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Isoniazid for the Prevention of Tuberculosis in HIV-Infected Children: A Systematic Review and Meta-Analysis

Jaykaran Charan, MD¹, Jagdish Prasad Goyal, MD², Tea Reljic, BS, MPH³, Patricia Emmanuel, MD⁴, Atul Patel, MD⁵, and Ambuj Kumar, MD, MPH³

¹Department of Pharmacology, All Indian Institute of Medical Sciences, Jodhpur, Rajasthan, India

²Department of Pediatrics, All Indian Institute of Medical Science, Rishikesh, Uttarakhand, India

³USF Health Program for Comparative Effectiveness Research, Morsani College of Medicine, University of South Florida, Tampa, FL, USA

⁴Department of Pediatrics, Morsani College of Medicine, University of South Florida, Tampa, FL, USA

⁵Vedanta Institute of Medical Sciences, Ahmedabad, Gujarat, India

Abstract

Background—Isoniazid is recommended for prevention of tuberculosis (TB) in HIV-infected adults but its efficacy in children living with HIV (CLHIV) is not known. We performed a systematic review to assess the efficacy of isoniazid for prevention of TB in CLHIV.

Methods—We searched PubMed, Cochrane Clinical Trial Registry, and Google Scholar from inception to December, 2016. Any randomized controlled trial (RCT) assessing the role of isoniazid for prevention of TB in CLHIV was eligible for inclusion. The primary endpoint was TB incidence; secondary end points were mortality, overall survival, and severe adverse events. Dual independent extraction of all data was performed. Data were pooled under a random effects model and summarized either as risk ratio (RR) or hazard ratio (HR) along with 95% confidence intervals (CI).

Results—Of 931 references, 3 RCTs enrolling 977 patients met the inclusion criteria. Pooled results showed a statistically non-significant reduction in TB incidence (RR=0.70; 95% CI 0.47 to 1.04; P=0.07), and mortality (RR=0.94; 95% CI 0.39 to 2.23; P=0.88) with use of isoniazid

Corresponding author: Ambuj Kumar, MD, MPH, 3515 E Fletcher Ave, Tampa, FL 33612, Phone: 813-396-9194, akumar1@health.usf.edu.

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Author contributions:

Dr. Kumar had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Charan, Goyal and Kumar

Acquisition, analysis, or interpretation of data: All authors.

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compared with placebo. One study was stopped early due to excess deaths in the placebo arm. However, results from subgroup analysis restricted to only completed trials did not change the overall findings.

Conclusion—Isoniazid did not reduce the incidence of TB in CLHIV. All included studies were performed in regions with high prevalence of TB making the overall generalizability limited.

An estimated 6 to 10% tuberculosis (TB) cases globally occur in children while, in high disease burden countries, childhood TB accounts for about 15 to 20% of all TB cases.(1, 2) Worldwide, in the year 2014 around one million children were infected with TB and 140,000 children died of either TB or related complications.(1, 2) While children are at a higher risk of progressing to active disease and developing more severe forms of TB (e.g. meningeal and disseminated TB) as compared to adults, some children exposed to TB may harbor latent infection for years and not develop disease until adulthood.(3, 4)

The emergence of HIV and its associated immunosuppression has led to an increase in incidence and prevalence of TB. The risk of developing TB is 26 to 31 times higher in HIV-infected subjects compared with those without HIV.(5) According to the 2013 estimates, one in four TB deaths globally were associated with HIV.(5) The convergence of these two epidemics wreaks havoc in high prevalence settings. The incidence of TB in children living with HIV (CLHIV) is declining with the use of antiretroviral therapy. However, TB rates in HIV-infected patients still remain high as compared to the HIV-uninfected population.(6)

The risk of latent TB is 8- to 10-fold higher among HIV-infected patients as compared to HIV-uninfected subjects.(7, 8) The complex interaction between HIV and TB includes mutual exacerbation of disease severity; hence, it is very important to identify infection and prevent reactivation of latent TB in HIV-infected patients to prevent associated morbidity and mortality.(8)

Isoniazid has the potential to prevent TB in HIV patients. Many studies support the role of isoniazid for prevention of TB in adults but its role in prevention of TB in children is not clear.(9–14) Treatment guidelines for TB by the World Health Organization (WHO), published in 2011, recommended isoniazid for adults and adolescents living with HIV. However, the guidelines panel also acknowledged the lack of conclusive evidence regarding the role of isoniazid for prevention of TB in CLHIV and the recommendation for the use of isoniazid in children was based on findings in adults.(2) Furthermore, a systematic review and meta-analysis found isoniazid to be beneficial as prophylactic therapy for TB in children.(15) A previous systematic review assessing the role of isoniazid for prevention of TB specifically in CLHIV concluded that isoniazid reduced TB incidence and death. (16) Since then additional studies have been published, warranting a reevaluation of the potential benefit and harms of isoniazid for prevention of TB in CLHIV. The objective of this systematic review is to synthesize all available evidence regarding the efficacy and safety of isoniazid for prevention of TB in CLHIV.

METHODS

The systematic review was performed as per the methodology documented *a priori* in a protocol.(17)

Eligibility criteria

Any randomized controlled trial (RCT) assessing the role of isoniazid versus any comparator in CLHIV regardless of publication or language status was eligible for inclusion. Any RCTs that had mix of adult and pediatric subjects and reported data separately for pediatric subjects were also eligible for inclusion.

Information sources and search

A comprehensive search of PubMed, Cochrane Clinical Trial Registry, and Google Scholar electronic databases was performed from inception to December 2016. The detailed search strategy is reported in Appendix 1. An additional hand search of references and Clinicaltrials.gov was undertaken to identify additional unpublished studies.

Study selection

Two authors (JC and AK) reviewed titles and abstracts of references retrieved from the searches independently against pre-defined inclusion criteria. All disagreements about the selection of studies were resolved by consensus accomplished through a joint meeting involving the third author (TR).

Outcomes

The primary outcome of this systematic review was the incidence of TB. Secondary outcomes were time to TB (time to event), mortality, overall survival (time to event) and any adverse events.

Data extraction and management

Two review authors (JC and AK) independently extracted data from included trials using a standardized data extraction form. Disagreements were resolved by consensus. Data were extracted on study characteristics (study design, inclusion/exclusion criteria, number randomized, study duration), participants (age, gender), treatment and comparison (dose and administration), risk of bias using Cochrane tool for randomized trials (18) and outcomes (mortality, survival, time to TB onset, and moderate to severe adverse events). In addition, we assessed the overall quality of evidence for each outcome according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines, which classify evidence as either very low, low, moderate, or high.(19)

Summary measures and synthesis

Data on similar outcomes was pooled under the random effects model. Time to event outcomes (e.g. overall survival and time to TB) were summarized as hazard ratio (HR) along with 95% confidence intervals (CI). Binary outcomes (e.g. incidence of TB) were summarized as relative risk (RR) along with 95% CI. The I square (I^2) measure was used for

assessment of heterogeneity among pooled studies and the same measure was used to assess for a test of interaction in sub-group analyses.(20) We considered an $I^2 > 50\%$ as high heterogeneity. All analyses were performed using Review Manager version 5.3.(21) The summary of findings table was generated using GRADE pro software. (22) The study was performed and reported per the PRISMA guidelines. (23)

Additional analyses

Additional subgroup and sensitivity analysis were planned according to differences in patient population, intervention, comparator and risk of bias characteristics. For all subgroup/sensitivity analysis a test of interaction was also assessed. We also planned for assessment of publication bias.(24) However, due to the availability of a limited number of studies (<10) we did not perform a formal assessment of publication bias.(24, 25)

RESULTS

Study selection and characteristics of included studies

The process of selection of eligible studies is illustrated in figure 1. The initial search yielded 931 citations of which 3 RCTs met the inclusion criteria.(12–14) The characteristics of the included studies are summarized in Table 1. All RCTs enrolled CLHIV ages 8 weeks and older with no known history of TB and were performed in South Africa except the Zar study which enrolled children with confirmed or probable tuberculosis but isoniazid was started only after the completion of standard tuberculosis treatment. The median follow-up was 5.7 months in the Zar study, 24 months in the Madhi study and 24 months in the Gray study. The primary outcome was mortality in the Zar study, TB-free survival in the Madhi and Gray study. The sample sizes ranged from 167 to 548. All subjects were prescribed co-trimoxazole for *Pneumocystis jirovecii* pneumonia prophylaxis and isoniazid was administered at a dose of 10–20 mg/kg for TB prevention. The Zar study was conducted in the pre-antiretroviral treatment (ART) era and only 9% of participants received ART at enrollment. In the Gray study all participants received ART and 31.5% of the subjects received ART at or before enrollment. The Zar study (13) was stopped early due to excess deaths in the placebo arm. To address the issue of early stopping, we performed additional subgroup analysis according to stopping time.

Definition of Tuberculosis

The diagnosis of TB was based on clinical symptoms in combination with findings on chest radiography, acid-fast staining of sputum, gastric aspirates or specimens from other sources, and culture.

Risk of bias within studies

Authors' judgment for each risk of bias element is illustrated in figure 2. Overall the methodological quality of included studies as per the GRADE method ranged from low to very low (Table 2). Briefly, all trials reported randomization sequence generation, described dropouts, and withdrawals, and performed the analysis according to intention-to-treat principle. Description of allocation concealment and blinding of participants was unclear in the Madhi trial.(12)

Outcomes

Incidence of tuberculosis—The incidence of TB, extractable from all 3 RCTs (977 patients) (Figure 3a), was not statistically significantly different between the isoniazid and placebo groups (RR=0.70; 95% CI 0.47 to 1.04; P=0.07). The observed heterogeneity between pooled studies was low ($I^2 = 2\%$).

In the subgroup analysis, there was no statistically significant difference in the incidence of TB with use of isoniazid versus placebo (RR=0.38; 95% CI 0.14 to 1.04, P = 0.06) in the trial stopped early (1 RCT; N=263)(13) or in the trials with complete follow-up (2 RCTs; 714 patients (12, 14); RR=0.78; 95% CI 0.51 to 1.18, P = 0.24, $I^2 = 0\%$). The test for interaction between subgroups was not statistically significant (P = 0.20, $I^2 = 40\%$; see figure 3a).

Time to tuberculosis—Time to TB, extractable from all 3 RCTs (977 patients), was not statistically significantly different between the isoniazid and placebo groups (HR=0.56; 95% CI 0.29 to 1.09; P = 0.09). The heterogeneity among studies was moderate ($I^2 = 45\%$; see figure 3b).

In the subgroup analysis, time to TB was significantly shorter with isoniazid versus placebo in the trial which was stopped early (1 RCT; N=263; HR=0.28; 95% CI 0.10 to 0.78, P = 0.02)(13) but not in the trials which had complete follow-up (2 RCTs; 714 patients; HR=0.77; 95% CI 0.49 to 1.19, P = 0.04, $I^2 = 0\%$).(12, 14) The test for interaction between subgroups was not statistically significant (P = 0.08, $I^2 = 68\%$; see figure 3b).

Mortality—Mortality, extractable from 3 RCTs (977 patients), was not statistically significantly different between isoniazid and placebo groups (RR=0.94; 95% CI 0.39 to 2.23; P=0.88). Heterogeneity between pooled trials was high ($I^2 = 58\%$; see figure 4a)

The findings from the subgroup analysis showed that, there was no statistically significant difference in mortality with use of isoniazid versus placebo (RR=0.52; 95% CI 0.26 to 1.03, P = 0.06) in the study with early termination (1 RCT; N=263)(13) as well as in pooled results from trials with complete follow-up (2 RCTs; N=714; RR=1.45; 95% CI 0.77 to 2.71, P = 0.25, $I^2 = 0\%$).(12, 14) The test for interaction between subgroups was statistically significant (P = 0.03, $I^2 = 78\%$; see figure 4a).

Overall Survival—Data on overall survival was extractable from only 2 RCTs (810 patients).(12, 13) There was no statistically significant difference in survival between the isoniazid and placebo groups (HR=0.89; 95% CI 0.25 to 3.17; P=0.86). The heterogeneity between pooled studies was high ($I^2 = 85\%$; see figure 4b).

In the subgroup analysis, there was a statistically significant survival benefit with the use of isoniazid versus placebo in the study that stopped early (1 RCT; 263 patients; HR=0.46; 95% CI 0.22 to 0.96, P = 0.04).(13) However, the difference in overall survival was not statistically significant in the study with complete follow-up (HR=1.68; 95% CI 0.86 to 3.28, P = 0.13). The test for interaction between subgroups was statistically significant (P = 0.01; $I^2 = 85\%$; see figure 4b).

Adverse Events—There was no statistically significant difference in the incidence of adverse events, available from all 3 RCTs (977 patients), with isoniazid versus placebo (RR=1.27; 95% CI 0.88 to 1.83, P=0.20). Heterogeneity between trials was low ($I^2 = 2\%$; figure 5).

The results from subgroup analysis showed no statistically significant difference in moderate to severe adverse events in the study with early stopping (RR=0.62; 95% CI 0.21 to 1.85, P=0.39)(13) as well as in pooled results from studies with complete follow-up (RR=1.39; 95% CI 0.96 to 2.01, P=0.08, $I^2 = 0\%$).(12, 14) The test for interaction between subgroups was not statistically significant (P = 0.17, $I^2 = 47\%$; see figure 5).

The most commonly reported moderate to severe adverse events were hematological events, infections, and hepatotoxicity.

DISCUSSION

This is the most comprehensive systematic review assessing the efficacy of isoniazid for prevention of TB in CLHIV. The pooled results showed no statistically significant effect of isoniazid prophylaxis on the incidence of TB, mortality or overall survival in HIV-infected children. However, the overall results for some outcomes (mortality and overall survival) were associated with statistically significant heterogeneity. We believe that primary reason for heterogeneity is due to inherent differences in the study conduct and differences between subjects in the Zar study and subjects in the other 2 studies. For example, the Zar study (13) was terminated early due to excess deaths in the placebo arm, while the other 2 RCTs (12, 14) had complete follow-up. This study enrolled an older, more malnourished and overall sicker group of patients. Furthermore, in the Zar trial (13), the majority of the children were not receiving antiretroviral therapy (ART) while in other two RCTs (12, 14) most subjects were receiving ART. Given that majority of events in the Zar study (13) were observed within first 30 to 40 days of treatment, it is very likely that children recruited in this study had primary TB at enrollment thus overestimating the benefit of isoniazid. Additionally, the Zar trial (13) did not report explicit criteria for ascertainment of TB prior to enrollment of subjects for excluding children exposed to TB. Therefore, we performed a subgroup analysis of trial stopped early (13) and compared it with trials with completed follow-up (12, 14). While the heterogeneity declined, the findings remained the same for all outcomes except overall survival and incidence of TB. While the Zar study (13) reported significant survival benefit and shorter time to TB with the use of isoniazid, the other two trials (12, 14) did not detect a significant difference.

Recent WHO guidelines recommend the 6 months of isoniazid preventive therapy as a part of comprehensive care for children (age > 12 months) living with HIV in areas with high TB prevalence and a conditional use in areas with moderate and low TB prevalence.(2) This recommendation was primarily based on the Zar trial (13) which included older children (median age of 24.7 months) despite the availability of the Madhi trial (12) enrolling relatively younger children (median age of 3–4 months). The Gray trial (14) was published later and its findings were not included in the WHO guidelines (2). Based on results of the available trials (12, 13), the WHO guidelines recommended isoniazid for children over age

12 months but not for children below age 12 months. It is worth noting that chances of progression from *Mycobacterium tuberculosis* infection to the development of TB disease are higher in the first two years of life (26). Therefore, if isoniazid prophylaxis is not effective in children under 12 months, it is unclear why it would be effective in children over 12 months of age. Another possibility is that isoniazid is not effective for primary prevention in infants, the focus of the study by Madhi et al.(12); however, it may be effective in preventing mortality and progression in children >12 months of age. Infants have more rapid progression of HIV disease, harder to diagnose TB and high overall mortality and, therefore, it is difficult to demonstrate clear efficacy. However, these findings point more towards the inconclusive nature of evidence associated with efficacy of isoniazid for prevention of TB in CLHIV, which needs further testing and warrants review of existing recommendations.

This systematic review also has limitations. While we followed the recommended methodological rigor in the field to perform this systematic review, the findings are limited by the availability of only three RCTs with moderate to high heterogeneity. Furthermore, all these RCTs were conducted on the African continent, in regions with high prevalence of TB making the overall global generalizability limited. Despite limitations, the results of this systematic review are in line with a previous systematic review assessing the role of isoniazid in HIV-infected adults for prevention of TB. The results from the systematic review by Akolo et al also concluded that isoniazid is not helpful for prevention of primary TB in adult HIV patients.(27)

In summary, results from this systematic review and meta-analysis show that evidence for isoniazid as an effective regimen for prevention of TB in CLHIV is inconclusive at best and emphasizes on the need for a large RCT to detect a clinically meaningful difference. For example, on the basis of results from this systematic review, to observe a reduction in the incidence of TB from 11% to 8% with 80% power at 5% significance a RCT would need about 3000 subjects. Until then, it would be advisable to revisit the available inconclusive evidence and potentially provide additional guidance for the use of isoniazid in the prevention of TB in HIV-infected children.

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Figure 1.
Flow diagram depicting the study selection process

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Gray DM 2014	+	+	+	+	+	+	+
Madhi SA 2011	+	?	?	+	+	+	?
Zar HJ 2007	+	+	+	+	+	+	?

Figure 2.
Risk of bias assessment for individual randomized controlled trials

Figure 3.

A) Forest plot for the outcome of incidence of tuberculosis with isoniazid versus placebo. B) Forest plot for the outcome of time to tuberculosis with isoniazid versus placebo. The summary effect estimate (risk ratio/hazard ratio) for individual randomized controlled trials are indicated by squares (the size of the square is proportional to the study weight), with the lines representing 95% confidence intervals (CIs). The overall summary effect estimate (risk ratio/hazard ratio) is represented by the diamond and the stretch of the diamond represents the 95% confidence intervals.

Figure 4.

A) Forest plot for the outcome of mortality with isoniazid versus placebo. B) Forest plot for the outcome of overall survival with isoniazid versus placebo. The summary effect estimate (risk ratio/hazard ratio) for individual randomized controlled trials are indicated by squares (the size of the square is proportional to the study weight), with the lines representing 95% confidence intervals (CIs). The overall summary effect estimate (risk ratio/hazard ratio) is represented by the diamond and the stretch of the diamond represents the 95% confidence intervals.

Figure 5.

Forest plot for the outcome of adverse events with isoniazid versus placebo. The summary effect estimate (risk ratio) for individual randomized controlled trials are indicated by squares (the size of the square is proportional to the study weight), with the lines representing 95% confidence intervals (CIs). The overall summary effect estimate (risk ratio) is represented by the diamond and the stretch of the diamond represents the 95% confidence intervals.

Table 1

Characteristics of included studies

	Zar HJ 2007	Gray DM 2014	Madhi SA 2011
Study design	Double blind randomized placebo controlled trial	Double blind randomized placebo controlled trial	Double blind randomized placebo controlled trial
Participants	<ul style="list-style-type: none"> - Children aged 8 weeks with HIV - No current evidence of tuberculosis infection 	<ul style="list-style-type: none"> - HIV-infected children aged >8 weeks on ART for >2 months. - No prior prolonged contact with a household member, teacher or regular visitor who was sputum- or respiratory specimen-positive for TB, within the last 12 months. Children with prior history of tuberculosis treatment or prophylaxis were eligible for inclusion. 	<ul style="list-style-type: none"> - HIV-infected infants (91 to 120 days of age) - No prior exposure to tuberculosis - Receipt of the BCG vaccine by 30 days of age
Intervention	<p>Isoniazid</p> <p>Enrolled 139</p> <p>Analyzed 132</p> <p>CD4 percent - median 21 (range – 14 to 29)</p> <p>Placebo</p> <p>Enrolled 138</p> <p>Analyzed 131</p> <p>CD4 percent - median 17 (range – 14 to 27)</p>	<p>Isoniazid</p> <p>Enrolled 85</p> <p>Analyzed 85</p> <p>CD4 percent - median 27 (range – 19 to 33)</p> <p>Placebo</p> <p>Enrolled 82</p> <p>Analyzed 82</p> <p>CD4 percent - median 27 (range – 22 to 34)</p>	<p>Isoniazid</p> <p>Enrolled 274</p> <p>Analyzed 273</p> <p>CD4 percent - median 29 (range – 6 to 53)</p> <p>Placebo</p> <p>Enrolled 274</p> <p>Analyzed 274</p> <p>CD4 percent - median 28 (range – 6 to 58)</p>
Intervention Schedule	<p>Isoniazid (10 mg/kg (Range 8–12 mg) and identical placebo</p> <p>Median follow up 5.7 months</p> <p>Treatment duration – 24 months</p>	<p>Isoniazid 10 mg/kg (Range 8–12 mg) and identical placebo</p> <p>Median follow up: 34 months</p> <p>Treatment duration – unclear</p>	<p>Isoniazid (10 to 20 mg/kg) and identical placebo</p> <p>Median follow up: 24 months</p> <p>Treatment duration – 22 months</p>
Outcomes	<p>Primary outcome: Mortality</p> <p>Secondary outcomes: Incidence of tuberculosis, Adverse events</p>	<p>Primary outcome: Tuberculosis-free survival</p> <p>Secondary outcomes: Incidence of tuberculosis, Mortality, Adverse events, Hospital admission and Adherence</p>	<p>Primary outcome: Disease-free survival (Tuberculosis disease or death)</p> <p>Secondary outcomes: Incidence of tuberculosis at 96 weeks, Mortality, and Adverse events</p>
Location of study	South Africa	South Africa	South Africa

Table 2

GRADE evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Isoniazid	placebo	Relative (95% CI)	Absolute (95% CI)	
Mortality											
3	randomized trials	serious ¹	serious ²	not serious	serious ³	none	33/490 (6.7%)	36/487 (7.4%)	RR 0.94 (0.39 to 2.23)	4 fewer per 1000 (from 45 fewer to 91 more)	⊕○○○ VERY LOW
Time to tuberculosis											
3	randomized trials	serious ¹	serious ⁴	not serious	serious ³	none	–/490	–/487	HR 0.56 (0.29 to 1.09)	-- per 1000 (from -- to --)	⊕○○○ VERY LOW
Overall Survival											
2	randomized trials	serious ¹	serious ⁵	not serious	serious ³	publication bias strongly suspected ⁶	–/405	–/405	HR 0.89 (0.25 to 3.17)	-- per 1000 (from -- to --)	⊕○○○ VERY LOW
Any Adverse Events											
3	randomized trials	serious ^{1,2}	serious ⁷	not serious	not serious	none	62/490 (12.7%)	49/487 (10.1%)	RR 1.27 (0.88 to 1.83)	27 more per 1000 (from 12 fewer to 84 more)	⊕⊕○○ LOW
Incidence of tuberculosis											
3	randomized trials	serious ^{1,2}	not serious	not serious	serious ³	none	40/490 (8.2%)	58/487 (11.9%)	RR 0.70 (0.47 to 1.04)	36 fewer per 1000 (from 5 more to 63 fewer)	⊕⊕○○ LOW

Abbreviations: **CI:** Confidence interval; **RR:** Risk ratio; **HR:** Hazard Ratio

- ¹ . Sufficient details were not provided in the trial by Madhi et al. to determine whether allocation concealment was adequate. Furthermore, it was unclear how blinding of outcome assessors and patients was accomplished.
- ² . The study by Zar et al. was stopped early due high incidence of deaths in the placebo arm and the results favored the isoniazid (although not statistically significant). However, the results from other two trials favored the placebo treatment (not statistically significant).
- ³ . The results were associated with wide confidence intervals.
- ⁴ . Two RCTs reported statistically non-significant results, the trial by Zar et al. that was stopped early reported statistically significant findings.
- ⁵ . The trial by Madhi et al. reported no difference between isoniazid and placebo. However, the trend favored placebo. The trial by Zar et al. showed a statistically significant benefit in favor of isoniazid.
- ⁶ . Out of 3 randomized controlled trials, only 2 reported this outcome
- ⁷ . The results from trial that was stopped early favored isoniazid. However, the pooled results from 2 randomized trials that had complete follow-up favored the placebo.