Published in final edited form as:

Int J Tuberc Lung Dis. 2016 August ; 20(8): 1065–1071. doi:10.5588/ijtld.15.0908.

Rifampicin resistance after treatment for latent tuberculous infection: a systematic review and meta-analysis

S. den Boon^{*}, A. Matteelli[†], and H. Getahun[†]

^{*}Independent consultant, Geneva, Switzerland [†]The Global TB Programme, World Health Organization, Geneva, Switzerland

Summary

Setting—Treatment for latent tuberculous infection (LTBI) reduces the risk of tuberculosis (TB) disease. Shorter, rifamycin-containing regimens have been shown to be as effective as 6 months of isoniazid and superior with regard to safety and completion rate. It is unknown whether preventive therapy with rifamycins increases resistance to the drugs used.

Objective—To determine whether treatment for LTBI with rifamycin-containing regimens leads to significant development of resistance against rifamycins.

Design—Systematic review and meta-analysis.

Results—We included six randomised-controlled trials of rifamycin-containing regimens for LTBI treatment that reported drug resistance. There was no statistically significant increased risk of rifamycin resistance after LTBI treatment with rifamycin-containing regimens compared to non-rifamycin-containing regimens (RR 3.45, 95% CI 0.72–16.56; $P = 0.12$) or placebo (RR 0.20, 95% CI 0.02–1.66; $P = 0.13$).

Conclusion—Preventive treatment with rifamycin-containing regimens does not significantly increase rifamycin resistance. Programmatic management of LTBI requires the creation of sound surveillance systems to monitor drug resistance.

Keywords

chemoprophylaxis; prevention; rifamycin

TREATMENT of latent tuberculous infection (LTBI) reduces the risk of tuberculosis (TB) by preventing progression from latent infection to active disease. Shorter, rifamycin-containing regimens have been shown to be as effective as 6-month isoniazid (INH) containing regimens and superior in terms of safety and completion rate,¹ and are recommended by the World Health Organization (WHO).² A possible downside to LTBI treatment is that it may increase resistance to the drug used when there is a failure to exclude active TB disease prior to starting treatment. While no increased risk of resistance was

Correspondence to: Saskia den Boon, Rue de Bourgogne 20A, 1203 Geneva, Switzerland. saskiadenboon@hotmail.com.

Conflicts of interest: none declared.

reported for INH preventive therapy (IPT),^{3,4} no information is available for rifamycin-containing regimens.

The objective of this systematic review and meta-analysis was to determine whether treatment for LTBI with rifamycin-containing regimens leads to significant development of resistance against rifamycins.

Study Population and Methods

Our search and study selection strategy consisted of three steps. First, we searched for randomised-controlled trials (RCTs) evaluating LTBI treatment. We searched PubMed, EMBASE and the Web of Science using a combination of the following search terms: 'chemoprevention', 'preventive therapy', 'chemoprophylaxis', or 'treatment' AND 'latent tuberculosis', 'tuberculous infection' or 'latent TB infection'. We used filters to select RCTs and human studies. We also searched the Cochrane Central Register of Controlled Trials, WHO International Clinical Trials Registry Platform, International Standardised Randomised Controlled Trial Number Register, ClinicalTrials.gov, and abstracts from international conferences of the International Union Against Tuberculosis and Lung Disease, the International AIDS Society, the American Thoracic Society and the European Respiratory Society from 2010 to 2013. Reference lists of included papers and review articles were also searched. Studies indexed before 1 November 2015 were included and we did not restrict inclusion on language. Animal studies were excluded, as were studies conducted only in children. Second, we included only RCTs that compared TB incidence in persons receiving rifamycin-containing preventive treatment vs. those receiving preventive treatment not containing a rifamycin, placebo or no preventive therapy. Third, we selected studies that reported the results of drug susceptibility testing (DST) of positive cultures for both rifamycin and control groups.

Two reviewers (SDB, AM) independently carried out title, abstract and full-text screening. They then independently extracted all relevant data items using a data extraction form. Disagreements were discussed to obtain consensus. The Cochrane Collaboration tool for assessing bias was used to assess the risk of bias in individual studies.

The rate of resistant TB was determined separately for the intervention and the control groups by dividing the number of persons with resistant TB by the total number in that group as reported in the respective studies. We calculated pooled estimates for studies that were clinically and methodologically homogeneous, and calculated relative risk (RR) summary statistics with 95% confidence intervals (CIs).

Results

We reviewed a total of 63 full-text papers for inclusion and exclusion criteria. Six studies met the inclusion criteria (Table 1).^{5–10} Four studies reported on more than one rifamycin-containing preventive treatment regimen. All six studies contained comparisons between rifamycin-containing preventive treatment regimens and INH, and two studies also contained a comparison with placebo. Four studies were conducted in human immunodeficiency virus (HIV) infected populations, one study included both HIV-infected and non-HIV-infected

individuals, and, in one study of Chinese men with silicosis in Hong Kong, information on HIV status was not provided. Different intervention regimens were used, including intermittent regimens (Table 1).

The studies included were of moderate quality, and we rated the risk of bias as unclear. One of the six studies was a double-blind placebo-controlled trial,⁵ while the rest were open-label randomised trials, which may have resulted in selection bias. Randomisation methods and treatment allocation were only described in about half of the studies. Intervention and control groups were similar in all studies. Loss to follow-up was generally well reported, and varied from 12% to 34% (Table 1). All studies included reported the full resistance profile; however, we extracted only information regarding rifamycin resistance.

We discuss below each of the studies in greater detail, first addressing studies that evaluated daily regimens and then those that studied intermittent regimens. The Hong Kong study involved 679 older Chinese men with silicosis for whom HIV status was not reported.⁵ More than half were tuberculin skin test (TST) positive. The study reported on daily rifampicin (RMP) for 12 weeks, and daily RMP and INH for 12 weeks vs. daily placebo for 24 weeks. Two cases of RMP resistance were detected in the placebo group.⁵ Two large studies looked at daily regimens in HIV-positive, TST-positive individuals. The first was a large study of 2736 adults in Uganda that evaluated daily RMP and INH for 3 months, daily RMP, pyrazinamide (PZA) and INH for 3 months, and daily INH for 6 months as well as placebo.¹⁰ None of the regimens led to the development of RMP resistance. The second study, conducted among 1583 HIV-positive persons aged 13 years with a positive TST, compared daily INH for 12 months with daily RMP and PZA for 2 months. Three cases of RMP resistance were detected in the RMP and PZA group (two cases with multidrug-resistant TB [MDR-TB] and one with resistance to RMP and ethambutol) vs. 1 case in the INH group (MDR-TB).⁸

The remaining three studies looked at intermittent regimens, two of which were in exclusively HIV-infected populations. The first, a large study, included 7731 participants and compared once-weekly INH and rifapentine (RPT) for 3 months with INH for 9 months in high-risk individuals such as contacts and new TST convertors.⁷ Approximately 2.5% were HIV-positive. Among seven TB cases in the intervention arm, one case had RMP monoresistance; this occurred in an HIV-positive individual with a CD4 count of 273/mm³ who had treatment interruptions and completed therapy late. There were 15 TB cases in the control arm, none of whom had rifamycin resistance. The second study, conducted among 44 HIV-positive, TST-positive adults, compared two different dosages of twice-weekly rifabutin (RBT) and INH for 3 months with daily INH for 6 months; there were two TB cases in the INH control group, none of whom had resistance to RBT (one had INH resistance). There were no TB cases in the RBT group.⁹ The last was a South African study that included 1148 HIV-positive, TST-positive individuals with a median CD4 count of 448/mm³.⁶ This study compared daily INH for 6 months, continuous INH, twice-weekly RMP and INH for 12 weeks, and once-weekly RPT and INH for 12 weeks. One case of RMP monoresistance and one case of MDR-TB were detected in the once-weekly RPT group, whereas there were no resistant cases in the twice-weekly RMP or INH control groups.⁶

Overall, there were very few cases of rifamycin resistance, which limited our study power. There were a total of 6 (0.09%) cases in 6808 individuals receiving LTBI treatment with a rifamycin-containing drug and 1 (0.01%) case in the 7415 individuals in the control group that received LTBI treatment with an alternative regimen (RR = 3.45, 95% CI 0.72–16.56; $P = 0.12$) (Table 2). As regards LTBI treatment with intermittent regimens, there were three studies with three cases of rifamycin resistance in 4673 individuals on rifamycin-containing regimens, and 0 cases with rifamycin resistance in 4427 in control regimens (RR = 3.89, 95% CI 0.44–34.56; $P = 0.22$).

Two studies also included comparisons of a rifamycin-containing regimen with a placebo control arm—both studies involved daily regimens with RMP.^{5,10} Two comparisons were retrieved in each study, giving a total of four comparisons (Table 2). In the group receiving preventive treatment with a rifamycin-containing regimen, 0/1344 (0%) individuals had resistance against rifamycins compared to 4/1892 (0.2%) individuals in those who received placebo (RR = 0.20, 95% CI 0.02–1.66; $P = 0.13$).

Discussion

In this systematic review, we showed that preventive treatment with rifamycin-containing regimens does not significantly increase rifamycin resistance, although our study power was limited by the small number of cases with drug resistance. A previous systematic review and meta-analysis of the risk for resistant TB following IPT showed a slight and non-significant increase in the relative risk compared to placebo (RR = 1.45, 95% CI 0.85–2.47).³ Another study, evaluating DST in TB patients exposed to IPT in a high HIV prevalence setting, found that the prevalence of drug resistance was comparable to a control group of TB cases that had not been exposed to IPT.⁴ As far as we know, our study is the first to systematically investigate whether preventive treatment with rifamycins leads to an increase in resistance.

Programmatic management of LTBI in high-risk populations in low TB incidence countries has recently received renewed attention, and has emerged as a core element of the WHO End TB Strategy and TB elimination efforts in low-incidence countries.^{2,11,12} INH is the cornerstone of LTBI treatment; however, the long duration of treatment, low completion rates and risk of liver toxicity and adverse events argue for the adoption of alternative regimens.¹³ Short-course rifamycin-containing regimens (including weekly RPT+INH for 12 weeks, daily RMP+INH for 3 months or daily RMP for 4 months) have advantages in terms of safety and likelihood of treatment completion, and could be more widely acceptable.

The intervention regimens in the studies included in our review differed: some provided RMP (with or without INH) daily, while others prescribed RPT (+INH) weekly or RBT (+INH) twice weekly. RMP, RBT and RPT differ in their pharmacokinetic properties: RPT and RBT have a longer half-life and are therefore suitable for intermittent regimens.¹⁴ Three cases of rifamycin-resistant TB were reported among 4673 individuals receiving intermittent regimens. Two were in a South African study that only included HIV-positive individuals, and the other was an HIV-positive individual from a predominantly American study, in which a small minority of patients were HIV-positive. Although intermittent (once-weekly)

RPT regimens have been shown to be ineffective for the treatment of active TB in people living with HIV, and led to the emergence of rifamycin resistance,¹⁵ we believe that they can be safely used for LTBI treatment because the mycobacterial burden and the rate of replication are significantly lower compared to active disease.¹⁶ Three cases of RMP resistance were detected in the RMP and PZA arm of one study.⁸ PZA-containing regimens are no longer recommended for LTBI treatment due to high rates of toxicity.²

There are a number of practical considerations regarding the implementation of LTBI treatment and choice of regimen. These include the cost of treatment and interventions to enhance adherence and client-friendly services, as well as the monitoring of adverse events and establishing a surveillance system to monitor the development of drug resistance. The exclusion of active TB remains a mainstay of the algorithm for programmatic testing and treatment of LTBI.² Absence of all of current cough, fever, night sweats and weight loss indicates a very low probability of having TB disease among people living with HIV in HIV-prevalent settings.¹⁷ In low TB incidence settings, the presence of any symptom suggestive of TB (i.e., any one of cough, haemoptysis, fever, night sweats, weight loss, chest pain, shortness of breath and fatigue) plus any abnormality on chest radiography offered the highest sensitivity and negative predictive value in ruling out active TB.¹²

Conclusions

Preventive treatment with rifamycin-containing regimens did not significantly increase rifamycin resistance. However, the results of this study should be interpreted with caution, as the number of resistant cases that were found was very small, leading to wide CIs around the effect estimates. Future RCTs should report DST results for both intervention and control groups, for both adults and children, to add to the body of evidence. Finally, establishing surveillance systems to monitor drug resistance in areas where preventive therapy programmes are rolled out will be of great value.

Acknowledgements

The authors would like to thank H Stagg and I Aboubaker for their support in the literature search.

References

1. Getahun H, Matteelli A, Chaisson RE, Ravigliione M. Latent *Mycobacterium tuberculosis* infection. N Engl J Med. 2015; 372:2127–2135. [PubMed: 26017823]
2. World Health Organization. Guidelines on the management of latent tuberculosis infection. Geneva, Switzerland: WHO; 2015. WHO/HTM/TB/2015.01
3. Balcells ME, Thomas SL, Godfrey-Faussett P, Grant AD. Isoniazid preventive therapy and risk for resistant tuberculosis. Emerg Infect Dis. 2006; 12:744–751. [PubMed: 16704830]
4. Van Halsema CL, Fielding KI, Chihota VN, et al. Tuberculosis outcomes and drug susceptibility in individuals exposed to isoniazid preventive therapy in a high HIV prevalence setting. AIDS. 2010; 24:1051–1055. [PubMed: 20299958]
5. Hong Kong Chest Service; Tuberculosis Research Centre, Madras; British Medical Research Council. A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. Am Rev Respir Dis. 1992; 145:36–41. [PubMed: 1731596]

6. Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J Med*. 2011; 365:11–20. [PubMed: 21732833]
7. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med*. 2011; 365:2155–2166.
8. Gordin F, Chaisson RE, Matts JP, et al. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons. An international randomized trial. *JAMA*. 2000; 283:1445–1450. [PubMed: 10732934]
9. Matteelli A, Olliaro P, Signorini L, et al. Tolerability of twice-weekly rifabutin-isoniazid combinations versus daily isoniazid for latent tuberculosis in HIV-infected subjects: a pilot study. *Int J Tuberc Lung Dis*. 1999; 3:1043–1046. [PubMed: 10587327]
10. Johnson JL, Okwera A, Hom DL, et al. Duration of efficacy of treatment of latent tuberculosis infection in HIV-infected adults. *AIDS*. 2001; 15:2137–2147. [PubMed: 11684933]
11. Uplekar M, Weil D, Lönnroth K, et al. WHO's new end TB strategy. *Lancet*. 2015; 385:1799–1801. [PubMed: 25814376]
12. Getahun H, Matteelli A, Abubakar I, et al. Management of latent *Mycobacterium tuberculosis* infection: WHO guidelines for low tuberculosis burden countries. *Eur Respir J*. 2015; 46:1563–1576. [PubMed: 26405286]
13. Getahun H, Granich R, Sculier D, et al. Implementation of isoniazid preventive therapy for people living with HIV worldwide: barriers and solutions. *AIDS*. 2010; 24(Suppl 5):S57–S65. [PubMed: 21079430]
14. Dooley K, Flexner C, Hackman J, et al. Repeated administration of high-dose intermittent rifapentine reduces rifapentine and moxifloxacin plasma concentrations. *Antimicrob Agents Chemother*. 2008; 52:4037–4042. [PubMed: 18765687]
15. Vernon A, Burman W, Benator D, Khan A, Bozeman L. Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. *Tuberculosis Trials Consortium. Lancet*. 1999; 353:1843. [PubMed: 10359410]
16. Young DB, Gideon HP, Wilkinson RJ. Eliminating latent tuberculosis. *Trends Microbiol*. 2009; 17:183–188. [PubMed: 19375916]
17. Getahun H, Kittikraisak W, Heilig CM, et al. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. *PLOS Med*. 2011; 8:e1000391. [PubMed: 21267059]

Table 1

Study characteristics for comparison of rifamycin resistance in those receiving a rifamycin-containing preventive regimen vs. those receiving a regimen without rifamycin*

Author, location, year, reference	Study description/design	Population	Intervention	Control	Follow-up	Description of participants
BMRC, Hong Kong, 1981–1987 ⁵	Double-blind placebo-controlled trial	Chinese men aged <65 years with silicosis	RMP 600 mg daily for 12 weeks, then placebo daily for 12 weeks (3R) RMP 600 mg + INH 300 mg daily for 12 weeks, then placebo daily for 12 weeks (3HR)	Placebo daily for 24 weeks	2 sputum specimens at 12 and 24 weeks and every 3 months from 9 months up to 5 years; postero-anterior CXR before starting regimen and then at weeks 8 and 24, months 9 and 12, and every 6 months thereafter	All males; majority (76%) between 45 and 64 years, 63% were current smokers and 10% had never smoked; 56% had a TST 15 mm
Johnson, Uganda, 1993–1995 ¹⁰	Randomised, placebo-controlled clinical trial	Age 18–50 years, HIV-positive, TST 5 mm or anergy (no induration)	RMP 600 mg + INH 300 mg daily for 3 months (3HR) RMP 600 mg + INH 300 mg + PZA 2 g daily for 3 months (3HRZ)	INH 300 mg daily for 6 months (6H) Placebo daily for 6 months	Monthly during study treatment and every 3 months thereafter; total follow-up was 4064 py; placebo 1557 py; 6H 1694 py; 3HR 1151 py; 3HRZ 800 py	The proportion of male subjects varied from 29% in the 3HR group to 34% in the 3HRZ group; mean age 29 or 30 years in all groups; PPD skin test on average 13 or 14 mm, except for the placebo and the 6H groups, for which patients with anergy were also included
Gordin, US, Mexico, Haiti, Brazil, 1991–1996 ⁸	Open-label, randomised controlled trial	13 years, HIV+, TST 5 mm	RMP 600 mg (or 450 mg for those weighing <50 kg) + PZA 20 mg/kg daily for 2 months	INH 300 mg + pyridoxine hydrochloride 50 mg daily for 12 months	Study visits scheduled at months 1, 2, 3, 6, 9, 12 and every 6 months thereafter; mean duration of follow-up was 37.2 months in the RMP + PZA group and 36.8 months in the INH group	29.2% females in the RMP+PZA group and 27.8% in the INH group; mean age 36.9 years in the RMP+PZA group and 37.7 in the INH group; TST 10 mm: 45% in the RMP+PZA group and 46% in the INH group; median CD4 count: $454 \times 10^6 / l$ in the RMP+PZA group and $427 \times 10^6 / l$ in the INH group
Sterling, US, Canada, Brazil, Spain, 2001–2008 ⁷	Open-label randomised non-inferiority trial	Age 12 years and close contact of a TST+, culture-confirmed TB patient, or conversion to TST+, or HIV + with TST+ or close contact, or	RPT 900 mg (with incremental adjustment for subjects weighing < 50 kg) + INH 15–25 mg/kg body weight (rounded up to the nearest 50 mg with a maximum of 900	INH 5–15 mg/kg body weight (rounded up to the nearest 50 mg with a maximum of 300 mg) daily for 9 months	For 33 months after enrolment and evaluated monthly during treatment; 10 327 patient-years of follow-up in the combination-therapy group and 9619 patient-years in the INH-only group in the modified	Males 55.4% in the RPT+INH group and 53.5% in the INH group; median age 36 years (IQR 25–47) in the RPT+INH group and 35 years (IQR 25–46) in the INH group; HIV infection: 2.6% in the RPT+INH group and 2.7% in the INH group

Author, location, year, reference	Study description/design	Population	Intervention	Control	Follow-up	Description of participants
		TST+ with fibrotic changes on CXR consistent with previously untreated TB	mg) once weekly for 3 months		intention-to-treat population	
Matteelli, Italy, 19949	Open-label, randomised comparative trial	Age 18 years, HIV- positive, TST 5 mm	RBT 300 mg + INH 750 mg twice weekly for 3 months RBT 600 mg + INH 750 mg twice weekly for 3 months	INH 300 mg daily for 6 months	Mean follow-up after end of treatment 18 months for the 300 mg RBT group, 19 months for the 600 mg RBT group, and 17 months for the control group; 9 subjects in all three groups had a follow-up of at least 24 months	Mean age 31.5 years in the two intervention groups and 34 years in the control group; CD4 cell counts averaged 500/mm ³ in all three groups
Martinson, South Africa, 2002–20056	Open-label randomised superiority trial	HIV-infected adults (18 years) with TST 5 mm diameter	RPT 900 mg + INH 900 mg weekly for 12 weeks RMP 600 mg + INH 900 mg twice weekly for 12 weeks	INH 300 mg daily for 6 months	Median follow-up 4.0 years in the RPT +INH group, 4.1 years in the RMP +INH group, and 3.9 years in the 6H group	Females 84.5% in the RPT+INH group, 81.2% in the RMP+INH group and 83.5% in the INH group; median age 30.3 years (IQR 26.3–35) in the RPT +NH group, 30.5 (IQR 27.0–34.3) in the RMP+INH group and 30.4 (IQR 26.3–34.9) in the INH group; median TST 14.5 mm (IQR 12–19) in the RPT +INH group, 15.0 (IQR 12–19) in the RMP+INH group and 15 (IQR 11–18) in the INH group

* Numbers before the letters indicate the duration in months of the phase of treatment.

BMRC = British Medical Research Council; RMP, R = rifampicin; INH, H = isoniazid; CXR = chest X-ray; TST = tuberculin skin test; HIV = human immunodeficiency virus; PZA, Z = pyrazinamide; py = person-years; PPD = purified protein derivative; += positive; RPT = rifapentine; IQR = interquartile range; RBT = rifabutin.

Table 2

Resistance to rifamycin: comparing rifamycin-containing regimens with non-rifamycin-containing regimens or placebo

Author, reference	Rifamycin-containing regimen	Control	Enrolled		Culture-positive TB/total TB		Resistant to a rifamycin/total underwent DST	
			Rifamycin	Control	Rifamycin	Control	Rifamycin	Control
Daily rifamycin-containing regimens								
BMRC5	RMP 600 mg daily for 12 weeks, then placebo daily for 12 weeks	INH 300 mg daily for 24 weeks	165	167	16/20	19/25	0/15	0/19
BMRC5	RMP 600 mg + INH 300 mg daily for 12 weeks, then placebo daily for 12 weeks	INH 300 mg daily for 24 weeks	161	167	22/26	19/25	0/21	0/19
Johnson10	RMP 600 mg + INH 300 mg daily for 3 months	INH 300 mg daily for 6 months	556	931	17/22	36/51	0/NR	0/20
Johnson10	RMP 600 mg + INH 300 mg + PZA 2 g daily for 3 months	INH 300 mg daily for 6 months	462	931	9/15	36/51	0/NR	0/20
Gordin8	RMP 600 mg [‡] + PZA 20 mg/kg daily for 2 months	INH 300 mg + pyridoxine hydrochloride 50 mg daily for 12 months	791	792	19/28	26/29	3/19	1/24
Intermittent rifamycin-containing regimens								
Sterling7	RPT 900 mg [*] + INH 15–25 mg/kg body weight [‡] once weekly for 3 months	INH 5–15 mg/kg body weight [§] daily for 9 months	3986	3745	NR/7	NR/15	1/NR	0/NR
Matteelli9	RBT 300 mg + INH 750 mg twice weekly for 3 months	INH 300 mg daily for 6 months	16	14	0/0	2/2	0/0	0/2
Matteelli9	RBT 600 mg + INH 750 mg twice weekly for 3 months	INH 300 mg daily for 6 months	14	14	0/0	2/2	0/0	0/2
Martinson6	RMP 600 mg + INH 900 mg twice weekly for 12 weeks	INH 300 mg daily for 6 months	329	327	18/24	18/22	0/16	0/16
Martinson6	RPT 900 mg + INH 900 mg weekly for 12 weeks	INH 300 mg daily for 6 months	328	327	21/24	18/22	2/21	0/16
Placebo-controlled trials								
BMRC5	RMP 600 mg daily for 12 weeks, then placebo daily for 12 weeks (3R)	Placebo daily for 24 weeks	165	159	16/20	29/36	0/15	2/28
BMRC5	RMP 600 mg + INH 300 mg daily for 12 weeks, then placebo daily for 12 weeks	Placebo daily for 24 weeks	161	159	22/26	29/36	0/21	2/28
Johnson10	RMP 600 mg + INH 300 mg daily for 3 months	Placebo: ascorbic acid 250 mg daily for 6 months	556	787	17/22	46/64	0/NR	0/24
Johnson10	RMP 600 mg + INH 300 mg + PZA 2 g daily for 3 months	Placebo: ascorbic acid	462	787	9/15	46/64	0/NR	0/24

Author, reference	Rifamycin-containing regimen	Control	Enrolled		Culture-positive TB/total TB		Resistant to a rifamycin/total underwent DST	
			Rifamycin	Control	Rifamycin	Control	Rifamycin	Control
		250 mg daily for 6 months						

* With incremental adjustment for subjects with >50 kg body weight.

[†] Rounded to the nearest 50 mg, with a maximum of 900 mg.

[‡] Or 450 mg for those weighing <50 kg.

[§] Rounded to the nearest 50 mg, with a maximum of 300 mg.

TB = tuberculosis; DST = drug susceptibility testing; BMRC = British Medical Research Council; RMP, R = rifampicin; INH, H = isoniazid; NR = not recorded; PZA = pyrazinamide; RPT = rifapentine; RBT = rifabutin.