EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original research article

Protective efficacy of 6-week regimen for latent tuberculosis infection treatment in rural China: 5-year follow-up of a randomised controlled trial

Henan Xin, Xuefang Cao, Haoran Zhang, Boxuan Feng, Ying Du, Bin Zhang, Dakuan Wang, Zisen Liu, Ling Guan, Fei Shen, Xueling Guan, Jiaoxia Yan, Yijun He, Yongpeng He, Zhusheng Quan, Shouguo Pan, Jianmin Liu, Qi Jin, Lei Gao

Please cite this article as: Xin H, Cao X, Zhang H, *et al*. Protective efficacy of 6-week regimen for latent tuberculosis infection treatment in rural China: 5-year follow-up of a randomised controlled trial. *Eur Respir J* 2021; in press (https://doi.org/10.1183/13993003.02359-2021).

Protective efficacy of 6-week regimen for latent tuberculosis infection treatment in rural China: 5-year follow-up of a randomized controlled trial

Henan Xin[1]*, Xuefang Cao[1]*, Haoran Zhang[1]*, Boxuan Feng[1], Ying Du[1], Bin Zhang[2], Dakuan Wang[2], Zisen Liu[2], Ling Guan[3], Fei Shen[3], Xueling Guan[3], Jiaoxia Yan[2], Yijun He[1], Yongpeng He[1], Zhusheng Quan[1], Shouguo Pan[2], Jianmin Liu[3], Qi Jin[1], Lei Gao[1]✉

1. NHC Key Laboratory of Systems Biology of Pathogens, Institute of Pathogen Biology, and Center for Tuberculosis Research, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, P.R. China.
2. Center for Diseases Control and Prevention of Zhongmu, Zhengzhou 451450, China.
3. The Sixth People's Hospital of Zhengzhou, Zhengzhou 400060, China.

* Contributed equally

Correspondence: Prof. Lei Gao, NHC Key Laboratory of Systems Biology of Pathogens, Institute of Pathogen Biology, Chinese Academy of Medical Sciences and Peking Union Medical College, No 9 Dong Dan San Tiao, Beijing 100730, China. Email: gaolei@ipbcams.ac.cn.

Take home message: Six-week twice-weekly rifapentine plus isoniazid regimen showed a protective efficacy over 60% in 5 years, which indicated that preventive treatment based on short-course regimen might be an optional tool for TB control in China.

Key words: Tuberculosis; Latent tuberculosis infection; 5-year protective efficacy; Short-course regimen; Preventive treatment.

Abstract

Background: Enlarging tuberculosis (TB) preventive treatment among at-risk populations is a critical component of the End TB Strategy. It is urgently needed to develop suitable latent tuberculosis infection (LTBI) testing and treatment tools according to local TB epidemic and available resources in worldwide.

Methods: Based on an open-labeled randomized controlled trial conducted since 2015 among rural residents aged 50-70 years with LTBI, the protective efficacy of the 6-week twice-weekly regimen of rifapentine plus isoniazid was further evaluated in a 5-year follow-up survey.

Results: A total of 1298 treated participants and 1151 untreated controls were included in the 5-year protective efficacy analysis. In the per-protocol analysis, the incidence rate was 0.49/100 person-years (95% confidence interval (CI): 0.30-0.67) in the untreated control group and 0.19/100 person-years (95% CI: 0.07-0.32) in the treated group, the protection rate was 61.22%. Subgroup analysis showed that the protection rate was 76.82% in the per-protocol analysis among participants with baseline IFN-γ levels in the highest quartile (≥3.25 IU/mL). The multiple logistic regression analysis indicated that participants with baseline BMI <18.5 $kg \cdot m^{-2}$ and with pulmonary fibrotic lesions had increased hazard of developing active disease with an adjusted hazard ratio (aHR) of 3.64 (95% CI: 1.20-11.00) and 5.99 (95% CI: 2.20-16.27), respectively. In addition, individuals with higher baseline IFN-γ levels showed an increased risk of TB occurrence (aHR 2.27, 95% CI 1.13-4.58).

Conclusions: Our findings suggested the 6-week twice-weekly regimen of rifapentine plus isoniazid for LTBI treatment might be an optional tool for TB control in Chinese population.

Introduction

It was estimated that about a quarter of the world's population was infected with *Mycobacterium tuberculosis* (*M.tb*) [1]. On average, 5%-10% of those infected might develop active tuberculosis (TB) over the course of their lives, usually within the first 2 years after initial infection [2]. Comprehensive control strategies had been implemented to control the seedbeds of TB. Among them, TB preventive treatment was reported to decline the risk of active TB development with an efficacy ranging from 60% to 90% [3]. Based on it, implementation of preventative treatment among individuals with latent tuberculosis infection (LTBI) under high-risk of developing active disease had been recommended by the World Health Organization (WHO), as one of critical components of the End TB strategy [4-6]. Currently, TB preventive treatment options can be broadly categorized into two types: monotherapy with isoniazid for at least 6 months or treatment with regimens containing isoniazid and a rifamycin (rifampicin or rifapentine). Isoniazid given for 6-9 months has been the preferred treatment regimen due to its low cost and proven efficacy. However, in consideration of the feasibility, resource requirements and acceptability to the treatment targets, short-course regimens with better tolerance and higher completion rate have been explored in the past decades. The 3-month weekly isoniazid plus rifapentine regimen (3HP) had been widely practiced in several populations [7-8]. By now, a 1-month regimen of rifapentine plus isoniazid (1HP) has been recommended for HIV-infections by WHO in the latest guidelines due to its equal protective efficacy and higher completion rate to 9 months of isoniazid alone [9-10].

China is a country with high burden for both TB and LTBI, it is more urgent to establish flexible preventive treatment policies to protect individuals under high-risk of *M.tb* infection and active disease development [11-12]. However, regimens suitable to Chinese population based on domestic medicine has not been developed and evaluated in China through randomized clinical trial (RCT). To explore short-course regimen for at-risk middle aged and elderly with LTBI in rural China, we conducted an open-label, pragmatic RCT in 2015. We initially wanted to evaluate two regimens, WHO

recommended 3HP and an innovative 2-month twice-weekly rifapentine plus isoniazid ($2H_2P_2$) regimen, however, the regimens were both modified due to unexpected high frequency of side-effects simultaneously. Fortunately, the modified innovative 6-week twice-weekly regimen obtained good protective efficacy at the 2-year follow-up survey [13]. Nevertheless, due to the new infection is still common in rural areas in China, one of the biggest worries about the implement of LTBI treatment lies in reinfection would definitely influence the protective efficacy and shorten protection period [14]. Thus, the aim of the present study was to further evaluate the 5-year protective efficacy of the innovative short-course regimen and to provide comprehensive estimation of the application of LTBI treatment in China and areas with similar situations.

Methods

Study design

This study was 5-year follow-up of an original open-label, pragmatic RCT aiming to explore protective efficacy of short-course LTBI treatment regimens for at-risk middle-aged and elderly in rural China. The detailed information of the original trial has been reported in elsewhere [13]. Briefly, all participants aged 50-70 years with QuantiFERON-TB Gold In-Tube (QFT-GIT) (QIAGEN, USA) positive result (a cut-off value of ≥ 0.35 IU/mL was used as recommended by the manufacturer) and without current active TB at baseline survey were included in the study. After randomization, eligible participants were classified into three groups: group A, 1284 for treatment with 3HP; group B, 1299 for treatment with an innovative $2H_2P_2$, and group C, 1155 as untreated controls. Before the intervention, we preset early termination criteria based on the existing evidence for the regimen of 3HP when the occurrence of hepatotoxicity (defined by aspartate transaminase/alanine transaminase (AST/ALT) >3×ULN with symptoms or AST/ALT >5×ULN) was higher than 1% [7]. The fact was both regimens were terminated in advance during implementation (3HP was modified to 8 weeks and $2H_2P_2$ was modified to 6 weeks). Thus, the protective rate of the modified regimens was evaluated and found to be 37% for 8-week once-weekly regimen and 69% for 6-week twice-weekly regimen at the 2-year follow-up investigation, respectively. Based

on the results of the 2-year follow-up survey, the present study aimed to explore the long-term protective rate of the 6-week twice-weekly regimen at the 5-year follow-up investigation. The 8-week once-weekly regimen was dropped in this study due to its limited protective effect observed in the 2-year follow-up. The protocols of the study were approved by the Ethics Committees of the Institute of Pathogen Biology, Chinese Academy of Medical Sciences (IDs: IPB-2015-5, IPB-2016-8 and IPB2019-11).

Follow-up examinations and end-points

Between 2018 and 2020, follow-ups were carried out quarterly by trained interviewers through door-to-door or telephone survey for active case finding based on suspected symptoms screening. At the 5-year follow-up, between November and December 2020, participants were invited for a closing survey with investigation of suspected symptoms and digital chest radiography. All participants in the cohorts were scheduled to be seen for a 5-year closing visit unless they migrated out of the area, refused to be followed up, or died. All participants suspected of having TB because of clinical symptoms or radiographic abnormalities were referred for diagnosis according to the national guidelines. In addition, the national Tuberculosis Information Management System (TBIMS) was screened as well to find potential registered patients among our study participants.

The primary study end-points were microbiologically confirmed active pulmonary TB or clinically determined pulmonary TB. Individuals with positive results by sputum smear, culture and/or GeneXpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) were confirmed as microbiologically confirmed active TB. Response to empiric TB treatment among participants suspected as having TB but negative to microbiological tests was evaluated for a diagnosis of clinical TB by consensus from a panel of experts consisting of four radiologists, two clinical experts and one laboratory expert. TB diagnosis was made by the expert panel blinded to treatment assignment. Additional secondary end-points was death from any cause.

Statistical analysis

The frequencies of categorical variables in the study participants were compared between the groups using Pearson's chi-square (χ^2) test. The Kruskal-Wallis tests were performed to assess differences in continuous variables. The distribution of baseline IFN-γ levels were presented and compared using Wilcoxon rank sum tests. The incidence rates of active TB were assessed during 5 years after the completion of therapy. For those with relapse TB during follow-up, only the first diagnostic information was used. The time duration for each participant involved in the study was calculated based on the quarterly follow-up records. The intention-to-treat analysis included all enrolled eligible subjects in each group. The per-protocol analysis included all eligible enrolled subjects who completed the assigned study regimen (defined as completed ≥90% doses of modified therapy). In subgroup analysis, all of the participants in each group were classified by the highest quartile of the baseline IFN-γ levels. Subjects with missing data of baseline IFN-γ levels were excluded in subgroup analysis. To identify potential variables related to active TB risk, the Cox proportional hazards regression models were fitted to estimate adjusted hazard ratio (aHR) with 95% confidence interval (CI).The other variables with $p<0.05$ (age, body mass index (BMI), baseline IFN-γ and presence of pulmonary fibrotic lesions) in the univariate model were also entered into the multivariable models as well. Statistical analyses were performed using SAS 9.4 version (SAS institute, Cary, NC) and Kaplan-Meier curves were performed GraphPad Prism 9 (GraphPad software, San Diego, CA).

Results

Characteristics of the study participants

As shown in **Figure 1**, a total of 1299 participants accepted treatment of the 6-week regimen and 1155 untreated controls were included in the original RCT. Among them, 935 (71.97%) and 825 (71.42%) completed the 5-year follow-up survey, respectively. Five participants were excluded because of self-reported preventative treatment after intervention performed by the study. Finally, a total of 1298 treated participants and 1151 untreated controls were included in the 5-year protective efficacy analysis. **Table**

1 shows the clinical and demographic characteristics of the population. Roughly, half of treated and untreated participants were males. No significant difference was found between the two groups with respect to age, BMI, history of silicosis, smoking and alcohol drinking. Untreated participants showed a trend with higher proportion of pulmonary fibrotic lesions found by chest radiography (p=0.015) and diabetes based on fasting blood glucose > 7 $mmol \cdot L^{-1}$ (p=0.046) than treated participants.

Protective efficacy of the treatment regimen

In total, 12 and 26 incident cases of active pulmonary TB were diagnosed for treated and untreated group during the 5-year follow-up post intervention, respectively. Eight cases were confirmed microbiologically, while 30 cases were diagnosed clinically based on their suspected symptoms, abnormal chest radiography and positive responses to anti-TB treatment (Detailed information of the identified TB cases please refer to **Supplementary Table 1**). Kaplan-Meier curve demonstrated that participants in the untreated group had a higher risk of developing active TB compared to the treated group (**Figure 2**). As shown in **Supplementary Figure 1,** the treated individuals who completed the assigned study regimen had lower risk of developing active TB (0.89%, 9/1013) as compared to those who did not complete the regimen (1.05%, 3/285), but the difference was statistically non-significant (p=0.706).

In the intention-to-treat analysis (**Table 2**), the cumulative incidence of active TB was 2.26% (95% CI: 1.40-3.12%) in the untreated control group and 0.92% (95% CI: 0.40-1.45%) in the treated group. The incidence density of active TB was 0.49 (95% CI: 0.30-0.67) per 100 person-years in the untreated control group and 0.20 (95% CI: 0.09-0.32) per 100 person-years in the treated group. As compared with the untreated controls, the risk of active disease was decreased among treated individuals (with an aHR of 0.41, (95% CI: 0.20-0.84). In the per-protocol analysis, the cumulative incidence of active TB was 2.26% (95% CI: 1.40-3.12%) in the untreated control group and 0.89% (95% CI: 0.31-1.41%) in the treated group. The incidence density of active TB was 0.49 (95% CI: 0.30-0.67) per 100 person-years in the untreated control group and 0.19 (95% CI: 0.07-0.32) per 100 person-years in the treated group. The 6-week

twice-weekly regimen showed a protection rate of 61.22%.

Protective efficacy of the treatment regimen among participants with baseline IFN-γ≥3.25 IU/mL

As shown in **Figure 3A**, with respect to QFT-GIT results, no significant difference was found for the median baseline levels of IFN-γ between treated and untreated participants. For the untreated participants, the median baseline levels of IFN-γ were significantly higher among those developed active TB than those stayed healthy (**Figure 3B**). Such a relation was found in the treated group as well, although the difference was not statistically significant.

The participants were classified into two subgroups by the highest quartile of the baseline IFN-γ levels (Table 3). For individuals with IFN-γ ≥3.25 IU/mL, in the per-protocol analysis, the incidence rate of active TB was 0.69 (95% CI: 0.23-1.13) per 100 person-years in the untreated control group and 0.16 (95% CI: 0.00-0.39) per 100 person-years in the treated group with a protection rate of 76.82%. No significant difference was found for major characteristics of the study participants between the groups as shown in **Supplementary Table 2**. In addition, participants developed active TB showed higher frequency of pulmonary fibrotic lesions than those stayed healthy (**Supplementary Table 3**).

Risk factors associated with active TB development among study participants

As shown in **Table 4**, the incidence of active TB increased along with age in a dose–response relationship. The multiple logistic regression analysis indicted that participant with baseline BMI <18.5 $kg \cdot m^{-2}$ had a much higher hazard of developing active disease with an aHR of 3.64 (95% CI: 1.20-11.00). Individuals with pulmonary fibrotic lesions identified by chest radiography were at a much higher risk of developing active TB compared with those with normal chest radiography with an aHR of 5.99 (95% CI: 2.20-16.27). In addition, individuals with higher baseline IFN-γ levels had an increased risk of TB occurrence compared to those with lower baseline IFN-γ levels with an aHR of 2.27 (95% CI: 1.13-4.58).

Discussion

As far as we know, this is the first RCT performed in the Chinese population aiming to explore short-course regimen composed of domestic drugs for LTBI treatment. Our results showed that the 6-week twice-weekly isoniazid plus rifapentine regimen still showed a protection rate of 61.22% in 5 years after the intervention. It indicated that under current TB epidemic situation in China, preventive treatment based on short-course regimen was an optional tool for TB control. Further analyses showed a higher protection rate of 76.82% among participants with higher baseline releasing level of IFN-γ, which provided important clues for further disclosing LTBI pathogenesis and developing precise intervention strategies.

Isoniazid prophylaxis has been reported to be effective in preventing TB in many different populations and under a variety of conditions, the protective efficacy has been shown to persist for as long as 19 years in areas with low burden of TB [15]. Rifapentine is a rifamycin derivative with a long half-life and greater potency against *M.tb* than rifampin. Using of rifapentine in combination with isoniazid provided an important opportunity for developing short-course and less-frequency regimens for LTBI treatment. As compared with the most recently reported short-course regimens [7, 9, 16], we developed 6-week twice-weekly regimen showing comparable safety and completion rate. In addition, we were glad to see that the regimen still showed a protective efficacy over 60% in 5 years after the intervention. As we all know, the duration of protection period was affected by multiple factors including the characters of the target population, local TB epidemic and TB control strategies. In high-burden areas like China with 0.8 million new TB cases annually, TB occurrence due to reinfection would definitely influence the protective efficacy and shorten protection period. Our previous study suggested that the annual TB infection rate was around 1.5% based on the persistent conversion of QFT-GIT testing in rural community [14]. Under such circumstances, whether reinfection yielded impact on the effect of preventive treatment has always been hotly discussed and worried. In addition, although participants were randomly divided into treated and untreated groups with the main

characteristics such as age and gender evenly distributed, the distribution of the other potential factors, which might influence the occurrence of active TB was difficult to investigate such as the onset of infection. As previously reported [17], parts of the baseline positives might be recently infected with a higher risk of developing active disease within the first 2 years follow-up. Thus, an overlap observed in Kaplan Meyer curves in the first 2 years might be explained by such uneven distributed factors between the two study groups. Considering the frequency of self-reported history of close contact with active TB patients during the 5-year follow-up was not significantly different between the groups and no outbreak of TB was reported in the study site, the protective effect observed in our study should not be remarkably affected by the occurrence of the new infection under current local TB epidemic situation. Despite our results need further verification in more populations and longer follow-up period, it provided further evidence and confidence on exploring short course or ultra-short course LTBI preventive treatment regimens which might be more suitable for application in China and countries with similar TB epidemic.

Positive relation was frequently observed between baseline IFN-γ levels and the risk of TB progression [18-19]. It was well accepted that the results of QFT-GIT could not be used for assessing the risk of active disease development due to the low predictive value [20]. However, whether individuals with variant IFN-γ levels in QFT-GIT testing had different responses to preventative treatment has been rarely studied. Therefore, we further evaluated the protection rate among participants with the highest quartile of the baseline IFN-γ levels in subgroup analysis and the protective efficacy was found to be as high as 76.82%. The finding might be explained by two potential reasons: first, higher IFN-γ levels might reflect more active *M.tb* replication in host and thus anti-bacterial effectiveness could be well presented by preventive treatment [21]. Second, individuals with higher IFN-γ levels might be recently infected with *M.tb* [22], and preventive treatment might be more effective for such high-risk individuals. Our present study could not provide positive evidence to support the above speculations (**Supplementary Table 4**). In any case, the subgroup analysis was limited because it

was not the original study objective. Therefore, it was hard to draw a solid conclusion on this finding, Our results need to be verified by mechanism research and observational studies with larger sample size.

Consistent with previous study [23], our results showed that the incidence rate of active pulmonary TB among participants with fibrotic lesions was higher than participants with normal chest radiography finding. Besides, similar to the link between lower BMI and increased risk of active TB, our results showed that BMI<18.5 $kg \cdot m^{-2}$ was independently associated with development of TB [24]. In addition, our study also found that participants with baseline BMI ≥28 $kg \cdot m^{-2}$ had a much lower hazard of developing active disease (aHR 0.13, 95% CI 0.02-1.00), which was similar with previous epidemiologic finding that obesity was associated with reduced risk of active TB in an inverse dose-response relationship [25–28]. Although currently we could not define target populations by these potential risk factors, they still deserve our attention, especially when they appear together with other risk factors like exposure to *M.tb* infection.

When interpreting the results of the study, several limitations should be kept in mind. First, study participants with pulmonary fibrotic lesions and diabetes mellitus based on fasting blood glucose >7 $mmol \cdot L^{-1}$ were not evenly distributed between the groups, which might influence the estimation of protection rate because they are potential risk factors for disease development from LTBI [23, 29]. However, after excluding participants with pulmonary fibrotic lesions and diabetes mellitus, the protective efficacy of the 6-week regimen was still 50.00% (**Supplementary Table 5**). Second, as active case finding based on digital chest radiography and suspected symptoms investigation were used for tacking TB during follow-up, most of the incident cases (30 out of 38) were clinically diagnosed in this study. In order to minimize the potential misclassification bias, the clinical diagnosis was determined by an expert team, blinded to group assignment, based on responses to diagnostic anti-TB treatment. Third, as the original study including the sample size was designed for the 2-year protection rate evaluation, the power to estimate the 5 years protective efficacy could not be sufficient.

As we retrospectively calculated, the power of the current study to identify a 60% protective rate in 5 years was 76%. In addition, as has been previously discussed [13], both of the studied regimens were terminated in advance in this RCT, and the group treated with modified once-weekly regimen was dropped in the present study due to its low protective efficacy in 2-year follow-up. Therefore, further studies with larger sample size are needed to verify our findings in different populations.

In conclusion, the 6-week twice-weekly rifapentine plus isoniazid regimen showed a protective efficacy over 60% in 5 years after the intervention in Chinese population with LTBI. Our findings provided more evidence and confidence to develop shorter and better-tolerated LTBI treatment regimens as potentially suitable tools for preventive treatment in China. However, the scale-up of LTBI treatment is a step-by-step process, besides suitable regimens, more innovative technologies, comprehensive strategies, resource input and government support are needed as well.

Reference

1. WHO. Global Tuberculosis Report 2020; World Health Organization: Geneva, Switzerland, 2020. Available at: https://apps.who.int/iris/handle/10665/336069?locale-attribute=en&. Accessed 24 December 2020.
2. Hartman-Adams H, Clark K, Juckett G. Update on latent tuberculosis infection. Am Fam Physician 2014;89(11):889-96.
3. Getahun H, Matteelli A, Chaisson RE, et al. Latent Mycobacterium tuberculosis Infection. N Engl J Med 2015;372(22):2127–35.
4. Uplekar M, Weil D, Lönnroth K, et al. WHO's new end TB strategy. Lancet 2015;385(9979):1799-801.
5. Implementing the End TB Strategy: the essentials (WHO/HTM/TB/2015.31). Geneva, World Health Organization. 2015. Available from: http://www.who.int/tb/publications/2015/end_tb_essential.pdf. Accessed 24 December 2020.
6. Lönnroth K, Migliori GB, Abubakar I, D, et al. Towards tuberculosis elimination: an action framework for low-incidence countries. Eur Respir J. 2015;45(4):928-52.
7. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med. 2011 Dec 8;365(23):2155-66.
8. Villarino ME, Scott NA, Weis SE, et al. Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and isoniazid. JAMA Pediatr. 2015 Mar;169(3):247-55.
9. Swindells S, Ramchandani R, Gupta A, et al. One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis. N Engl J Med. 2019 Mar 14;380(11):1001-1011.
10. WHO consolidated guidelines on tuberculosis, Module 1: Prevention Tuberculosis preventive treatment. Geneva: World Health Organization, 2020. Available at:https://www.who.int/publications-detail/who-consolidated-guidelines-on-tuberculosis-module-1-prevention-tuberculosis-preventive-treatment. Accessed 24 March 2020.

11. Gao L, Li XW, Liu JM, et al. Incidence of active tuberculosis among individuals with latent tuberculosis infection in rural China: follow-up results of a population-based multicenter prospective cohort study. Lancet Infect Dis 2017; 17: 1053-1061.
12. Gao L, Zhang H, Xin H, et al. Short-course regimens of rifapentine plus isoniazid to treat latent tuberculosis infection in older Chinese patients: a randomised controlled study. Eur Respir J 2018;52(6):1801470.
13. Gao L, Lu W, Bai L, et al. Latent tuberculosis infection in rural China: baseline results of a population-based, multicenter, prospective cohort study. Lancet Infect Dis 2015; 15: 310–19.
14. Gao L, Bai L, Liu J, et al. Annual risk of tuberculosis infection in rural China: a population-based prospective study. Eur Respir J 2016; 48:168-178.
15. Comstock GW, Baum C, Snider DE Jr. Isoniazid prophylaxis among Alaskan Eskimos: a final report of the bethel isoniazid studies. Am Rev Respir Dis 1979;119 (5):827-30.
16. Ronald LA, FitzGerald JM, Bartlett-Esquilant G, et al. Treatment with isoniazid or rifampin for latent tuberculosis infection: population-based study of hepatotoxicity, completion and costs. Eur Respir J. 2020 Mar 20;55(3):1902048.
17. Xin H, Zhang H, Yang S, et al. 5-Year Follow-up of Active Tuberculosis Development From Latent Infection in Rural China. Clin Infect Dis. 2020 Feb 14;70 (5):947-950.
18. Winje BA, White R, Syre H, et al. Stratification by interferon-γ release assay level predicts risk of incident TB. Thorax. 2018: thoraxjnl-2017-211147.
19. Xin H, Cao X, Zhang H, et al. Dynamic changes of interferon gamma release assay results with latent tuberculosis infection treatment. Clin Microbiol Infect 2020;26(11): 1555.e1-1555.e7.

20. Abubakar I, Drobniewski F, Southern J, et al. Prognostic value of interferon-γ release assays and tuberculin skin test in predicting the development of active tuberculosis (UK PREDICT TB): a prospective cohort study. Lancet Infect Dis. 2018 Oct;18(10):1077-1087.
21. Liang L, Shi R, Liu X, et al. Interferon-gamma response to the treatment of active pulmonary and extra-pulmonary tuberculosis. Int J Tuberc Lung Dis. 2017 Oct 1;21(10):1145-1149.
22. del Corral H, París SC, Marín ND, et al. IFN gamma response to Mycobacterium tuberculosis, risk of infection and disease in household contacts of tuberculosis patients in Colombia. PLoS One 2009;4(12): e8257.
23. Shimouchi A, Ozasa K. The incidence rate of active pulmonary tuberculosis among adult population with fibrotic lesions. Kekkaku 2003;78(1):5-13.
24. Cegielski JP, McMurray DN. The relationship between malnutrition and tuberculosis: evidence from studies in humans and experimental animals. Int J Tuberc Lung Dis 2004;8(3):286-98.
25. Leung CC, Lam TH, Chan WM, et al. Lower risk of tuberculosis in obesity. Arch Intern Med 2007;167(12):1297–304.
26. Lonnroth K, Williams BG, Cegielski P, et al. A consistent log-linear relationship between tuberculosis incidence and body mass index. Int J Epidemiol 2010;39(1):149-55.
27. Cegielski JP, Arab L, Cornoni-Huntley J. Nutritional risk factors for tuberculosis among adults in the United States, 1971-1992. Am J Epidemiol 2012;176(5):409-22.
28. Yen YF, Hu HY, Lee YL, et al. Obesity/overweight reduces the risk of active tuberculosis: a nationwide population-based cohort study in Taiwan. Int J Obes (Lond) 2017;41(6):971-975.
29. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Med 2008 Jul 15;5(7): e152.

Acknowledgements: We thank Dr. Dingyong Sun from Center for Diseases Control and Prevention of Henan province for his support on study implement. We thank Prof. Yu Ma and Prof. Zongde Zhang from Beijing Chest Hospital for their help on quality control of reading chest radiography. We thank all the investigators in the study team for their contributions.

Ethics approval and consent to participate: All participants included in the study signed the informed consent and the ethics committees of the Institute of Pathogen Biology and the Chinese Academy of Medical Sciences approved the study protocol (IPB-2015-5, IPB-2016-8 and IPB2019-11).

Data sharing: This study is registered at www.chictr.org.cn with identifier ChiCTR-IOR-15007202. The corresponding author can provide, upon request, individual participant data that underlie the results reported in this article or protocol after applying necessary measures to guarantee that no individual is identified or identifiable.

Consent for publication: Not applicable

Contributors: LG and QJ designed the study. LG, JL, SP, BZ, DW, ZL and JY organized the implement of the study. HX, HZ, XC, YD, BF, LG, FS, YH, YH, ZQ did epidemiological investigation and quality control. XG interpreted radiographs. XC, HX and HZ did data management and data analysis. HX, XC and LG wrote the report. All authors contributed to review and revision and have seen and approved the final version of manuscript.

Conflict of interest: All co-authors declare that we have no conflicts of interest.

Role of the Funding source: This work was supported by the National Science and Technology Major Project of China [2017ZX10201302-009], the CAMS Innovation Fund for Medical Sciences (CIFMS) [2016-I2M-1-013] and [2019-I2M-2-005]. They did not involve in trial design, patient recruitment, data collection, analysis, interpretation or any aspect pertinent to the study.

Figure legend

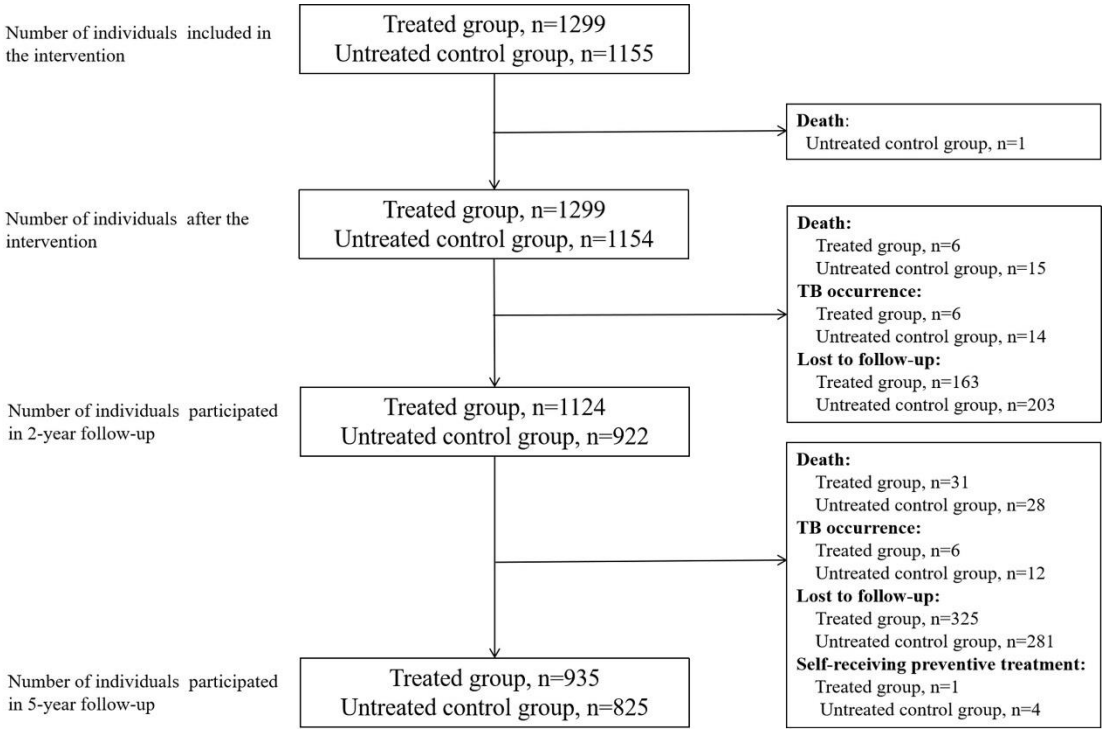


Figure 1 Flowchart of study participant intervention and follow-up

A total of 1299 participants accepted treatment of the 6-week regimen and 1155 untreated controls were included in the original RCT. There were 83.37% (2046/2454) and 71.71% (1760/2454) of the subjects finished in the 2-year and 5-year follow-up survey, respectively. Five subjects (one in treated group and four in untreated control group) were excluded because of self-reported preventative treatment after intervention performed by the study. Finally, a total of 1298 treated participants and 1151 untreated controls were included in the protective efficacy analysis.

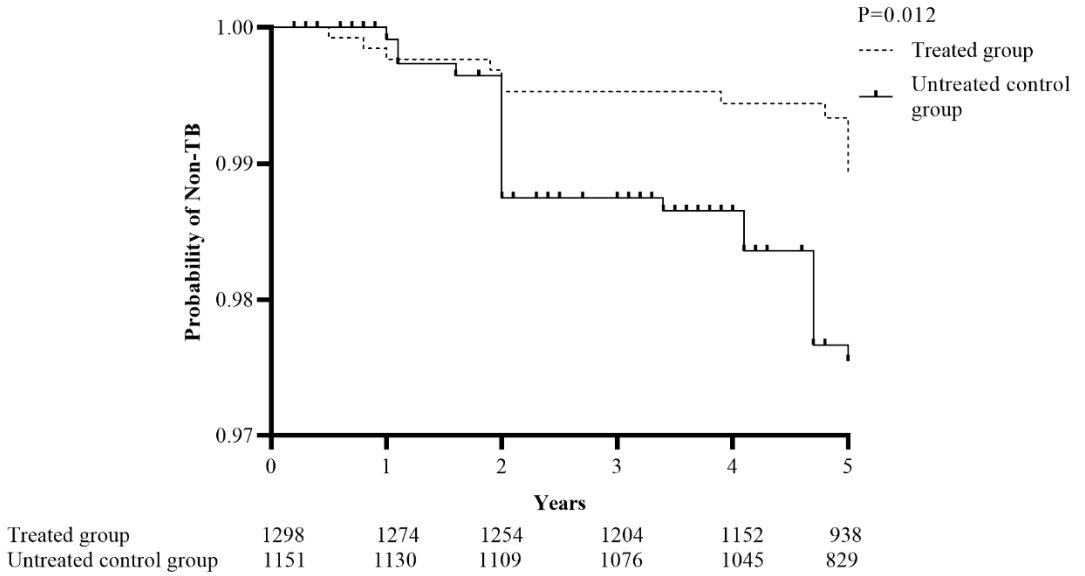
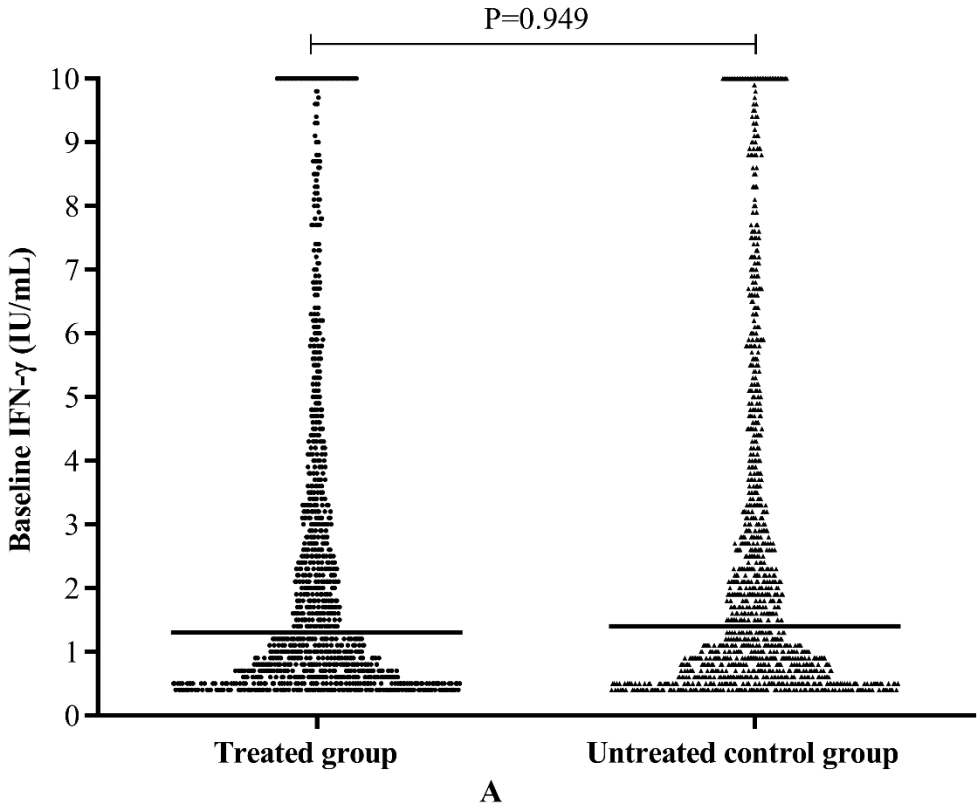
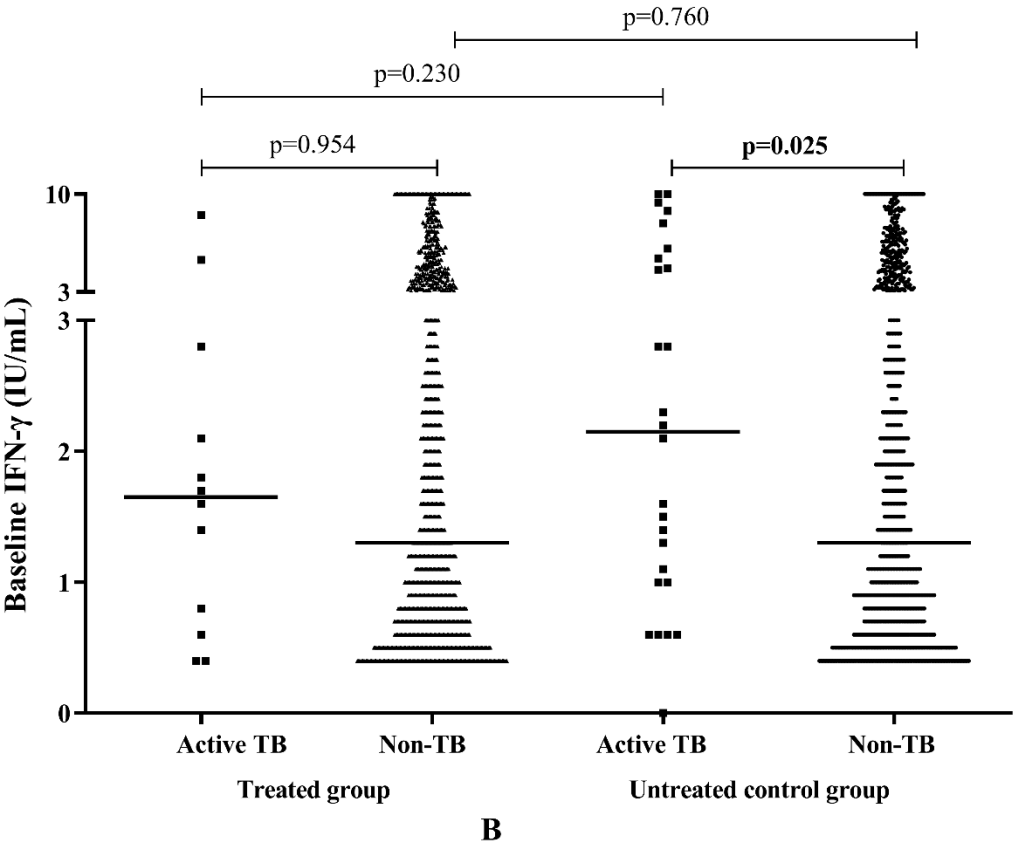


Figure 2 Kaplan-Meier curve of time to tuberculosis by study arm

Numbers of participants stayed without disease were listed by study arm. Most of the cases were identified in yearly examinations with chest radiography screening based active case-finding. Kaplan-Meier curve demonstrated that participants in the untreated group had an increased risk of developing active TB compared to the treated control group. TB, tuberculosis.


P=0.949
Baseline IFN-γ (IU/mL)
10
9
8
7
6
5
4
3
2
1
0
Treated group
Untreated control group

A


p=0.760
p=0.230
p=0.954
p=0.025
Baseline IFN-γ (IU/mL)
10
3
3
2
1
0
Active TB
Non-TB
Active TB
Non-TB
Treated group
Untreated control group

B

Figure 3 Subgroup distributions and comparisons of IFN-γ levels at baseline

Distribution of baseline IFN-γ levels between treated and untreated participants (the difference was tested by p for Wilcoxon rank sum test) (A). Distribution of baseline IFN-γ levels between subjects with and without TB disease development classified by treatment (the difference was tested by p for Wilcoxon rank sum test) (B). Horizontal lines represent median IFN-γ levels. TB, tuberculosis.

Table 1 Characteristics of the study participants included in the intention-to-treat analysis

Variables	Treated group[#] n (%)	Untreated control group n (%)	p for χ^2 test
Total	1298	1151	
Age (years), n (%)			
50-55	317 (24.42)	264 (22.94)	0.637
56-60	343 (26.43)	295 (25.63)	
61-65	333 (25.65)	299 (25.98)	
66-70	305 (23.50)	293 (25.46)	
Gender, n (%)			
Female	590 (45.45)	512 (44.48)	0.630
Male	708 (54.55)	639 (55.52)	
BMI (Kg/m^2), n (%)			
<18.5	542 (41.76)	471 (40.92)	0.755
18.5–<24	30 (2.31)	22 (1.91)	
24–<28	493 (37.98)	458 (39.79)	
⩾28	233 (17.95)	200 (17.38)	
Smoking, n (%)			
Never smoked	765 (58.94)	691 (60.03)	0.581
Ever smoked	533 (41.06)	460 (39.97)	
Presence of TB history, n (%)			
No	1284 (98.92)	1124 (97.65)	**0.015**
Yes	14 (1.08)	27 (2.35)	
Alcohol drinking, n (%)			
No	901 (69.41)	810 (70.37)	0.606
Yes	397(30.59)	341(29.63)	
Fasting blood glucose, n (%)			
≤7 mmol·L^{-1}	1211(93.30)	1049 (91.14)	**0.046**
>7 mmol·L^{-1}	87(6.70)	102 (8.86)	
History of silicosis, n (%)			
No	1270 (97.84)	1127 (97.91)	0.902
Yes	28 (2.16)	24 (2.09)	

Abbreviation: BMI, body mass index; TB, tuberculosis.

[#]: Treated group completed 6 weeks of twice-weekly rifapentine plus isoniazid (both with a maximum dose of 600 mg).

Table 2 Incidence of active tuberculosis in the study groups

	Treated group[#]	Untreated control group
Intention-to-treat analysis		
Subjects, n	1298	1151
Person-years, n	5876	5337
Incident cases, n	12	26
Cumulative incidence, % (95% CI)	0.92 (0.40, 1.45)	2.26 (1.40, 3.12)
Protective rate[+], %	59.29	
Incidence rate per 100 person-years (95% CI)	0.20 (0.09, 0.32)	0.49 (0.30, 0.67)
Protective rate[§], %	59.18	
Adjusted hazard ratio (95% CI) [ƒ]	0.41 (0.20, 0.84)	Ref.
Per-protocol analysis		
Subjects, n	1012	1151
Person-years, n	4654	5337
Incident cases, n	9	26
Cumulative incidence, % (95% CI)	0.89 (0.31, 1.41)	2.26 (1.40, 3.12)
Protective rate[+], %	60.62	
Incidence rate per 100 person-years (95% CI)	0.19 (0.07, 0.32)	0.49 (0.30, 0.67)
Protective rate[§], %	61.22	
Adjusted hazard ratio (95% CI) [ƒ]	0.39 (0.17, 0.88)	Ref.

Abbreviation: TB, tuberculosis; CI, confidence interval.

[#]: Treated group completed 6 weeks of twice-weekly rifapentine plus isoniazid (both with a maximum dose of 600 mg);

[+]: calculating protective rate by using cumulative incidence;

[§]: calculating protective rate by using incidence rate per 100 person-years;

[ƒ]: adjusted for age, body mass index, baseline IFN-γ and presence of pulmonary fibrotic lesions.

Table 3 Subgroup analysis of active tuberculosis incidence classified by baseline IFN-γ levels

	0.35 IU/mL≤ Baseline IFN-γ <3.25 IU/mL		Baseline IFN-γ ≥3.25 IU/mL	
	Treated group[#]	Untreated control group	Treated group[#]	Untreated control group
Intention-to-treat analysis				
Subjects, n	961	861	337	288
Person-years, n	4322	4026	1554	1304
Incident cases, n	10	16	2	9
Cumulative incidence, % (95% CI)	1.04 (0.40, 1.68)	1.86 (0.96, 2.76)	0.59 (0.00, 1.41)	3.13 (1.12, 5.13)
Protective rate[&], %	44.09		81.15	
Incidence rate per 100 person-years (95% CI)	0.23 (0.08, 0.37)	0.40 (0.20, 0.59)	0.13 (0.00, 0.31)	0.69 (0.23, 1.13)
Protective rate[§], %	42.50		81.16	
Adjusted hazard ratio (95% CI) [ƒ]	0.50 (0.22, 1.13)	Ref.	0.26 (0.05, 1.25)	Ref.
Per-protocol analysis				
Subjects, n	748	861	264	288
Person-years, n	3021	4026	1233	1304
Incident cases, n	7	16	2	9
Cumulative incidence, % (95% CI)	0.94 (0.24, 1.63)	1.86 (0.96, 2.76)	0.76 (0.00, 1.80)	3.13 (1.12, 5.13)
Protective rate[+], %	49.46		75.72	
Incidence rate per 100 person-years (95% CI)	0.23 (0.06, 0.40)	0.40 (0.20, 0.59)	0.16 (0.00, 0.39)	0.69 (0.23, 1.13)
Protective rate[§], %	42.50		76.82	
Adjusted hazard ratio (95% CI) [ƒ]	0.46 (0.18, 1.15)	Ref.	0.33 (0.07, 1.56)	Ref.

Abbreviation: TB, tuberculosis; CI, confidence interval.

*:3.25 IU/mL was the 75% quantile level of baseline IFN-γ.

[#]: Treated group completed 6 weeks of twice-weekly rifapentine plus isoniazid (both with a maximum dose of 600 mg);

[&]: calculating protective rate by using cumulative incidence;

[§]: calculating protective rate by using incidence rate per 100 person-years;

[ƒ]: adjusted for age, body mass index, and presence of pulmonary fibrotic lesions.

Two subjects without baseline IFN-γ level were treated as missing value in this analysis

Table 4. Risk factors related with the incidence of active tuberculosis

Variables	Incidence of TB* n/N (%)	p for χ^2 test	Adjusted HR# (95% CI)
Age (years)			
50-55	2/581 (0.34)	**<0.001**	Ref.
56-60	5/638 (0.78)		1.56 (0.29, 8.55)
61-65	12/632 (1.90)		**4.88 (1.09, 21.89)**
66-70	19/598 (3.18)		**5.07 (1.13, 22.62)**
p for trend		**<0.001**	
Gender			
Female	12/1102 (1.09)	0.094	
Male	26/1347 (1.93)		
BMI (Kg/m^2)			
<18.5	4/52 (7.69)	**<0.001**	**3.64 (1.20, 11.00)**
18.5–<24	22/1013 (2.17)		Ref.
24–<28	11/951 (1.16)		0.63 (0.30,1.32)
⩾28	1/433 (0.23)		**0.13 (0.02, 1.00)**
p for trend		**<0.001**	
Ever-smoker			
No	17/1456 (1.17)	0.063	
Yes	21/993 (2.11)		
Current alcohol drinking			
No	27/1711 (1.58)	0.872	
Yes	11/738 (1.49)		
With a history of silicosis			
No	37/2397 (1.54)	0.827	
Yes	1/52 (1.92)		
CXR identified prior TB			
No	33/2408 (1.37)	**<0.001**	Ref.
Yes	5/41 (12.20)		**5.99 (2.20, 16.27)**
Fasting blood glucose			
≤7 mmol/L	35/2260 (1.55)	0.967	
>7 mmol/L	3/189 (1.59)		
Groups			
Treated group: completed the regimen	9/1012 (0.89)	**0.028**	**0.40 (0.18, 0.89)**
Treated group: uncompleted the regimen	3/286 (1.05)		0.42 (0.12, 1.50)
Untreated control group	26/1151 (2.26)		Ref.
Baseline IFN-γ level&			
<1.34 IU/mL	12/1218 (0.99)	**0.034**	Ref.
≥1.34 IU/mL	25/1229 (2.03)		**2.27 (1.13, 4.58)**

Abbreviation: BMI, Body mass index; CI, confidence interval; CXR, chest radiography; HR, hazard ratio; TB, tuberculosis. *: The events in both groups were pooled for this analysis.
#: All variables with p values < 0.05 in univariate model were entered into the multivariate models.
&: It was classified by median level of baseline IFN-γ.

Supplementary Table 1 Detailed information of the active tuberculosis cases identified during 5 year follow-up

ID	Age	Sex	Group	Time for diagnosis	Smear	Culture	Gene X-pert	Diagnosis
1201020181	59	male	Untreated control group	Nov-17	negative	negative	negative	Clinical diagnosis
3241010621	70	male	Untreated control group	Nov-17	negative	negative	negative	Clinical diagnosis
3151030171	66	female	Untreated control group	Jun-17	negative	negative	negative	Clinical diagnosis
1032040081	58	male	Untreated control group	Nov-17	negative	negative	negative	Clinical diagnosis
1131020122	60	female	Untreated control group	Nov-17	negative	negative	negative	Clinical diagnosis
1201030011	70	male	Untreated control group	Nov-17	negative	negative	negative	Clinical diagnosis
1231040132	51	female	Untreated control group	Nov-17	negative	negative	negative	Clinical diagnosis
3071080142	55	female	Untreated control group	Nov-17	negative	negative	negative	Clinical diagnosis
3211040312	58	male	Untreated control group	Nov-17	negative	negative	negative	Clinical diagnosis
3431020172	64	male	Untreated control group	Nov-17	negative	negative	negative	Clinical diagnosis
3431050401	59	female	Untreated control group	Dec-16	negative	negative	negative	Clinical diagnosis
4021050461	69	male	Untreated control group	Dec-16	negative	negative	negative	Clinical diagnosis
4061030252	63	male	Untreated control group	Nov-16	positive	positive	positive	Microbiological confirmed
6044050031	53	male	Untreated control group	Nov-17	negative	negative	negative	Clinical diagnosis
1181040172	64	male	Untreated control group	Dec-19	negative	negative	negative	Clinical diagnosis
3063040171	66	male	Untreated control group	Dec-19	negative	negative	negative	Clinical diagnosis
7031040361	65	male	Untreated control group	Dec-19	negative	negative	negative	Clinical diagnosis
5081040202	64	female	Untreated control group	Apr-19	negative	negative	negative	Clinical diagnosis
2173070321	64	male	Untreated control group	Aug-20	negative	negative	negative	Clinical diagnosis
3251060271	67	male	Untreated control group	Aug-20	negative	negative	negative	Clinical diagnosis
1042040381	66	male	Untreated control group	Aug-20	negative	positive	positive	Microbiological confirmed
3152060882	64	male	Untreated control group	Aug-20	negative	positive	negative	Microbiological confirmed
4141040201	66	male	Untreated control group	Aug-20	negative	positive	positive	Microbiological confirmed
5041030051	70	female	Untreated control group	Aug-20	negative	positive	positive	Microbiological confirmed
6066020021	61	male	Untreated control group	Aug-20	positive	positive	positive	Microbiological confirmed
4061030091	69	male	Untreated control group	Dec-20	negative	negative	negative	Clinical diagnosis
1241020241	68	female	Treated group	Nov-17	negative	negative	negative	Clinical diagnosis
3071070301	67	male	Treated group	May-16	negative	negative	negative	Clinical diagnosis
3231020332	62	male	Treated group	Oct-17	negative	negative	negative	Clinical diagnosis
4141090242	69	female	Treated group	Nov-17	negative	negative	negative	Clinical diagnosis
6022040081	65	female	Treated group	Aug-16	negative	negative	negative	Clinical diagnosis
3301070171	68	male	Treated group	Nov-16	negative	negative	negative	Clinical diagnosis
5081010531	62	male	Treated group	Sep-20	positive	positive	positive	Microbiological confirmed
1061030361	68	male	Treated group	Dec-20	negative	negative	negative	Microbiological confirmed
3251020041	69	female	Treated group	Dec-20	negative	negative	negative	Clinical diagnosis
3301060042	66	female	Treated group	Dec-20	negative	negative	negative	Clinical diagnosis
3431010121	70	male	Treated group	Dec-20	negative	negative	negative	Clinical diagnosis
4131080101	61	male	Treated group	Oct-19	negative	negative	negative	Clinical diagnosis

Abbreviations: TB, tuberculosis.

Supplementary Table 2 Characteristics of the study participants with the highest quartile baseline IFN-γ levels included in the intention-to-treat analysis

Variables	Treated group[#] n (%)	Untreated control group n (%)	p for χ^2 test
Total	337	288	
Age (years), n (%)			
50-55	93 (27.60)	62 (21.53)	0.371
56-60	86 (25.52)	79 (27.43)	
61-65	84 (24.93)	76 (26.39)	
66-70	74 (21.96)	71 (24.65)	
Gender, n (%)			
Female	138 (40.95)	120 (41.67)	0.856
Male	199 (59.05)	168 (58.33)	
BMI (Kg/m^2), n (%)			
<18.5	139 (41.25)	120 (41.67)	0.941
18.5–<24	5 (1.48)	6 (2.08)	
24–<28	129 (38.28)	110 (38.19)	
⩾28	64 (18.99)	52 (18.06)	
Smoking, n (%)			
Never smoked	186 (55.19)	158 (54.86)	0.934
Ever smoked	151 (44.81)	130 (45.14)	
Presence of TB history, n (%)			
No	333 (98.81)	277 (96.18)	**0.032**
Yes	4 (1.19)	11 (3.82)	
Alcohol drinking, n (%)			
No	231 (68.55)	194 (67.36)	0.752
Yes	106 (31.45)	94 (32.64)	
Fasting blood glucose, n (%)			
≤7 mmol·L^{-1}	314 (93.18)	264 (91.67)	0.476
>7 mmol·L^{-1}	23 (6.82)	24 (8.33)	
History of silicosis, n (%)			
No	331 (98.22)	280 (97.22)	0.401
Yes	6 (1.78)	8 (2.78)	

Abbreviations: BMI, body mass index; TB, tuberculosis.

[#]: Treated group completed 6 weeks of twice-weekly rifapentine plus isoniazid (both with a maximum dose of 600 mg).

Supplementary Table 3 Characteristics of active tuberculosis and non-tuberculosis participants with the highest quartile baseline IFN-γ levels

Variables	Active TB	Non-TB	p for χ^2 test
Age (years), n (%)			
50-55	0 (0.00)	155 (25.24)	0.078
56-60	2 (18.18)	163 (26.55)	
61-65	6 (54.55)	154 (25.08)	
66-70	3 (27.27)	142 (23.13)	
Gender, n (%)			
Female	2 (18.18)	256 (41.69)	0.116
Male	9 (81.82)	358 (58.31)	
BMI (Kg/m^2), n (%)			
<18.5	1 (9.09)	10 (1.63)	**0.025**
18.5–<24	8 (72.73)	251 (40.88)	
24–<28	2 (18.18)	237 (38.60)	
≥28	0 (0.00)	116 (18.89)	
Ever-smoker, n (%)			
No	3 (27.27)	341 (55.54)	0.062
Yes	8 (72.73)	273 (44.46)	
Current alcohol drinking, n (%)			
No	6 (54.55)	419 (68.24)	0.335
Yes	5 (45.45)	195 (31.76)	
With a history of silicosis, n (%)			
No	10 (90.91)	601 (97.88)	0.121
Yes	1 (9.09)	14 (2.12)	
CXR identified prior TB, n (%)			
No	9 (81.82)	601 (97.88)	**<0.001**
Yes	2 (18.18)	13 (2.12)	
Fasting blood glucose, n (%)			
≤7 mmol/L	11 (100.00)	567 (92.35)	0.340
>7 mmol/L	0 (0.00)	47 (7.65)	
Groups, n (%)			
Treated group	2 (18.18)	335 (54.56)	**0.016**
Untreated control group	9 (81.82)	279 (45.44)	

Abbreviations: BMI, Body mass index; CI, confidence interval; CXR, chest radiography; HR, hazard ratio; TB, tuberculosis.

Supplementary Table 4 Subgroup analysis of incidence of active tuberculosis according to median baseline IFN-γ and timing of tuberculosis occurrence

Treated group[#]			
	The first 2-year after intervention	**The last 3-year after intervention**	**p for χ^2 test** [+]
Baseline IFN-γ <1.34 IU/mL	0.08 (2/2471) /100 person-years	0.06 (2/3405) /100 person-years	1.000
Baseline IFN-γ ≥1.34 IU/mL	0.16 (4/2471) /100 person-years	0.12 (4/3405) /100 person-years	0.922
p for χ^2 test[§]	0.683	0.683	
Untreated control group			
	The first 2-year after intervention	**The last 3-year after intervention**	**p for χ^2 test** [+]
Baseline IFN-γ <1.34 IU/mL	0.19 (4/2057) /100 person-years	0.27 (9/3280) /100 person-years	0.564
Baseline IFN-γ ≥1.34 IU/mL	0.19 (4/2057) /100 person-years	0.24 (8/3280) /100 person-years	0.941
p for χ^2 test[§]	1.000	0.808	

Abbreviations: TB, tuberculosis;

[#]: Treated group completed 6 weeks of twice-weekly rifapentine plus isoniazid (both with a maximum dose of 600 mg);

+： p value of incidence of active TB according to timing of TB occurrence;

§： p value of incidence of active TB according to median baseline IFN-γ;

Supplementary Table 5 Incidence of active tuberculosis after excluding those with prior tuberculosis and diabetes mellitus

	Treated group[#]	Untreated control group
Intention-to-treat analysis		
Subjects, n	1197	1023
Person-years, n	5433	4753
Incident cases, n	11	19
Cumulative incidence, % (95% CI)	0.92 (0.38, 1.45)	1.86 (1.03, 2.68)
Protective rate[+], %	50.54	
Incidence rate per 100 person-years (95% CI)	0.20 (0.08, 0.32)	0.40 (0.22, 0.58)
Protective rate§, %	50.00	
Per-protocol analysis		
Subjects, n	935	1023
Person-years, n	4312	4753
Incident cases, n	8	19
Cumulative incidence, % (95% CI)	0.86 (0.27, 1.45)	1.86 (1.03, 2.68)
Protective rate[+], %	53.76	
Incidence rate per 100 person-years (95% CI)	0.19 (0.06, 0.31)	0.40 (0.22, 0.58)
Protective rate[§], %	52.50	

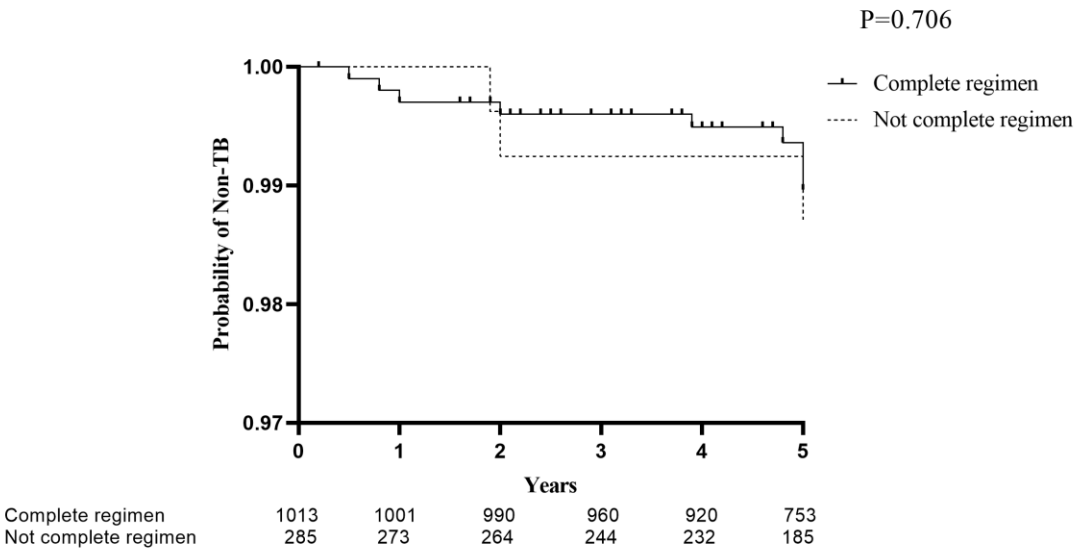
Abbreviations: TB, tuberculosis; CI, confidence interval.

[#]: Treated group completed 6 weeks of twice-weekly rifapentine plus isoniazid (both with a maximum dose of 600 mg);

[+]: calculating protective rate by using cumulative incidence;

[§]: calculating protective rate by using incidence rate per 100 person-years.

Figure legend



Supplementary Figure 1 Kaplan-Meier curve of tuberculosis occurrence by completion of the regimen.

Numbers of participants stayed without disease were listed by study arm. Kaplan-Meier curve demonstrated that there was no significant difference in the risk of developing active TB between the participants who completed the regimen and who did not (p=0.706). TB, tuberculosis.