Short-Course Therapy with Rifampin plus Isoniazid, Compared with Standard Therapy with Isoniazid, for Latent Tuberculosis Infection: A Meta-analysis

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Background. A major difficulty associated with the use of standard therapy with isoniazid for latent tuberculosis infection is poor patient adherence to therapy because of the prolonged course required. Shorter courses of therapy involving ≥2 drugs have been proposed as an alternative to standard therapy, but they have not undergone enough testing.

Methods. We performed a meta-analysis to determine the equivalence of daily short-course therapy with rifampin plus isoniazid for 3 months and standard therapy with isoniazid for 6–12 months. The end points that were evaluated were development of active tuberculosis, severe adverse drug reactions, and death. We searched published information in the Cochrane Library, MEDLINE, and Embase databases, as well as unpublished information in the Cambridge Scientific Abstracts Internet database, Conference Papers Index, AIDS and Cancer Research Abstracts, and ClinicalTrials.gov. We also scanned the reference lists of articles. We only included trials in which individuals were randomly allocated to receive treatment. Two reviewers independently applied the criteria for trial selection, assessed trial quality, and extracted data.

Results. Five trials comprising 1926 adults from Hong Kong, Spain, and Uganda were identified. The mean duration of follow-up varied from 13 to 37 months. Overall, development of active tuberculosis was equivalent in association with both regimens (pooled risk difference, 0%; 95% confidence interval [CI], −1% to 2%; percentage of total variation across the studies that is the result of heterogeneity rather than chance [I^2], 0%; $P = .86$). Severe adverse effects were reported with a similar frequency for both regimens (pooled risk difference, −1%; 95% CI, −7% to 5%) but with statistically significant heterogeneity detected (I^2, 78%; $P = .001$). However, a subanalysis of high-quality trials (including 74% of the sample size) suggested that both regimens were equally safe. In 3 trials (comprising 1390 patients) that provided data on mortality, the regimens showed equivalence (pooled risk difference, −1%; 95% CI, −4% to 2%; I^2, 2.7%; $P = .38$).

Conclusion. Short-course therapy with rifampin plus isoniazid was equivalent to standard therapy with isoniazid in terms of efficacy, the proportion of severe side effects that occurred, and mortality.

The rationale behind prevention of tuberculosis disease is to eradicate latent infection before active disease develops. Currently, treatment is recommended for patients with suspected infection (as determined by a positive result of a tuberculin skin test) and for patients with a high risk of developing active disease [1].

Previous clinical trials have shown that isoniazid substantially reduces the incidence of active tuberculosis [2].

Therapy with isoniazid for 6–12 months has been proposed as the standard regimen for treatment of latent tuberculosis infection, in spite of the high rate of poor adherence associated with the regimen's prolonged course. Thus, shorter courses of treatment have been proposed. A 2-month regimen of pyrazinamide and rifampin has been found to result in a substantial rate of severe hepatic injury and death [3, 4]. In 1998, the British Thoracic Society recommended a 3-month regimen of rifampin plus isoniazid as an alternative short-course therapy for latent infection, although the recommendation was based on very limited information [5].

We conducted a comprehensive search of the literature and performed a meta-analysis of randomized controlled trials that compared a 3-month regimen of rifampin plus isoniazid with a regimen of isoniazid giv-

en for ≥6 months as prophylaxis for latent tuberculosis infection. We specifically investigated whether these 2 regimens were equally effective in preventing tuberculosis and death, and whether the proportions of severe side effects associated with the 2 regimens were equivalent.

METHODS

Criteria for the selection of trials for review. We included only randomized controlled trials that compared a 3-month regimen of daily therapy with rifampin plus isoniazid with a 6–12-month regimen of daily standard therapy with isoniazid for latent tuberculosis infection. "Latent tuberculosis infection" was defined as infection with *Mycobacterium tuberculosis* (as determined by a positive PPD skin test result) in a person who has no symptoms of active tuberculosis and whose infection is not contagious. PPD skin test reactions were interpreted according to the sensitivity and specificity of the tuberculin skin test used and the prevalence of tuberculosis in the different patient groups. To be eligible for review, trials had to include a human population with latent tuberculosis infection, an intervention involving random allocation of participants to receive either daily treatment with rifampin plus isoniazid or daily treatment with isoniazid, and the following outcomes: (1) frequency of active tuberculosis, which was defined either microbiologically (preferably by culture) or histologically, or as a clinical syndrome consisting of typical symptoms (as assessed by chest radiography and documented by response to treatment), (2) frequency of serious adverse drug reactions requiring cessation of the study drug, and/or (3) death. For HIV-infected patients or otherwise immunocompromised patients, anergy testing has been used to assist in guiding the treatment of individuals in countries where the prevalence of tuberculosis is high [1].

Search strategy. We searched published information in MEDLINE (January 1966 to June 2004), Embase (up to June 2004), and the Cochrane Controlled Trial Register (Cochrane Library 2004, issue 2). In addition, we searched for unpublished information (up to June 2004) in the following databases: Conference Papers Index (the Cambridge Scientific Abstracts Internet database), AIDS and Cancer Research Abstracts, and ClinicalTrials.gov. The search strategy is depicted in figure 1. We scanned the reference lists of all relevant articles to ensure that all completed trials had been identified.

Review procedure. Two reviewers (J.E. and V.V.) considered trials for inclusion in the analysis, and data were collated and checked by both reviewers and were abstracted in a pretested, predefined form. Discrepancies were resolved by consensus. The quality of each trial included in the present analysis was graded by use of a validated score that includes the following items [6]: randomization of participants, double-blind evaluation, and a full description of participants who withdrew from or dropped out of the trial. The scoring gives 1 point for each item present. If randomization is concealed and the method of double-blind evaluation (e.g., use of identical placebo, active placebo, or dummy) is appropriate, the study is assigned 1 additional point, thus yielding a score of 0–5 points.

Statistical analysis. We used the κ statistic to measure the chance-corrected agreement between the 2 independent reviewers with regard to trial inclusion and quality assessment [7]. Treatment effects were summarized as risk differences with 95% CIs, and they were pooled using the DerSimonian and Laird random-effects model [8]. Risk difference values of zero denoted no difference for the outcome. Analysis was performed according to the intention-to-treat principle. To demonstrate equivalence between regimens, the 95% CI of the risk difference should be within −5% to 5%. These values were selected on the basis of the recommendations of the limits of equivalence proposed by the European Agency for the Evaluation of Medicinal Products [9]. The heterogeneity of treatment effects between studies was investigated using the Cochran Q test (a χ^2 test for heterogeneity) and I^2 statistics. "I^2" denotes the percentage of total variation across the studies that is the result of heterogeneity rather than chance (an I^2 value of 0% denotes no observed heterogeneity, and greater I^2 values denote increasing heterogeneity) [10]. The subgroup analysis planned to explore possible sources of heterogeneity, including HIV status, duration of treatment, and trial quality. We assessed for the presence of publication bias by use of a funnel plot [11]. All analyses were performed using RevMan software, version 4.2 (The Cochrane Collaboration).

RESULTS

Trials included in the analysis. The present analysis is based on 5 randomized controlled trials that comprised 1926 adult participants [12–16] (figure 1). The agreement between the 2 reviewers showed that $\kappa = 1$ for inclusion of trials and that $\kappa = 0.79$ for the 5 methodological aspects considered. The quality of 2 of the trials [12, 16] was rated as 5 points (the highest score), and the quality of the 3 remaining trials was rated as 2 points [13–15]. Table 1 provides information about the characteristics of the trials included in the analysis. In each of the trials, the prognosis variables were equally distributed between groups at the beginning of the trial.

Three trials included subjects with HIV infection ($n = 1390$), and 2 trials included patients without HIV infection or patients who had not been tested for HIV infection ($n = 536$). Two trials used isoniazid regimens of >6 months' duration; the 3 remaining trials used regimens of 6 months' duration. Adherence to treatment was reported in 4 of 5 trials, and it was reported as being equal or greater among patients receiving short-course treatment with rifampin plus isoniazid than among patients receiving standard therapy with isoniazid. One
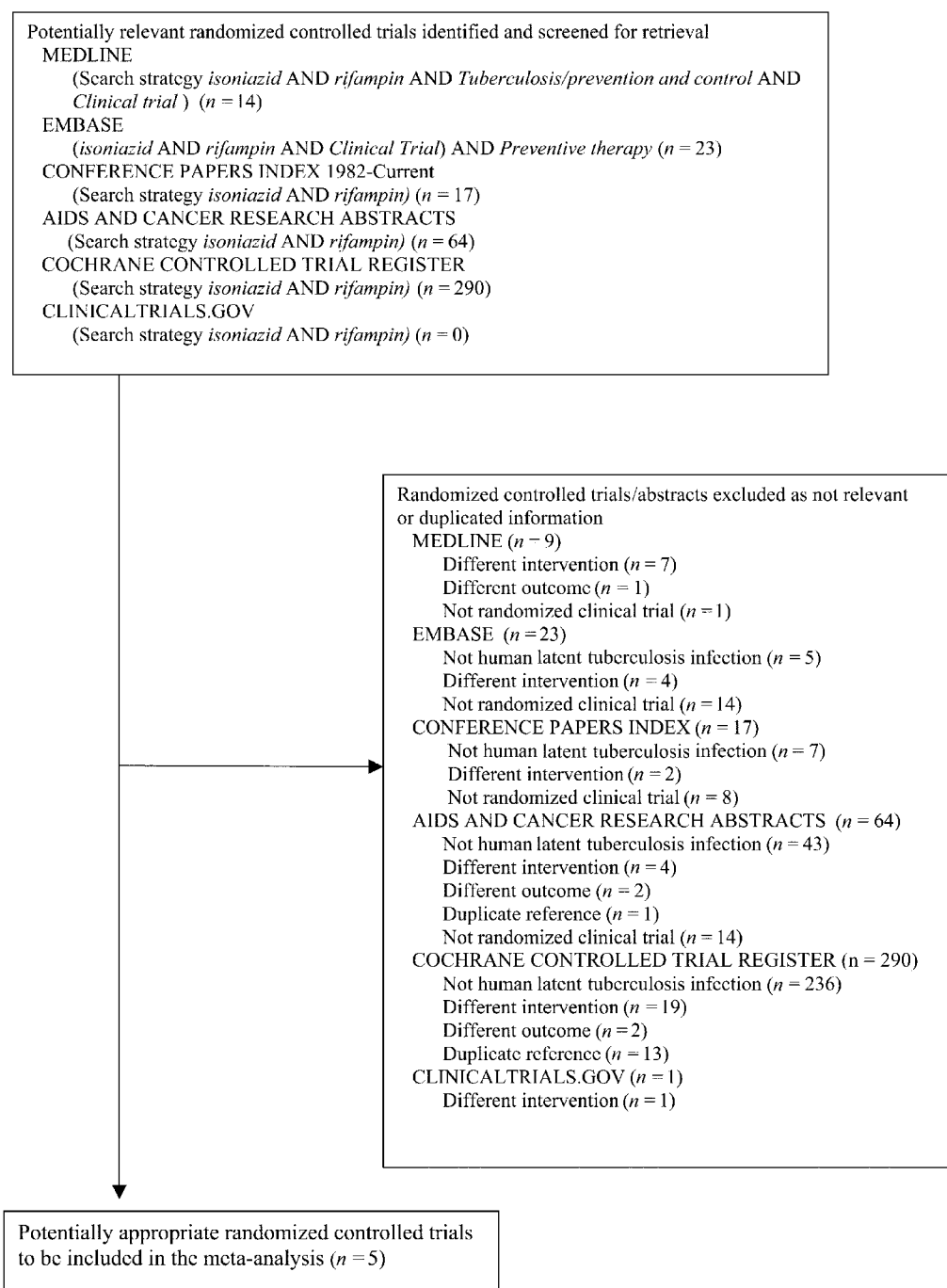
Potentially relevant randomized controlled trials identified and screened for retrieval
  MEDLINE
      (Search strategy *isoniazid* AND *rifampin* AND *Tuberculosis/prevention and control* AND
      Clinical trial) (*n* = 14)
  EMBASE
      (*isoniazid* AND *rifampin* AND *Clinical Trial*) AND *Preventive therapy* (*n* = 23)
  CONFERENCE PAPERS INDEX 1982-Current
      (Search strategy *isoniazid* AND *rifampin*) (*n* = 17)
  AIDS AND CANCER RESEARCH ABSTRACTS
      (Search strategy *isoniazid* AND *rifampin*) (*n* = 64)
  COCHRANE CONTROLLED TRIAL REGISTER
      (Search strategy *isoniazid* AND *rifampin*) (*n* = 290)
  CLINICALTRIALS.GOV
      (Search strategy *isoniazid* AND *rifampin*) (*n* = 0)

Randomized controlled trials/abstracts excluded as not relevant
or duplicated information
    MEDLINE (*n* − 9)
        Different intervention (*n* = 7)
        Different outcome (*n* = 1)
        Not randomized clinical trial (*n* = 1)
    EMBASE (*n* = 23)
        Not human latent tuberculosis infection (*n* = 5)
        Different intervention (*n* = 4)
        Not randomized clinical trial (*n* = 14)
    CONFERENCE PAPERS INDEX (*n* = 17)
        Not human latent tuberculosis infection (*n* = 7)
        Different intervention (*n* = 2)
        Not randomized clinical trial (*n* = 8)
    AIDS AND CANCER RESEARCH ABSTRACTS (*n* = 64)
        Not human latent tuberculosis infection (*n* = 43)
        Different intervention (*n* = 4)
        Different outcome (*n* = 2)
        Duplicate reference (*n* = 1)
        Not randomized clinical trial (*n* = 14)
    COCHRANE CONTROLLED TRIAL REGISTER (n = 290)
        Not human latent tuberculosis infection (*n* = 236)
        Different intervention (*n* = 19)
        Different outcome (*n* = 2)
        Duplicate reference (*n* = 13)
    CLINICALTRIALS.GOV (*n* = 1)
        Different intervention (*n* = 1)

Potentially appropriate randomized controlled trials
to be included in the meta-analysis (*n* = 5)

Figure 1. Results of the search for trials for inclusion in the present analysis, as well as reasons for exclusion of trials from analysis

trial was conducted in Uganda, 1 in Hong Kong, and 3 in Spain (table 1).

The present analysis included 972 patients treated with rifampin and isoniazid and 954 patients treated with isoniazid. The mean duration of follow-up varied from 13 to 36.51 months. Funnel plot analysis failed to suggest significant publication bias.

Incidence of tuberculosis. A total of 41 patients (4.2%) who

received therapy with rifampin plus isoniazid developed tuberculosis, compared with 39 patients (4.1%) who received standard therapy with isoniazid. Overall, the frequency of tuberculosis was equivalent among patients receiving each regimen (pooled risk difference, 0%; 95% CI, −1% to 2%) (figure 2). The result of the test for heterogeneity among trials was not statistically significant (I^2, 0%; $P = .83$).

Side effects requiring drug withdrawal. A total of 48 pa-

Table 1. Characteristics of randomized controlled trials that included comparisons of short-course therapy with rifampin (Rif) plus isoniazid (INH) with standard therapy with INH for the treatment of latent tuberculosis.

Trial (country) [reference]	Trial quality score[a]	Trial participants	PPD skin test and/or anergy testing result	Patient adherence rate, %			Participants who completed the trial, by regimen received			Intervention	Mean follow-up, months	Outcome
				Rif + INH	INH	Overall	Rif + INH, %	INH, %	All, n/N (%)[b]			
Hong Kong Chest Service (China) [12]	5	Patients with silicosis who did not undergo HIV testing	Induration of ≥10 mm (86% of patients)	76	73	NA	66	67	227/340 (67)	Rif (600 mg) plus INH (300 mg) daily for 3 months, compared with INH (300 mg) daily for 6 months	36.5	Development of active tuberculosis (culture confirmed for 84% of patients); severe side effects; death
Martinez-Alfaro et al. (Spain) [13]	2	HIV-negative patients or patients who did not undergo HIV testing	Induration of ≥5 mm (tuberculosis contacts; 85% of patients); ≥10 mm (with risk factors; 10% of patients), or ≥15 mm (without risk factors; 5% of patients)	63	57	NA	97	89	196/196 (100)	Rif (600 mg) plus INH (300 mg) daily for 3 months, compared with INH (300 mg) daily plus vitamin B₆ (50 mg) for 9 months	16	Development of active tuberculosis (culture confirmed for 100% of patients); severe side effects; death
Martinez-Alfaro et al. (Spain) [14]	2	HIV-infected patients	Induration of ≥5 mm (35% of patients); anergy (7 antigens not specified; 65% of patients)	97	89	NA	80	75	124/133 (93)	Rif (600 mg) plus INH (300 mg) daily for 3 months, compared with INH (300 mg) daily plus vitamin B₆ (50 mg) for 12 months	17	Development of active tuberculosis (culture confirmed for unknown percentage of patients); severe side effects
Rivero et al. (Spain) [15]	2	HIV-infected patients	Anergy (skin induration of 0 mm) for tuberculin, Candida albicans antigen, and parotiditis antigen testing	69	65	NA	73	82	134/165 (81)	Rif (600 mg) plus INH (300 mg) daily for 3 months, compared with INH (300 mg) daily for 6 months	13	Development of active tuberculosis (culture confirmed for 100% of patients); severe side effects; death
Whalen et al. (Uganda) [16]	5	HIV-infected patients	Included only patients with induration of ≥5 mm (100% of patients)	NA	NA	75	86	88	950/1092 (87)	Rif (600 mg) plus INH (300 mg) daily for 3 months, compared with INH (300 mg) daily for 6 months	15	Development of active tuberculosis (culture confirmed for 50% of patients); severe side effects; death

NOTE. PPD, protein purified derivative.

[a] As defined by Jadad et al. [6].

[b] No. of participants who completed the trial/total no. of participants in the trial (% of total participants who completed the trial).
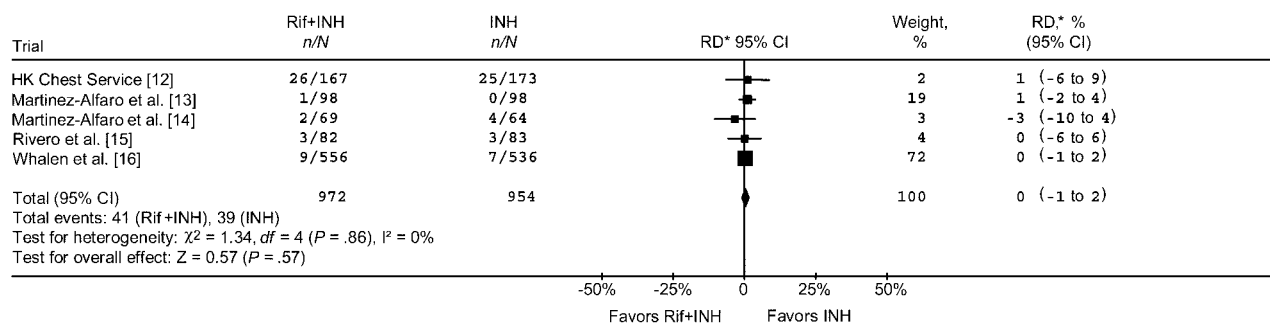
Trial	Rif+INH n/N	INH n/N	RD* 95% CI	Weight, %	RD,* % (95% CI)
HK Chest Service [12]	26/167	25/173		2	1 (−6 to 9)
Martinez-Alfaro et al. [13]	1/98	0/98		19	1 (−2 to 4)
Martinez-Alfaro et al. [14]	2/69	4/64		3	−3 (−10 to 4)
Rivero et al. [15]	3/82	3/83		4	0 (−6 to 6)
Whalen et al. [16]	9/556	7/536		72	0 (−1 to 2)
Total (95% CI)	972	954		100	0 (−1 to 2)

Total events: 41 (Rif+INH), 39 (INH)
Test for heterogeneity: $\chi^2 = 1.34$, $df = 4$ ($P = .86$), $I^2 = 0\%$
Test for overall effect: $Z = 0.57$ ($P = .57$)

-50% -25% 0 25% 50%
Favors Rif+INH   Favors INH

Figure 2. Pooled risk difference (RD) for development of active tuberculosis. HK, Hong Kong; I^2, percentage of total variation across the studies that is the result of heterogeneity rather than chance; INH, isoniazid; n/N, total no. of trial participants who developed tuberculosis/total no. of trial participants who received the regimen specified; Rif, rifampin; weight, contribution of the study to the overall result. *, RDs pooled using a random-effects model.

tients (4.9%) who received rifampin plus isoniazid required drug withdrawal because of severe side effects, compared with 46 patients (4.8%) who received standard therapy with isoniazid. Table 2 shows the proportion of side effects associated with required drug discontinuation among the trials. Although some trials provided a detailed description of the type and severity of side effects that resulted in drug discontinuation [13–15], it was difficult to gather such information from the remaining trials [12, 16]. Drug-related mortality was not among the side effects.

The summary estimate pooling all side effects requiring drug withdrawal indicated a trend toward an increased risk associated with the regimen of rifampin plus isoniazid, compared with the standard regimen of isoniazid (pooled risk difference, −1%; 95% CI, −7% to 5%) (figure 3A). Because the 95% CIs were greater than the prespecified margin of equivalence, it was not possible to conclude that both regimens were equally safe. Nevertheless, there was statistically significant heterogeneity among the trials (I^2, 78.1%; $P = .001$). To assess the source of heterogeneity, we performed 3 predefined subanalyses that compared (1) HIV-positive patients with HIV-negative patients or patients who had not undergone HIV testing, (2) standard therapy with isoniazid for 6 months versus >6 months, and (3) high-quality trials versus trials of moderate to low quality. The quality of the trials proved to be the source of heterogeneity.

In high-quality trials (74% of the sample size) and in trials in which assessors were blinded to outcome [12, 16], both regimens proved to be equally safe (pooled risk difference, 2%; 95% CI, 1%–3%; I^2, 0%; $P = .54$) (figure 3B). However, in trials of low to moderate quality [13–15], statistically significant heterogeneity remained (pooled risk difference, −2%; 95% CI, −16% to 12%; I^2, 82.9%; $P = .003$).

Mortality. Three trials (comprising 1390 patients) provided data on mortality. A total of 67 patients (9.5%) who received therapy with rifampin plus isoniazid died, compared with 71 patients (10.4%) who received standard therapy with isoniazid. The pooled risk difference for death was −1% (95% CI, −4% to 2%. There was no statistically significant heterogeneity among the trials (I^2, 2.7%; $P = .36$) (figure 4).
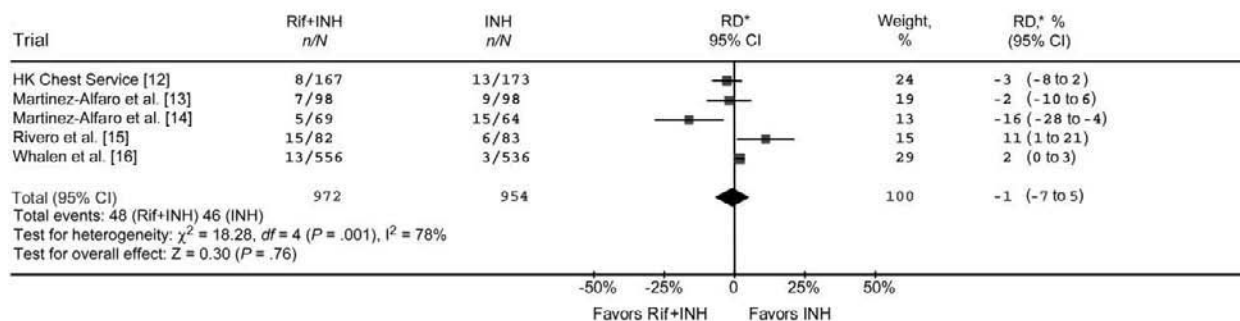
DISCUSSION

The present meta-analysis shows that a 3-month regimen of rifampin plus isoniazid and a standard 6–12-month regimen of isoniazid were equivalent in terms of effectiveness and safety. Although there was significant heterogeneity among the trials with regard to the outcome of severe adverse drug reactions, a subanalysis that included only high-quality studies in which assessors were blinded to outcome showed that both regimens were equally safe.

Table 2. Severe side effects requiring drug discontinuation, according to therapy received.

Trial [reference]	Hepatotoxicity		Rash		Gastrointestinal intolerance		Other		Not specified		Total	
	Rif + INH	INH	Rif + INH	INH	Rif + INH	INH	Rif + INH	INH	Rif + INH	INH	Rif + INH	INH
Hong Kong Chest Service [12]	...	...	...	...	...	...	...	...	8 (5)	13 (8)	8 (5)	13 (8)
Martinez-Alfaro et al. [13]	6 (6)	8 (8)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	7 (10)	9 (13)
Martinez-Alfaro et al. [14]	4 (6)	11 (18)	...	...	...	...	...	...	1 (1)	4 (6)	5 (7)	15 (24)
Rivero et al. [15]	1 (1)	4 (5)	7 (8)	1 (1)	5 (6)	1 (1)	2 (2)	0 (0)	0 (0)	0 (0)	15 (18)	6 (7)
Whalen et al. [16]	...	...	...	...	...	...	...	...	13 (2)	3 (1)	13 (2)	3 (1)

NOTE. Data are the no. (%) of patients who required drug discontinuation because of a severe side effect. INH, isoniazid; Rif, rifampin.

A Overall results

Trial	Rif+INH n/N	INH n/N	RD* 95% CI	Weight, %	RD,* % (95% CI)
HK Chest Service [12]	8/167	13/173		24	−3 (−8 to 2)
Martinez-Alfaro et al. [13]	7/98	9/98		19	−2 (−10 to 6)
Martinez-Alfaro et al. [14]	5/69	15/64		13	−16 (−28 to −4)
Rivero et al. [15]	15/82	6/83		15	11 (1 to 21)
Whalen et al. [16]	13/556	3/536		29	2 (0 to 3)
Total (95% CI)	972	954		100	−1 (−7 to 5)

Total events: 48 (Rif+INH) 46 (INH)
Test for heterogeneity: $\chi^2 = 18.28$, $df = 4$ ($P = .001$), $I^2 = 78\%$
Test for overall effect: $Z = 0.30$ ($P = .76$)

-50% -25% 0 25% 50%
Favors Rif+INH Favors INH

B Results of high-quality trials

Trial	Rif+INH n/N	INH n/N	RD* 95% CI	Weight, %	RD,* % (95% CI)
HK Chest Service [12]	8/167	13/173		39	−3 (−8 to 2)
Whalen et al. [16]	13/556	3/536		61	2 (0 to 3)
Total (95% CI)	723	709		100	0 (−5 to 5)

Total events: 21 (Rif+INH) 16 (INH)
Test for heterogeneity: $\chi^2 = 3.97$, $df = 1$ ($P = .05$), $I^2 = 74.8\%$
Test for overall effect: $Z = 0.01$ ($P = 1.00$)

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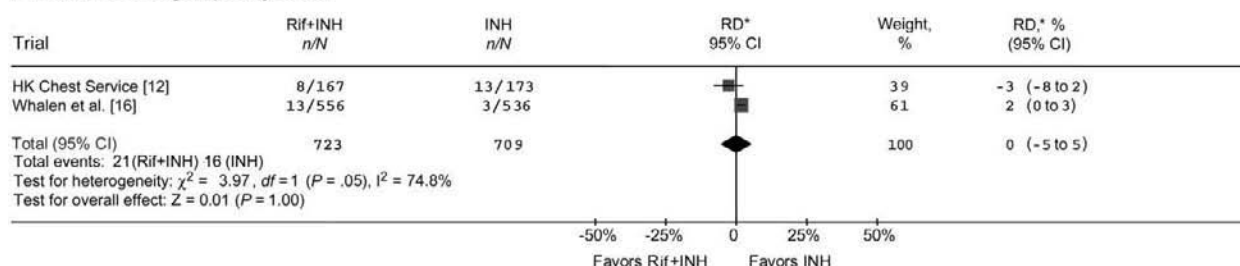Favors Rif+INH Favors INH

Figure 3. Pooled risk difference (RD) for development of severe adverse effects. HK, Hong Kong; I^2, percentage of total variation across the studies that is the result of heterogeneity rather than chance; INH, isoniazid; n/N, total no. of trial participants who developed severe adverse effects and required drug discontinuation/total no. of trial participants who received the regimen specified; Rif, rifampin; weight, contribution of the study to the overall result. *, RDs pooled using a random-effects model.

The strengths of the present analysis include its explicit inclusion and exclusion criteria (limiting eligible studies to randomized trials), a comprehensive literature search, and a sample size large enough to detect clinically meaningful differences. The sample size, which was estimated under the assumption of an average efficacy of isoniazid of 60% [17, 18] and an 80% power to detect a difference of ≤5% in the outcomes evaluated between the standard regimen of isoniazid and the multiple-drug regimen, required at least 749 subjects in each group.

However, there are some limitations associated with the results of the present analysis, as well as their interpretation. The quality of the trials varied considerably, which could lead to

bias [19]. There was only 1 randomized trial that specified concealed randomization, and there were only 2 trials in which assessors were blinded to the outcomes. However, these differences in quality were identified as a cause for heterogeneity among trials only with regard to the outcome for severe side effects. That the mean duration of follow-up also varied throughout the trials (from 13 to 36.51 months) could explain the higher rates of tuberculosis observed in the study from Hong Kong [12]. There were also differences in the percentages of patients lost to follow-up, although this percentage was <20% in 4 of 5 trials (1586 patients). In addition, trials reported that the rate of adherence to either drug regimen was equal or
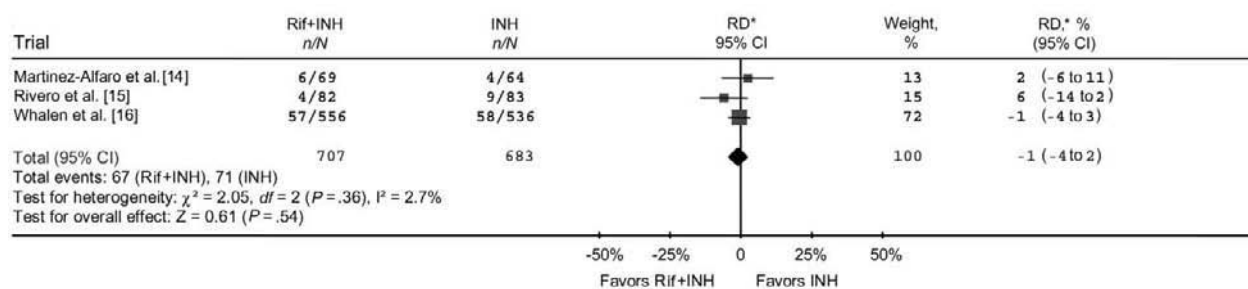
Trial	Rif+INH n/N	INH n/N	RD* 95% CI	Weight, %	RD,* % (95% CI)
Martinez-Alfaro et al. [14]	6/69	4/64		13	2 (−6 to 11)
Rivero et al. [15]	4/82	9/83		15	6 (−14 to 2)
Whalen et al. [16]	57/556	58/536		72	−1 (−4 to 3)
Total (95% CI)	707	683		100	−1 (−4 to 2)

Total events: 67 (Rif+INH), 71 (INH)
Test for heterogeneity: $\chi^2 = 2.05$, $df = 2$ ($P = .36$), $I^2 = 2.7\%$
Test for overall effect: $Z = 0.61$ ($P = .54$)

-50% -25% 0 25% 50%
Favors Rif+INH Favors INH

Figure 4. Pooled risk difference (RD) for death. HK, Hong Kong; I^2, percentage of total variation across the studies that is the result of heterogeneity rather than chance; INH, isoniazid; INH, isoniazid; n/N, total no. of trial participants who died/total no. of trial participants who received the regimen specified; Rif, rifampin; weight, contribution of the study to the overall result. *, RDs pooled using a random-effects model.

greater among patients receiving short-course therapy than among patients receiving standard therapy. Only a very small proportion of patients had negative results of tuberculin skin tests (not anergy); therefore, it was not possible to perform a subanalysis to evaluate the efficacy of these regimens as prophylaxis instead of treatment for latent tuberculosis infection. In spite of these shortcomings, there is enough burden of evidence to assume the equivalence of both regimens.

The choice of which regimen to implement in clinical practice will likely depend on anticipated adherence, cost, availability of drugs, and prevalence of drug resistance in the population. In addition to an equivalent effectiveness, compared with standard isoniazid therapy, short-course regimens of rifampin plus isoniazid could provide a priori greater adherence, equivalent cost (because of the reduced number of clinical and liver monitoring tests required), and good access to therapy (because of the existence of commercialized coformulations).

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