Isoniazid prophylaxis for tuberculosis in HIV infection: a meta-analysis of randomized controlled trials

Authors' objectives
To evaluate the efficacy of isoniazid (INH) for the prevention of tuberculosis in tuberculin skin test-positive and negative (TST) individuals with HIV infection.

Searching
The authors searched MEDLINE, EMBASE, CAB Health, BIOSIS Previews, HEALTHSTAR, IDIS Drug File, DHSS-Data, Medical Toxicology and Health, Drug Information Full Text, AIDSLINE, AIDSTRIAL, AIDS DRUG and the Cochrane Library (1985 to October 1997) using the search terms: 'isoniazid', 'tuberculosis', human immunodeficiency syndrome', 'acquired immunodeficiency syndrome', 'HIV infection', and the textword 'randomized', and 'randomized controlled trial' as a publication type.

The authors also scanned the Proceedings of the International and European Conference on AIDS and the references from identified trials.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with an intention-to-treat analysis comparing isoniazid with placebo or no prophylaxis. Only studies that reported the number of patients who developed TB and the number who died were included in the review. Mean follow-up in trials varied from 0.4 to 3.2 years.

Specific interventions included in the review
Comparison of isoniazid 300 mg with placebo or no prophylaxis.

Participants included in the review
Individuals with HIV infection free from tuberculosis.

Outcomes assessed in the review
Tuberculosis, death, and drug-related adverse effects.

How were decisions on the relevance of primary studies made?
Pairs of two reviewers independently performed the methodological quality assessment. Reviewers resolved disagreement by consensus.

Assessment of study quality
The authors used the Jadad validated score, which assessed the following: randomisation of the participants; double-blind evaluation, and full description of withdrawals and drop-outs. The score ranged from 0 to 5 points. (see Other Publications of Related Interest no.1).

Pairs of two reviewers independently performed the methodological quality assessment. Reviewers resolved disagreement by consensus.

Data extraction
Reviewers abstracted data from eligible studies in duplicate. Data were extracted for the categories of study identification, trial location, drug regimen, duration of intervention (months), quality score, patients (%) with culture-proven TB, mean age (years), mean follow-up (years), risk of TB in controls per 100 person-years, number of patients,
number with TB, number of deaths, and number of any side-effects.

**Methods of synthesis**

**How were the studies combined?**

Risk ratios (RRs) and computed summary estimates with 95% confidence intervals (CIs) were calculated using a random-effects model. These are presented as forest plots. The authors also calculated summary incidence ratios but these are not reported.

Two subgroup analyses were performed to: test the efficacy of INH in people with or without a positive TST at study onset; and to test the calculations by excluding two unpublished trials.

**How were differences between studies investigated?**

A formal statistical test for heterogeneity was performed for each analysis and sub-group analysis. Also for the effect of INH on mortality, the analyses were repeated excluding the unpublished studies with a quality score of 1.

**Results of the review**

Seven RCTs were included in the review with 2,367 participants in the intervention group and 2,162 participants in the control groups.

There was complete agreement between reviewers for relevance of eligible studies.

Agreement for methodological quality of included studies was K = 0.80.

For INH prophylaxis and the incidence of TB: The pooled RR (7 trials) for persons treated with isoniazid for developing tuberculosis was 0.58 (95% CI: 0.43, 0.80). In groups of tuberculin skin test- positive and negative persons, the RR of tuberculosis was 0.40 (95% CI: 0.24, 0.65) and 0.84 (95% CI: 0.54, 1.30), respectively. The difference in the effectiveness of isoniazid versus placebo between these groups was statistically significant (P = 0.03 for the difference of summary estimates).

For INH prophylaxis and mortality: The pooled RR (7 trials) for persons treated with isoniazid for death was 0.94 (95% CI: 0.83, 1.07). In groups of tuberculin skin test-positive and negative persons (5 trials), the RR of death was 0.79 (95% CI: 0.37, 1.70) and 1.02 (95% CI: 0.90, 1.17) respectively. There was no statistically significant difference between the summary estimates in TST-positives and negatives (P = 0.52 for the difference of summary estimates). The results were not altered by excluding unpublished studies (quality score 1) from the analysis.

For side-effects and drug-limiting toxicity of INH prophylaxis: The pooled RR (4 trials) indicated a trend towards an increased risk in INH compared with placebo (RR 1.36, 95% CI: 1.0, 1.86). The RR for drug-limiting toxicity of INH compared with placebo was 1.66 (95% CI: 0.83, 3.32). The RR for hepatotoxicity of INH versus placebo was 1.80 (95% CI: 1.05, 3.10).

**Authors' conclusions**

The authors state that prophylaxis with isoniazid reduces the risk of tuberculosis in persons with HIV infections but does not reduce mortality from HIV infection. The effect is restricted to skin test-positive persons.

**CRD commentary**

The authors have stated their research question and some inclusion and exclusion criteria. The literature search appears thorough although there is no reporting of language restrictions. The authors report how many of the authors performed the selection of studies and the data extraction. There is a formal assessment of the included studies using the Jadad validity score.

The studies were statistically pooled with further sub-group analyses. There were tests for heterogeneity and the sub-groupings were explored further in assessing heterogeneity. There was further discussion about the differences between
the included studies and sources of possible bias.

The authors’ conclusions appear to follow from the results.

**Implications of the review for practice and research**

Practice: The authors state that the case for preventative therapy will be strongest in TST-positive patients at high risk of TB. Preventative therapy programmes are likely to do most good when resources for the exclusion of active TB and proper monitoring of patients with dual infection are available.

Research: The authors did not state any implications for further research.

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