MAJOR ARTICLE

4 Months of Rifampin Compared with 9 Months of Isoniazid for the Management of Latent Tuberculosis Infection: A Meta-analysis and Cost-Effectiveness Study That Focuses on Compliance and Liver Toxicity

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Background. One-third of the world's population is infected with tuberculosis, and 9 months of isoniazid monotherapy is the treatment of choice for latent tuberculosis infection. However, this approach has been associated with hepatotoxicity and poor compliance. A shorter (4-month) rifampin regimen has been evaluated in recent clinical trials.

Methods. We performed a meta-analysis of the published studies to compare compliance, toxicity, and cost-effectiveness between the 2 strategies. Pooled effects were calculated as risk ratios (RRs) by means of random-effects and fixed-effects models.

Results. Pooled data from 3586 patients suggested that 4-month rifampin therapy was associated with a significant reduction in the risk of noncompletion (RR for random-effects model, 0.53; 95% confidence interval [CI], 0.44–0.63). Noncompletion rates were lower among patients who received 4-month rifampin therapy (range, 8.6%–28.4%), compared with noncompletion rates among patients who received 9-month isoniazid therapy (range, 24.1%–47.4%). Also, rates of hepatotoxicity (defined as grade 3 or 4 liver failure leading to drug discontinuation) were lower for patients who received 4-month rifampin therapy (range, 0%–0.7%), compared with the corresponding rates for patients who received 9-month isoniazid therapy (range, 1.4%–5.2%), and rifampin was associated with significant reduction in the risk of hepatotoxicity (RR for fixed-effects model, 0.12; 95% CI, 0.05–0.30). Notably, with the data from our meta-analysis, we calculated that the 4-month rifampin strategy is also cost-effective and results in $213 savings per patient treated ($90/patient when doctor fees are not included).

Conclusions. The improved compliance, safety, and cost associated with the 4-month rifampin therapy suggest that the efficacy of this approach needs to be evaluated in detail. An extended posttreatment follow-up in future studies will clarify the unresolved issue of tuberculosis reactivation rates.

One-third of the world's population is infected with tuberculosis [1], and the lifetime cumulative risk for active tuberculosis is >10% [2]. For >40 years isoniazid (INH) has been the treatment of choice for latent tuberculosis infection (LTBI). However, this agent is associated with a number of shortcomings. Specifically, the need for a lengthy period of daily administration has been associated with low compliance [3], and the potential of liver toxicity profile [4] and the increasing resistance rates undermine the effectiveness of this approach [5]. A shorter (4-month) course of rifampin (RIF) has been evaluated as a viable alternative to INH in LTBI, given its low toxicity and high efficacy profile [6–8]. We conducted a pooled meta-analysis of published clinical trials to compare the efficacy, toxicity, and cost of the 4-month RIF treatment (4-RIF) with the standard 9-month INH strategy (9-INH).

METHODS

Studies eligible for inclusion were studies comparing 4-RIF with 9-INH for the treatment of LTBI (9-INH is the control group, because it is considered the standard

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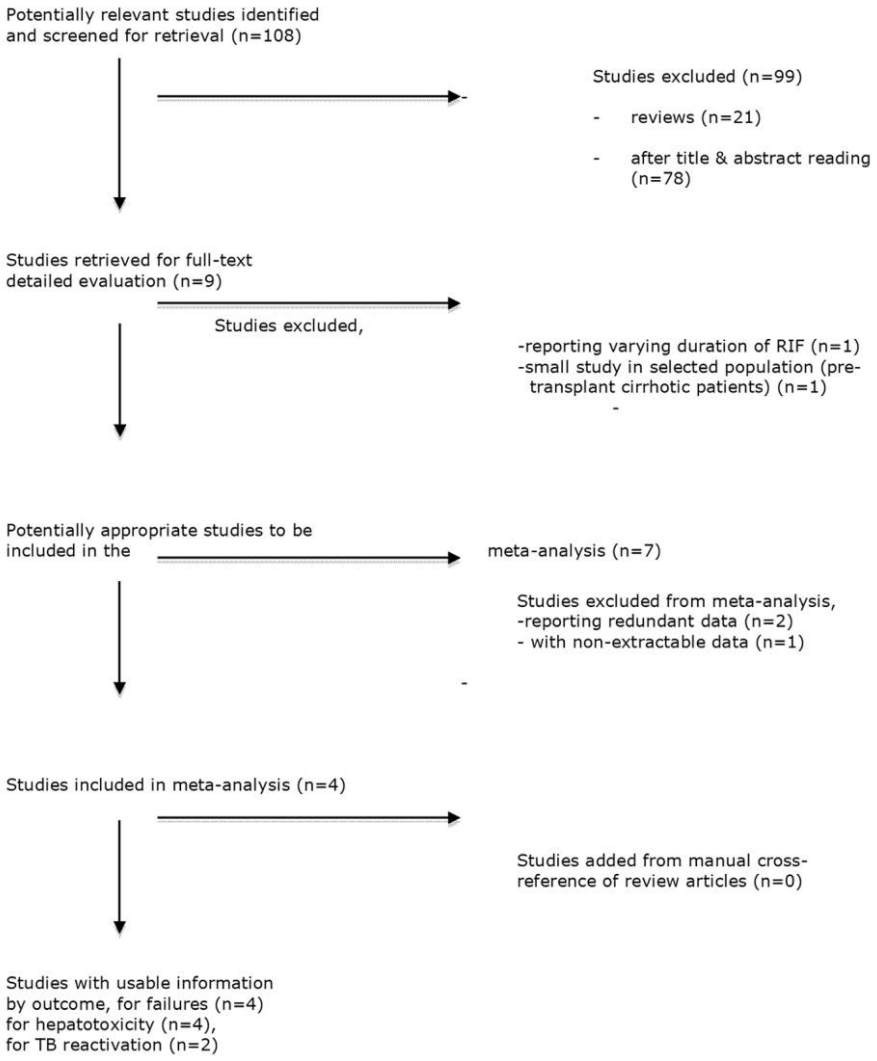

Figure 1. Flow chart of the study selection process.

regimen). Our main outcome measures were noncompletion rates (percentage of patients not completing each treatment arm), hepatotoxicity (defined as percentage of patients meeting criteria for grade 3 or 4 liver failure [9] leading to study drug discontinuation), and failures (defined as percentage of patients reactivating tuberculosis).

MEDLINE searches were conducted using "rifampin," "isoniazid," "latent," and "tuberculosis" as search terms and included studies published up to July 2009. We independently performed the literature review and assessed all potentially relevant publications. The reference lists of included studies and reviews were searched for additional studies. Data were extracted, and any emerging discrepancies were resolved by consensus of the authors.

We calculated the risk ratio (RR) for each outcome by means of the pooled effect of each therapy, in accordance with the Mantel-Haenszel method for fixed effects [10] and the DerSimonian and Laird method for random effects [11, 12]. Statistical heterogeneity was measured using the I^2 statistic. Random-effects pooling was used when there was a possibility of heterogeneity ($I^2 > 0$), and fixed-effects pooling was used when there was no evidence to suggest heterogeneity ($I^2 = 0$). The use of random-effects pooling in the calculation of confidence intervals (CIs) results in wider intervals and thus a more conservative estimate of effects. Whenever heterogeneity was limited, a fixed-effects model appeared more appropriate [13, 14]. RevMan5 module (Nordic Cochrane Centre) was used for data analysis.

The mean cost (C), the effectiveness (E) expressed as a percentage of patients completing treatment, and the cost-effectiveness ratio (C/E) for each strategy were calculated using the meta-analysis data and the costs for drugs, doctor fees, and laboratory tests adapted to guidelines for managing tuberculosis infection [15]. Costs for drugs were estimated after consultation

Table 1. Characteristics of Studies Included in Meta-analysis of Management of Latent Tuberculosis Infection

Type of study	Location	No. of patients receiving daily dose	
		Of RIF (10 mg/kg)[a]	Of INH (5 mg/kg)[b]
Single-center, historical [16]	Chest clinic, central New Jersey	261	213
Single-center, randomized, open label [17]	Canadian University Respiratory Hospital, Montreal, Canada	58	58
Single center, retrospective [18]	Prince George's County Health Department, Maryland	1412	843
Multicenter, randomized, open label [19]	9 centers (7 in Canada, 1 in Saudi Arabia, and 1 in Brazil)	420	427

NOTE. INH, isoniazid; RIF, rifampin.

[a] Maximum, 600 mg.

[b] Maximum, 300 mg.

with the Massachusetts General Hospital pharmacy (Petra M. Khoury, oral communication, July 2009) and include the current hospital price for both INH and RIF (assuming a daily dose of 300 mg and 600 mg, respectively). Costs for laboratory tests were also based on nosocomial prices (Linda J. Ardisson, oral communication, July 2009).

RESULTS

The initial Medline search resulted in 108 potentially relevant publications. Twenty-one review articles were initially excluded. Seventy-eight studies were excluded on the basis of relevance after title and abstract reading. Nine publications remained for detailed full-text evaluation. After full-text reading by both authors, 5 publications were eliminated (2 reported redundant data, 1 reported a varying duration of RIF treatment, 1 included a preselected population [only cirrhotic patients], and 1 had nonextractable data). Four articles [16–19] were ultimately included in the analysis. The review articles added no further studies. The study was performed in accordance with the Quality of Reporting of Meta-analyses (QUOROM) statement [20], and the study selection process is presented in the flow chart (Figure 1). The studies included in the systematic review are summarized in Table 1. Two studies [17, 19] were randomized clinical trials. The remaining studies [16, 18] retrospectively assessed the 2 treatment strategies. With regard to using the raw data from the 2 nonrandomized studies, pooling of data from different sources was valid because the 2 studies contained patients with similar diagnosis, clinical severity, treatment, and outcomes. Results were unidirectional; that is, in all studies, calculated treatment effects were in favor of the 4-RIF strategy with regard to fewer serious adverse events and better compliance.

Noncompletion rates in the RIF arm ranged from 8.6% to 28.4%, whereas noncompletion rates ranged from 24.1% to 47.4% in the INH arm. Among 2118 patients in the 4-RIF arm and 1468 patients in the 9-INH arm, the pooled effect of RIF was protective under the random-effects model (RR, 0.53; 95% CI, 0.44–0.63) with moderate statistical heterogeneity ($I^2 =$ 54%), that is, with moderate quantitative difference of calculated effects between studies (Figure 2A). On clinical grounds, patients in the 4-RIF arm have half the risk of not completing treatment course that patients in the 9-INH arm have.

Hepatotoxicity rates ranged from 0% to 0.7% in the 4-RIF arm and from 1.4% to 5.2% in the 9-INH arm. Regarding hepatotoxicity, the pooled effect of 4-RIF was also protective under the fixed-effects model (RR, 0.12; 95% CI, 0.05–0.30), with no evidence of statistical heterogeneity between studies (Figure 2B), that is, with no quantitative difference of estimated treatment effects between studies. Importantly, there was limited information regarding tuberculosis reactivation in the included studies.

As discussed below, one of the major findings of this report is the need for studies that compare the rates of tuberculosis reactivation between the 2 strategies. Page et al [18] did address the issue of treatment failures by reviewing medical records and tuberculosis case registries for Maryland and Washington, DC, from 1999 to mid-2005, a time frame that overlapped with patient enrollment. The study reported 1 case of active tuberculosis in the RIF arm, compared with none among patients who received 9-INH (the patient developed tuberculosis lymphadenopathy 1 year after the end of treatment with RIF, and the relapse was not associated with immune suppression or reinfection) [18]. Lardizabal et al [16] reported 1 tuberculosis case in the 9-INH group that occurred during treatment with INH and resulted in cessation of therapy for LTBI. Notably, in the studies by Menzies et al [17, 19], primary and secondary outcomes included on-time treatment completion and frequency of adverse events within the time limits defined by the treatment protocols.

The mean costs for each strategy were calculated according to costs presented (Table 2). For simplicity, we used these basic assumptions: (1) patients have a full clinical and laboratory evaluation at first visit and for a total of 7 visits in the 9-INH and 4 visits in the 4-RIF if they complete therapy [17], (2) hepatotoxicity results in early withdrawal that occurs at first trimester [17], (3) withdrawals due to poor compliance occur on average in the middle of treatment [18], and (4) there is

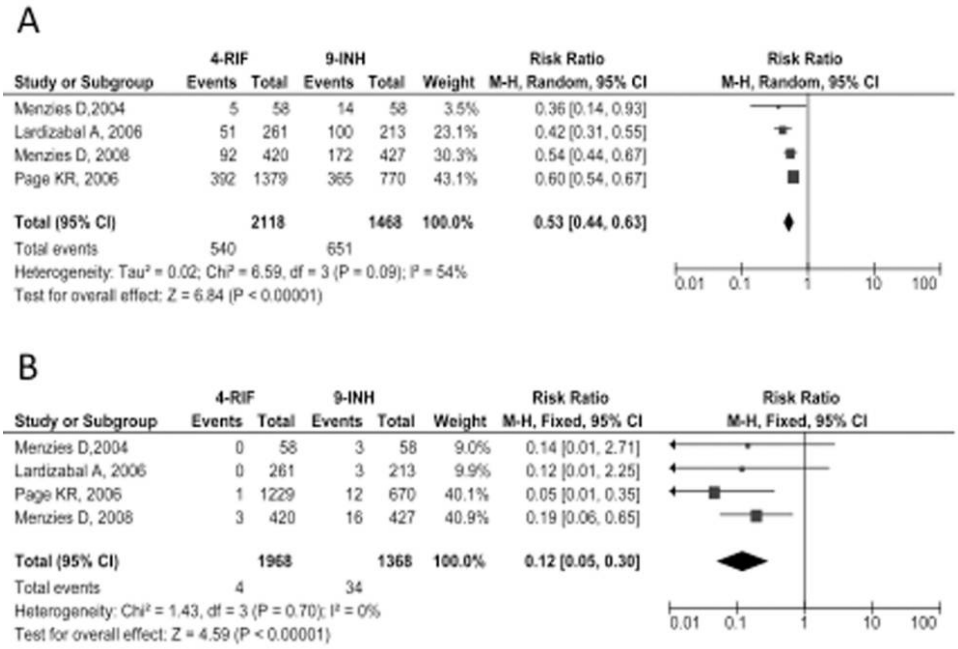

Figure 2. *A,* Forest plot of included studies presenting the pooled effect (calculated as risk ratios [RRs]) of 4-month rifampin therapy (4-RIF) on noncompletion of therapy for latent tuberculosis infection. Data were drawn from 3586 patients, and the standard 9-month isoniazid therapy (9-INH) group was the control. Cumulative data suggest that 4-RIF reduced the risk of failures by half, compared with the risk of failures with 9-INH. *B,* Forest plot of included studies presenting the pooled effect (RR) of 4-RIF on hepatotoxicity. Data were drawn from 3336 patients, and the 9-INH group was the control. Cumulative data suggest that the 4-RIF strategy results in an 8-fold decrease in the risk of hepatotoxicity, compared with the risk of hepatotoxicity with 9-INH.

no cross-over between treatment arms. The RIF strategy appears cost-effective regardless of charges for expert consultation, because calculated costs vary proportionally between the 2 arms for any change in expert fees.

Cost-effectiveness analysis revealed the 4-RIF strategy is optimal for both mean cost and compliance with a saving of $213 per patient treated including doctor fees, with an incremental C/E of −$24 (Table 3). One-way sensitivity analysis for noncompletion rates reported in this analysis for each treatment arm always favored the 4-RIF strategy, and threshold values were not reached. Specifically for the 4-RIF arm (with 8.6% to 28.4% of patients not completing therapy), the mean cost per patient treated ranged from $1125 to $1258. In the INH arm (with 24.1% to 47.4% of patients not completing therapy), the mean cost per patient treated ranged from $1271 to $1431. All calculations were based on a presumed cost of $50 per visit for consultation and follow-up, which is a moderate estimate. In the article by Menzies et al [17], specialist consultation in 2004 ranged from $19 to $94 for each visit.

If no fees are included, RIF was again better, with a saving of $90 per patient treated, with an incremental C/E of −$10 (Table 3). Specifically for the 4-RIF arm, the mean cost per patient treated ranged from $954 to $1067. In the INH arm, the mean cost per patient treated ranged from $993 to $1118. Importantly, threshold analysis reveals that the 4-month strategy will remain the least expensive strategy provided that RIF cost remains below $127 monthly. In addition, the decision in favor of 4-RIF remains unchanged provided that laboratory costs remain >80% of the baseline value.

DISCUSSION

In this study, we performed a meta-analysis of the published controlled trials that compare a shorter-course RIF therapy to the standard 9-INH approach for LTBI. Interestingly, we found that the shorter-course RIF therapy was associated with better compliance rates and lower risk for discontinuation (RR, 0.53; 95% CI, 0.44–0.63). In addition, the pooled effect of these 4 trials suggested significant reduction in hepatotoxicity when using the RIF regimen (RR, 0.12; 95% CI, 0.05–0.30). These effects are large enough to support the use of 4-RIF, because hepatotoxicity rates appear negligible and compliance rates are significantly higher. Moreover, our study suggests that the cost of the 4-RIF approach appears to be significantly lower, although the current studies do not allow conclusive evaluation of posttreatment failures due to tuberculosis reactivation. Villarino et al [6] reported no case of tuberculosis reactivation during the 2 years of a study among 157 patients who were exposed to INH-resistant *Mycobacterium tuberculosis* and who received RIF for 6 months. However, with the exception of the

Table 2. Estimated Costs per Person for Each Different Scenario of Treatment Completion or Failure

Scenario	% of patients	Doctor and/or nurse practitioner fees ($50)	Laboratory tests[a] ($177)	Monthly cost of RIF ($101.40)	Monthly cost of INH ($1.50)
Treatment completed					
4-RIF arm	74.5	× 4	× 4	× 4	…
9-INH arm	65.5	× 7	× 7	…	× 9
Treatment failed					
Because of poor compliance					
4-RIF arm	25.3[b]	× 2	× 2	× 2	…
9-INH arm	32.0[b]	× 4	× 4	…	× 4.5
Because of hepatotoxicity					
4-RIF arm	0.2	× 3	× 3	× 3	
9-INH arm	2.5	× 3	× 3	…	× 3

Note. We expected a mean of 2 visits plus tests for 4-month rifampin therapy (4-RIF) vs 4 visits plus tests for 9-month isoniazid therapy (9-INH) in case of poor compliance. We expected a mean of 3 visits plus tests for 4-RIF vs 3 visits plus tests for 9-INH in case of hepatotoxicity.

[a] Laboratory tests include complete blood counts ($53), aspartate transaminase level ($42), alanine transaminase level ($42), and bilirubin level (total, $40), with prices based on those of Massachusetts General Hospital (Linda J. Ardisson, oral communication, July 2009).

[b] The percentage of patients with poor compliance was calculated as the total percentage with failed treatment minus the percentage with hepatotoxicity.

study by Page et al [18], all studies included in our analysis lack a prospective or retrospective evaluation of tuberculosis reactivation rates after completion of therapy for LTBI. The limited, albeit promising, results emphasize the lack of data regarding efficacy of the 4-month monotherapy. Exact calculation of tuberculosis reactivation is not feasible in the absence of prolonged posttreatment follow-up.

From 1993 to 2006, the number of tuberculosis cases in the United States decreased by 45%, and by 2006 the number of cases of tuberculosis in the United States reached historic lows [21, 22]. The success in reducing the tuberculosis burden reflects several factors, including the current health policies that outline the treatment of individuals with LTBI. However, the efficacy of the standard treatment for LTBI entails the daily use of INH for 9 months and is associated with decreased compliance [16–19]. In addition to compliance, liver toxicity remains a major concern linked to INH therapy. INH preventive therapy for LTBI has been debated because of the risk of hepatotoxicity. The frequency of hepatotoxicity is 0.5% to 2.0%, and increases with age and abnormal liver enzymes at baseline, and decreases with frequent monitoring [23–25]. Short-course regimens have higher completion rates than longer INH regimens [26], and there is a need for a short-course, single-agent, nontoxic strategy for LTBI. The need to maximize compliance and minimize treatment discontinuation is particularly significant in certain populations, such as individuals with limited access to health care facilities and prison inmates.

Another shorter regimen (2 months RIF plus pyrazinamide) was previously recommended on the basis of published evidence [27, 28]. However, subsequent reports of severe and fatal

Table 3. Baseline Cost-Benefit Cost-Effectiveness Analysis With and Without Doctor Fees for Patients with Latent Tuberculosis Infection

Strategy	Cost, $	Effectiveness, % of patients completing therapy	Incremental cost per patient, $	Incremental effectiveness, % of patients	Incremental C/E, $[a]
Doctor and/or nurse practitioner fees included					
9-INH	1359.50	65.5			
4-RIF	1146.80	74.5	−212.70	9	−23.60
Doctor and/or nurse practitioner fees not included					
9-INH	1062.50	65.5			
4-RIF	972.20	74.5	−90.30	9	−10.00

Note. C/E, cost-effectiveness ratio; 4-RIF, 4-month rifampin therapy; 9-INH, 9-month INH therapy.

[a] In dollars per 1-unit gain in effectiveness.

hepatotoxicity [29, 30] have rendered this regimen unacceptable for most patients [31]. The 4-RIF strategy may provide a more appropriate balance between shorter course and toxicity. Notably, there are studies that report more detailed data on the incidence of liver failure associated with 4-RIF therapy. These studies did not include a control population that received 9-INH treatment and thus were not included in our analysis; however, they provide useful data on toxicity. For example, Fountain et al [32] reported 4 cases of hepatotoxicity among 205 patients with evaluable data (1.95%; 95% CI, 0%-4.33%). Hepatotoxicity occurred in none of the 49 patients reported by Polesky et al [7], in 1 (0.6%) of 157 adolescents who received 6 months of RIF in the study by Villarino et al [6], and in 3 (0.4%) of the 749 patients reported by Haley et al [8]. Finally, none of the 5 patients who were receiving 4-RIF had elevations in liver enzymes in a small trial among compensated cirrhotic patients (asymptomatic patients with no stigmata of end-stage liver disease) during the transplant candidacy period [33]. Importantly, no deaths related to hepatoxicity were reported, and all published trials suggest that this risk is very low.

Notably, the hepatic toxicity of RIF is dose related and has been observed mainly in patients with underlying liver disease [34]. Moreover, it should be noted that we did not include in the analysis the rare hematologic complications of immune-mediated thrombocytopenia or anemia related to RIF, because the clinical implication of hematologic changes is unclear and in the latest controlled trial [19] no patient exhibited clinical manifestations of changes in hematologic variables.

Our cost-effectiveness analysis demonstrated that the 4-RIF strategy is superior to 9-INH in terms of mean cost per patient treated, with savings of $213 per patient treated ($90 if medical fees are not included). The higher cost of the RIF diminishes when we take into account the shorter duration and the lack of hepatotoxicity that result in less frequent monitoring and laboratory evaluation. Practically, assuming a very low cost for INH, the 4-RIF strategy will remain the optimal choice unless RIF cost markedly increases or full laboratory evaluation is omitted. Our cost analysis complements previous reports that also studied the cost associated with the different options available for the management of LTBI [17, 35–37]. Among the studies included in our meta-analysis, the study by Menzies et al [17] also found a higher cost associated with 9-INH therapy, compared with the cost associated with the 4-RIF approach, whereas INH was cost saving compared with a shorter combination regimen that included 2-month RIF plus pyrazinamide therapy [36]. Moreover, Holland et al [37] found that the 4-RIF approach was associated with significant life-long cost savings. Notably, the study by Holland et al [37] is not a meta-analysis but a cost-effectiveness analysis that is based on estimated effects; data on tuberculosis reactivation for RIF treatment were assumed or interpolated, and by design the study was unable to provide any information on compliance and hepatotoxicity. The meta-analysis approach allowed us to evaluate the significantly better completion rates, the lower hepatotoxicity rates, and the consistently lower cost per treated patient that are associated with the RIF therapy. Recently, Young et al [35] reported that 4-RIF is associated with higher completion rates (91.3% vs 77.2% for 9-INH) and less hepatotoxicity, yet this study reported a higher total cost, with the monthly cost of INH being $2 versus $41 for RIF [35] and medical fees at $57 per visit. The lower mean cost of INH is largely attributed to the absence of a periodical full laboratory evaluation, other than alanine transaminase monitoring. However, this study was not included in this meta-analysis because it did not provide the raw data and it excluded early withdrawals (<1 month) from the analysis.

In conclusion, study effects and pooled effects are unidirectional toward the superiority of the 4-RIF regimen in the treatment of LTBI, in terms of both safety and compliance. Given the lack of solid evidence on tuberculosis reactivation rates in this arm, 9-INH therapy remains the standard of care. However, a large trial is warranted to define the risk of tuberculosis reactivation among persons who received 4-RIF treatment. The low cost and short duration of 4-RIF therapy may make this approach especially attractive for patients in areas with high incidence of INH resistance [38, 39], those with limited access to health care, and special populations, such as jail inmates.

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