Emerging Microbes & Infections
2025, VOL. 14, 2502010 (8 pages)
https://doi.org/10.1080/22221751.2025.2502010

Efficacy and safety of a novel short course rifapentine and isoniazid regimen for the preventive treatment of tuberculosis in Chinese silicosis patients: a pilot study (SCRIPT-TB)

Qiao-Ling Ruan[a#], Qing-Luan Yang[a#], Chun-Lian Ma[b#], Miao-Yao Lin[b], Xi-Tian Huang[b], Ya-Pin Mao[c], Ji-Mei Gao[c], Jin-Ju Li[c], Xia-Ning Zhang[c], Zhi-Xiang You[c], Quan-Qing Zheng[c], Yan-Fei Ren[d], Xue-Feng Liu[b], Ling-Yun Shao[a] and Wen-Hong Zhang[a,d]

[a]Department of Infectious Diseases, Shanghai Key Laboratory of Infectious Diseases and Biosafety Emergency Response, National Medical Center for Infectious Diseases, Huashan Hospital, Fudan University, Shanghai, People's Republic of China; [b]The First People's Hospital of Wenling, Zhejiang, People's Republic of China; [c]Taizhou Sanmen County Xiaoxiong Health Center, Zhejiang, People's Republic of China; [d]Shanghai Sci-Tech Inno Center for Infection & Immunity, Shanghai, People's Republic of China

ABSTRACT

Background: Tuberculosis preventive treatment (TPT) is essential for the end TB Strategy, but shorter and better tolerated regimens are needed to boost its coverage and acceptance.

Methods: Silicosis patients aged 18 to 65 years received a novel 1H3P3 regimen (400 mg isoniazid and 450 mg rifapentine, thrice-weekly for 4 weeks) under direct observation and were actively followed up for 3 years. The safety and efficacy were compared to the 3-month, once-weekly isoniazid/rifapentine (3HP) group and observation group from our previous trials.

Results: A total of 279 eligible participants were enrolled, and 238 participants provided informed consent. All eligible participants had a median age of 56 years (IQR 52–60), 163 (68.5%) participants had a Bacillus Calmette-Guerin vaccine scar, and 74 (31.1%) participants were QuantiFERON-TB Gold In-Tube positive. There were 88 adverse events from 66 (27.7%) participants and only one (0.4%) participant had a Grade 3 adverse event. The completion rate was 92.0% (219/238). Six (2.5%) participants were diagnosed with active TB, five of which were bacterial confirmed cases. The cumulative active TB rate was 1.67 cases per 100 person-years. Compared to the previous study, the 1H3P3 regimen significantly reduced the 3-year cumulative active TB rate than the observation group (HR = 0.26, Log-rank $P = 0.02$) and was comparable with the 3HP group (HR = 0.74, Log-rank $P = 0.69$), while significantly reducing adverse events.

Conclusion: The $1H_3P_3$ TPT regimen was both safe and effective among silicosis patients. Further work is necessary to test the regimen in other high-risk populations.

Trial registration: ClinicalTrials.gov identifier: NCT06022146 and NCT03900858.

ARTICLE HISTORY Received 27 December 2024; Revised 22 April 2025; Accepted 30 April 2025

KEYWORDS Controlled clinical trial; tuberculosis; preventive treatment; rifapentine; isoniazid

Introduction

Tuberculosis (TB) remains one of the most significant infectious diseases globally. One-fourth of the world's population is infected with *Mycobacterium tuberculosis*, and serves as a reservoir for incident tuberculosis disease [1]. In 2015, the World Health Organization (WHO) called for the implementation of the End TB Strategy. Preventive treatment for individuals at the highest risk of TB progressing to an active disease is one of the pillars of successful TB control [2,3]. However, according to the WHO TB Report, only 15.5 million people at high risk of TB progression were reached between 2018 and 2022, and the goal of reaching 30 million people was missed by a substantial margin [4]. Exposure to silica dust or the development of silicosis predisposes to active TB [5]. In our pilot cross-sectional study of 1656 subjects with silicosis, the prevalence of TB was 6.34 per 100 persons, and the proportion of patients with latent TB infection was 50.6% [6]. WHO guidelines recommended patients with silicosis to be systematically tested and treated for TB infection [7].

According to the cascade of care in tuberculosis preventive treatment (TPT), completion of treatment

CONTACT Ling-yun Shao lingyun26@fudan.edu.cn Department of Infectious Diseases, Shanghai Key Laboratory of Infectious Diseases and Biosafety Emergency Response, National Medical Center for Infectious Diseases, Huashan Hospital, Fudan University, People's Republic of China; Wen-Hong Zhang zhangwenhong@fudan.edu.cn Department of Infectious Diseases, Shanghai Key Laboratory of Infectious Diseases and Biosafety Emergency Response, National Medical Center for Infectious Diseases, Huashan Hospital, Fudan University, People's Republic of China Shanghai Sci-Tech Inno Center for Infection & Immunity, Shanghai, People's Republic of China
[#]These authors contribute equally to this work.

Supplemental data for this article can be accessed online at https://doi.org/10.1080/22221751.2025.2502010

if started is one of the steps in the cascade associated with greater losses [8]. A previous study indicated that the shorter the duration of treatment, the better the patient compliance and the higher the treatment completion rate [9]. For preventive TB treatment, balancing the potential long-term benefit and immediate risk of therapy-related adverse events is a challenge. Thus, shorter, better-tolerated, cost-effective TPT regimens are highly desirable.

The 3-month once-weekly therapy with rifapentine (RPT) and isoniazid (INH) (3HP, both with a maximum dose of 900 mg) is a recommended TPT regimen by the WHO because of its short duration and good safety profile. However, when the regimen was evaluated in randomized controlled trials in China, the performance was not as good as anticipated. High frequency and fast-growing drug-related side effects were reported for older adults (age, 50–70 years) receiving the 3HP regimen, which led to premature termination after 8 weeks [10]. In our open-label, randomized clinical trial targeting individuals exposed to silica dust, only 54.7% (139/254) of participants completed the 3HP regimen, and 28.3% (72/254) of participants permanently discontinued drug intake due to drug-associated side effects [11]. Pharmacokinetic analysis revealed higher rifapentine and metabolite concentrations than those in the TBTC and PREVENT TB studies [12,13].

These adverse reactions may be related to the high drug dosage of 3HP and the intermittent administration of rifampicin. Therefore, based on our pharmacokinetic studies and clinical experience, our team designed a novel one-month, thrice-weekly rifapentine and isoniazid TPT regimen, referred to as the $1H_3P_3$ regimen, aimed at reducing peak drug concentrations by lowering the single dose of the medication and increasing the frequency of administration to avoid systemic drug reactions (SDRs) caused by intermittent dosing. The $1H_3P_3$ regimen exhibited potent bactericidal activity against *M. tuberculosis* within 4 weeks in a murine model of latent tuberculosis infection (LTBI) [14]. In the present study, we further evaluated this novel $1H_3P_3$ TPT regimen to prevent TB among individuals exposed to silica dust in real-world settings in China.

Methods

Study participants

Between February and April 2019, we targeted individuals with silicosis in Taizhou City; the same population in which we previously conducted a randomized controlled trial using the 3HP regimen [11]. All eligible subjects were required to be: (1) individuals with silica exposure or diagnosed with silicosis; (2) aged 18–65 years; (3) willing to provide signed informed consent, or parental consent, and participant assent. The exclusion criteria were (1) clinical or bacterial confirmed active TB (ATB); (2) a history of treatment for >14 consecutive days with a rifamycin or >30 consecutive days with INH during the previous 2 years; (3) a documented history of completing an adequate course of treatment for ATB or latent TB infections; (4) allergy to isoniazid, rifampin, or rifapentine; (5) human immunodeficiency virus (HIV) infection; (6) a history of hepatitis B/C infection or liver cirrhosis; (7) serum aspartic transaminase (AST) or alanine transaminase (ALT) > 2 upper limit of normal (ULN) or total bilirubin >2.5 mg/dL; (8) receiving immunosuppressants or biological agents; (9) life expectancy <3 years; (10) the presence of a mental disorder; and (11) participation in other clinical trials in the prior three months; or (12) other conditions that the investigators considered not suitable for participation.

Intervention and follow-up

Eligible participants were assigned to the one-month $1H_3P_3$ regimen (12 doses), which included thrice-weekly rifapentine treatments at a dose of 450 mg plus isoniazid at a dose of 400 mg. Treatments were administered under direct observation. Screening for latent tuberculosis infection was performed using QuantiFERON-TB Gold In-Tube (QFT; Cellestis). Active pulmonary TB disease was screened by symptoms, digital chest radiography, and sputum cultures for Mycobacteria. Once diagnosed with ATB, the strains of bacterially confirmed cases were isolated and went through a drug susceptibility test. Patients were evaluated for 37 months after enrollment, examined every 6 months, and screened for both active pulmonary and extrapulmonary TB every year (see Supplement material). Participants and their primary caretakers were encouraged to report symptoms or other signs of suspected ATB. We provided free examinations to individuals with suspected tuberculosis. Participants were evaluated every two weeks during intervention and followed up one month after intervention using routine blood tests, liver function tests, and self-reported adverse events (AEs).

Outcome measurements

The primary study endpoint was bacterial confirmed or clinically diagnosed ATB disease. A bacterial confirmed case was defined with a positive sputum smear, culture, and/or GeneXpert MTB/RIF® assays. Clinically diagnosed ATB refers to a condition where an individual does not meet the criteria for bacteriological confirmation but has been diagnosed based on symptoms, radiographic abnormalities, and response to empiric TB treatment among participants suspected to have TB. A clinical TB diagnosis was

made based on the consensus of three experts who were blinded to the treatment assignment.

Secondary endpoints included drug discontinuation for any reason, any grade 3 or 4 adverse events, death for any reason, and completion of the treatment regimen. Adverse events and side effects were graded using the Common Terminology Criteria for Adverse Events (CTCAE 5.0), including hepatoxicity grade (see Supplement material). SDRs were evaluated using the criteria in the PREVENT TB Study [13,15]. All eligible enrolled subjects who completed ≥11 of 12 doses of the $1H_3P_3$ regimen were regarded as having completed the regimen.

Participants who complied with the required blood sampling schedule and provided written informed consent were included in the pharmacokinetic analysis. Serial plasma samples were collected to determine the concentrations of rifapentine, isoniazid, and their metabolites (25-desacetyl-rifapentine, acetyl-isoniazid) for pharmacokinetic analysis (see Supplement material).

Statistical analysis

The rates of ATB disease were based on person-time of follow-up. TB rates were calculated using the follow-up period and rate ratios were estimated to compare TB incidence rates. Patients who were lost to follow-up or died contributed to person-time until the date of their last contact or death. To gain more information about the efficacy of the treatment regimen, we incorporated an external cohort as a reference. The cohort was derived from a randomized controlled trial (RCT) conducted by our team within the same Chinese city, focussing on prophylactic anti-tuberculosis therapy for patients with silicosis [11]. The intention-to-treat (ITT) population encompassed all eligible participants who were enrolled, while the per-protocol (PP) population comprised all eligible participants who adhered to the treatment regimen, completing 11 out of the 12 prescribed doses, as well as all individuals in the observation group. To ensure the comparability between different studies, we used 1:1 propensity score matching (PSM) to balance all baseline variables between the $1H_3P_3$ group and observation group, as well as between the $1H_3P_3$ group and the 3HP group, separately. The primary PSM analysis was based on the ITT population. Furthermore, to assess the comparative therapeutic efficacy of the regimen, we deliberately selected a subset of the silicosis population with latent tuberculosis infection. To identify potential variables related to active disease risk, Kaplan–Meier analysis was used to estimate the probability of progress to TB. The hazard ratio (HR) was determined by the Cox proportional-hazard regression model, and the P value was calculated using the log-rank test. $P < 0.05$ was considered statistically significant.

Ethics approval

The study protocol was approved by the ethics committees of the First People's Hospital of Wengling, Zhejiang (ethics approval number: 2019-01-10). Considering the limited educational background of the participants, we provided a detailed explanation to ensure that they were aware of their rights and duties in the study. Written informed consent was obtained from all study participants before screening and randomization.

Results

From February to April 2019, we identified and screened 452 adults diagnosed with silicosis. A total of 238 (52.7%) individuals were finally enrolled and assigned to treatment with the $1H_3P_3$ regimen (Figure 1). The main ineligibility reasons included participants being over 65 years of age (55 patients), having chronic hepatitis or abnormal liver function (55 patients), receiving previous TB treatments (49 patients), or had current ATB disease (19 patients).

The demographic and clinical characteristics are shown in Table 1. The median age of the patients was 56 years and most patients had silicosis categories over 2. A BCG scar was present in 68.5% (163/238) of patients, and the QFT-positive rate was 31.1% (74/238). The median follow-up time was 37 months and 237 of 238 (99.6%) patients completed the follow-up or a date of death was recorded. There were three deaths during the follow-up period, none of which were related to TB disease.

Tuberculosis incidence

Among the 238 individuals included in the primary outcome analysis, six (2.5%) participants were diagnosed with TB, five of whom had confirmed TB, and one was clinically diagnosed with probable pulmonary TB and tuberculous pleuritis (Table S1). Among the five confirmed ATB cases, all were rifampicin-sensitive. The overall incidence of TB was 1.67 cases per 100 person-years. In the ITT population, after 1:1 PSM between the $1H_3P_3$ group and the observation group from the previous study, most baseline variables were balanced (Table S2). The Kaplan–Meier cumulative incidence curve demonstrated a significantly lower incidence of ATB in the $1H_3P_3$ group compared to the observation group (HR = 0.26, 95% CI 0.07-0.93, Log-rank $P = 0.025$) (Figure 2A). However, after 1:1 PSM between the $1H_3P_3$ group and the 3HP group (Table S3), the difference in incidence between the $1H_3P_3$ group and the 3HP group was not statistically significant (HR = 0.74, 95% CI 0.17 - 3.31, Log-rank $P = 0.69$) (Figure 2B). Sensitivity analyses between 2 treatment groups ($1H_3P_3$ and 3HP) in the matched PP population revealed an HR with an implausibly wide confidence interval (0.00 to >100),

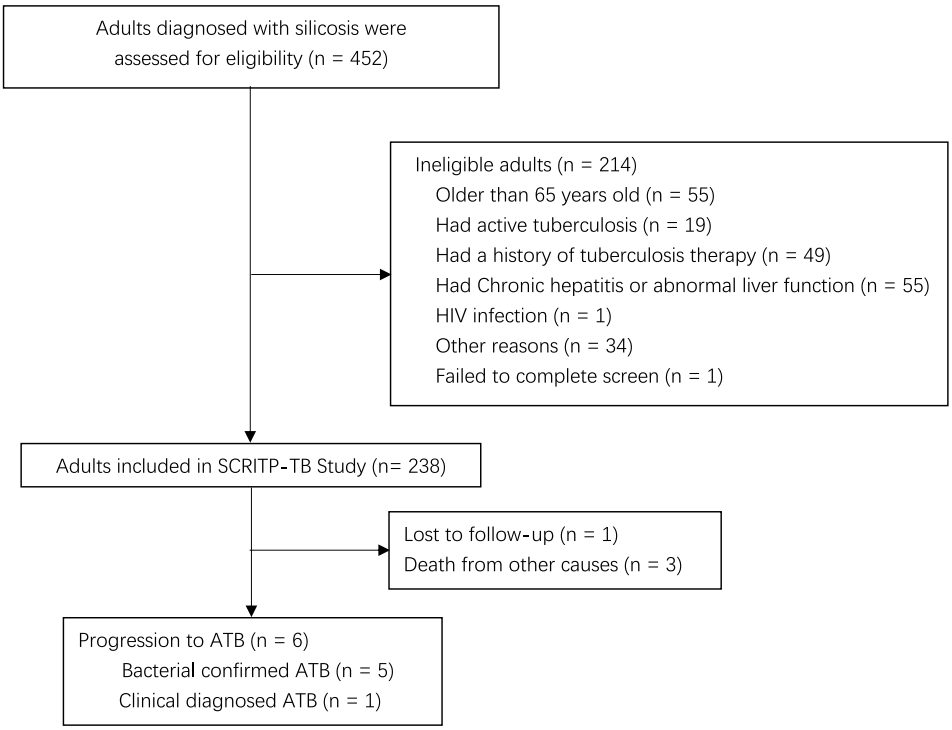

Figure 1. Flow chart of the enrolment and follow-up of study participants.

suggesting model instability. This is likely attributable to the reduced sample size after excluding non-adherent participants ($n = 159$ in the PP cohort vs. $n = 220$ in the ITT cohort). In the pre-matched PP population, both the $1H_3P_3$ group and the 3HP group exhibited significantly lower incidences of ATB compared to the observation group (HR = 0.338, Log-rank $P = 0.015$; HR = 0.092, Log-rank $P = 0.004$, respectively). However, no statistically significant difference was observed between the 3HP group and the $1H_3P_3$ group (Log-rank $P = 0.1949$). Further analysis of the subgroup with LTBI revealed that although the incidence of ATB was lower in both preventive treatment groups than in the observation group, the differences did not reach statistical significance (all Log-rank $P > 0.05$) (Figure 3).

Table 1. Clinical and demographic characteristics of 238 subjects enrolled in the study.

Characteristic		$1H_3P_3$ Group
Age at randomization (years)	Median	56
	Interquartile range	52–60
Body mass index (kg/m^2)	Median	24.0
	Interquartile range	22.0–25.9
Silicosis categories*	0	14 (5.9)
	1	43 (18.1)
	2	82 (34.5)
	3	99 (41.5)
Completed primary school – no. (%)		172 (72.3)
Risk factors – no. (%)	Frequent alcohol user	107 (45.0)
	Current smoker	57 (23.9)
	Diabetes mellitus	9 (3.8)
BCG scar – no. (%)	Absent	59 (24.8)
	Present	163 (68.5)
	Uncertain	16 (6.7)
QFT results – no. (%)	Positive	74 (31.1)
	Negative	164 (68.9)

BCG = Bacillus Calmette-Guerin; QFT = QuantiFERON-TB Gold In-Tube.
*Silicosis categories were determined according to the revised edition (2011) of the ILO Guidelines for the use of the ILO International Classification of Radiographs of Pneumoconioses.

Adherence and adverse events

In total, 219 of the 238 (92.0%) participants took more than 90% of their $1H_3P_3$ doses (11 out of 12 doses). For those who discontinued treatment, three out of 19 permanently discontinued drug intake because of side effects related to the regimen. There was no irreversible sequelae.

The safety analysis set included all subjects who took at least one dose of the study regimen. Although 3 subjects were excluded soon after taking the first dose because of delayed ATB diagnosis at baseline, those subjects were still considered eligible for safety analysis. Among 241 subjects who received ≥1 dose of the drug, the proportion of subjects that experienced any adverse event was 27.4% (66/241). There were 85 Grade 1 adverse events, two Grade 2 adverse events (one fatigue and one hepatotoxicity), and only one Grade 3 adverse event (one hepatotoxicity). Fatigue (19.1%) was the most common adverse event, followed by dizziness (5.8%) and headache (2.5%). Notably, only one individual experienced SDRs of flu-like symptoms. Three cases (1.26%) had hepatotoxicity caused by the drugs in the $1H_3P_3$ regimen, and 28.3% (72/254) of participants had hepatotoxicity due to drug-associated side effects. Compared to our previous study in the same population, the numbers and proportion of different AEs from the original safety analysis set revealed a possible reduction from

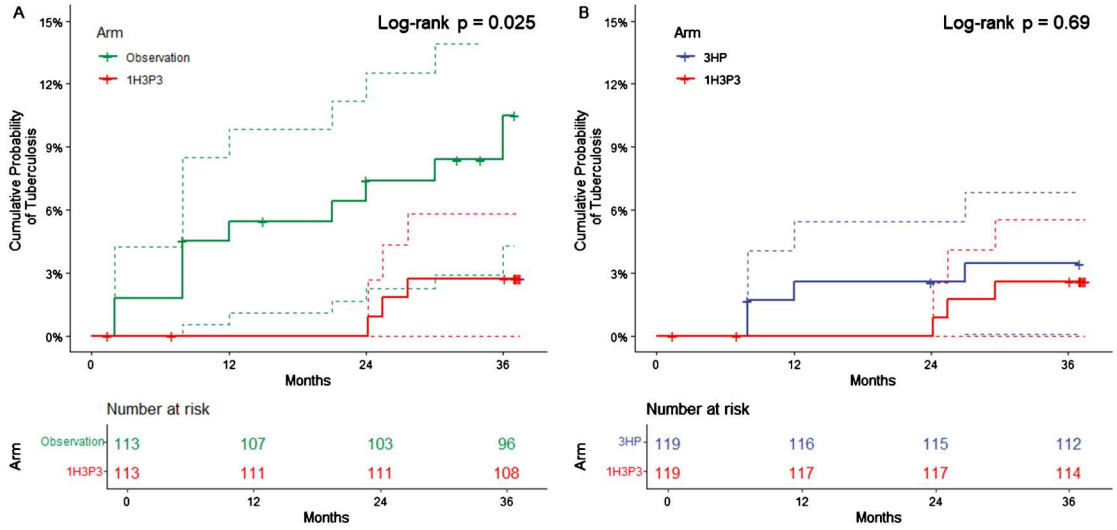

Figure 2. (A) Kaplan–Meier estimates of tuberculosis risk of $1H_3P_3$ and observation groups. *P* value was determined by the log-rank test. (B) Kaplan–Meier estimates of tuberculosis risk of the $1H_3P_3$ and 3HP groups. *P* value was determined by the log-rank test.

the 3HP regimen (Table 2). Subset analysis using matched data between the two groups showed significant differences favouring the $1H_3P_3$ regimen (Table S4).

Pharmacokinetic analysis

Out of 238 participants who received the 1-month $1H_3P_3$ regimen, 140 participants completed the full blood concentration testing. Blood concentration patterns were measured for rifapentine and isoniazid, along with their respective metabolites, between TB progressors and non-progressors. Specifically, the blood concentration of rifapentine in TB progressors 4 h post-administration was 14.9 (11.4, 21.7) μg/mL, which was lower than non-progressors, who had a concentration of 20.2 (14.3, 26.2) μg/mL. By 48 and 72 h post-administration, the blood concentrations of rifapentine between the two groups were similar. Consistently lower blood concentrations of rifapentine metabolites were observed in TB progressors at all time points (4, 48, and 72 h post-administration). In contrast, the blood concentrations of isoniazid and its metabolites 4 h post-administration did not differ between TB progressors and non-progressors (Table 3).

Discussion

Based on our experience in TPT practice and pharmacokinetic analysis, we proposed a novel one-month, thrice-weekly preventive therapy with INH plus RPT (the $1H_3P_3$ regimen). In this single-arm interventional pilot trial, we evaluated the safety and effectiveness of the regimen among Chinese patients with silicosis. Patients on the $1H_3P_3$ regimen exhibited a low incidence of adverse events and a high level of adherence. Furthermore, the reduced incidence of ATB compared to our previous trial in a similar population is indicative of the clinical efficacy of this shorter regimen.

Shortening the duration of tuberculosis preventive therapy is currently an international priority and area of effort. By maintaining non-inferiority, abbreviated regimens can enhance safety and adherence, thereby rendering such preventive treatments more feasible and widely applicable worldwide. In 2020, a new conditional recommendation for daily RPT plus INH for one month (1HP) was added to the TPT regimen based on emerging evidence. However, this regimen has not been widely adopted in China due to concerns that RPT, with its long-acting nature, might be more effective when administered intermittently.

The 3HP regimen is recommended by the WHO for its non-inferiority and safety, and higher completion rate compared to the 6–9 months regimen of daily isoniazid monotherapy [13,16,17]. However, a recent meta-analysis indicated that the 3HP regimen had a higher risk of treatment-related adverse events compared to a 4-month rifampicin regimen [18]. Subsequent studies have further confirmed that the 3HP regimen is associated with a higher frequency of systemic drug reactions (SDRs), including flu-like syndromes and dizziness, as well as uncommon Grade 3 or 4 adverse events such as hypotension, syncope, and bronchospasm [19]. Also, the 3HP regimen was associated with the highest incidence of drug discontinuation due to AEs among the regimens currently recommended, which was estimated at 8.2% (95% CI, 6.1% to 10.8%) [20].

In our previous trial, 28.3% of participants permanently discounted the 3HP regimen because of side effects, while only 54.7% (139/254) completed the treatment [11]. This result is consistent with a contemporaneous clinical trial conducted among Chinese elderly

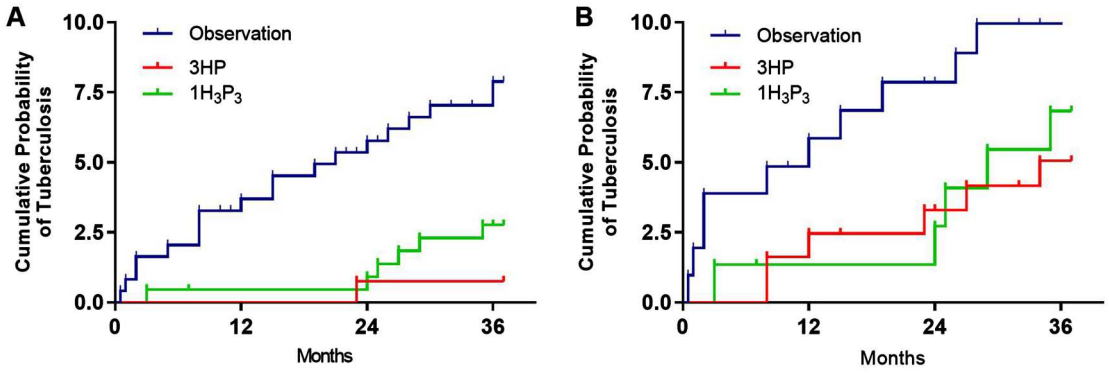

Figure 3. (A) Kaplan–Meier estimates of the risk of tuberculosis in the per-protocol population based on the groups. $1H_3P_3$ group vs observation group: HR = 0.338, Log-rank $P = 0.015$; 3HP group and the observation group: HR = 0.092, Log-rank $P = 0.004$. (B) Kaplan–Meier estimates of the risk of tuberculosis in the intention-to-treat population with LTBI based on the groups (all Log-rank $P > 0.05$).

individuals by Gao et al. [10], where high rates of adverse events were reported for adults aged 50–70 years who received the 3HP regimen. Such high rates of adverse events subsequently led to the premature interruption of the original protocol. Flu-like and other systemic drug reactions were observed in 3.5% of patients receiving the 3HP regimen in the PREVENT TB Trial [15]. We also observed a higher rate of SDRs (10.8%) in our previous RCT. The underlying mechanism leading to the high level of AEs is unclear, but most previous studies indicated that flu-like SDRs occur among persons receiving intermittent rifampin, and usually follow a high dose [21,22]. The present $1H_3P_3$ regimen reduced the single dose of rifampin and increased the frequency of administration. Flu-like SDRs occurred in only one of 238 cases (0.8%) in the $1H_3P_3$ group, whereas they were an important barrier (10.8%, 26/254) to completing the regimen in the 3HP group. Meanwhile, there were significantly fewer treatment interruptions or discontinuations because of drug toxicity in the $1H_3P_3$ group than in the 3HP group. All types of AEs were reduced significantly compared to the 3HP group and cases of hepatotoxicity further decreased from 2.1% to 1.2%.

Regarding the effectiveness of the $1H_3P_3$ regimen, we observed a low rate (2.5%) of ATB cases in this cohort of silicosis patients over a 37-month follow-up period. In our previous trial, the ATB rate was 7.3% in the observational group and 3.5% in the 3HP group over the same period. In PSM analysis, compared to the previous study, the $1H_3P_3$ regimen significantly reduced the 3-year cumulative ATB rate than the observation group (HR = 0.26, Log-rank $P = 0.02$) and was comparable with the 3HP group (HR = 0.74, Log-rank $P = 0.69$), while significantly reducing adverse events. Further analysis of the subgroup with LTBI revealed that although the incidence of ATB was lower in both preventive treatment groups than in the observation group, the differences did not reach statistical significance (all Log-rank $P > 0.05$). We speculate it was because of the small sample size.

In our study, we also explored the plasma drug concentrations of patients undergoing the $1H_3P_3$ regimen to identify any correlations with treatment efficacy.

Table 2. Adverse events in the $1H_3P_3$ group and groups in the previous study [8].

Adverse events#	$1H_3P_3$ group¶ ($n = 241$)	3HP group† ($n = 239$)	Observation group‡ ($n = 259$)
Fatigue	46 (19.1)	128 (53.3)	10 (3.9)
Fever	2 (0.8)	57 (23.8)	12 (4.6)
Gastrointestinal reaction			
Anorexia	5 (2.1)	33 (13.8)	0
Nausea	5 (2.1)	30 (12.5)	0
Abdominal distension	3 (1.2)	14 (5.9)	0
Dizziness	14 (5.8)	55 (22.9)	0
Headache	6 (2.5)	20 (8.3)	0
Back pain	1 (0.4)	–	–
Thrombocytopenia	2 (0.8)	–	–
Hepatotoxicity	3 (1.2)	5 (2.1)	1 (0.4)
Systemic drug reactions	1 (0.4)	26 (10.8)	0
Grade 3/4 reactions*	1 (0.4)	19 (7.9)	0

Adverse events were analysed among subjects who received ≥1 dose of assigned treatment. Data are n(%).
¶ Three participants were excluded after the first dose because of delayed diagnosis of baseline active TB but were eligible for safety analysis.
† Previously published data.
‡ Previously published data.
*Grade 3/4 reactions were identified and graded by physicians using the Common Terminology Criteria for Adverse Events (CTCAE 5.0).

Table 3. Plasma drug concentrations of TB progressors and non-progressors in the $1H_3P_3$ regimen*.

	TB progressors ($n = 5$)	TB non-progressors ($n = 135$)
Rifapentine (μg/mL)		
C4	14.9 (11.4, 21.7)	20.2 (14.3, 26.2)
C48	4.1 (3.3, 5.8)	4.0 (2.0, 6.5)
C72	0.5 (0.2, 0.9)	0.6 (0.3, 1.7)
25-Desacetyl-rifapentine (μg/mL)		
C4	4.3 (2.4, 7.8)	5.6 (3.7, 8.0)
C48	3.4 (2.6, 5.2)	4.3 (2.0, 6.8)
C72	0.4 (0.3, 0.7)	0.7 (0.3, 1.4)
Isoniazid (μg/mL)		
C4	2.3 (1.7, 3.4)	2.0 (1.2, 3.3)
Acetyl-isoniazid (μg/mL)		
C4	1.8 (1.6, 3.9)	2.2 (1.2, 3.6)

C4/48/72; concentration at 4/48/72 h after drug administration.
*Data are reported as the median (25% percentile, 75% percentile).

Rifamycin drugs are pivotal to anti-tuberculosis strategies, yet their effectiveness can vary significantly among individuals, thus, underscoring the critical need for drug concentration monitoring [23]. Our findings indicated a discernible trend: the blood concentrations of rifapentine and its metabolites tended to be lower in TB progressors compared to non-progressors, particularly 4 h after drug administration. However, no significant difference was observed in the levels of isoniazid and its metabolites between the two groups. Weight-based dosing adjustment of rifapentine is not currently recommended when treating LTBI [24]. $1H_3P_3$ maintains a standardized dosage regimen, which ensures therapeutic drug levels in patients with lower body weights, potentially improving treatment efficacy.

Our trial had several limitations. First, it was a single-arm cohort study without a contemporaneous control group. Instead, we used data from a previous study as an external control. The use of historical controls may introduce potential biases such as selection bias, temporal bias, and so on. Thus, we performed PSM to maximally reduce them. However, this study was not designed to establish differences from other groups, and the new regimen needs to be verified in large-scale, parallel controlled trials. Second, the study included only patients with silicosis. Given the high risk of TB in this population, it was more feasible to evaluate the effectiveness of the novel regimen among this population. Moving forward, we are conducting a large-scale randomized trial to confirm the efficacy of the novel $1H_3P_3$ regimen in other high-risk populations (TB-YOUTH study, ClinicalTrials.gov ID: NCT06022146).

In conclusion, the present study indicated that the $1H_3P_3$ regimen was a promising option for the preventive treatment of tuberculosis in high-risk populations of patients with silicosis.

Acknowledgements

We thank all of the subjects for participating in this study; Sanmen County Xiaoxiong Health Centre for study-site support, study enrolment, patient and education; and Sanmen People's Hospital for imaging diagnosis of Pulmonary CT.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the National Key Research and Development Program of China: [Grant Number 2024YFC2311201]; and the Guangzhou National Laboratory Project: [Grant Number GZNL2024A01030]; and the Key Technologies Research and Development Program for Infectious Diseases of China: [Grant Number 2017ZX10201302-004].

Access to data

Individual participant data that underlie the results reported in this article, the study protocol, and the statistical analysis plan are available to researchers who provide a methodologically sound proposal. Proposals should be directed to qlruan07@fudan.eud.cn. Data are available beginning 3 months and ending 3 years following article publication.

Author contributions

Qiao-ling Ruan, Qing-luan Yang, and Chun-lian Ma contributed to the design of the study, directed the field work and collection of the study data, analysis and interpretation of the data, co-writing of the first draft, and approval of the manuscript. Miao-yao Lin, Xi-tian Huang, Ya-pin Mao, Ji-mei Gao, Jin-ju Li, Xia-ning Zhang, Zhi-xiang You, Quan-qing Zheng, and Xue-feng Liu contributed to enrolling the participants, follow-up with participants, collection of data, analysis of the published data, and approval of the manuscript. Wen-hong Zhang and Ling-yun Shao contributed to the design of the study, supervised the field trial and collection of the data, analysis of the published data, and writing and approval of the manuscript. All authors read and approved the final manuscript.

References

[1] Shah M, Dorman SE. Latent tuberculosis infection. N Engl J Med. 2021;385:2271–2280. doi:10.1056/NEJMcp2108501

[2] Uplekar M, et al. WHO's new end TB strategy. Lancet. 2015;385:1799–1801. doi:10.1016/S0140-6736(15)60570-0

[3] World Health Organizaiton. Guidelines on the management of latent tuberculosis infection. (2015).

[4] World Health Organizaiton. Global tuberculosis report 2023. Geneva: World Health Organization; 2023; Licence: CC BY-NC-SA 3.0 IGO. (2023).

[5] Leung CC, Yu IT, Chen W. Silicosis. Lancet. 2012;379:2008–2018. doi:10.1016/S0140-6736(12)60235-9

[6] Yang Q, et al. Mycobacterium tuberculosis infection among 1,659 silicosis patients in zhejiang province, China. Microbiol Spectr. 2022;10:e0145122. doi:10.1128/spectrum.01451-22

[7] World Health Organization. WHO consolidated guidelines on tuberculosis: Module 1: Prevention – Tuberculosis preventive treatment, second edition. Geneva: WHO Guidelines Approved by the Guidelines Review Committee (2024).

[8] Alsdurf H, Hill PC, Matteelli A, et al. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. Lancet Infect Dis. 2016;16:1269–1278. doi:10.1016/S1473-3099(16)30216-X

[9] Pease C, et al. Efficacy and completion rates of rifapentine and isoniazid (3HP) compared to other treatment regimens for latent tuberculosis infection: a systematic

review with network meta-analyses. BMC Infect Dis. 2017;17:265–275. doi:10.1186/s12879-017-2377-x

[10] Gao L, 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. doi:10.1183/13993003.01470-2018

[11] Ruan QL, et al. Efficacy and safety of weekly rifapentine and isoniazid for tuberculosis prevention in Chinese silicosis patients: a randomized controlled trial. Clin Microb Infect Offic Publicat Eur Soc Clin Microbiol Infect Dis. 2021;27:576–582. doi:10.1016/j.cmi.2020.06.008

[12] Weiner M, et al. Tuberculosis Trials, Pharmacokinetics of rifapentine at 600, 900, and 1,200 mg during once-weekly tuberculosis therapy. Am J Respir Crit Care Med. 2004;169:1191e7.

[13] Sterling TR, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med. 2011;365:2155–2166.

[14] Ruan QL, et al. Novel thrice-weekly isoniazid plus rifapentine short-course regimen for the treatment of latent tuberculosis infection in a murine model. Infect Dis Immun. 2024;4:138–141. doi:10.1097/ID9.0000000000000121

[15] Sterling TR, et al. Flu-like and other systemic drug reactions Among persons receiving weekly rifapentine plus isoniazid or daily isoniazid for treatment of latent tuberculosis infection in the PREVENT tuberculosis study. Clin Infect Dis. 2015;61:527–535. doi:10.1093/cid/civ323

[16] Martinson NA, et al. New regimens to prevent tuberculosis in adults with HIV infection. N Engl J Med. 2011;365:11–20.

[17] Villarino ME, 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;169:247–255. doi:10.1001/jamapediatrics.2014.3158

[18] Winters N, et al. Completion, safety, and efficacy of tuberculosis preventive treatment regimens containing rifampicin or rifapentine: an individual patient data network meta-analysis. Lancet. Respirat Med. 2023;11:782–790. doi:10.1016/S2213-2600(23)00096-6

[19] Bhargava A. The 3 HP regimen for tuberculosis preventive treatment: safety, dosage and related concerns during its large-scale implementation in countries like India. Lancet Reg Health Southeast Asia. 2024;31:100422. doi:10.1016/j.lansea.2024.100422

[20] Melnychuk L, Perlman-Arrow S, Lisboa Bastos M, et al. A systematic review and meta-analysis of tuberculous preventative therapy adverse events. Clin Infect Dis. 2023;77:287–294. doi:10.1093/cid/ciad246

[21] Riska NV, Mattson K. Systemic reactions to intermittent rifampicin. Bull Int Union Tuberc. 1974;49(suppl 1):280–285.

[22] Grosset J, Leventis S. Adverse effects of rifampin. Rev Infect Dis. 1983;5(Suppl 3):S440–S450.

[23] Choi R, Jeong BH, Koh WJ, et al. Recommendations for optimizing tuberculosis treatment: therapeutic drug monitoring, pharmacogenetics, and nutritional status considerations. Ann Lab Med. 2017;37:97–107. doi:10.3343/alm.2017.37.2.97

[24] Hibma JE, et al. Rifapentine population pharmacokinetics and dosing recommendations for latent tuberculosis infection. Am J Respir Crit Care Med. 2020;202:866–877. doi:10.1164/rccm.201912-2489OC