI due to their exposure to TB patients. Also, our study was compatible with several studies that

showed relatively low rate of treatment initiation for LTBI among HCWs.¹¹⁻¹³ Although we attributed a high rate to the comprehensive program for active follow-up of HCWs with TB skin testing, physician counseling, phone consultation, and free medications provided on-site, the study's low rate of treatment initiation among HCWs was not consistent with another study by Shukla et al,¹⁵ which had the initiation rate of 98% among HCWs

at their institution. Most of HCWs declined to start INH because of adverse effects or perhaps their decision to control themselves for LTBI reactivation instead of the treatment.

Additionally, there were several barriers for the acceptance and completion of INH therapy. Adherence was lower in the regimens with longer duration and more complexity. In this study, the completion of INH treatment in the 6-month group was better than in the 9-month group. Most HCWs stopped the INH treatment within 2 months. However, no adverse effects were noted from the INH therapy.

TB reactivation usually occurs in the first few years of acquiring TB infection.^{1,16-17} Therefore, the 5-year observation may be appropriate to assess the reduction of TB rate in HCWs with recent LTBI. Many studies have shown that LTBI treatment with INH is 69% to 93% effective in preventing the development of active TB, but the effectiveness depends on the level of adherence.²⁰⁻²¹

Despite the TB reactivation in the first few years of acquiring TB infection^{1,18-19} and the appropriateness to assess reduction of TB rate in HCWs during the 5-year observation, there were no new active tuberculosis cases in the INH treatment group compared with the control group after 5 years of observation. It may from most HCWs in this study were healthy persons who have lower probability to develop active TB disease. The results in our study was different from those of the United States Public Health Service (USPHS) in the 1950s which enrolled a total of nearly 14,000 patients per arm with up to 10 years of follow-up and the 60% reduction of TB cases in the INH group.^{16,20-21}

The International Union Against Tuberculosis (IUAT) conducted a controlled trial in Eastern Europe with multiple INH durations for patients with inactive TB and no history of prior TB treatment. The patients were anticipated to be followed for 5 years from study entry, and the primary outcome of interest was culture positive TB per 1,000 persons at risk. Compared with placebo, the reduction in TB rate after INH was 21% for the 12 weeks, 65% for the 24 weeks, and the 75% for the 52 weeks.²²

The findings in this study lead to questions of relevance for HCW health improvement and safety in middle-income and developing countries regarding the INH treatment among HCWs with LTBI. Nevertheless, there are some limitations to the study for the reduction of active TB cases in the INH group. Firstly, it may need more sample sizes and durations to assess the effectiveness in preventing active tuberculosis among HCWs. In a follow-up paper of one study, it was demonstrated that the protective effect of INH persisted through the final evaluation of 19 years after the study began.²² Therefore, it may be possible to extend more duration of the observation. Secondly, liver enzymes were not done after the INH treatment, and hepatotoxicity caused by the INH could not be evaluated. About 10% to 20% of persons taking INH will have some mild, asymptomatic elevation of liver enzymes. Finally, the adherence of INH treatment which was evaluated by self reports was not the best method of adherence assessment.

CONCLUSION

There was no active tuberculosis disease in HCWs with positive TST with or without INH prophylaxis during the 5-year follow up period.

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