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Treatment of latent tuberculosis infection in HIV infected persons (Review)

Akolo C, Adetifa I, Shepperd S, Volmink J

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TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
BACKGROUND 3
OBJECTIVES 3
METHODS 4
Figure 1. 6
RESULTS 7
DISCUSSION 9
AUTHORS' CONCLUSIONS 10
ACKNOWLEDGEMENTS 10
REFERENCES 11
CHARACTERISTICS OF STUDIES 13
DATA AND ANALYSES 22
Analysis 1.1. Comparison 1 Any TB drug vs placebo, Outcome 1 Incidence of active TB (confirmed, probable or possible). 23
Analysis 1.2. Comparison 1 Any TB drug vs placebo, Outcome 2 Incidence of confirmed TB. 24
Analysis 1.3. Comparison 1 Any TB drug vs placebo, Outcome 3 Incidence of death (all cause). 25
Analysis 1.4. Comparison 1 Any TB drug vs placebo, Outcome 4 Incidence of AIDS. 26
Analysis 1.5. Comparison 1 Any TB drug vs placebo, Outcome 5 Incidence of adverse events leading to stopping treatment. ... 26
Analysis 1.9. Comparison 1 Any TB drug vs placebo, Outcome 9 Mean time to AIDS. 27
Analysis 2.1. Comparison 2 Isoniazid vs placebo, Outcome 1 Incidence of active TB (confirmed, probable or possible). 28
Analysis 2.2. Comparison 2 Isoniazid vs placebo, Outcome 2 Incidence of confirmed TB. 29
Analysis 2.3. Comparison 2 Isoniazid vs placebo, Outcome 3 Incidence of death (all cause). 30
Analysis 2.4. Comparison 2 Isoniazid vs placebo, Outcome 4 Incidence of AIDS. 30
Analysis 2.5. Comparison 2 Isoniazid vs placebo, Outcome 5 Incidence of adverse events leading to stopping treatment. 31
Analysis 2.9. Comparison 2 Isoniazid vs placebo, Outcome 9 Mean time to AIDS. 32
Analysis 3.1. Comparison 3 Isoniazid + rifampicin vs placebo, Outcome 1 Incidence of active TB (confirmed, probable or possible). 33
Analysis 3.2. Comparison 3 Isoniazid + rifampicin vs placebo, Outcome 2 Incidence of confirmed TB. 34
Analysis 3.3. Comparison 3 Isoniazid + rifampicin vs placebo, Outcome 3 Incidence of death (all cause). 34
Analysis 3.5. Comparison 3 Isoniazid + rifampicin vs placebo, Outcome 5 Incidence of adverse events leading to stopping treatment. 35
Analysis 4.1. Comparison 4 Rifampicin + pyrazinimide vs placebo, Outcome 1 Incidence of active TB (confirmed, probable or possible). 36
Analysis 4.2. Comparison 4 Rifampicin + pyrazinimide vs placebo, Outcome 2 Incidence of confirmed TB. 37
Analysis 4.3. Comparison 4 Rifampicin + pyrazinimide vs placebo, Outcome 3 Incidence of death (all cause). 38
Analysis 4.5. Comparison 4 Rifampicin + pyrazinimide vs placebo, Outcome 5 Incidence of adverse events leading to stopping treatment. 38
Analysis 5.1. Comparison 5 Isoniazid + rifampicin + pyrazinamid vs placebo, Outcome 1 Incidence of active TB (confirmed, probable or possible). 40
Analysis 5.3. Comparison 5 Isoniazid + rifampicin + pyrazinamid vs placebo, Outcome 3 Incidence of death (all cause). 41
Analysis 5.5. Comparison 5 Isoniazid + rifampicin + pyrazinamid vs placebo, Outcome 5 Incidence of adverse events leading to stopping treatment. 41
Analysis 6.1. Comparison 6 Isoniazid vs rifampicin + pyrazinimide, Outcome 1 Incidence of active TB (confirmed, probable or possible). 43
Analysis 6.2. Comparison 6 Isoniazid vs rifampicin + pyrazinimide, Outcome 2 Incidence of confirmed TB. 43
Analysis 6.3. Comparison 6 Isoniazid vs rifampicin + pyrazinimide, Outcome 3 Incidence of death (all cause). 44
Analysis 6.5. Comparison 6 Isoniazid vs rifampicin + pyrazinimide, Outcome 5 Incidence of adverse events leading to stopping treatment. 45
Analysis 7.1. Comparison 7 Isoniazid vs isoniazid + rifampicin, Outcome 1 Incidence of active TB (confirmed, probable or possible). 46
Analysis 7.2. Comparison 7 Isoniazid vs isoniazid + rifampicin, Outcome 2 Incidence of confirmed TB. 47

Analysis 7.3. Comparison 7 Isoniazid vs isoniazid + rifampicin, Outcome 3 Incidence of death (all cause). 48
Analysis 7.5. Comparison 7 Isoniazid vs isoniazid + rifampicin, Outcome 5 Incidence of adverse events leading to stopping treatment. 49
Analysis 8.1. Comparison 8 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide, Outcome 1 Incidence of active TB (confirmed, probable or possible). 50
Analysis 8.2. Comparison 8 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide, Outcome 2 Incidence of confirmed TB. 51
Analysis 8.3. Comparison 8 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide, Outcome 3 Incidence of death (all cause). 51
Analysis 8.5. Comparison 8 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide, Outcome 5 Incidence of adverse events leading to stopping treatment. 52
Analysis 9.1. Comparison 9 Isoniazid vs isoniazid + rifampicin + Pyrazinamide, Outcome 1 Incidence of active TB (confirmed, probable or possible). 53
Analysis 9.3. Comparison 9 Isoniazid vs isoniazid + rifampicin + Pyrazinamide, Outcome 3 Incidence of death (all cause). 54
Analysis 9.5. Comparison 9 Isoniazid vs isoniazid + rifampicin + Pyrazinamide, Outcome 5 Incidence of adverse events leading to stopping treatment. 55
Analysis 10.1. Comparison 10 Isoniazid + rifampicin vs isoniazid + rifampicin + Pyrazinamide, Outcome 1 Incidence of active TB (confirmed, probable or possible). 56
Analysis 10.3. Comparison 10 Isoniazid + rifampicin vs isoniazid + rifampicin + Pyrazinamide, Outcome 3 Incidence of death (all cause). 57
Analysis 10.5. Comparison 10 Isoniazid + rifampicin vs isoniazid + rifampicin + Pyrazinamide, Outcome 5 Incidence of adverse events leading to stopping treatment. 57
Analysis 11.1. Comparison 11 Isoniazid vs placebo (stratified by AIDS status at baseline), Outcome 1 Incidence of confirmed TB. 58
Analysis 11.2. Comparison 11 Isoniazid vs placebo (stratified by AIDS status at baseline), Outcome 2 Incidence of death (all cause). 59
Analysis 12.1. Comparison 12 Isoniazid vs rifampicin + pyrazinimide (stratified by AIDS status at baseline), Outcome 1 Incidence of confirmed TB. 60
Analysis 12.2. Comparison 12 Isoniazid vs rifampicin + pyrazinimide (stratified by AIDS status at baseline), Outcome 2 Incidence of death (all cause). 60
APPENDICES 61
WHAT'S NEW 66
HISTORY 66
CONTRIBUTIONS OF AUTHORS 66
DECLARATIONS OF INTEREST 66
SOURCES OF SUPPORT 66
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 67
INDEX TERMS 67

[Intervention Review]

Treatment of latent tuberculosis infection in HIV infected persons

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ABSTRACT

Background

Individuals with human immunodeficiency virus (HIV) infection are at an increased risk of developing active tuberculosis (TB). It is known that treatment of latent TB infection (LTBI), also referred to as TB preventive therapy or chemoprophylaxis, helps to prevent progression to active disease in HIV negative populations. However, the extent and magnitude of protection (if any) associated with preventive therapy in those infected with HIV should be quantified. This present study is an update of the original review.

Objectives

To determine the effectiveness of TB preventive therapy in reducing the risk of active tuberculosis and death in HIV-infected persons.

Search methods

This review was updated using the Cochrane Controlled Trials Register (CCTR), MEDLINE, EMBASE, AIDSLINE, AIDSTRIALS, AIDSearch, NLM Gateway and AIDSDRUGS (publication date from 01 July 2002 to 04 April 2008). We also scanned reference lists of articles and contacted authors and other researchers in the field in an attempt to identify additional studies that may be eligible for inclusion in this review.

Selection criteria

We included randomized controlled trials in which HIV positive individuals were randomly allocated to TB preventive therapy or placebo, or to alternative TB preventive therapy regimens. Participants could be tuberculin skin test positive or negative, but without active tuberculosis.

Data collection and analysis

Three reviewers independently applied the study selection criteria, assessed study quality and extracted data. Effects were assessed using relative risk for dichotomous data and mean differences for continuous data.

Main results

12 trials were included with a total of 8578 randomized participants. TB preventive therapy (any anti-TB drug) versus placebo was associated with a lower incidence of active TB (RR 0.68, 95% CI 0.54 to 0.85). This benefit was more pronounced in individuals with a positive tuberculin skin test (RR 0.38, 95% CI 0.25 to 0.57) than in those who had a negative test (RR 0.89, 95% CI 0.64 to 1.24). Efficacy was similar for all regimens (regardless of drug type, frequency or duration of treatment). However, compared to INH monotherapy, short-course multi-drug regimens were much more likely to require discontinuation of treatment due to adverse effects. Although there was reduction in mortality with INH monotherapy versus placebo among individuals with a positive tuberculin skin test (RR 0.74, 95% CI 0.55 to 1.00) and with INH plus rifampicin versus placebo regardless of tuberculin skin test status (RR 0.69, 95% CI 0.50 to 0.95), overall, there was no evidence that TB preventive therapy versus placebo reduced all-cause mortality (RR 0.94, 95% CI 0.85 to 1.05).

Authors' conclusions

Treatment of latent tuberculosis infection reduces the risk of active TB in HIV positive individuals especially in those with a positive tuberculin skin test. The choice of regimen will depend on factors such as availability, cost, adverse effects, adherence and drug resistance. Future studies should assess these aspects. In addition, trials evaluating the long-term effects of anti-tuberculosis chemoprophylaxis, the optimal duration of TB preventive therapy, the influence of level of immunocompromise on effectiveness and combination of anti-tuberculosis chemoprophylaxis with antiretroviral therapy are needed.

PLAIN LANGUAGE SUMMARY

Treatment of latent tuberculosis (TB) with isoniazid in people infected with HIV reduces their risk of developing active TB

Most people infected with tuberculosis (TB) never get TB symptoms. This is called latent TB. People infected with HIV/AIDS are at increased risk of getting TB and about 30% of people with HIV who have latent TB will eventually get active TB. This results in an increase in the risk of earlier death. This update of the review of available clinical trials found that the risk of developing active TB was reduced when people infected with both HIV and TB used isoniazid. Isoniazid for latent TB is usually taken for six to 12 months, but more research is still needed to show optimal duration of treatment, the best treatment regime for people with HIV, and especially the best regimen in combination with HIV drugs.

BACKGROUND

Although the availability of antiretroviral therapy (ART) has transformed human immunodeficiency virus (HIV) infection into a chronic and manageable disease in those who are able to access treatment; the successes recorded can easily be destroyed by the high burden of tuberculosis (TB) co-infection in the HIV-infected population. Even after the initiation of ART, the incidence of HIV-related TB remains unacceptably high (Badri 2002; Lawn 2005; Girardi 2005).

According to the WHO Global TB Control report of 2008, worldwide, about 9.2 million new cases and 1.7 million deaths from TB occurred in 2006 and of these around 709,000 (7.7%) new cases and 200,000 deaths were estimated to have occurred in HIV-positive individuals (WHO 2008 (1)).

Therefore, prevention of TB is one of the most important measures that may help in reducing the morbidity and mortality associated with HIV infection particularly in countries with high burden of both infections.

Latent TB (LTB) infection is the presence of *Mycobacterium tuberculosis* (*M. tuberculosis*), the organism that causes TB, in an individual in a non-active phase and without producing clinical symptoms. Although, one third of the world's population is believed to be latently infected with *M. tuberculosis,* most of those infected will never have symptoms (Dye 1999). Whereas in the general population the lifetime risk of progression from latent TB infection to active disease is about 10%, HIV positive persons who are infected with *M. tuberculosis* have a 5-8% annual risk and a 30% lifetime risk of developing active tuberculosis (Selwyn 1989) and this risk increases as immune deficiency worsens (Williams 2003). HIV infection by impairing cell-mediated immunity is the most potent known risk factor for the reactivation of latent *M. tuberculosis* infection (McShane 2005).

The tuberculin skin test (TST) is the primary screening test for the diagnosis of latent TB. Although this test is over 100 years old, it represents the second longest standing test in use for TB after sputum microscopy (Mendelson 2007). In this test, purified protein derivative (PPD), a material derived from *M. tuberculosis* is injected into the skin of an individual and the reaction on the skin as indicated by the degree of induration is evaluated after about 48-72 hours.

A person is said to be positive to the TST (PPD positive) if there is a strong skin reaction. In HIV infected persons, a reaction greater than 5mm is considered positive while a reaction of less than 5mm is said to be a negative reaction. An individual without a reaction to TST and other common antigens such as mumps and candida is said to be anergic. PPD positive individuals are at a greater risk of progressing to active TB disease than people not infected with *M. tuberculosis* (Watkins 2000). Despite being an imperfect test, with both false positive and false negative results, TST remains a very useful and indeed a critical tool, both for epidemiologic research and the control and prevention of clinical tuberculosis (Nelson 2007).

HIV infection also has implications for the diagnosis and clinical presentation of TB. The proportion of PPD negative individuals with tuberculosis infection seems to be higher in HIV positive populations than in those who are not infected with HIV (Daniel 2000). Similarly, the percentage of sputum smear negative patients with active tuberculosis is higher in HIV infected populations compared with HIV negative populations raising concerns for TB detection. Furthermore, extra-pulmonary tuberculosis is more common in patients with HIV infection than those who are not HIV-infected (Harries 1994).

The treatment of LTB (also known as TB preventive therapy or chemoprophylaxis) is the administration of one or combination of anti-TB drugs to people with latent infection with *M. tuberculosis* with the aim of eradicating latent infection before it develops into active disease. The use of isoniazid preventive therapy (IPT) is one of the strategies recommended by the World Health Organization (WHO) to decrease the burden of TB in people living with HIV in addition to establishing intensified TB case finding and ensuring the control of TB infection in health-care and congregate settings (WHO 2004).

Several placebo-controlled trials in HIV negative people infected with *M. tuberculosis* have shown that daily isoniazid given for 6-12 months substantially reduces the subsequent risk of active tuberculosis (O'Brien 1994; Smieja 2003). Similarly, several placebo-controlled trials have shown that treatment of latent TB is effective in HIV-infected individuals (Gordin 1997; Halsey 1998; Hawken 1997; Mwinga 1998; Pape 1993; Quigley 1998; Whalen 1997). Following the publication of these trials, a systematic review that included 10 trials was published in 2004 and the results showed that treatment of LTB infection reduces the risk of active TB in HIV positive individuals especially those with a positive TST (Woldehanna 2004). We hereby report an update of this review.

OBJECTIVES

The objective of this review was to determine the effectiveness of TB preventive therapy (PT) in reducing the risk of active TB and death in persons infected with HIV. The following hypotheses were proposed for testing depending on available evidence:

1. PT does not reduce the incidence of, and interval to active TB in HIV infected persons. If PT is effective in reducing the incidence of active TB, the effect is not dependent on the following factors:

- PPD status (whether the TST is positive or negative)
- Degree of immunocompromise (stage of HIV disease)
- TB drug regimen including type, dosage and duration of treatment
- Time since completion of therapy

2. PT does not reduce the frequency of death from all causes in HIV infected persons.
3. PT does not slow the progression of HIV disease through reducing the incidence of AIDS and delay of time to the development of AIDS.
4. PT is not associated with an increased incidence of adverse drug reactions and different drug regimens do not have different rates of adverse reactions

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomized controlled trials in which participants were randomly allocated to TB preventive therapy and placebo, or to alternative TB preventive therapy regimens.

Preventive therapy is defined as TB chemotherapy given to people at high risk of developing TB to prevent active disease.

Types of participants

Participants had to be HIV infected individuals (at least 13 years of age) who did not have active TB at the start of trial. Participants could be male or female and from any setting. They could be either tuberculin skin test positive or negative. Anergic patients were considered TST negative.

Types of interventions

Experimental group: Any anti-TB drug or drug combination
Control group: Inactive placebo or an alternative anti-TB drug or drug combination

Types of outcome measures

Primary outcomes:
1. Active TB based upon microbiological diagnosis (preferably by culture), histological diagnosis, or as a defined clinical syndrome (typical symptoms, consistent and independently assessed chest X-ray, and a documented response to anti-TB treatment) (ATS 1990)
2. Interval to active TB from initiation of preventive therapy.
3. Survival including incidence of death and interval to death

Secondary outcomes:
1. Progression of HIV disease. This could include incidence of, interval to, and types of HIV-related disease, change in CD4 count or incidence of, and time to, AIDS.
2. Incidence of adverse drug reactions leading to discontinuation of treatment.

Search methods for identification of studies

We attempted to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress).

We used the following terms to search for eligible randomized controlled trials or review articles: (HIV AND tuberculosis) AND (preventive therapy OR chemoprophylaxis or treatment). "Treatment" was used as a search term because we discovered some studies that discussed treatment of latent tuberculosis were indexed incorrectly under treatment.

The following databases were searched for relevant articles (Note: Since the original review included studies published up to July 2002, the publication dates used were from 01 July 2002 to 04 April 2008):

- The Cochrane Controlled Trials Register (CCTR)
- MEDLINE
- EMBASE
- AIDSLINE
- AIDSTRIALS
- AIDSDRUGS
- AIDS Search
- NLM Gateway

The Cochrane Controlled Trials Register (CCTR)

We also scanned the reference lists of review articles and included studies to identify further studies. We contacted study authors and other researchers in the field in an attempt to identify additional studies that may be eligible for inclusion in this update.

Data collection and analysis

We independently applied the pre-specified study eligibility criteria to determine which studies should be included in the review. We also independently evaluated the quality of the studies according to the following predefined criteria for quality assessment
1. Generation of allocation sequence - trials were classified as

- Adequate: if appropriate methods, such as random numbers generated by computer, or throwing dice were used.
- Inadequate: if sequences such as case record number, date of birth, day, month or years of admission were used.
- Unclear: if methods were not described

2. Concealment of allocation - trials were classified as

- Adequate: if measures were used to prevent foreknowledge of assignment, such as centralized randomization or numbered, sealed, opaque envelopes.
- Inadequate: if researchers reported an approach that could not be considered adequate e.g. alternation
- Unclear: if methods were not described

3. Blinding - trials were assessed for provider, participant and assessor blinding

4. Inclusion of all randomized participants in the analysis- trials were labelled as adequate if more than 90% of the randomized participants were included.

We independently extracted the following information using a standardized data collection form specifically designed for the update of this review: study setting, demographics of participants, details of interventions, methods of randomization and blinding, follow-up, degree of adherence to treatment, and outcomes. Where we were able to obtain information from either published or unpublished data, we stratified results by PPD status and HIV/AIDS status at baseline. We also extracted information on adherence to therapy.

Differences between reviewers (CA, IA & SS) in relation to data extraction or quality assessment were resolved by discussion and re-examination of the relevant studies.

We pooled data using relative risk (RR) with 95% confidence intervals using a fixed effects model. We tested for statistical heterogeneity of trial results at the 0.1 level. For continuous data such as time to AIDS, we used the weighted mean difference (WMD). Heterogeneity was quantified by the I^2 statistic, which quantifies the percentage of the total variation across studies that

is due to heterogeneity rather than chance (Higgins 2003); smaller percentages suggest less observed heterogeneity.

See Figure 1 for the Bias Assessment table.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

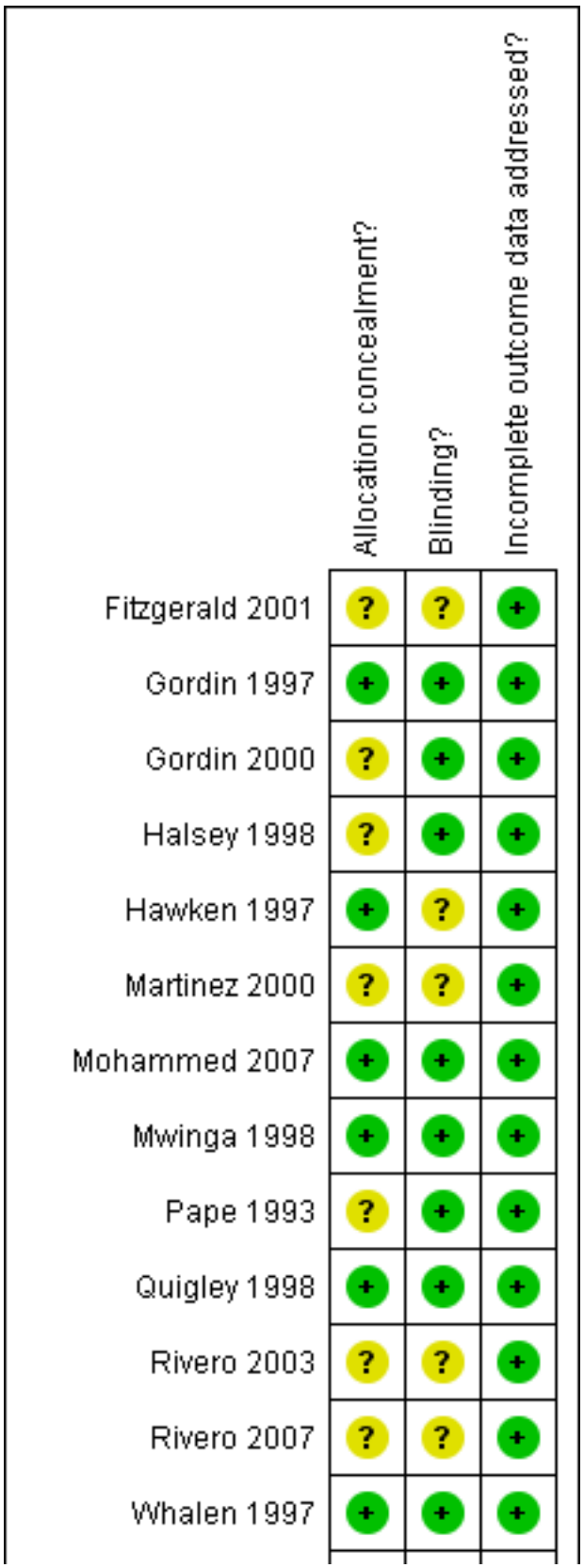
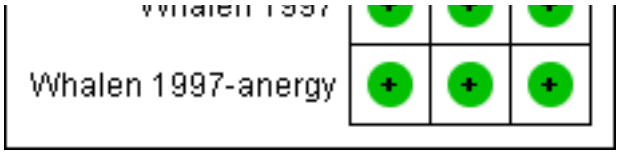


Figure 1. (Continued)



RESULTS

Description of studies

In addition to the 10 trials included in the original systematic review, we initially identified a possible four new trials that met the inclusion criteria. Of these, one trial (Grant 2005) was later excluded because it assessed the effect on incidence of TB at a clinic that offered INH under routine conditions and participants were not randomized to receive INH or placebo. The study by Lim 2006 (Lim 2006) was an additional publication from the Whalen trial (Whalen 1997), which was already included in the review. Lim et al reported data on the rate of disease progression to AIDS or death, with results reported for PPD positive persons and those with anergy (Lim 2006).Long-term follow-up results of Mwinga 1998 were published in Quigley 1998.

This current update thus includes 12 trials with a total of 8578 randomized participants. Study size varied from 98 to 2018 participants. The two new trials included in this update are Rivero 2007 and Mohammed 2007. The study by Rivero et al. that was included in the original review recruited anergic individuals Rivero 2003. The study identified in this update recruited PPD+ individuals Rivero 2007.

Full details of the studies included in this review are provided in the table of included studies. In addition ongoing trials are summarised in appendix 1 (Churchyard GJ 2007).

Summary of included studies:

The trials were conducted in both developed and developing countries: Haiti (Fitzgerald 2001; Halsey 1998; Pape 1993), Uganda (Whalen 1997; Lim 2006), Kenya (Hawken 1997), Zambia (Mwinga 1998), South Africa (Mohammed 2007), Spain (Martinez 2000; Rivero 2003; Rivero 2007) and the USA (Gordin 1997). One multi-national study included participants from Mexico, USA, Haiti and Brazil (Gordin 2000).

Study participants were 13 years of age or older (mean age 33 years). 47% were female, with a range of 20% to 69% across trials. Mean duration of follow up ranged from 1 to 3 years.

Some reports included only individuals who were PPD+ (Gordin 2000; Halsey 1998; Rivero 2007) and others involved only those known to be anergic (Gordin 1997; Rivero 2003; Mohammed 2007). One trial included both PPD+ and anergic individuals as separately randomized groups (Whalen 1997; Lim 2006) and another as one group with stratification by PPD status in the analysis (Martinez 2000). A further trial among PPD negative individuals did not test for anergy (Fitzgerald 2001). The remaining trials included individuals regardless of PPD status (Hawken 1997; Mwinga 1998; Pape 1993) with only two of these providing stratified data (Hawken 1997; Pape 1993)

In all, 4811 individuals were PPD+, 2030 were PPD- (of which 1640 were known to be anergic) and in 1737 individuals the PPD status was unknown.

Five trials compared isoniazid (INH) with placebo (Fitzgerald 2001;Gordin 1997 Hawken 1997 Mohammed 2007; Mwinga 1998), three with rifampicin (RIF) (Gordin 2000; Halsey 1998; Martinez 2000), one with pyridoxine (Pape 1993), one to either placebo or INH +RIF (Whalen 1997) and two to RIF or RIF + PZA (Rivero 2003; Rivero 2007)

Treatment dosage varied among the trials: INH 300 mg or 600 mg for daily regimens; 600 mg or 900 mg for twice weekly regimens; RIF 450 mg or 600 mg; and PZA 20 mg/kg body weight to a total of 3500 mg. Dosage frequency was daily except in two trials (Halsey 1998; Mwinga 1998) which offered treatment twice a week. The duration of INH treatment varied as follows: 12 months (Fitzgerald 2001; Gordin 2000; Martinez 2000; Pape 1993; Mohammed 2007) and 6 months (Gordin 1997; Halsey 1998; Hawken 1997; Mwinga 1998; Rivero 2003; Whalen 1997; Rivero 2007).

We collected data for active TB diagnosed either by culture or other methods of diagnosis as defined by the study authors (confirmed, probable and possible). Active TB data were available for all participants.

Risk of bias in included studies

Allocation concealment was adequate in five studies (Gordin 1997; Hawken 1997;Mohammed 2007; Mwinga 1998; Whalen 1997) and unclear in the remaining seven (Fitzgerald 2001; Gordin 2000; Halsey 1998; Martinez 2000; Pape 1993; Rivero 2003; Rivero 2007). In 7 trials both providers and participants were blinded (Gordin 1997, Gordin 2000; Halsey 1998; Mohammed 2007; Mwinga 1998; Pape 1993; Whalen 1997).

The inclusion of randomized participants was adequate in all the included trials. All randomized participants were included in the analysis in 10 of the trials. Participant loss to follow-up ranged from 0 to 31%.
(See Table of Included Studies for details of individual studies.)

Effects of interventions

ACTIVE TUBERCULOSIS

Preventive therapy (any anti-TB drug) versus placebo reduced the risk of active TB by 32% (10 trials; 5762 participants; RR 0.68, 95% CI 0.54 to 0.85). There was a small amount of statistical heterogeneity among the trials (I^2 = 31%; Chi ^{2} =18.93, p = 0.13). For confirmed (culture-proven) TB, the result was similar (4 trials; 2573 participants; RR 0.73, 95% CI 0.49 to 1.08) although not statistically significant.

All drug regimens (regardless of type, frequency or duration of treatment) reduced the incidence of active TB compared with placebo:

- INH: RR 0.67, 95% CI 0.51 to 0.87 [n=4136] Analysis 2.1
- INH+RIF: RR 0.41, 95% CI 0.21 to 0.81 [n=1179] Analysis 3.1
- RIF+PZA: RR 0.54, 95% CI 0.34 to 0.86 [n=855] Analysis 4.1
- INH+RIF+PZA: RR 0.48, 95% CI 0.23 to 1.00 [n=926] Analysis 5.1

In trials that directly compared drug regimens we found no differences in effectiveness:

- INH vs. RIF+PZA: 6 trials; RR 1.03, 95% CI 0.75 to 1.40 Analysis 6.1
- INH vs. INH+RIF: 5 trials; RR 0.97, 95% CI 0.52 to 1.83 Analysis 7.1
- INH + RIF vs. RIF+PZA: 2 trials; RR 2.64, 95% CI 0.71 to 9.8 Analysis 8.1
- INH vs. INH+RIF+PZA: 1 trial; RR 0.60, 95% CI 0.23 to 1.57 Analysis 9.1
- INH + RIF vs. INH+RIF+PZA: 1 trial; RR 0.75, 95% CI 0.31 to 1.82 Analysis 10.1

We detected no heterogeneity in the outcome across the trials.

We found no trials that compared the effects of different drug dosages, treatment frequency or duration of therapy on clinical outcomes. Current trials do not provide sufficient data to assess the impact of preventive therapy on interval to active TB.

We assessed the influence of various factors on the incidence of active TB:

PPD status
Among individuals who were tuberculin skin test positive, preventive therapy reduced the risk of active TB by 62% (4 trials; 2378 participants; RR 0.38, 95% CI 0.25 to 0.57). There was no evidence of effect for individuals with a negative tuberculin test (7 trials; 2822 participants; RR 0.89, 95% CI 0.64 to 1.24).Analysis 1.1

Stage of HIV disease at baseline
We found limited data stratified by stage of HIV/AIDS at baseline. In Gordin 1997, which compared INH to placebo, the relative risk (95% CI) for the development of confirmed TB was 3.42 (0.14 to 82.33) for those with AIDS and 0.32 (0.06 to 1.54) for those without AIDS; neither of these findings being statistically significant. Similarly, in Gordin 2000 comparing INH with RIF+PZA, the risk of confirmed TB was not statistically significant in subgroups defined by AIDS status: AIDS RR 0.97, 95% CI 0.28 to 3.43; no AIDS RR 1.42, 95% CI 0.74 to 2.74.

Time since treatment
We found limited information on the duration of the protective effect of preventive therapy. Mwinga 1998 provided data for a median follow-up of 1.8 years in a mixture of PPD positive and negative people found a reduction in the risk of active TB in the intervention groups versus placebo (INH: RR 0.62, 95% CI 0.39 to 0.97; RIF plus PZA: RR 0.57, 95% CI 0.35 to 0.91). In a subsequent report (Quigley 1998) presenting findings after a mean follow-up of 3 years, Kaplan Meier analysis demonstrated a diminishing effect over time. Nevertheless, compared to placebo the reported cumulative risk in the first 2.5 years remained lower for INH (RR 0.52, 95% CI 0.27 to 1.00), for RIF plus PZA (RR 0.58, 95% CI 0.30 to 1.09) and for both intervention arms combined (RR 0.55, 95% CI 0.32 to 0.93).

In another study (Whalen 1997) involving PPD positive individuals, INH (RR 0.29, 95% CI 0.12 to 0.67), INH + RIF (RR 0.36, 95% CI 0.17 to 0.77) and INH + RIF + PZA (RR 0.48, 95% CI 0.23 to 1.00) were each shown to significantly lower the risk of active TB after a mean of 15 months. This benefit remained statistically significant on long-term follow-up for the rifampicin containing regimens but not for INH alone (Johnson 2001). Based on a Cox regression analysis the adjusted relative risk at 3 years was 0.67 (95% CI 0.42 to 1.07) for INH, 0.49 (95% CI 0.29 to 0.82) for INH + RIF, and 0.41 (95% CI 0.22 to 0.76) for INH+RIF+PZA. For anergic participants the initial statistically non-significant benefit 1 year after INH treatment (RR 0.74, 95% CI 0.30 to 0.1.79) (Whalen 1997-anergy) remained at 2 years (adjusted relative risk 0.61 (95% CI 0.32 to 1.16) (Johnson 2001 -anergy).

The long-term follow-up results for the studies mentioned above should be interpreted with caution as there was substantial loss to follow-up in all trials which may have introduced bias.

DEATH FROM ALL CAUSES

We found no evidence that preventive therapy versus placebo reduced all-cause mortality (9 trials; 5762 participants; RR 0.94, 95% CI 0.85 to 1.05) or reduced mortality among those who were PPD positive (4 trials, 2378 participants, RR 0.80, 95% CI 0.63 to 1.02), however these findings were heterogeneous (p=0.04).

The single placebo-controlled trial that assessed the effect of INH by stage of HIV/AIDS at baseline found no difference (Gordin 1997): with AIDS (RR 0.96, 95% CI 0.79 to 1.17), without AIDS (RR 1.07, 95% CI 0.84 to 1.35).

There was reduction in mortality with INH monotherapy versus placebo among individuals with a positive tuberculin skin test (RR 0.74, 95% CI 0.55 to 1.00).

We found no differences in the effect on death by study drug with the exception of INH+RIF, which was associated with a significant reduction in the risk of death (2 trials; 1179 participants; OR 0.69, 95% CI 0.50 to 0.95). Direct comparison of different drug regimens revealed no differences.Analysis 3.3.

AIDS

Based on data from two trials of an INH based regimen versus placebo (Fitzgerald 2001; Pape 1993), we found no evidence of a reduction in the incidence of AIDS (RR 0.88, 95% CI 0.60 to 1.28). However, one trial (Pape 1993) found a lower risk of AIDS in PPD + individuals (RR 0.36, 95% CI 0.15 to 0.85), but not in those with a negative skin test (RR 0.78, 95% CI 0.27 to 2.20). Pape 1993 also found a significant increase in the mean time to AIDS (in months) (WMD 7.8, 95% CI 1.71 to 13.89) Analysis 2.4.

ADVERSE EVENTS

We extracted available data on adverse events deemed by the investigators as serious enough to discontinue treatment. Compared to placebo, preventive therapy led to more adverse events (6 trials; 5525 participants; RR 2.55, 95% CI 1.70 to 3.85) Analysis 1.5.

The likelihood of stopping treatment due to adverse effects was higher for combination therapies than for INH monotherapy:

Compared with placebo (i.e. indirect comparison)

- INH: 6 trials; RR 1.66, 95% CI 1.09 to 2.51 Analysis 2.5
- INH+RIF: 2 trials; RR 16.72, 95% CI 3.29 to 84.89 Analysis 3.5
- RIF+PZA: 2 trials; RR 7.84, 95% CI 2.60 to 23.67 Analysis 4.5
- INH+RIF+PZA: 1 trial; RR 26.11, 95% CI 3.56 to 191.63 Analysis 5.5

Direct comparisons:

- INH vs RIF+PZA: 5 trials; RR 0.63, 95% CI 0.48 to 0.84 Analysis 6.5
- INH vs INH+RIF: 4 trials; RR 0.79, 95% CI 0.50 to 1.23 Analysis 7.5
- INH+RIF vs RIF+PZA: 2 trials; RR 0.85, 95% CI 0.50 to 1.46 Analysis 8.5
- INH vs INH+RIF+PZA: 1 trial; RR 0.10, 95% CI 0.03 to 0.33 Analysis 9.5
- INH+RIF vs INH+ RIF+PZA: 1 trial; RR 0.42, 95% CI 22 to 0.80 Analysis 10.5

ADHERENCE

Overall, about half of the studies reported on adherence to therapy (Halsey 1998; Hawken 1997; Martinez 2000; Mohammed 2007; Mwinga 1998; Rivero 2007; Whalen 1997). Differences in the definition of adherence and the level of detail varied across the studies. There is some evidence that the length of treatment may be related to degree of adherence. Halsey 1998 reported higher rates of adherence with a 2 months course of RIF+PZA as compared to 6 months of INH. Martinez 2000 reported better adherence with 3 months INH+RIF compared to 12 months INH. On the other hand, Whalen 1997, reported no difference among treatment groups which included INH for 6 months, INH+RIF for 3 months and INH+RIF+PZA for 3 months. Hawken 1997, a placebo-controlled trial of INH for 6 months, found no difference in adherence rates between the two study arms. Mohammed 2007 reported a median adherence of 87% in the INH group and 81.2% in the placebo group while Rivero 2007 reported an adherence of 64.5%, 63.0% and 62.4% in the INH, INH+RIF and RIF+PZA treatment groups respectively. We did not have sufficient data to assess adherence as an effect modifier in the studies included in the review.

DISCUSSION

Despite the availability of ART, many patients living with HIV are still dying from TB and measures to control opportunistic infections such as TB are especially important. This systematic review which updates a previous Cochrane review (Woldehanna 2004) confirms that treatment of latent TB reduces the risk of clinical tuberculosis in HIV infected populations by 32%. Although there was reduction in mortality with INH monotherapy versus placebo among individuals with a positive tuberculin skin test and in those treated with INH plus rifampicin versus placebo regardless of tuberculin skin test status, overall, there was no evidence that TB preventive therapy versus placebo reduced all-cause mortality. The impact of INH preventive therapy on mortality is of public health importance as INH is commonly used in most resource poor countries and it's being scaled up as part of the WHO Three I's initiative (WHO 2008 (2)). Globally, less than 30, 000 HIV-infected people were reported to have been started on INH preventive therapy in 2007 – equivalent to just 0.1% of the 33 million people estimated to be infected with HIV (WHO 2009). Though the major findings of this updated review are not different from those reported in the original review, overall, they provide more up-to-date evidence in support of the use of TB preventive therapy in people living with HIV.

For INH monotherapy, compared with placebo, the short-term reduction in relative risk of one-third is only half of that in people who are HIV-negative (Smieja 2003), the absolute risk reduction (ARR) for active tuberculosis is greater (2% vs 1%). In HIV positive and negative individuals the pooled number-needed-to-treat (NNT) to prevent one case of TB is therefore 50 and 100, respectively. However, among people infected with HIV who have a positive tuberculin test, chemoprophylaxis appears to be substantially more beneficial (INH: ARR 5%, NNT 20). The combined NNT should, however, be interpreted with caution as NNTs in individual trials will be influenced by a number of factors, including baseline incidence rates, misclassification of cases and duration of follow-up.

How long the initial benefit conferred by anti-tuberculosis drugs on the incidence of active tuberculosis persists is not known with certainty. Based on one study with limited follow-up (median duration of follow-up 1.8 years), it seems that the initial protection conferred by chemoprophylaxis may diminish over time (Mwinga 1998). Whether HIV positive individuals living in areas of high TB prevalence should receive repeated courses of preventive treatment or even remain on life-long treatment cannot be answered from currently available research.

Although there appears to be no difference in benefit from alternative anti-tuberculosis drugs/drug combinations for the outcomes examined, current trials do not provide sufficient data on drug resistance and adherence to treatment which, along with information on cost, would be important for choosing a particular drug regimen. Adverse effects leading to discontinuation of treatment were more common in trials using multi-drug combination therapy as opposed to INH alone.

The finding from one study that preventive therapy may reduce the incidence of AIDS and time to full-blown disease is plausible (Pape 1993). It is known that *M. tuberculosis* can activate HIV-infected CD4 lymphocytes and this may lead to progression from HIV infection to clinical AIDS (Daniel 2000). This observation, however, awaits confirmation in further trials.

Currently available trials do not provide sufficient data to draw firm conclusions about the value of preventive therapy for improving survival in persons infected with HIV. It was also not possible to determine whether the effects of treatment are influenced by the stage of HIV disease at baseline and also evidence on the optimal duration of TB preventive therapy is still lacking.

Potential limitations of the review

In this updated review, a comprehensive search strategy was used to identify all new studies and one author was contacted for clarification of reported findings. Methods to minimize systematic error were used in the extraction of data and assessment of methodological quality of included studies. While all trials seemed to be of good quality some key components, such as allocation concealment, were not reported in all the studies. Although the trial characteristics varied, there was no statistical heterogeneity for the primary outcomes assessed in this updated review. As

non-tuberculous Mycobacteria also occur commonly among HIV-infected patients, studies that did not speciate positive cultures might erroneously have included non-tuberculous Mycobacteria as cases of TB. Furthermore, there were no studies that examined the combination of TB preventive therapy and ART. Finally, as most of the trials were conducted in developing countries, the results of this review are likely to be applicable to the situations where the burden of tuberculosis is high and preventive therapy is most needed.

AUTHORS' CONCLUSIONS

Implications for practice

Current guidelines and policy statements regarding the use of preventive therapy in HIV infected individuals who are TST positive (CDC 1998; WHO 1998; WHO 2004) are supported by the results of this review. However, in developing countries, especially in Africa, where the rates of both tuberculosis and HIV infection are high, logistical and financial barriers to wide-scale use of TB preventive therapy need to be critically examined. There is evidence to show that ART can be feasibly administered in resource-limited settings (Akileswaran 2005).Therefore, the experiences from ART scale-up may be beneficial in the scale-up of TB preventive therapy. Importantly, care should be taken to ensuring that programmes of TB preventive therapy do not divert resources from treating active tuberculosis or from offering ART to the large numbers of people who may need these treatments. In addition, poor adherence and drug resistant TB disease potentially associated with the use of long courses of isoniazid monotherapy should be considered although available evidence does not show a significant increase in the risk of INH resistance (Balcells 2006). Policy makers should take all these factors into consideration when designing broad public health interventions in the area of TB control in people living with HIV.

Implications for research

Trials assessing the long-term effects of anti-TB chemoprophylaxis are needed to more adequately assess the duration of benefit in various settings. These trials should be large enough to assess overall mortality as an endpoint and should also assess the impact of preventive treatment on progression of HIV disease. Whether the level of immunocompromise in HIV positive individuals influences the efficacy of preventive therapy is still not known and this question warrants further study. With the current scale-up of ART services, trials that will evaluate the effectiveness of the combination of TB preventive therapy and ARTneed to be conducted particularly in developing countries and the cost-effectiveness of anti-tuberculosis drugs compared to highly active antiretroviral therapy for preventing active tuberculosis should also be evaluated.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Fitzgerald 2001

Methods	237 individuals "randomized"; blinding: providers unclear, participants unclear, assessors unclear. 54 (23%) lost to follow-up; intention to treat analysis.
Participants	HIV positive, PPD negative individuals living in Haiti. Inclusion criteria: Age >18 years; HIV symptom free (CDC category A); PPD < 5mm induration; informed consent; negative sputum examination results by smear and culture; negative chest x-ray; no history of TB. Exclusion Criteria: Positive sputum examination results by smear and culture; a history of TB; pregnant.
Interventions	1) Control (placebo) plus pyridoxine (vitamin B6): 50 mg daily for 1 year. 2) INH 300 mg plus pyridoxine 50 mg daily for 1 year.
Outcomes	1) Active TB: ATS definition- 2 of the following required a) clinical symptoms suggesting TB, b) AFB on Ziehl Nielsen stain or MTb cultured from sputum or biopsy sample, c) chest X-ray independently evaluated as highly suggestive of TB. If no microbiological confirmation, response to anti-TB meds required. 2) AIDS: CDC classification of HIV infection. 3) Death. -- Mean duration of follow-up 2.5 years.
Notes	All patients were treated for opportunistic infections but none were on ART. 91% had +ve reactions to candida + mumps.

Risk of bias

Bias	Authors' judgement	Support for judgement

Fitzgerald 2001 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear
Blinding? All outcomes	Unclear risk	Unclear for providers, participants and assessors
Incomplete outcome data addressed? All outcomes	Low risk	23% lost to follow-up

Gordin 1997

Methods	517 individuals, centralized randomisation, stratified by study unit, permuted blocks; blinding: providers yes, participants yes, assessors yes. 34 (7%) lost to follow-up; intention to treat analysis
Participants	HIV positive patients attending AIDS research clinics in the US. Inclusion criteria: Anergic (PPD less than 5mm induration AND less than 2mm induration to mumps antigen and tetanus toxoid); age >= 13+ years; no active TB; written consent. Exclusion Criteria: household TB contact in past year, on drugs with activity against TB, acute hepatitis, peripheral neuropathy, history of positive PPD, intolerance to study drug, treatment for >= 1 month with drug active against TB.
Interventions	1) Control (Placebo) plus pyridoxine 50mg daily for 6months. 2) INH 300mg plus pyridoxine 50mg daily for 6months.
Outcomes	1) Active TB (primary end point): positive culture from any source. 2) Probable TB: clinical features of TB plus a response to anti-TB drugs or autopsy evidence of granulomata containing AFB. 3) Progression of HIV disease: first occurrence of an AIDS-defining condition. 4) Death. 5) Adverse effects.-- Mean duration of follow-up 33.5 months.
Notes	Use of ART 73.2% in control arm and 72.7% in INH arm.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate
Blinding? All outcomes	Low risk	Blinding of providers, participants and assessors
Incomplete outcome data addressed? All outcomes	Low risk	7% lost to follow-up

Gordin 2000

Methods	1583 individuals "randomized," stratified by clinic; blinding: providers no, participants no, assessors yes. 115 (7%) lost to follow-up; intention to treat analysis.
Participants	Patients attending HIV/AIDS clinics in US, Mexico, Haiti and Brazil. Inclusion criteria: HIV positives, age >= 13 years, >=5mm induration to 5 U PPD or documented history of positive test, informed consent. Exclusion Criteria: Active TB, current treatment with fluoroquinolones or history of >2 mo treatment with anti-TB drugs, intolerance to study drugs, acute hepatitis or peripheral neuropathy, pregnancy.

Gordin 2000 *(Continued)*

Interventions	1) INH 300mg plus pyridoxine 50mg daily for 12 months. 2) RIF 600mg plus PZA 20mg/kg, daily for 2 months.
Outcomes	1) Active TB: positive culture from any source. 2) Probable TB: clinical evidence from a physical examination. 3) Clinical progression of HIV disease: first occurrence of AIDS defining condition. 4) Death. 5) Adverse Effects. -- Mean duration of follow-up 37months.
Notes	Use of ART at baseline 35.8% in INH arm and 36.8% in RIF/PZA arm. "Progression of HIV was not reliably diagnosed in Haiti."

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear
Blinding? All outcomes	Low risk	Blinding of assessors only, no blinding of providers or participants
Incomplete outcome data addressed? All outcomes	Low risk	7% lost to follow-up

Halsey 1998

Methods	784 individuals "randomized" with assignment in blocks of 4 or 6; sealed, sequentially numbered envelopes but not described as opaque; blinding: providers no, participants no, assessors yes. 85 (11%) lost to follow-up; 96% included in analysis.
Participants	HIV-1 positive individuals living in Haiti. Inclusion criteria: Adults 16 to 77 years, verbal consent, PPD >=5mm, HIV-1 positive (2 positive EIA or rapid test followed by positive EIA confirmed by Western blot). Exclusion Criteria: Evidence of TB, pregnant, negative or indeterminate western blot.
Interventions	1) INH 600 mg plus pyridoxine 25mg twice weekly for 6 months. 2) RIF 450mg plus PZA1500mg twice weekly, for 2 months.
Outcomes	1) Confirmed TB: positive culture with a compatible clinical illness. 2) Probable TB: positive smear or characteristic morphology and clinically compatible disease. 3) Possible TB: clinically compatible disease responding to anti-TB therapy. 4) Adverse reactions. -- Median duration of follow-up 2.5 years.
Notes	Reasons for exclusion from analysis: 23 HIV-1 neg or indeterminate on Western blot; 10 had a PPD <5mm; 1 had a abnormal CXR .

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear
Blinding? All outcomes	Low risk	Blinding of assessors only, no blinding of providers or participants
Incomplete outcome data addressed? All outcomes	Low risk	11% lost to follow-up

Hawken 1997

Methods	684 individuals randomized using computer generated random numbers, permuted blocks of 10; labelled tablet packs; blinding: providers yes, participants yes, assessors unclear. 151 (22%) lost to follow-up; 98% included in analysis.
Participants	HIV-1 positive commercial sex workers and patients attending STD clinics in Nairobi Kenya. Inclusion criteria: HIV-1 positive (two ELISA tests), local residents, age 14-65 years. Consent- not mentioned. Exclusion Criteria: Past history of TB, current TB suspected, abnormal liver enzymes, life threatening intercurrent illness, pregnant.
Interventions	1) Control (Placebo) daily for 6 months. 2) INH 300mg daily for 6months.
Outcomes	1) TB: symptoms plus either a) >= 1 positive culture or b) TB histology and no response to broad-spectrum antibiotics for 7 days, and a resolution of symptoms and X-ray findings on anti-TB treatment by 12 weeks. 2) Death. 3) Adverse effects. 4) HIV disease progression: decline in CD4 counts. -- Median duration of follow-up 1.83 years.
Notes	12 patients were excluded after enrolment for the following reasons: TB within 30 days of enrolment (3), abnormal chest X ray at enrolment found on review (3), abnormal liver enzymes at enrolment (1), HIV-negative (4), needed hospital referral after enrolment (1).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate
Blinding? All outcomes	Unclear risk	Blinding of providers and participants, unclear if blinding of assessors
Incomplete outcome data addressed? All outcomes	Low risk	22% lost to follow-up

Martinez 2000

Methods	133 individuals assigned by "random number method"; blinding: providers no, participants no, assessors unclear. 30 (23%) lost to follow-up; intention to treat analysis.
Participants	HIV positive patients living in areas of high tuberculosis incidence in Spain. Inclusion criteria: HIV positive, PPD >=5mm or anergic (a negative PPD and induration <2 mm after 48 hours to 7 antigens Multitest IMC), Institut Merieux, Lyon, France), consent. Exclusion Criteria: Contraindications to the study drugs, liver disease, pregnant or lactating, on drugs that could interfere with RIF metabolism, active TB, previous TB prophylaxis.
Interventions	1) INH 300 mg daily for 12 months. 2) RIF 600mg plus INH 300 mg daily for 3 months.
Outcomes	1) Active TB: positive microscopy and confirmation by culture. 2) Adverse effects. -- Mean duration of follow-up= 17 months.
Notes	

Risk of bias

Martinez 2000 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear
Blinding? All outcomes	Unclear risk	Unclear if blinding of assessors only, no blinding of providers or participants
Incomplete outcome data addressed? All outcomes	Low risk	23% lost to follow-up

Mohammed 2007

Methods	98 individuals, using computer generated randomization in blocks of 20; sealed envelopes; blinding: providers yes, participants yes, asserssors yes. 23 (23.5%) lost to follow-up; intention to treat analysis.
Participants	PPD negative HIV positive patients with clinically advanced disease attending three University affliated HIV clinics in Cape Town, South Africa. Inclusion criteria: HIV infection, adults (aged ≥18 years), WHO clinical stage 3 or 4, signed informed consent, known TST status and nomination of a treatment supervisor. Exclusion criteria: activeTB, history of TB within the past 5 years, active alcoholabuse, pregnancy and treatment with antiretroviraltherapy (ART).
Interventions	1) Control (matching placebo) daily twice weekly for 12 months. 2) INH (15 mg/kg/dose: 900 mg for those ≥55 kg and 800 mg for those ≤55 kg).
Outcomes	1) Definite TB: culture-positive together with appropriate symptoms or radiographic appearances. 2) Probable TB: smear positive. 3) Possible TB: clinical diagnosis together with a response to therapy. 4) Death. 5) Hospitalization. 6) Adherence. 7) Change in CD4+ lymphocyte count. 8) Adverse effects.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate
Blinding? All outcomes	Low risk	Blinding of providers, participants and assessors
Incomplete outcome data addressed? All outcomes	Low risk	23.5% lost to follow-up

Mwinga 1998

Methods	1053 individuals assigned using computer generated random method and blocks of 30; serially numbered sealed envelopes not stated to be opaque; blinding: providers yes participants yes, assessors yes. 332 (32%) lost to follow-up; 98% included in analysis
Participants	HIV positive patients in Lusaka, Zambia. Inclusion criteria: HIV positive (2 positive ELISA tests); over 15 years of age; written consent. Exclusion Criteria: Previous history of treatment of TB; abnormal liver function tests; evidence of TB; pregnant; unable to attend study clinic.

Mwinga 1998 *(Continued)*

Interventions	1) Placebo twice a week for 6 months or 3 months. 2) INH 900 mg, twice a week, for 6 months. 3) RIF 600mg plus PZA 3500 mg twice a week for 3 months.
Outcomes	1) Active TB (confirmed and presumed): includes a) Confirmed TB: positive smear or culture or positive histopathology; b) Presumed TB: abnormal X-ray and clinical symptoms responding to TB treatment in 2 months or pleural or pericardial effusion with a documented response to TB treatment within 2 months. 2) Probable tuberculosis. 3) Death. 4) Adverse events. -- Median duration of follow-up 1.8 years.
Notes	27 individuals were excluded after enrolment because they did not meet inclusion criteria: 22 were HIV negative, 3 were duplicates, 1 revealed previous history of TB treatment and 1 subject was discovered to have a TB positive culture. The long-term results of this study are published in the Quigley01

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate
Blinding? All outcomes	Low risk	Blinding of providers, participants and assessors
Incomplete outcome data addressed? All outcomes	Low risk	32% lost to follow-up

Pape 1993

Methods	118 individuals randomized using computer generated numbers; blinding: providers no, participants no, assessors yes. No loss to follow up; intention to treat analysis.
Participants	HIV positive patients living in Haiti. Inclusion criteria: Adults 18 to 65 years, symptom free, newly diagnosed as HIV positive (ELISA confirmed by western blot). Consent - non mentioned. Exclusion Criteria: History of TB, abnormal chest X ray or liver function tests.
Interventions	1) Pyridoxine 50 mg, daily for 12 months. 2) INH 300mg plus pyridoxine 50 mg daily for 12 months.
Outcomes	1) Active TB: Clinical response to TB therapy and at least 2 of: a) TB symptoms 4 weeks b) positive smear, culture or histology; c) chest X-ray suggestive of TB. 2) HIV disease: CDC class II or IVA. 3) AIDS: CDC class IV. 4) Death. -- Mean duration of follow-up= 36 months.
Notes	After 1989, control patients were offered INH- 21 of the 60 patients accepted.. Anergy screen included mumps, tricophyton and candida. The % of PPD+ in the INH plus pyridoxine group was significantly higher than the placebo group (66% vs. 38%).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear
Blinding? All outcomes	Low risk	Blinding of assessors only, no blinding of providers or participants
Incomplete outcome data addressed?	Low risk	No loss to follow-up

Pape 1993 *(Continued)*
All outcomes

Quigley 1998

Methods	1053 individuals using computer generated randomization and blocks of 30; serially numbered sealed envelopes not stated to be opaque; blinding: providers no (discontinued after initial phase), assessors yes. Awaiting data on patients lost to follow up.
Participants	As in Mwinga 98
Interventions	As in Mwinga 98
Outcomes	As in Mwinga 98. -- Mean duration of follow-up 3 years.
Notes	Long-term follow up of Mwinga98 study. Placebo group was offered 6 mo of INH after initial analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate
Blinding? All outcomes	Low risk	Blinding of providers, participants and assessors
Incomplete outcome data addressed? All outcomes	Low risk	32% lost to follow-up

Rivero 2003

Methods	319 individuals "randomized"; blinding: providers no, participants no, assessors unclear. 17 (5%) lost to follow-up; intention to treat analysis.
Participants	HIV positive anergy patients attending hospitals in Spain. Inclusion criteria: Confirmed HIV infection; age 18-65 yrs; anergy (defined as 0 mm induration after 48-72 hrs to 3 antigens applied by the Mantoux method: PPD, candida albicans and mumps antigens). Consent: none mentioned. Exclusion Criteria: Presence of active TB; previous treatment or chemoprohylaxis for TB; history of hypersensitivity to study drugs; Aspartate aminotransferase (ALT) > 4x normal values; Bilirubin > 2 mg/ml; Creatinine > 2 mg/ml; pregnancy.
Interventions	1) Control (No treatment). 2) INH 5 mg/kg (max 300 mg) daily for 6 months. 3) RIF 10 mg/kg (max 600 mg) plus INH 5 mg/kg (max 300 mg) daily for 3 months. 4) RIF 10 mg/kg (max 600 mg) plus PZA 2000 mg daily for 2 months.
Outcomes	1) Confirmed Tuberculosis: Confirmation by MTb culture. 2) Probable TB. 3) Death. 4) Adverse events. -- Mean duration of follow-up= 1.23 years.
Notes	

Risk of bias

Rivero 2003 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear
Blinding? All outcomes	Unclear risk	Blinding of assessors unclear, no blinding of providers or participants
Incomplete outcome data addressed? All outcomes	Low risk	5% lost to follow-up

Rivero 2007

Methods	316 individuals "randomized"; blinding: providers no, participants no, assessors unclear. 31 (9.8%) lost to follow-up; intention to treat analysis.
Participants	PPD positive HIV positive patients attending 12 hospitals in Spain. Inclusion criteria: HIV infection confirm by ELISA and western blot; age 18-65 yrs; life expectancy greater than 2 years; positive tuberculin skin reaction (defined as ≥5 mm induration after 48-72 hrs to 3 antigens applied by the Mantoux method). Consent: obtained from all selected subjects. Exclusion Criteria: Presence of active TB; previous treatment or chemoprophylaxis for TB; history of hypersensitivity to study drugs; Aspartate aminotransferase (ALT) > 4x normal values; Bilirubin > 2 mg/ml; Creatinine > 2 mg/ml; pregnancy.
Interventions	1) INH 5 mg/kg (max 300 mg) daily for 6 months. 2) RIF 10 mg/kg (max 600 mg) plus INH 5 mg/kg (max 300 mg) daily for 3 months. 3) RIF 10 mg/kg (max 600 mg) plus PZA 1500 mg daily for patients weighing <50 kg, 2000 mg daily for those weighing between 50 and 70 kg and 2500 mg for those weighing >70 kg all for 2 months.
Outcomes	1) Confirmed Tuberculosis: Confirmation by MTb culture. 2) Probable TB. 3) Probable TB: Clinical illness with response to tuberculosis treatment. 4) Adverse events. -- Mean duration of follow-up= ?.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear
Blinding? All outcomes	Unclear risk	Unclear if blinding of assessors, no blinding of providers or participants
Incomplete outcome data addressed? All outcomes	Low risk	9.8% lost to follow-up

Whalen 1997

Methods	2018 individuals "randomized" in blocks of 6; sequentially numbered, sealed opaque envelopes; blinding: providers no, participants no, assessors yes. No loss to follow up; intention to treat analysis.
Participants	PPD+ adults attending clinics or counselling centres for persons with HIV-1 infection in Kampala, Uganda. Inclusion criteria: Adults (18 to 50 years) with HIV-1 infection (ELISA test), PPD >=5mm, Karnofsky

Whalen 1997 *(Continued)*

	performance score >50, verbal consent. Exclusion Criteria: Active TB, previous treatment for TB, use of antiviral drugs, anaemia, liver or kidney disease, pregnancy test, home >20km from project clinic, advanced HIV disease, serious medical illness not related to HIV.
Interventions	1) Control (Placebo) 250mg ascorbic acid daily for 6 months. 2) INH 300mg daily for 6 months. 3) INH 300mg plus RIF 600mg daily for 3 months. 4) INH 300mg plus RIF 600mg plus PZA 2000mg, daily for 3months.
Outcomes	1) Definite TB: Culture confirmed. 2) Probable TB: Clinical illness consistent with TB based on at least 2 of the following: a) results of chest X-ray; b) positive smear c) response to anti-TB therapy. 3) Adverse reactions. 4) Death. -- Mean duration of follow-up= 15 months.
Notes	After interim analysis INH was offered to placebo group. The long-term results of this study are published in Johnson01.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate
Blinding? All outcomes	Low risk	Blinding of assessors only, no blinding of providers or participants
Incomplete outcome data addressed? All outcomes	Low risk	No loss to follow-up

Whalen 1997-anergy

Methods	718 individuals "randomized" in blocks of 6. Sequentially numbered, sealed opaque envelopes; blinding: providers no, participants no, assessors yes. 103 (14%) lost to follow-up; intention to treat analysis.
Participants	As in Whalen 97 except patients had to be anergic. Anergy was defined as 0mm induration in reaction to both PPD and candida antigens.
Interventions	1) Control (placebo) Ascorbic acid 250mg daily for 6 months. 2) INH 300mg, daily for 6 months.
Outcomes	As in Whalen 97. -- Mean duration of follow-up 12 months.
Notes	The long-term results of this study are published in Johnson01anergy.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate
Blinding? All outcomes	Low risk	Blinding of assessors only, no blinding of providers or participants
Incomplete outcome data addressed? All outcomes	Low risk	14% loss to follow-up

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Fitzgerald 2000	Only evaluated preventive therapy to reduce recurrence of TB in individuals who had previously had the disease, not to prevent occurrence of 1st TB.
Garcia 1993	Assessed drug tolerability rather than prevention of active TB
Grant 2005	Assessed the effect on incidence of TB of enrolment in a clinic that offered INH under routine conditions. Participants were not randomized into INH or placebo.
Matteelli 1998	Assessed drug tolerability rather than prevention of active TB
Saenghirunvatta 1996	Described only as "prospective, comparative"

DATA AND ANALYSES

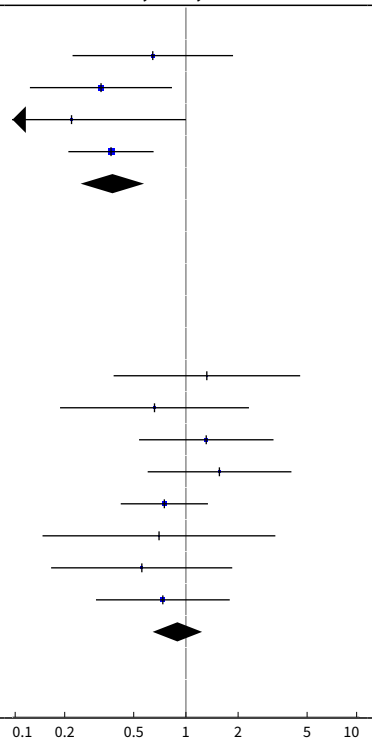
Comparison 1. Any TB drug vs placebo

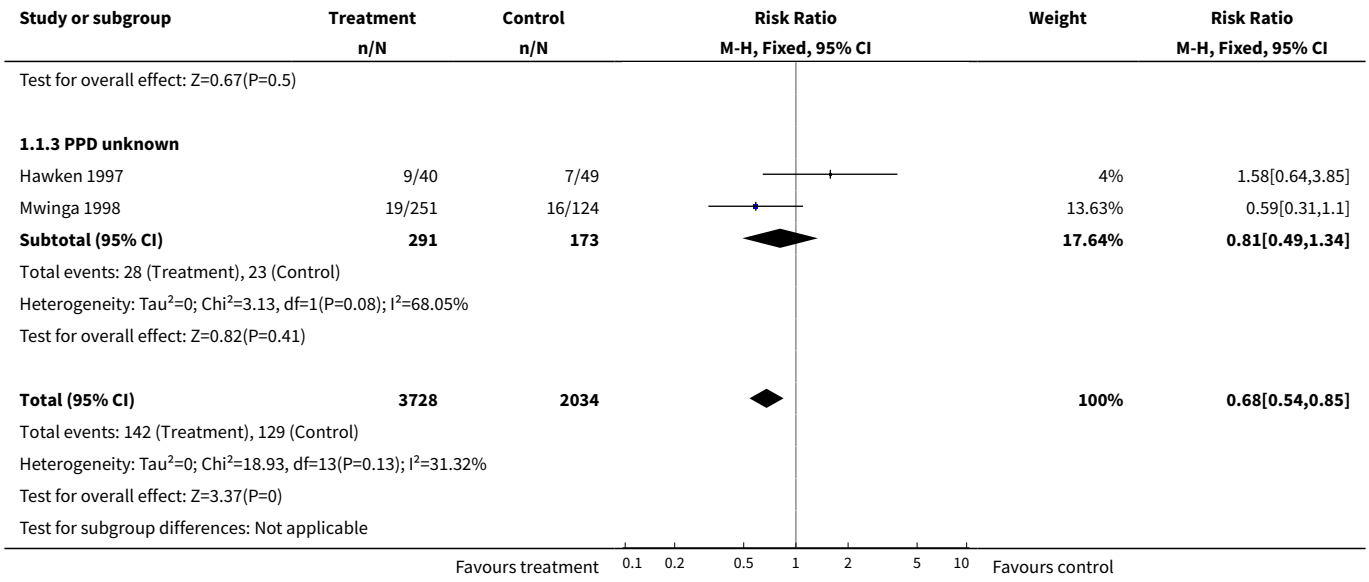
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of active TB (confirmed, probable or possible)	9	5762	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.54, 0.85]
1.1 PPD+	4	2378	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.25, 0.57]
1.2 PPD-	8	2920	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.64, 1.24]
1.3 PPD unknown	2	464	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.49, 1.34]
2 Incidence of confirmed TB	4	2573	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.49, 1.08]
2.1 PPD+	1	161	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.06, 1.57]
2.2 PPD-	3	1353	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.38, 1.45]
2.3 PPD unknown	2	1059	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.47, 1.32]
3 Incidence of death (all cause)	9	5762	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.85, 1.05]
3.1 PPD+	4	2378	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.63, 1.02]
3.2 PPD-	8	2920	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.89, 1.14]
3.3 PPD unknown	2	464	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.58, 1.24]
4 Incidence of AIDS	2	355	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.60, 1.28]
4.1 PPD+	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.15, 0.85]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.2 PPD-	2	292	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.72, 1.69]
4.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Incidence of adverse events leading to stopping treatment	8	5525	Risk Ratio (M-H, Fixed, 95% CI)	2.55 [1.70, 3.85]
6 Mean CD4 count	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.1 PPD+	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 PPD-	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 PPD unknown	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Mean time to TB	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Mean time to death	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Mean time to AIDS	1	118	Mean Difference (IV, Fixed, 95% CI)	7.80 [1.71, 13.89]

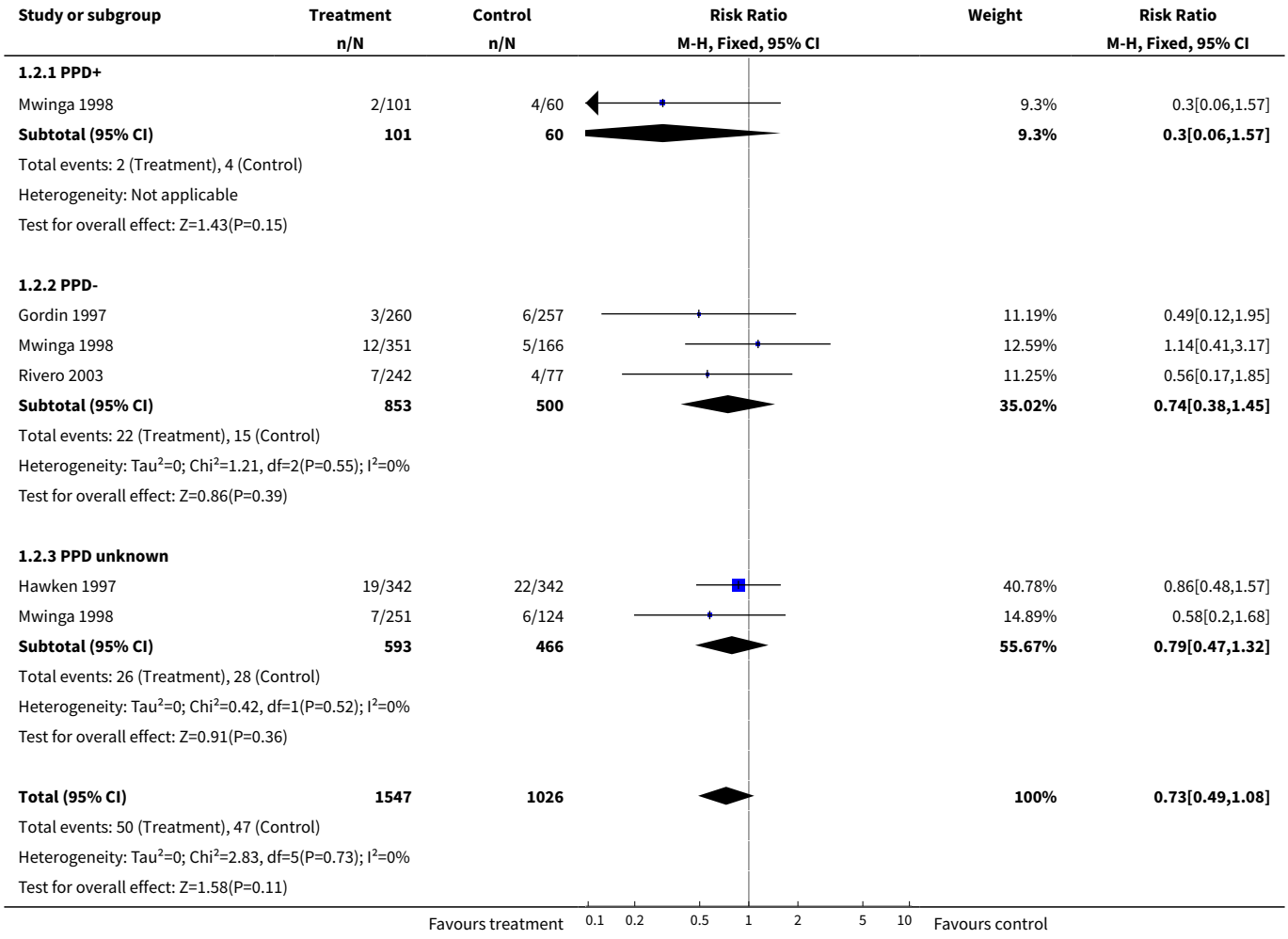
Analysis 1.1. Comparison 1 Any TB drug vs placebo, Outcome 1 Incidence of active TB (confirmed, probable or possible).

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 PPD+					
Hawken 1997	5/67	8/69		5.02%	0.64[0.22,1.87]
Mwinga 1998	6/101	11/60		8.78%	0.32[0.13,0.83]
Pape 1993	2/38	6/25		4.61%	0.22[0.05,1]
Whalen 1997	26/1554	21/464		20.58%	0.37[0.21,0.65]
Subtotal (95% CI)	**1760**	**618**		**38.99%**	**0.38[0.25,0.57]**
Total events: 39 (Treatment), 46 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.56, df=3(P=0.67); I^2=0%					
Test for overall effect: Z=4.55(P<0.0001)					
1.1.2 PPD-					
Fitzgerald 2001	6/126	4/111		2.71%	1.32[0.38,4.56]
Gordin 1997	4/260	6/257		3.84%	0.66[0.19,2.31]
Hawken 1997	11/235	8/224		5.21%	1.31[0.54,3.2]
Mohammed 2007	9/48	6/50		3.74%	1.56[0.6,4.06]
Mwinga 1998	27/351	17/166		14.69%	0.75[0.42,1.34]
Pape 1993	2/20	5/35		2.31%	0.7[0.15,3.28]
Rivero 2003	7/242	4/77		3.86%	0.56[0.17,1.85]
Whalen 1997-anergy	9/395	10/323		7%	0.74[0.3,1.79]
Subtotal (95% CI)	**1677**	**1243**		**43.37%**	**0.89[0.64,1.24]**
Total events: 75 (Treatment), 60 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.86, df=7(P=0.8); I^2=0%					

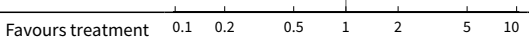




Analysis 1.2. Comparison 1 Any TB drug vs placebo, Outcome 2 Incidence of confirmed TB.

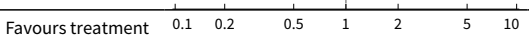


Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for subgroup differences: Not applicable					



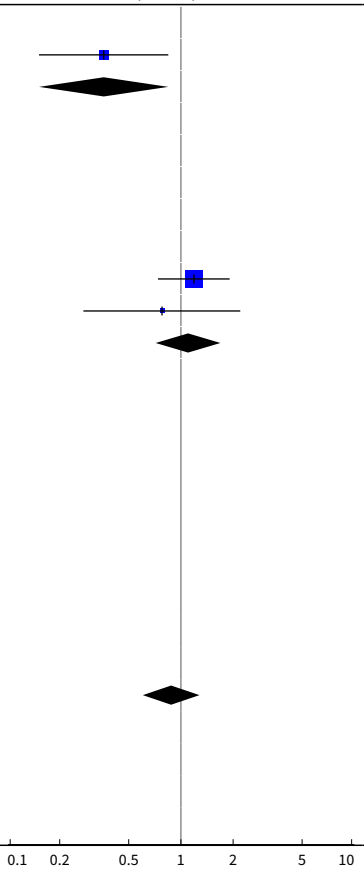
Analysis 1.3. Comparison 1 Any TB drug vs placebo, Outcome 3 Incidence of death (all cause).

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 PPD+					
Hawken 1997	3/67	9/69		1.75%	0.34[0.1,1.21]
Mwinga 1998	16/101	4/60		0.99%	2.38[0.83,6.78]
Pape 1993	3/38	7/25		1.67%	0.28[0.08,0.99]
Whalen 1997	173/1554	64/464		19.49%	0.81[0.62,1.05]
Subtotal (95% CI)	**1760**	**618**		**23.9%**	**0.8[0.63,1.02]**
Total events: 195 (Treatment), 84 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.53, df=3(P=0.04); I^2=64.82%					
Test for overall effect: Z=1.77(P=0.08)					
1.3.2 PPD-					
Fitzgerald 2001	19/126	15/111		3.15%	1.12[0.6,2.09]
Gordin 1997	129/260	126/257		25.06%	1.01[0.85,1.21]
Hawken 1997	50/235	37/224		7.49%	1.29[0.88,1.89]
Mohammed 2007	14/48	18/50		3.49%	0.81[0.46,1.44]
Mwinga 1998	69/351	28/166		7.52%	1.17[0.78,1.74]
Pape 1993	2/20	5/35		0.72%	0.7[0.15,3.28]
Rivero 2003	18/242	11/77		3.3%	0.52[0.26,1.05]
Whalen 1997-anergy	86/395	76/323		16.53%	0.93[0.71,1.21]
Subtotal (95% CI)	**1677**	**1243**		**67.26%**	**1.01[0.89,1.14]**
Total events: 387 (Treatment), 316 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.7, df=7(P=0.46); I^2=0%					
Test for overall effect: Z=0.09(P=0.93)					
1.3.3 PPD unknown					
Hawken 1997	9/40	11/49		1.96%	1[0.46,2.18]
Mwinga 1998	42/251	26/124		6.88%	0.8[0.51,1.24]
Subtotal (95% CI)	**291**	**173**		**8.84%**	**0.84[0.58,1.24]**
Total events: 51 (Treatment), 37 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.25, df=1(P=0.62); I^2=0%					
Test for overall effect: Z=0.88(P=0.38)					
Total (95% CI)	**3728**	**2034**		**100%**	**0.94[0.85,1.05]**
Total events: 633 (Treatment), 437 (Control)					
Heterogeneity: Tau^2=0; Chi^2=18.57, df=13(P=0.14); I^2=30%					
Test for overall effect: Z=1.09(P=0.28)					
Test for subgroup differences: Not applicable					



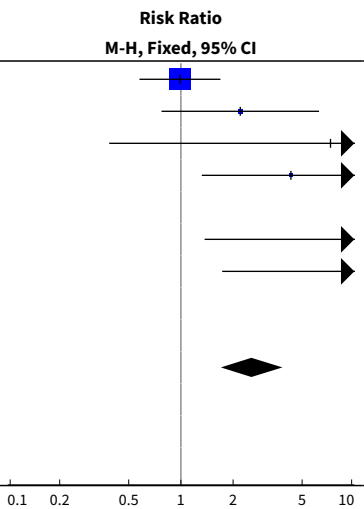
Analysis 1.4. Comparison 1 Any TB drug vs placebo, Outcome 4 Incidence of AIDS.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 PPD+					
Pape 1993	6/38	11/25		29.97%	0.36[0.15,0.85]
Subtotal (95% CI)	**38**	**25**		**29.97%**	**0.36[0.15,0.85]**
Total events: 6 (Treatment), 11 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.34(P=0.02)					
1.4.2 PPD-					
Fitzgerald 2001	31/126	23/111		55.24%	1.19[0.74,1.91]
Pape 1993	4/20	9/35		14.78%	0.78[0.27,2.2]
Subtotal (95% CI)	**146**	**146**		**70.03%**	**1.1[0.72,1.69]**
Total events: 35 (Treatment), 32 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.52, df=1(P=0.47); I^2=0%					
Test for overall effect: Z=0.44(P=0.66)					
1.4.3 PPD unknown					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**184**	**171**		**100%**	**0.88[0.6,1.28]**
Total events: 41 (Treatment), 43 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.79, df=2(P=0.06); I^2=65.44%					
Test for overall effect: Z=0.68(P=0.5)					
Test for subgroup differences: Not applicable					

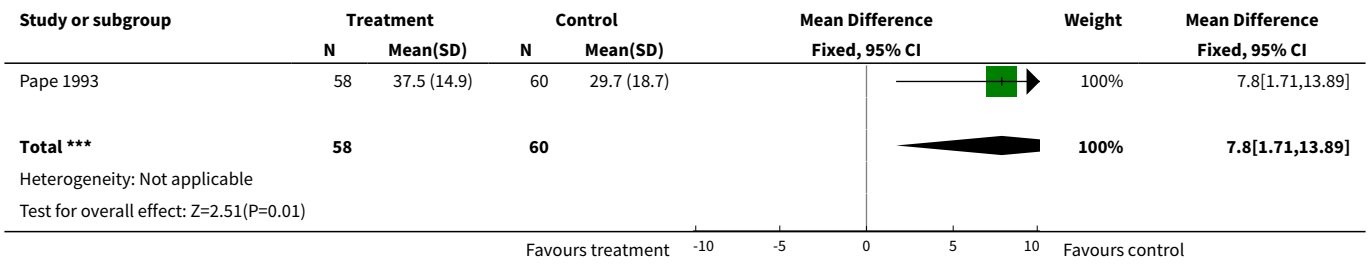


Analysis 1.5. Comparison 1 Any TB drug vs placebo, Outcome 5 Incidence of adverse events leading to stopping treatment.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Gordin 1997	24/260	24/257		67.18%	0.99[0.58,1.69]
Hawken 1997	11/342	5/342		13.92%	2.2[0.77,6.26]
Mohammed 2007	3/48	0/50		1.36%	7.29[0.39,137.42]
Mwinga 1998	26/703	3/350		11.15%	4.31[1.32,14.16]
Pape 1993	0/58	0/60			Not estimable
Rivero 2003	34/242	0/77		2.11%	22.15[1.37,357.06]
Whalen 1997	42/1554	1/464		4.29%	12.54[1.73,90.87]
Whalen 1997-anergy	0/395	0/323			Not estimable
Total (95% CI)	**3602**	**1923**		**100%**	**2.55[1.7,3.85]**
Total events: 140 (Treatment), 33 (Control)					
Heterogeneity: Tau^2=0; Chi^2=18.04, df=5(P=0); I^2=72.28%					
Test for overall effect: Z=4.48(P<0.0001)					



Analysis 1.9. Comparison 1 Any TB drug vs placebo, Outcome 9 Mean time to AIDS.



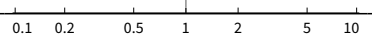
Comparison 2. Isoniazid vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of active TB (confirmed, probable or possible)	8	4136	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.51, 0.87]
1.1 PPD+	4	1311	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.22, 0.61]
1.2 PPD-	7	2490	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.59, 1.26]
1.3 PPD unknown	2	335	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.48, 1.52]
2 Incidence of confirmed TB	4	2063	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.47, 1.11]
2.1 PPD+	1	112	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 2.32]
2.2 PPD-	3	1021	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.36, 1.61]
2.3 PPD unknown	2	930	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.46, 1.36]
3 Incidence of death (all cause)	8	4136	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.85, 1.06]
3.1 PPD+	4	1311	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.55, 1.00]
3.2 PPD-	7	2490	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.90, 1.16]
3.3 PPD unknown	2	335	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.52, 1.27]
4 Incidence of AIDS	2	355	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.60, 1.28]
4.1 PPD+	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.15, 0.85]
4.2 PPD-	2	292	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.72, 1.69]
4.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Incidence of adverse events leading to stopping treatment	7	3899	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [1.09, 2.51]

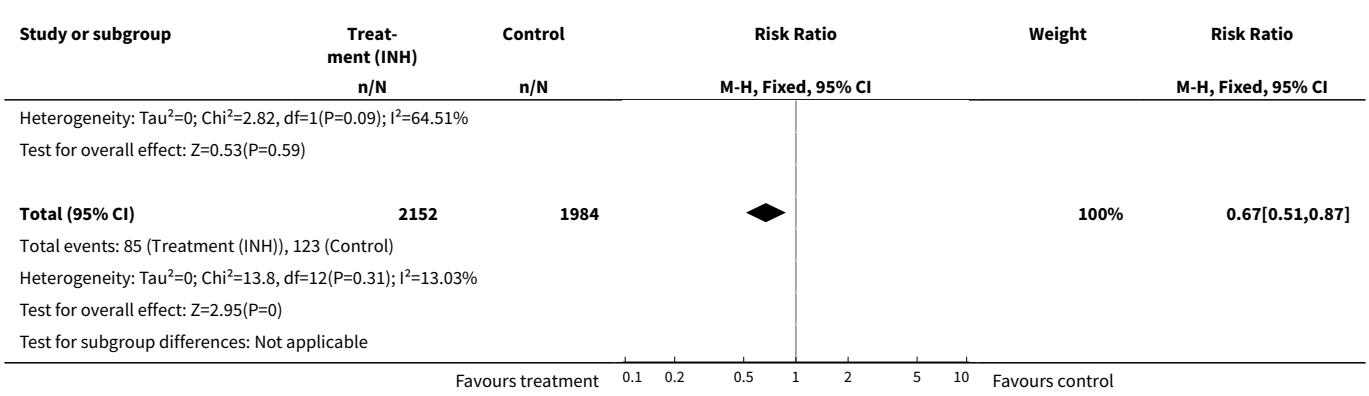
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6 Mean CD4 count	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.1 PPD+	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 PPD-	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 PPD unknown	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Mean time to TB	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Mean time to death	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Mean time to AIDS	1	118	Mean Difference (IV, Fixed, 95% CI)	7.80 [1.71, 13.89]

Analysis 2.1. Comparison 2 Isoniazid vs placebo, Outcome 1 Incidence of active TB (confirmed, probable or possible).

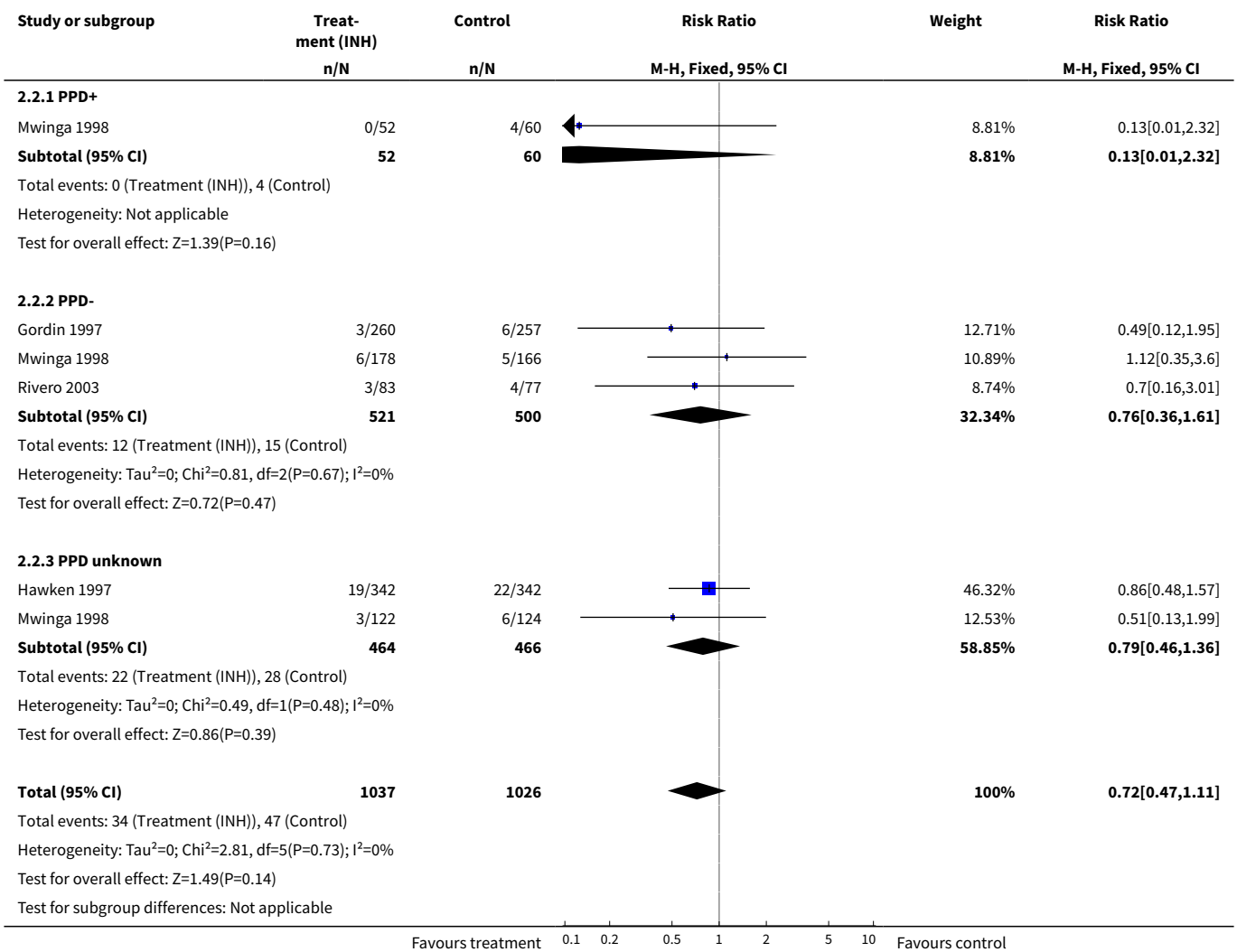
Study or subgroup	Treat-ment (INH) n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 PPD+					
Hawken 1997	5/67	8/69		6.31%	0.64[0.22,1.87]
Mwinga 1998	4/52	11/60		8.18%	0.42[0.14,1.24]
Pape 1993	2/38	6/25		5.8%	0.22[0.05,1]
Whalen 1997	7/536	21/464		18.03%	0.29[0.12,0.67]
Subtotal (95% CI)	**693**	**618**		**38.32%**	**0.36[0.22,0.61]**
Total events: 18 (Treatment (INH)), 46 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.88, df=3(P=0.6); I^2=0%					
Test for overall effect: Z=3.78(P=0)					
2.1.2 PPD-					
Fitzgerald 2001	6/126	4/111		3.41%	1.32[0.38,4.56]
Gordin 1997	4/260	6/257		4.83%	0.66[0.19,2.31]
Hawken 1997	11/235	8/224		6.56%	1.31[0.54,3.2]
Mwinga 1998	14/178	17/166		14.09%	0.77[0.39,1.51]
Pape 1993	2/20	5/35		2.91%	0.7[0.15,3.28]
Rivero 2003	3/83	4/77		3.32%	0.7[0.16,3.01]
Whalen 1997-anergy	9/395	10/323		8.81%	0.74[0.3,1.79]
Subtotal (95% CI)	**1297**	**1193**		**43.93%**	**0.86[0.59,1.26]**
Total events: 49 (Treatment (INH)), 54 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.87, df=6(P=0.93); I^2=0%					
Test for overall effect: Z=0.76(P=0.45)					
2.1.3 PPD unknown					
Hawken 1997	9/40	7/49		5.04%	1.58[0.64,3.85]
Mwinga 1998	9/122	16/124		12.71%	0.57[0.26,1.24]
Subtotal (95% CI)	**162**	**173**		**17.75%**	**0.86[0.48,1.52]**
Total events: 18 (Treatment (INH)), 23 (Control)					



Favours treatment — Favours control

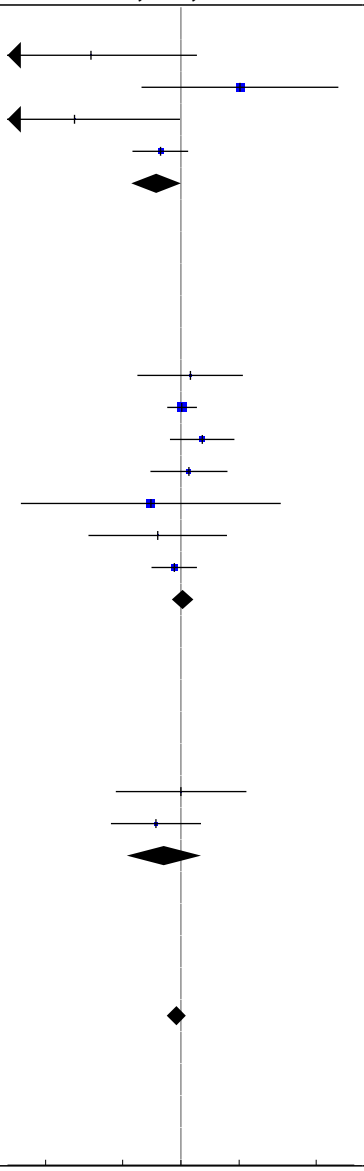


Analysis 2.2. Comparison 2 Isoniazid vs placebo, Outcome 2 Incidence of confirmed TB.



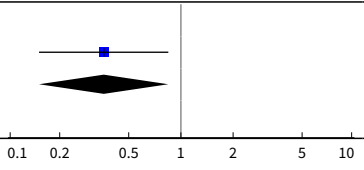
Analysis 2.3. Comparison 2 Isoniazid vs placebo, Outcome 3 Incidence of death (all cause).

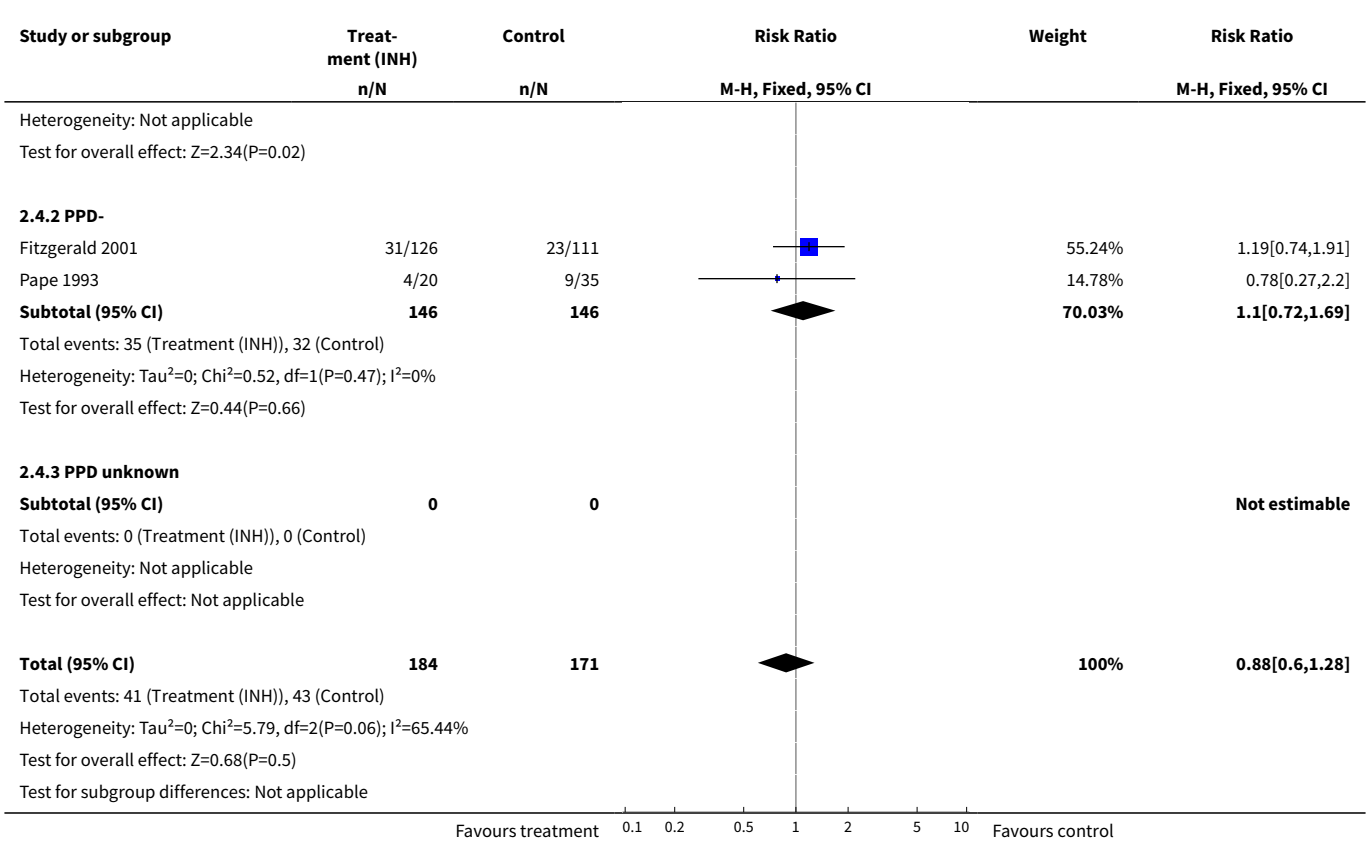
Study or subgroup	Treatment (INH) n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 PPD+					
Hawken 1997	3/67	9/69		2.05%	0.34[0.1,1.21]
Mwinga 1998	7/52	4/60		0.86%	2.02[0.63,6.51]
Pape 1993	3/38	7/25		1.95%	0.28[0.08,0.99]
Whalen 1997	58/536	64/464		15.83%	0.78[0.56,1.09]
Subtotal (95% CI)	**693**	**618**		**20.68%**	**0.74[0.55,1]**
Total events: 71 (Treatment (INH)), 84 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.63, df=3(P=0.08); I^2=54.74%					
Test for overall effect: Z=1.96(P=0.05)					
2.3.2 PPD-					
Fitzgerald 2001	19/126	15/111		3.68%	1.12[0.6,2.09]
Gordin 1997	129/260	126/257		29.23%	1.01[0.85,1.21]
Hawken 1997	50/235	37/224		8.74%	1.29[0.88,1.89]
Mwinga 1998	33/178	28/166		6.68%	1.1[0.7,1.74]
Pape 1993	2/20	5/35		0.84%	0.7[0.15,3.28]
Rivero 2003	9/83	11/77		2.63%	0.76[0.33,1.73]
Whalen 1997-anergy	86/395	76/323		19.29%	0.93[0.71,1.21]
Subtotal (95% CI)	**1297**	**1193**		**71.09%**	**1.02[0.9,1.16]**
Total events: 328 (Treatment (INH)), 298 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.83, df=6(P=0.83); I^2=0%					
Test for overall effect: Z=0.34(P=0.73)					
2.3.3 PPD unknown					
Hawken 1997	9/40	11/49		2.28%	1[0.46,2.18]
Mwinga 1998	19/122	26/124		5.95%	0.74[0.43,1.27]
Subtotal (95% CI)	**162**	**173**		**8.23%**	**0.81[0.52,1.27]**
Total events: 28 (Treatment (INH)), 37 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.39, df=1(P=0.53); I^2=0%					
Test for overall effect: Z=0.91(P=0.36)					
Total (95% CI)	**2152**	**1984**		**100%**	**0.95[0.85,1.06]**
Total events: 427 (Treatment (INH)), 419 (Control)					
Heterogeneity: Tau^2=0; Chi^2=13.84, df=12(P=0.31); I^2=13.3%					
Test for overall effect: Z=0.9(P=0.37)					
Test for subgroup differences: Not applicable					



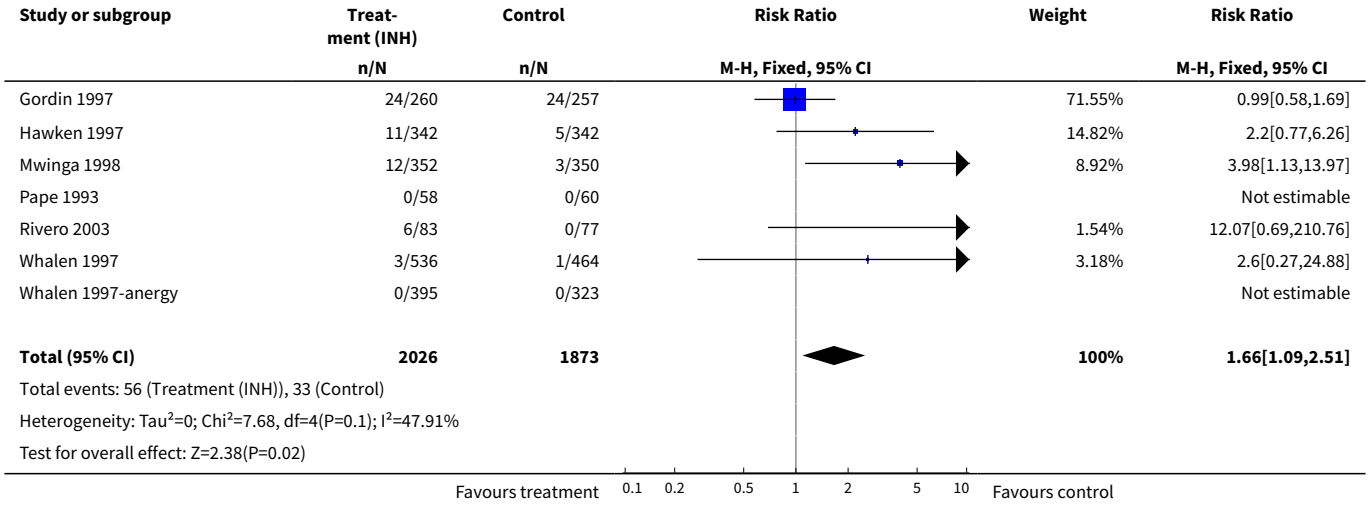
Analysis 2.4. Comparison 2 Isoniazid vs placebo, Outcome 4 Incidence of AIDS.

Study or subgroup	Treatment (INH) n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.1 PPD+					
Pape 1993	6/38	11/25		29.97%	0.36[0.15,0.85]
Subtotal (95% CI)	**38**	**25**		**29.97%**	**0.36[0.15,0.85]**
Total events: 6 (Treatment (INH)), 11 (Control)					

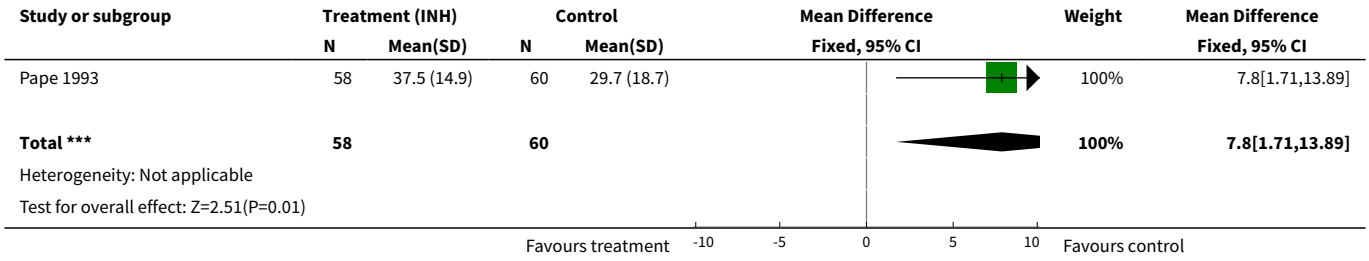




Analysis 2.5. Comparison 2 Isoniazid vs placebo, Outcome 5 Incidence of adverse events leading to stopping treatment.



Analysis 2.9. Comparison 2 Isoniazid vs placebo, Outcome 9 Mean time to AIDS.



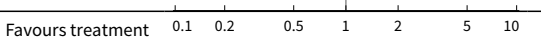
Comparison 3. Isoniazid + rifampicin vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of active TB (confirmed, probable or possible)	2	1179	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.21, 0.81]
1.1 PPD+	1	1020	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.17, 0.77]
1.2 PPD-	1	159	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.16, 3.05]
1.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Incidence of confirmed TB	1	159	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.16, 3.05]
2.1 PPD+	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 PPD-	1	159	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.16, 3.05]
2.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Incidence of death (all cause)	2	1179	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.50, 0.95]
3.1 PPD+	1	1020	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.53, 1.04]
3.2 PPD-	1	159	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.11, 1.03]
3.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Incidence of AIDS	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.1 PPD+	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 PPD-	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Incidence of adverse events leading to stopping treatment	2	1179	Risk Ratio (M-H, Fixed, 95% CI)	16.72 [3.29, 84.89]
6 Mean CD4 count	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 PPD+	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 PPD-	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 PPD unknown	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Mean time to TB	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Mean time to death	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Mean time to AIDS	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

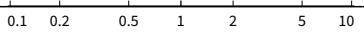
Analysis 3.1. Comparison 3 Isoniazid + rifampicin vs placebo, Outcome 1 Incidence of active TB (confirmed, probable or possible).

Study or subgroup	Treatment (INH+RIF) n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 PPD+					
Whalen 1997	9/556	21/464		84.73%	0.36[0.17,0.77]
Subtotal (95% CI)	**556**	**464**		**84.73%**	**0.36[0.17,0.77]**
Total events: 9 (Treatment (INH+RIF)), 21 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.61(P=0.01)					
3.1.2 PPD-					
Rivero 2003	3/82	4/77		15.27%	0.7[0.16,3.05]
Subtotal (95% CI)	**82**	**77**		**15.27%**	**0.7[0.16,3.05]**
Total events: 3 (Treatment (INH+RIF)), 4 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.47(P=0.64)					
3.1.3 PPD unknown					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatment (INH+RIF)), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**638**	**541**		**100%**	**0.41[0.21,0.81]**
Total events: 12 (Treatment (INH+RIF)), 25 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.64, df=1(P=0.42); I^2=0%					
Test for overall effect: Z=2.58(P=0.01)					
Test for subgroup differences: Not applicable					



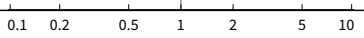
Analysis 3.2. Comparison 3 Isoniazid + rifampicin vs placebo, Outcome 2 Incidence of confirmed TB.

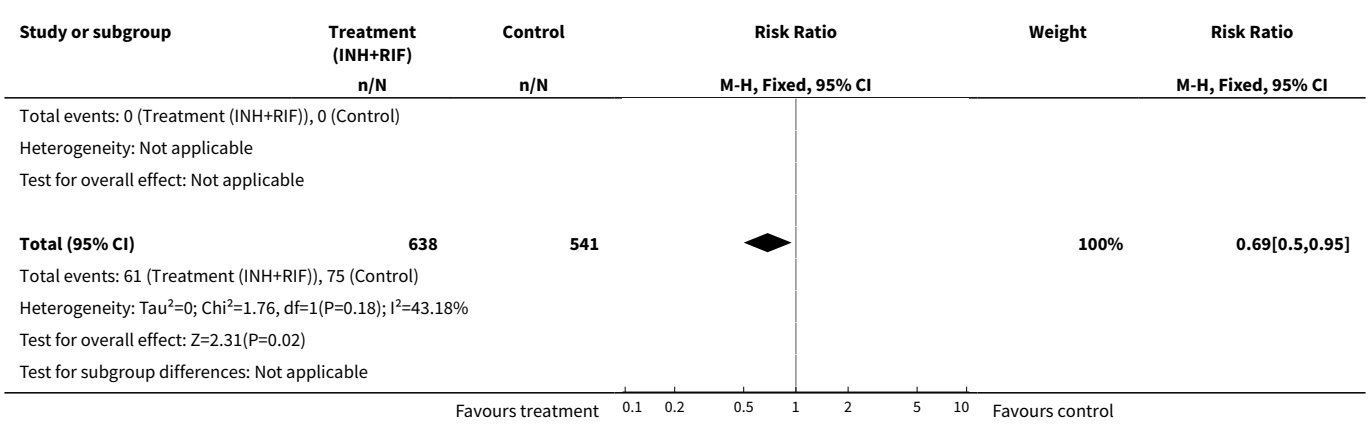
Study or subgroup	Treatment (INH+RIF) n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 PPD+					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatment (INH+RIF)), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.2.2 PPD-					
Rivero 2003	3/82	4/77		100%	0.7[0.16,3.05]
Subtotal (95% CI)	**82**	**77**		**100%**	**0.7[0.16,3.05]**
Total events: 3 (Treatment (INH+RIF)), 4 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.47(P=0.64)					
3.2.3 PPD unknown					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatment (INH+RIF)), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**82**	**77**		**100%**	**0.7[0.16,3.05]**
Total events: 3 (Treatment (INH+RIF)), 4 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.47(P=0.64)					
Test for subgroup differences: Not applicable					



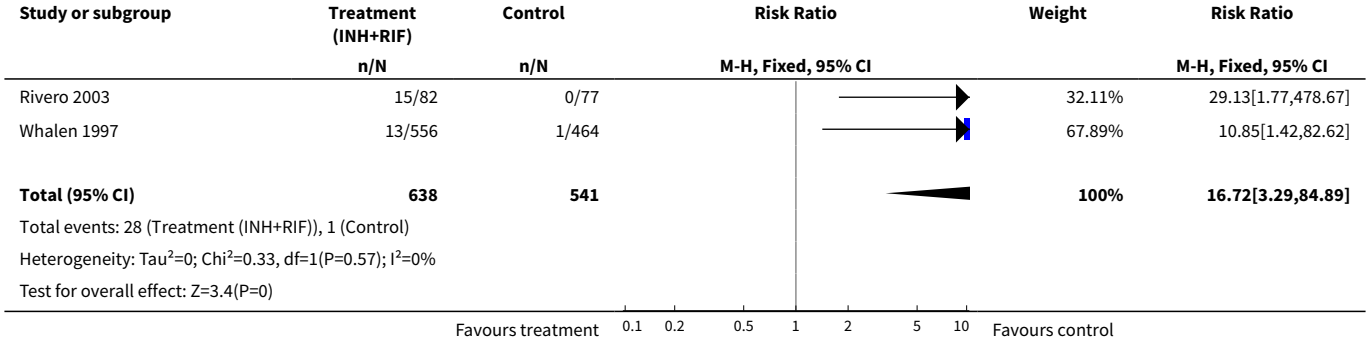
Analysis 3.3. Comparison 3 Isoniazid + rifampicin vs placebo, Outcome 3 Incidence of death (all cause).

Study or subgroup	Treatment (INH+RIF) n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.3.1 PPD+					
Whalen 1997	57/556	64/464		86.01%	0.74[0.53,1.04]
Subtotal (95% CI)	**556**	**464**		**86.01%**	**0.74[0.53,1.04]**
Total events: 57 (Treatment (INH+RIF)), 64 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.74(P=0.08)					
3.3.2 PPD-					
Rivero 2003	4/82	11/77		13.99%	0.34[0.11,1.03]
Subtotal (95% CI)	**82**	**77**		**13.99%**	**0.34[0.11,1.03]**
Total events: 4 (Treatment (INH+RIF)), 11 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.91(P=0.06)					
3.3.3 PPD unknown					
Subtotal (95% CI)	**0**	**0**			**Not estimable**





Analysis 3.5. Comparison 3 Isoniazid + rifampicin vs placebo, Outcome 5 Incidence of adverse events leading to stopping treatment.



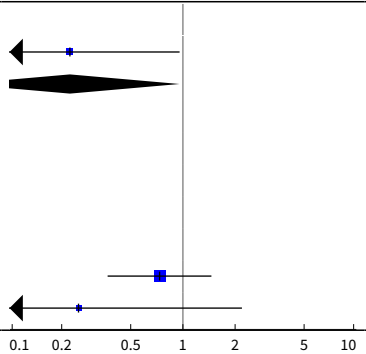
Comparison 4. Rifampicin + pyrazinimide vs placebo

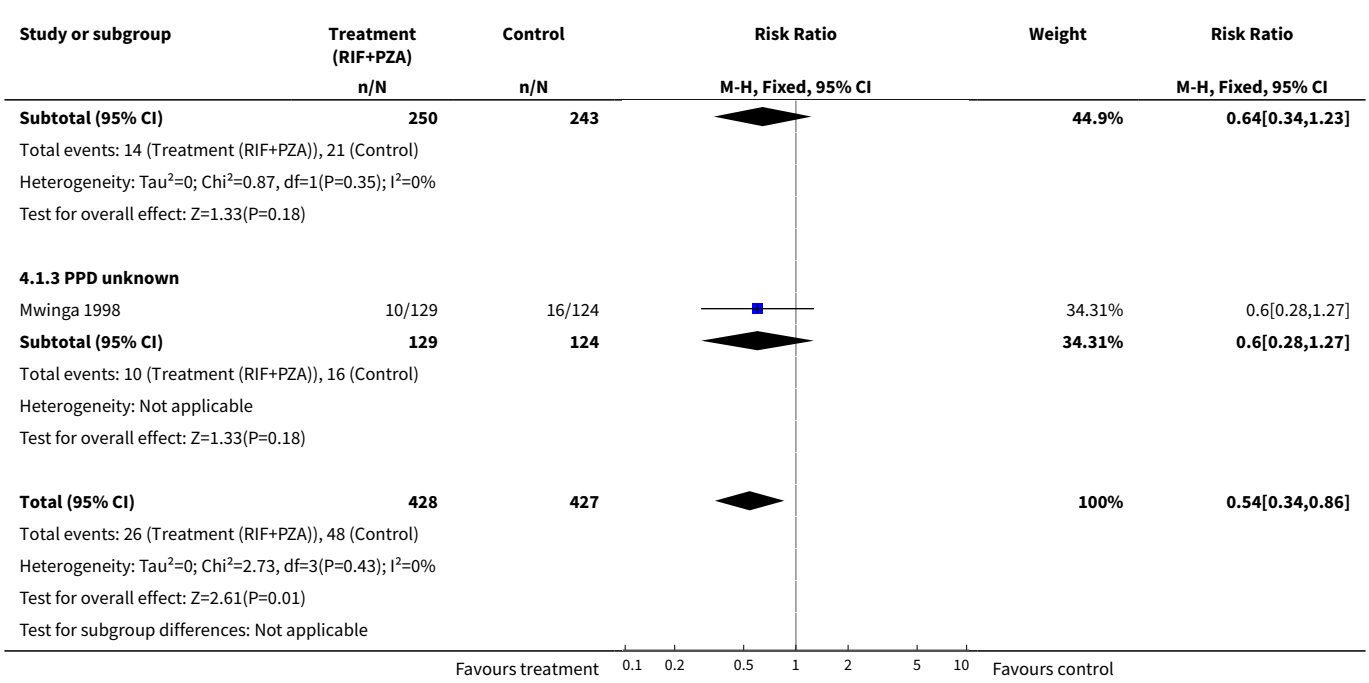
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of active TB (confirmed, probable or possible)	2	855	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.34, 0.86]
1.1 PPD+	1	109	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.05, 0.96]
1.2 PPD-	2	493	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.34, 1.23]
1.3 PPD unknown	1	253	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.28, 1.27]
2 Incidence of confirmed TB	2	855	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.34, 1.38]
2.1 PPD+	1	109	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.12, 3.20]
2.2 PPD-	2	493	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.28, 2.01]
2.3 PPD unknown	1	253	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.19, 2.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Incidence of death (all cause)	2	855	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.77, 1.41]
3.1 PPD+	1	109	Risk Ratio (M-H, Fixed, 95% CI)	2.76 [0.90, 8.41]
3.2 PPD-	2	493	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.68, 1.52]
3.3 PPD unknown	1	253	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.51, 1.41]
4 Incidence of AIDS	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.1 PPD+	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 PPD-	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Incidence of adverse events leading to stopping treatment	2	855	Risk Ratio (M-H, Fixed, 95% CI)	7.84 [2.60, 23.67]
6 Mean CD4 count	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.1 PPD+	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 PPD-	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 PPD unknown	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Mean time to TB	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Mean time to death	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Mean time to AIDS	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

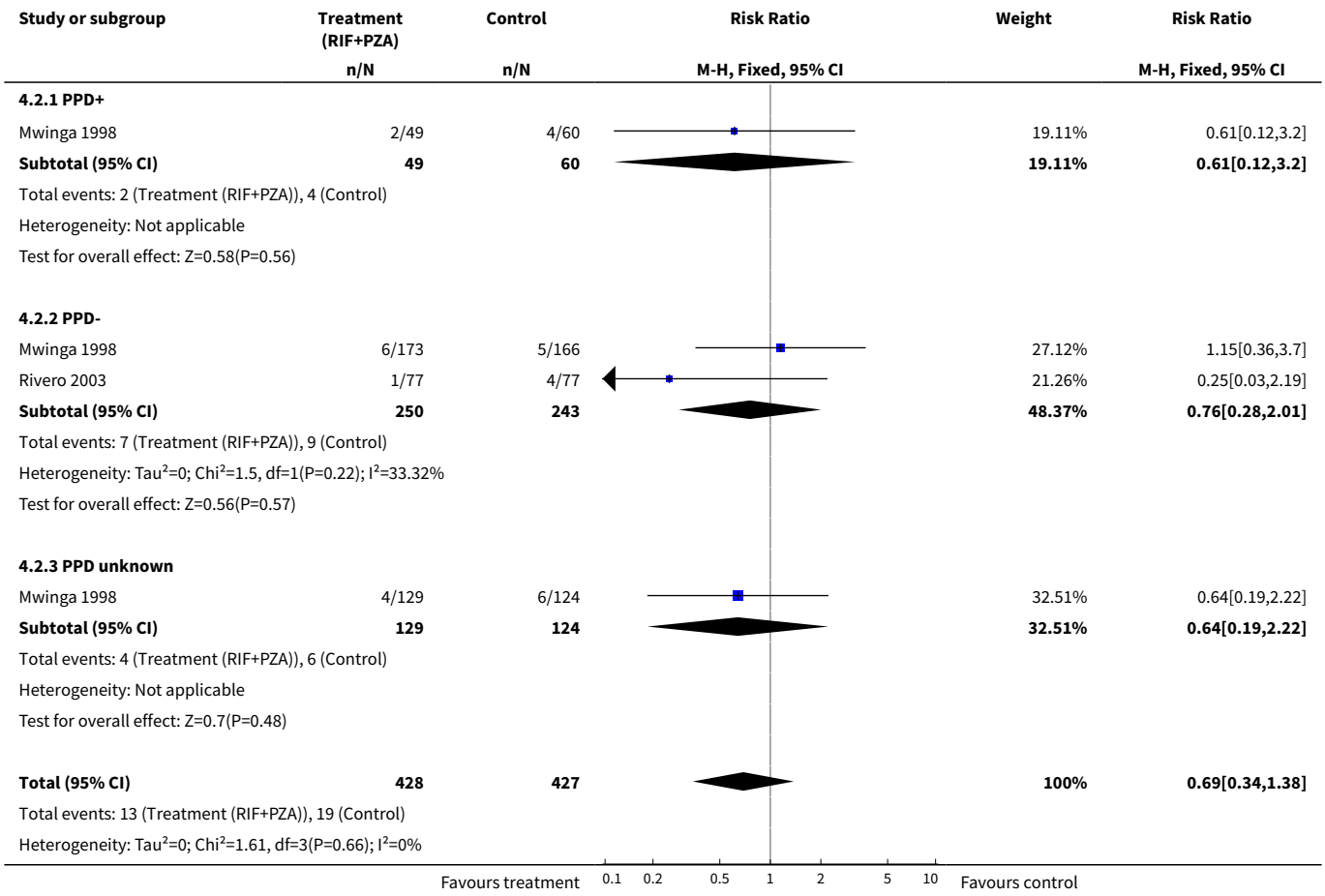
Analysis 4.1. Comparison 4 Rifampicin + pyrazinimide vs placebo, Outcome 1 Incidence of active TB (confirmed, probable or possible).

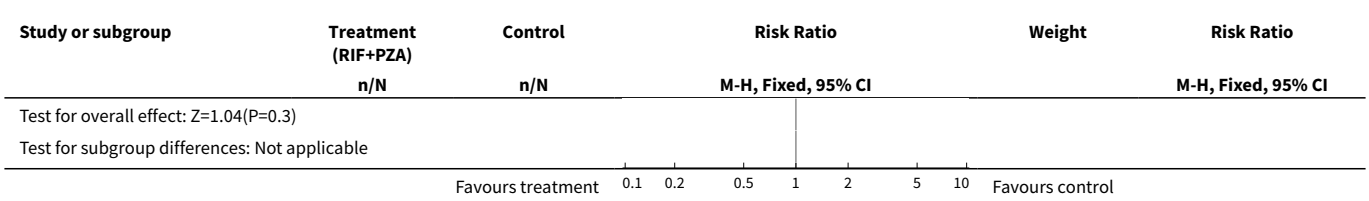
Study or subgroup	Treatment (RIF+PZA) n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 PPD+					
Mwinga 1998	2/49	11/60		20.8%	0.22[0.05,0.96]
Subtotal (95% CI)	**49**	**60**		**20.8%**	**0.22[0.05,0.96]**
Total events: 2 (Treatment (RIF+PZA)), 11 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=2.02(P=0.04)					
4.1.2 PPD-					
Mwinga 1998	13/173	17/166		36.48%	0.73[0.37,1.46]
Rivero 2003	1/77	4/77		8.41%	0.25[0.03,2.19]



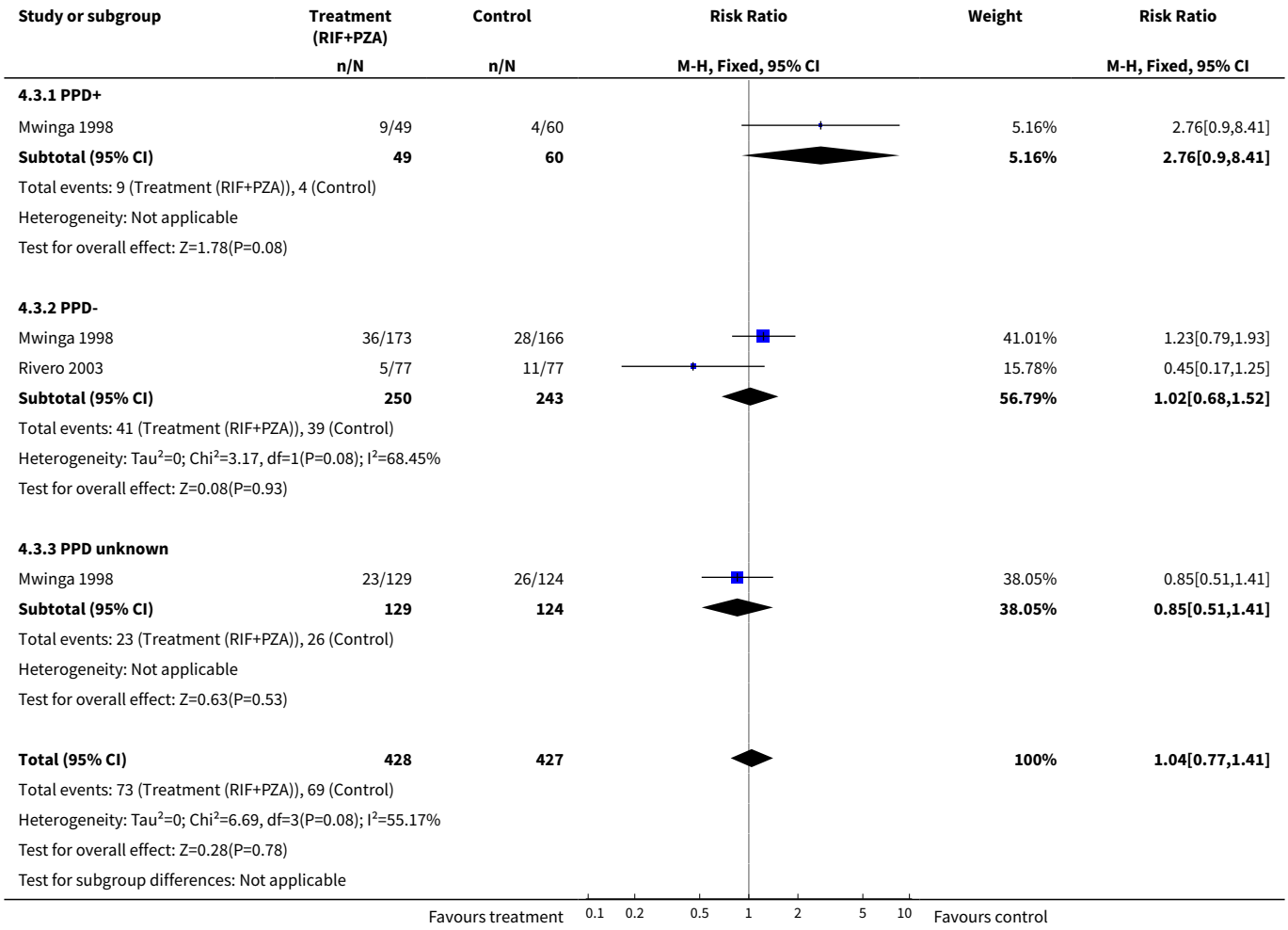


Analysis 4.2. Comparison 4 Rifampicin + pyrazinimide vs placebo, Outcome 2 Incidence of confirmed TB.

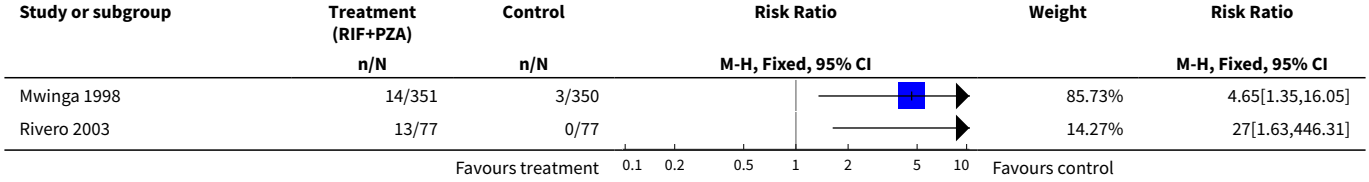


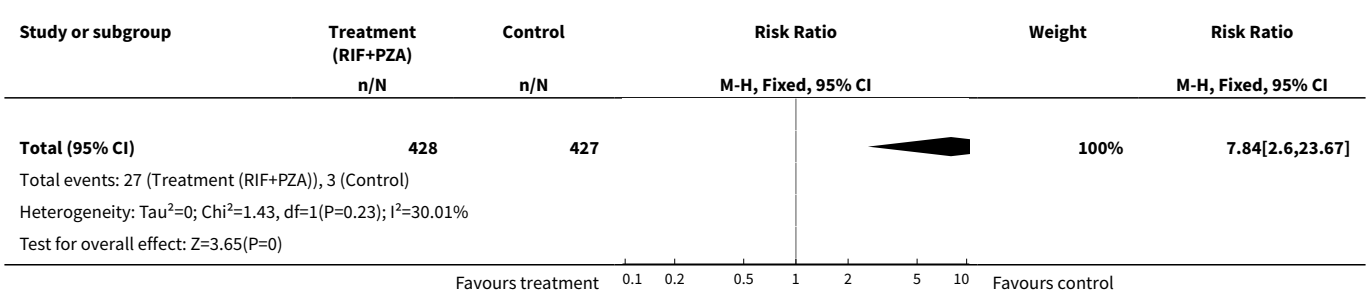


Analysis 4.3. Comparison 4 Rifampicin + pyrazinimide vs placebo, Outcome 3 Incidence of death (all cause).



Analysis 4.5. Comparison 4 Rifampicin + pyrazinimide vs placebo, Outcome 5 Incidence of adverse events leading to stopping treatment.





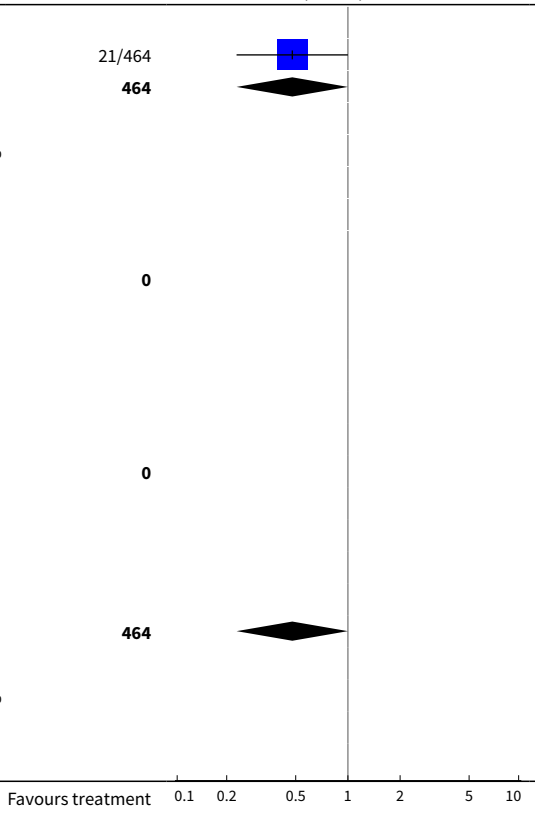
Comparison 5. Isoniazid + rifampicin + pyrazinamid vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of active TB (confirmed, probable or possible)	1	926	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.23, 1.00]
1.1 PPD+	1	926	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.23, 1.00]
1.2 PPD-	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Incidence of confirmed TB	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.1 PPD+	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 PPD-	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Incidence of death (all cause)	1	926	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.65, 1.27]
3.1 PPD+	1	926	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.65, 1.27]
3.2 PPD-	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Incidence of AIDS	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.1 PPD+	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 PPD-	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Incidence of adverse events leading to stopping treatment	1	926	Risk Ratio (M-H, Fixed, 95% CI)	26.11 [3.56, 191.63]
6 Mean CD4 count	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 PPD+	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 PPD-	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 PPD unknown	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Mean time to TB	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Mean time to death	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Mean time to AIDS	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

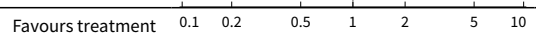
Analysis 5.1. Comparison 5 Isoniazid + rifampicin + pyrazinamid vs placebo, Outcome 1 Incidence of active TB (confirmed, probable or possible).

Study or subgroup	Treatm (INH +RIF+PZA) n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.1.1 PPD+					
Whalen 1997	10/462	21/464		100%	0.48[0.23,1]
Subtotal (95% CI)	**462**	**464**		**100%**	**0.48[0.23,1]**
Total events: 10 (Treatm (INH+RIF+PZA)), 21 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=1.95(P=0.05)					
5.1.2 PPD-					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatm (INH+RIF+PZA)), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
5.1.3 PPD unknown					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatm (INH+RIF+PZA)), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**462**	**464**		**100%**	**0.48[0.23,1]**
Total events: 10 (Treatm (INH+RIF+PZA)), 21 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=1.95(P=0.05)					
Test for subgroup differences: Not applicable					



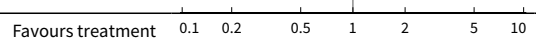
Analysis 5.3. Comparison 5 Isoniazid + rifampicin + pyrazinamid vs placebo, Outcome 3 Incidence of death (all cause).

Study or subgroup	Treatm (INH +RIF+PZA) n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.3.1 PPD+					
Whalen 1997	58/462	64/464		100%	0.91[0.65,1.27]
Subtotal (95% CI)	**462**	**464**		**100%**	**0.91[0.65,1.27]**
Total events: 58 (Treatm (INH+RIF+PZA)), 64 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.56(P=0.58)					
5.3.2 PPD-					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatm (INH+RIF+PZA)), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
5.3.3 PPD unknown					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatm (INH+RIF+PZA)), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**462**	**464**		**100%**	**0.91[0.65,1.27]**
Total events: 58 (Treatm (INH+RIF+PZA)), 64 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.56(P=0.58)					
Test for subgroup differences: Not applicable					



Analysis 5.5. Comparison 5 Isoniazid + rifampicin + pyrazinamid vs placebo, Outcome 5 Incidence of adverse events leading to stopping treatment.

Study or subgroup	Treatm (INH +RIF+PZA) n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Whalen 1997	26/462	1/464		100%	26.11[3.56,191.63]
Total (95% CI)	**462**	**464**		**100%**	**26.11[3.56,191.63]**
Total events: 26 (Treatm (INH+RIF+PZA)), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.21(P=0)					



Comparison 6. Isoniazid vs rifampicin + pyrazinimide

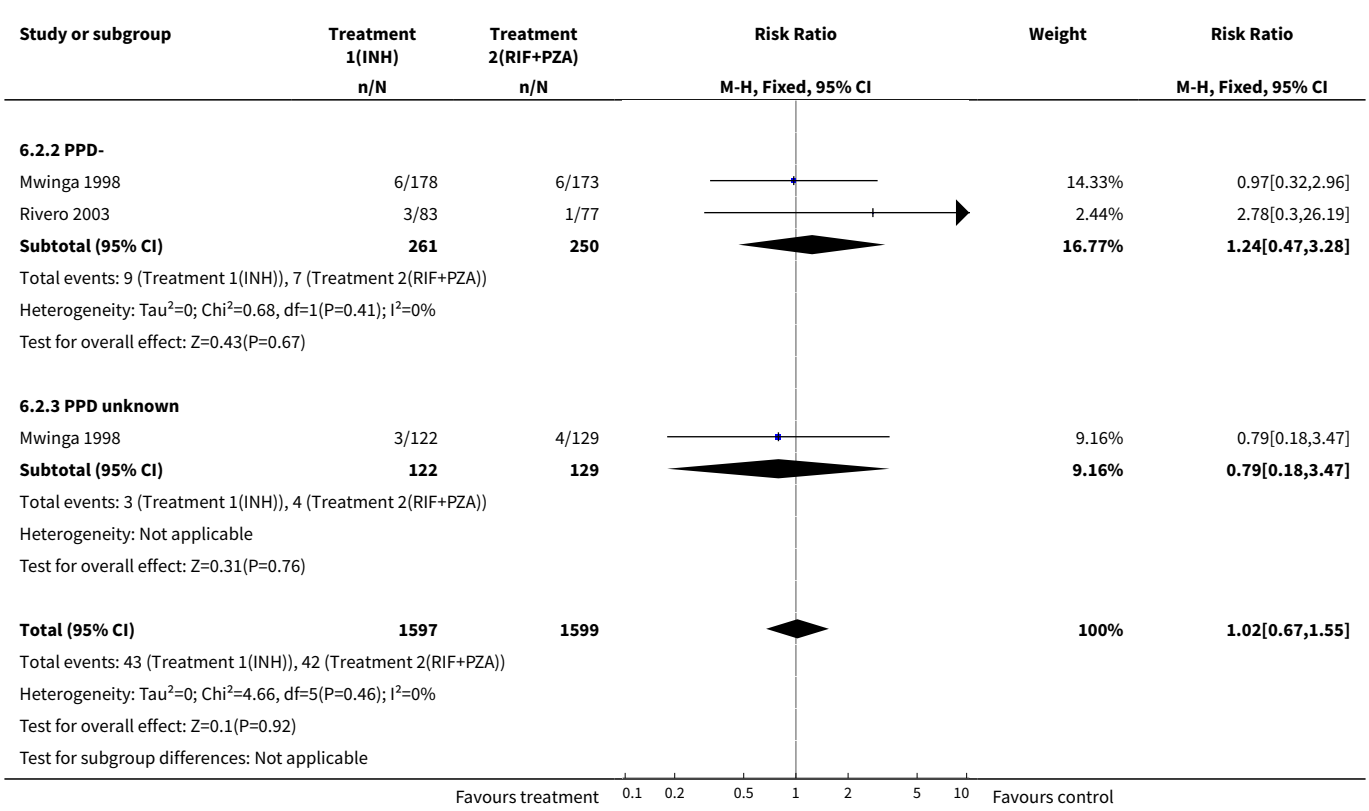
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of active TB (confirmed, probable or possible)	5	3409	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.75, 1.40]
1.1 PPD+	4	2647	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.68, 1.47]
1.2 PPD-	2	511	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.59, 2.32]
1.3 PPD unknown	1	251	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.40, 2.26]
2 Incidence of confirmed TB	4	3196	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.67, 1.55]
2.1 PPD+	3	2434	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.62, 1.63]
2.2 PPD-	2	511	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.47, 3.28]
2.3 PPD unknown	1	251	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.18, 3.47]
3 Incidence of death (all cause)	4	3137	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.89, 1.19]
3.1 PPD+	3	2434	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.93, 1.29]
3.2 PPD-	2	452	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.54, 1.17]
3.3 PPD unknown	1	251	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.50, 1.52]
4 Incidence of AIDS	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.1 PPD+	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 PPD-	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Incidence of adverse events leading to stopping treatment	5	3409	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.48, 0.84]
6 Mean CD4 count	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.1 PPD+	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 PPD-	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 PPD unknown	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Mean time to TB	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Mean time to death	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Mean time to AIDS	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 6.1. Comparison 6 Isoniazid vs rifampicin + pyrazinimide, Outcome 1 Incidence of active TB (confirmed, probable or possible).

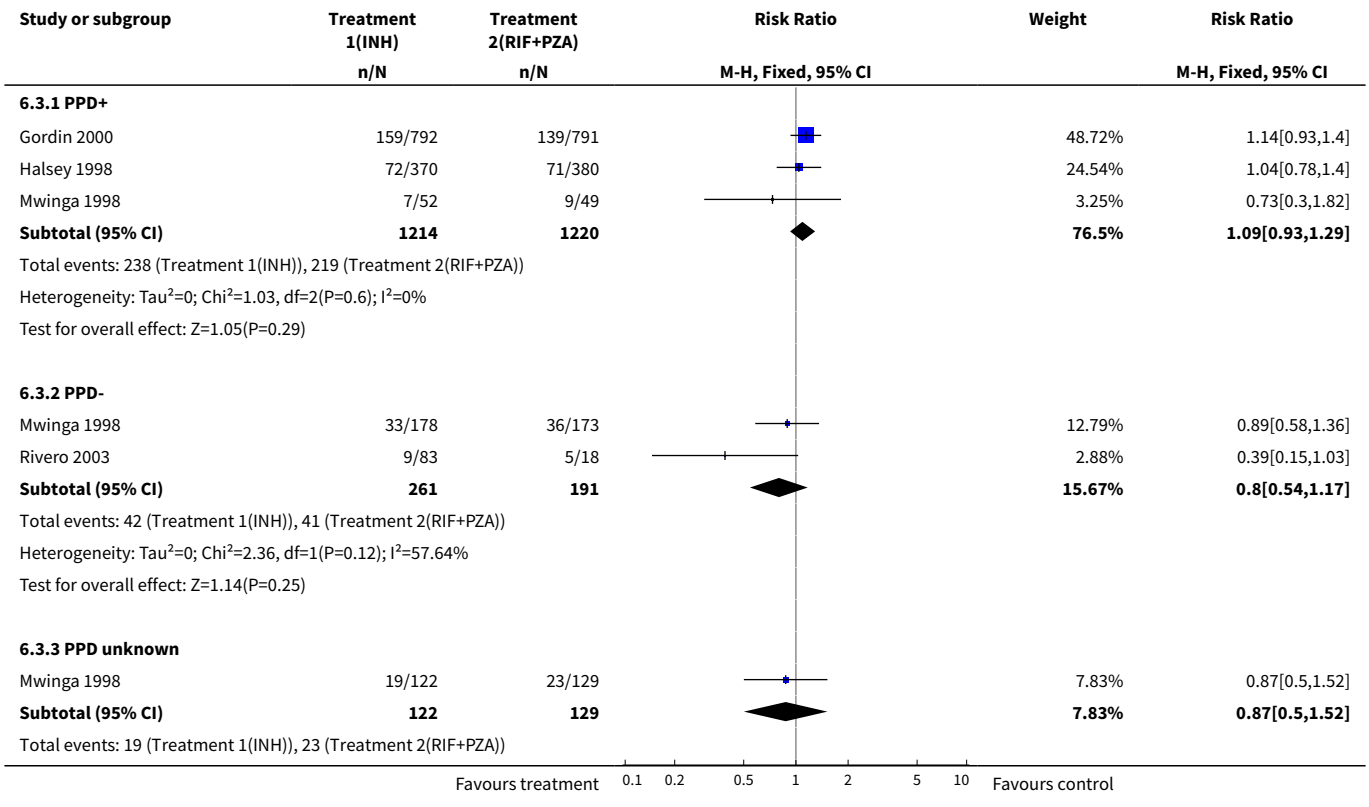
Study or subgroup	Treatment 1(INH) n/N	Treatment 2(RIF+PZA) n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.1.1 PPD+					
Gordin 2000	29/792	28/791		37.46%	1.03[0.62,1.72]
Halsey 1998	14/370	19/380		25.06%	0.76[0.39,1.49]
Mwinga 1998	4/52	2/49		2.75%	1.88[0.36,9.83]
Rivero 2007	4/108	2/105		2.71%	1.94[0.36,10.39]
Subtotal (95% CI)	**1322**	**1325**		**67.99%**	**1[0.68,1.47]**
Total events: 51 (Treatment 1(INH)), 51 (Treatment 2(RIF+PZA))					
Heterogeneity: Tau^2=0; Chi^2=1.84, df=3(P=0.61); I^2=0%					
Test for overall effect: Z=0.01(P=0.99)					
6.1.2 PPD-					
Mwinga 1998	14/178	13/173		17.63%	1.05[0.51,2.16]
Rivero 2003	3/83	1/77		1.39%	2.78[0.3,26.19]
Subtotal (95% CI)	**261**	**250**		**19.02%**	**1.17[0.59,2.32]**
Total events: 17 (Treatment 1(INH)), 14 (Treatment 2(RIF+PZA))					
Heterogeneity: Tau^2=0; Chi^2=0.67, df=1(P=0.41); I^2=0%					
Test for overall effect: Z=0.46(P=0.65)					
6.1.3 PPD unknown					
Mwinga 1998	9/122	10/129		13%	0.95[0.4,2.26]
Subtotal (95% CI)	**122**	**129**		**13%**	**0.95[0.4,2.26]**
Total events: 9 (Treatment 1(INH)), 10 (Treatment 2(RIF+PZA))					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.11(P=0.91)					
Total (95% CI)	**1705**	**1704**		**100%**	**1.03[0.75,1.4]**
Total events: 77 (Treatment 1(INH)), 75 (Treatment 2(RIF+PZA))					
Heterogeneity: Tau^2=0; Chi^2=2.66, df=6(P=0.85); I^2=0%					
Test for overall effect: Z=0.18(P=0.86)					
Test for subgroup differences: Not applicable					

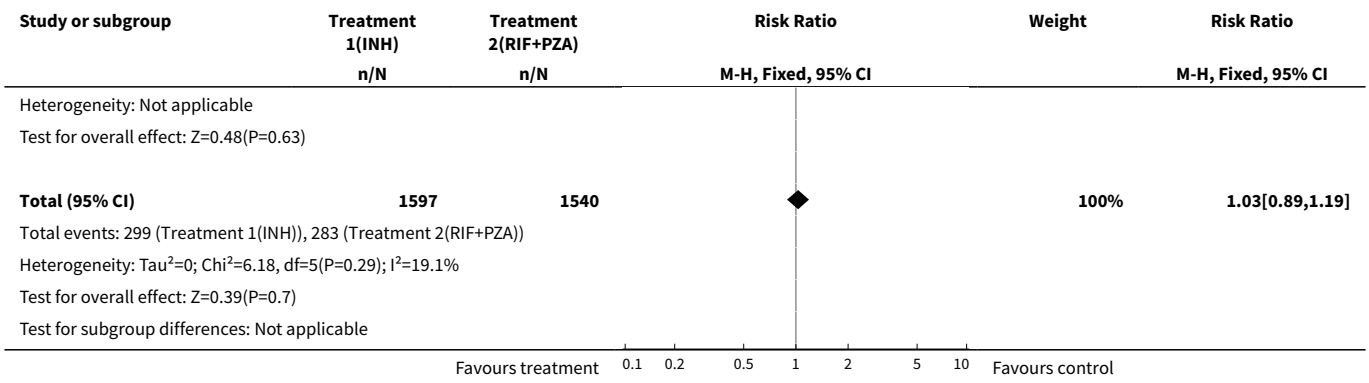
Analysis 6.2. Comparison 6 Isoniazid vs rifampicin + pyrazinimide, Outcome 2 Incidence of confirmed TB.

Study or subgroup	Treatment 1(INH) n/N	Treatment 2(RIF+PZA) n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.2.1 PPD+					
Gordin 2000	26/792	19/791		44.77%	1.37[0.76,2.45]
Halsey 1998	5/370	10/380		23.24%	0.51[0.18,1.49]
Mwinga 1998	0/52	2/49		6.06%	0.19[0.01,3.83]
Subtotal (95% CI)	**1214**	**1220**		**74.07%**	**1[0.62,1.63]**
Total events: 31 (Treatment 1(INH)), 31 (Treatment 2(RIF+PZA))					
Heterogeneity: Tau^2=0; Chi^2=3.78, df=2(P=0.15); I^2=47.15%					
Test for overall effect: Z=0.01(P=0.99)					

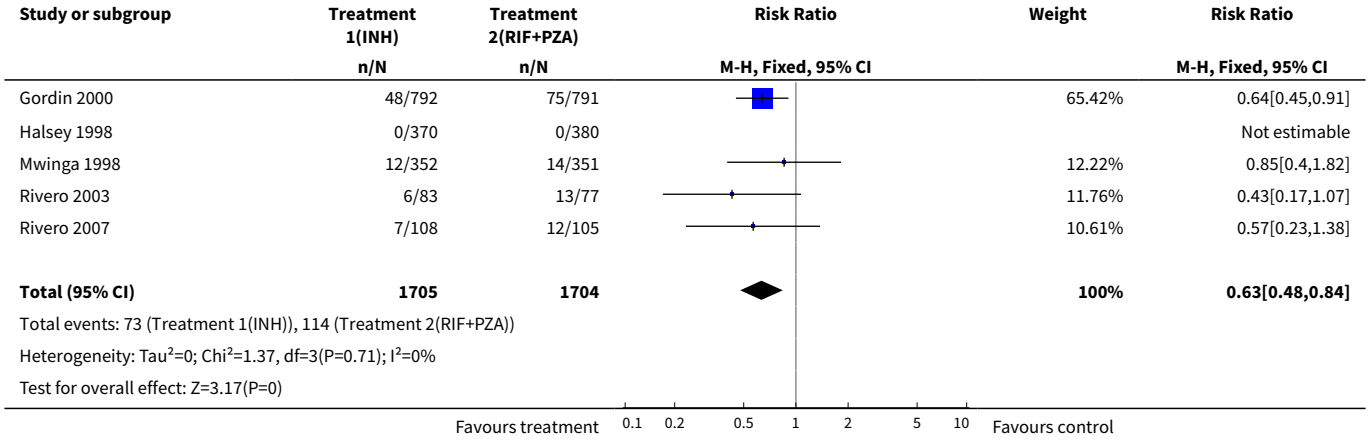


Analysis 6.3. Comparison 6 Isoniazid vs rifampicin + pyrazinimide, Outcome 3 Incidence of death (all cause).





Analysis 6.5. Comparison 6 Isoniazid vs rifampicin + pyrazinimide, Outcome 5 Incidence of adverse events leading to stopping treatment.



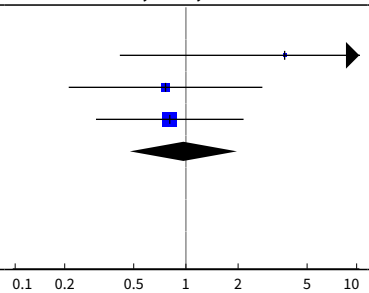
Comparison 7. Isoniazid vs isoniazid + rifampicin

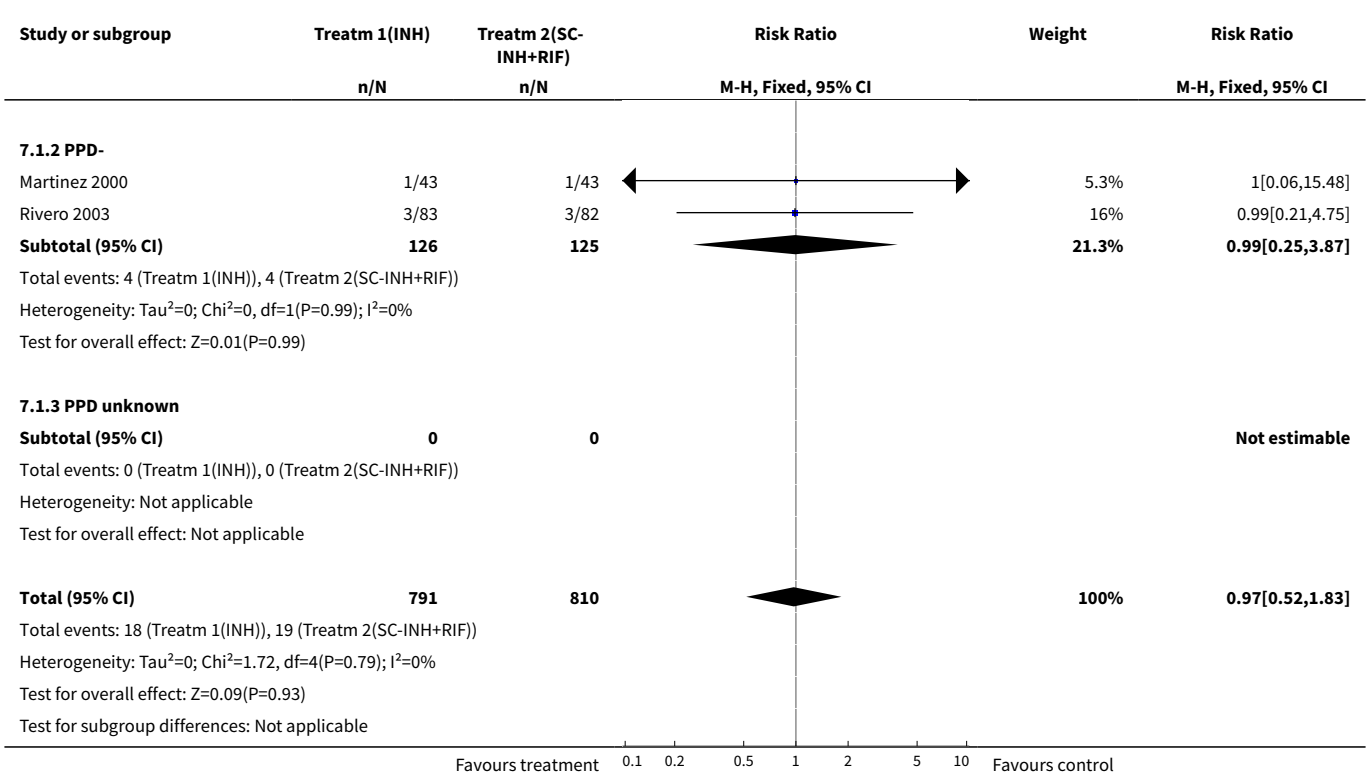
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of active TB (confirmed, probable or possible)	4	1601	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.52, 1.83]
1.1 PPD+	3	1350	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.47, 1.97]
1.2 PPD-	2	251	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.25, 3.87]
1.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Incidence of confirmed TB	2	298	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.49, 4.50]
2.1 PPD+	1	47	Risk Ratio (M-H, Fixed, 95% CI)	3.71 [0.42, 33.15]
2.2 PPD-	2	251	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.25, 3.87]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Incidence of death (all cause)	3	1385	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.80, 1.50]
3.1 PPD+	2	1134	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.75, 1.49]
3.2 PPD-	2	251	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.59, 2.84]
3.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Incidence of AIDS	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.1 PPD+	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 PPD-	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Incidence of adverse events leading to stopping treatment	4	1601	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.50, 1.23]
6 Mean CD4 count	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.1 PPD+	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 PPD-	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 PPD unknown	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Mean time to TB	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Mean time to death	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Mean time to AIDS	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

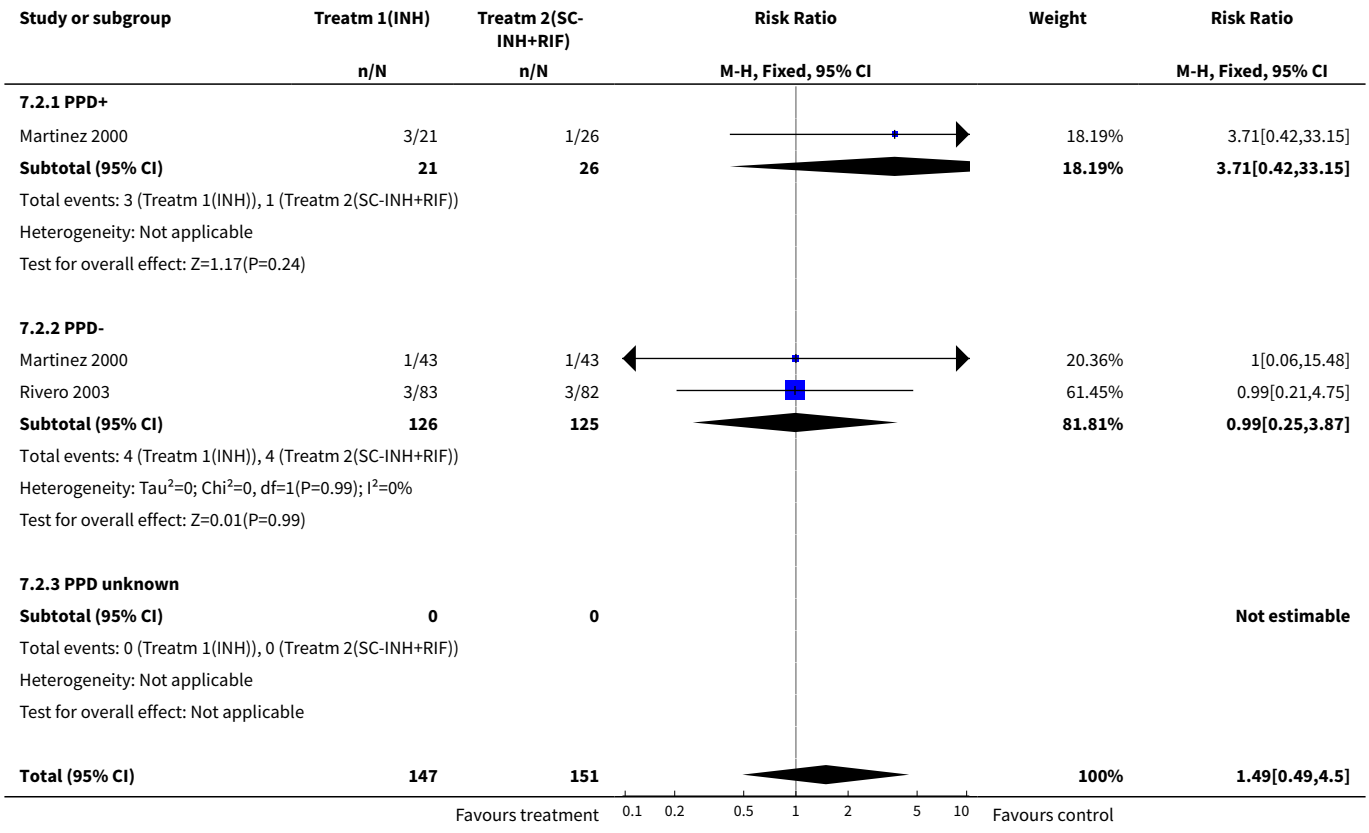
Analysis 7.1. Comparison 7 Isoniazid vs isoniazid + rifampicin, Outcome 1 Incidence of active TB (confirmed, probable or possible).

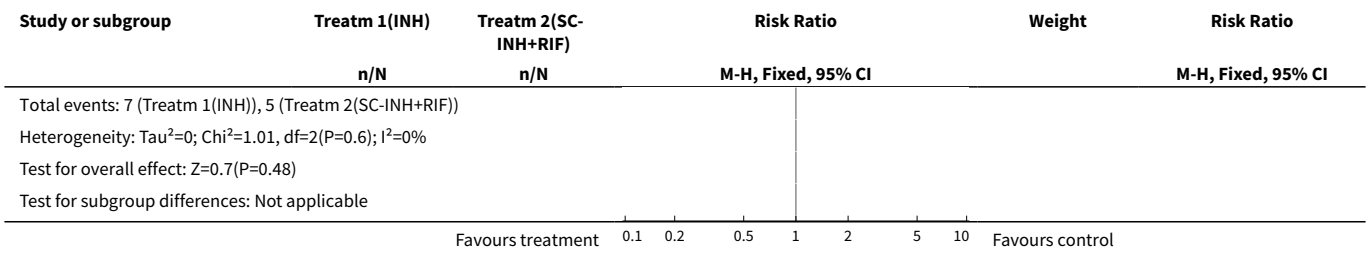
Study or subgroup	Treatm 1(INH) n/N	Treatm 2(SC-INH+RIF) n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
7.1.1 PPD+					
Martinez 2000	3/21	1/26		4.74%	3.71[0.42,33.15]
Rivero 2007	4/108	5/103		27.13%	0.76[0.21,2.76]
Whalen 1997	7/536	9/556		46.83%	0.81[0.3,2.15]
Subtotal (95% CI)	**665**	**685**		**78.7%**	**0.97[0.47,1.97]**
Total events: 14 (Treatm 1(INH)), 15 (Treatm 2(SC-INH+RIF))					
Heterogeneity: Tau^2=0; Chi^2=1.71, df=2(P=0.42); I^2=0%					
Test for overall effect: Z=0.09(P=0.93)					



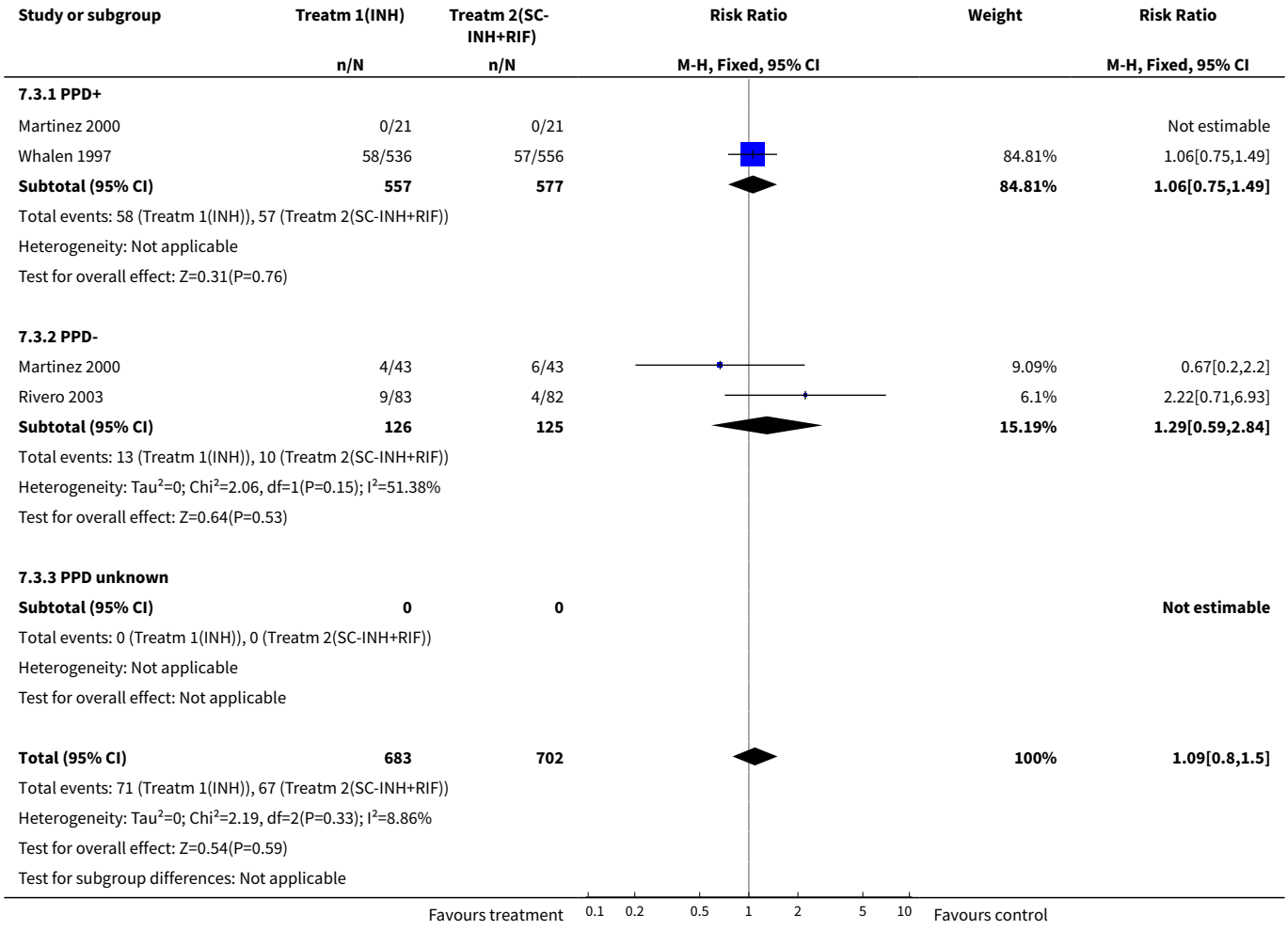


Analysis 7.2. Comparison 7 Isoniazid vs isoniazid + rifampicin, Outcome 2 Incidence of confirmed TB.

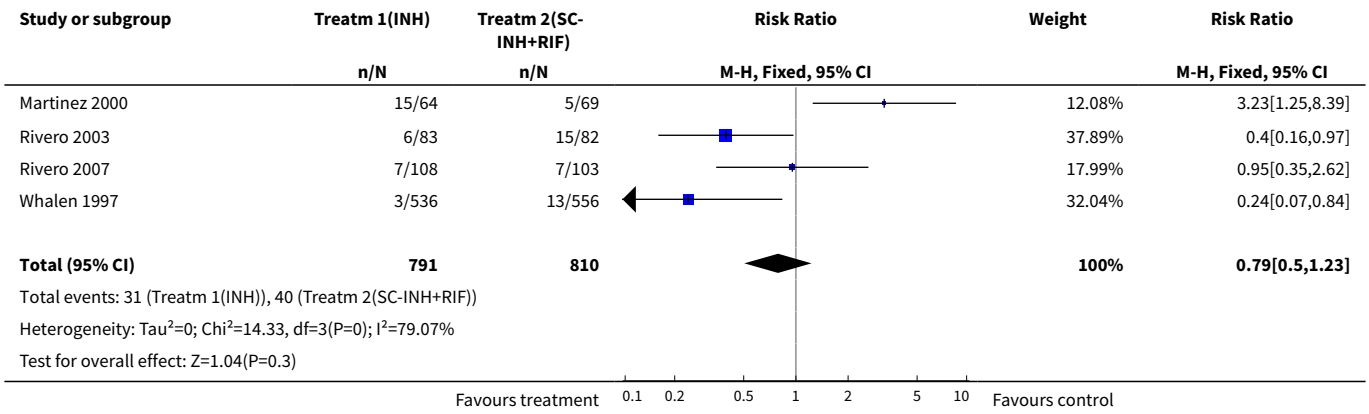




Analysis 7.3. Comparison 7 Isoniazid vs isoniazid + rifampicin, Outcome 3 Incidence of death (all cause).



Analysis 7.5. Comparison 7 Isoniazid vs isoniazid + rifampicin, Outcome 5 Incidence of adverse events leading to stopping treatment.



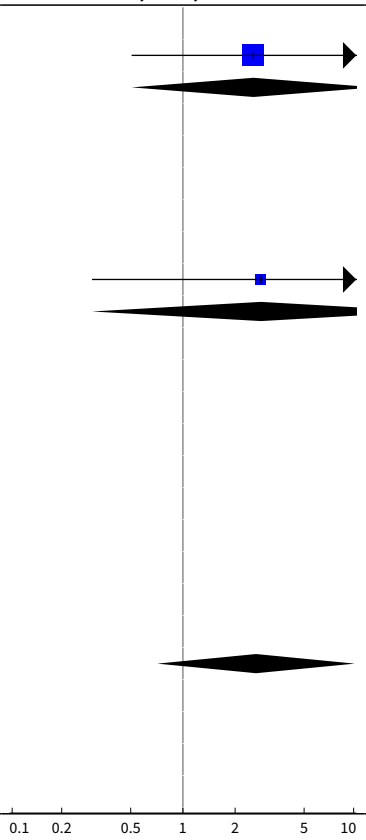
Comparison 8. Isoniazid + rifampicine vs Rifampicin + Pyrazinimide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of active TB (confirmed, probable or possible)	2	367	Risk Ratio (M-H, Fixed, 95% CI)	2.64 [0.71, 9.80]
1.1 PPD+	1	208	Risk Ratio (M-H, Fixed, 95% CI)	2.55 [0.51, 12.84]
1.2 PPD-	1	159	Risk Ratio (M-H, Fixed, 95% CI)	2.82 [0.30, 26.51]
1.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Incidence of confirmed TB	1	159	Risk Ratio (M-H, Fixed, 95% CI)	2.82 [0.30, 26.51]
2.1 PPD+	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 PPD-	1	159	Risk Ratio (M-H, Fixed, 95% CI)	2.82 [0.30, 26.51]
2.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Incidence of death (all cause)	1	159	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.21, 2.70]
3.1 PPD+	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 PPD-	1	159	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.21, 2.70]
3.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Incidence of AIDS	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.1 PPD+	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 PPD-	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5 Incidence of adverse events leading to stopping treatment	2	367	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.50, 1.46]
6 Mean CD4 count	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.1 PPD+	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 PPD-	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 PPD unknown	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Mean time to TB	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Mean time to death	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Mean time to AIDS	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

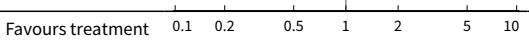
Analysis 8.1. Comparison 8 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide, Outcome 1 Incidence of active TB (confirmed, probable or possible).

Study or subgroup	Treatm 1(INH+RIF) n/N	Treatm 2(RIF+PZA) n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
8.1.1 PPD+					
Rivero 2007	5/103	2/105		65.76%	2.55[0.51,12.84]
Subtotal (95% CI)	**103**	**105**		**65.76%**	**2.55[0.51,12.84]**
Total events: 5 (Treatm 1(INH+RIF)), 2 (Treatm 2(RIF+PZA))					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.13(P=0.26)					
8.1.2 PPD-					
Rivero 2003	3/82	1/77		34.24%	2.82[0.3,26.51]
Subtotal (95% CI)	**82**	**77**		**34.24%**	**2.82[0.3,26.51]**
Total events: 3 (Treatm 1(INH+RIF)), 1 (Treatm 2(RIF+PZA))					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.91(P=0.37)					
8.1.3 PPD unknown					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatm 1(INH+RIF)), 0 (Treatm 2(RIF+PZA))					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**185**	**182**		**100%**	**2.64[0.71,9.8]**
Total events: 8 (Treatm 1(INH+RIF)), 3 (Treatm 2(RIF+PZA))					
Heterogeneity: Tau²=0; Chi²=0.01, df=1(P=0.94); I²=0%					
Test for overall effect: Z=1.45(P=0.15)					
Test for subgroup differences: Not applicable					



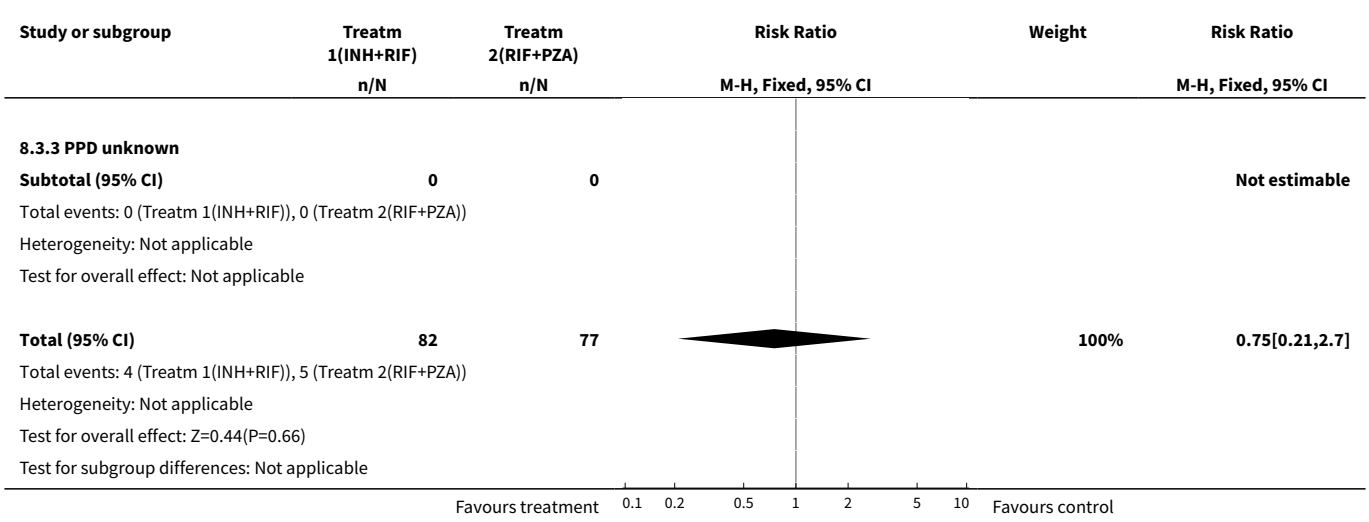
Analysis 8.2. Comparison 8 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide, Outcome 2 Incidence of confirmed TB.

Study or subgroup	Treatm 1(INH+RIF) n/N	Treatm 2(RIF+PZA) n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
8.2.1 PPD+					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatm 1(INH+RIF)), 0 (Treatm 2(RIF+PZA))					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
8.2.2 PPD-					
Rivero 2003	3/82	1/77		100%	2.82[0.3,26.51]
Subtotal (95% CI)	**82**	**77**		**100%**	**2.82[0.3,26.51]**
Total events: 3 (Treatm 1(INH+RIF)), 1 (Treatm 2(RIF+PZA))					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.91(P=0.37)					
8.2.3 PPD unknown					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatm 1(INH+RIF)), 0 (Treatm 2(RIF+PZA))					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**82**	**77**		**100%**	**2.82[0.3,26.51]**
Total events: 3 (Treatm 1(INH+RIF)), 1 (Treatm 2(RIF+PZA))					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.91(P=0.37)					
Test for subgroup differences: Not applicable					

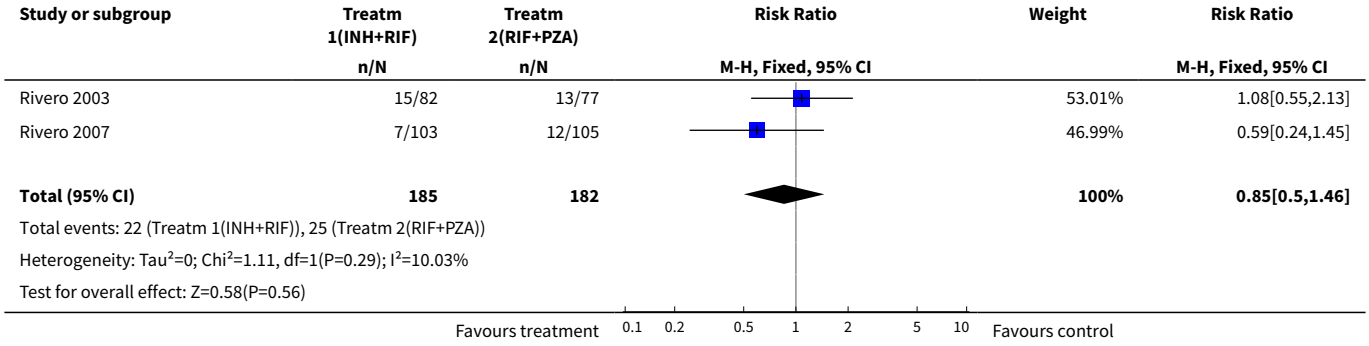


Analysis 8.3. Comparison 8 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide, Outcome 3 Incidence of death (all cause).

Study or subgroup	Treatm 1(INH+RIF) n/N	Treatm 2(RIF+PZA) n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
8.3.1 PPD+					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatm 1(INH+RIF)), 0 (Treatm 2(RIF+PZA))					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
8.3.2 PPD-					
Rivero 2003	4/82	5/77		100%	0.75[0.21,2.7]
Subtotal (95% CI)	**82**	**77**		**100%**	**0.75[0.21,2.7]**
Total events: 4 (Treatm 1(INH+RIF)), 5 (Treatm 2(RIF+PZA))					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.44(P=0.66)					



Analysis 8.5. Comparison 8 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide, Outcome 5 Incidence of adverse events leading to stopping treatment.



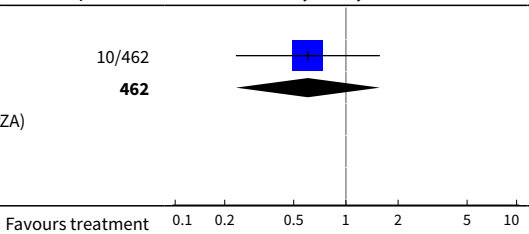
Comparison 9. Isoniazid vs isoniazid + rifampicin + Pyrazinamide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of active TB (confirmed, probable or possible)	1	998	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.23, 1.57]
1.1 PPD+	1	998	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.23, 1.57]
1.2 PPD-	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Incidence of confirmed TB	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.1 PPD+	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

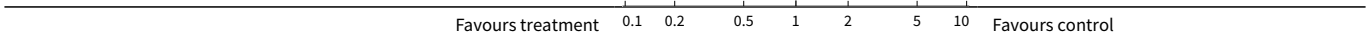
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 PPD-	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Incidence of death (all cause)	1	998	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.61, 1.21]
3.1 PPD+	1	998	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.61, 1.21]
3.2 PPD-	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Incidence of AIDS	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.1 PPD+	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 PPD-	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Incidence of adverse events leading to stopping treatment	1	998	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.03, 0.33]
6 Mean CD4 count	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.1 PPD+	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 PPD-	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 PPD unknown	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Mean time to TB	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Mean time to death	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Mean time to AIDS	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 9.1. Comparison 9 Isoniazid vs isoniazid + rifampicin + Pyrazinamide, Outcome 1 Incidence of active TB (confirmed, probable or possible).

Study or subgroup	Treatm 1(INH) n/N	Treatm 2-INH+RIF+PZA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
9.1.1 PPD+					
Whalen 1997	7/536	10/462		100%	0.6[0.23,1.57]
Subtotal (95% CI)	**536**	**462**		**100%**	**0.6[0.23,1.57]**
Total events: 7 (Treatm 1(INH)), 10 (Treatm 2-INH+RIF+PZA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.03(P=0.3)					

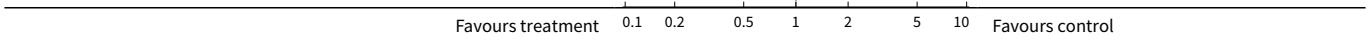


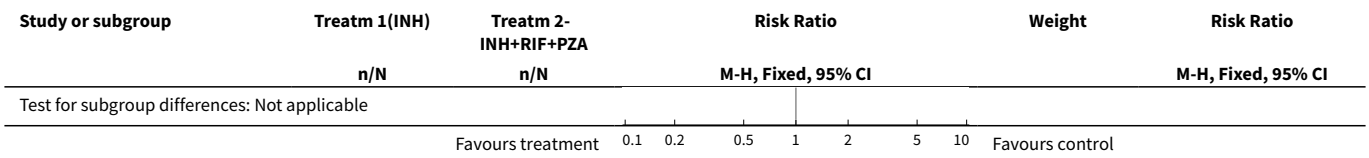
Study or subgroup	Treatm 1(INH) n/N	Treatm 2-INH+RIF+PZA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
9.1.2 PPD-					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatm 1(INH)), 0 (Treatm 2-INH+RIF+PZA)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
9.1.3 PPD unknown					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatm 1(INH)), 0 (Treatm 2-INH+RIF+PZA)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**536**	**462**		**100%**	**0.6[0.23,1.57]**
Total events: 7 (Treatm 1(INH)), 10 (Treatm 2-INH+RIF+PZA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.03(P=0.3)					
Test for subgroup differences: Not applicable					



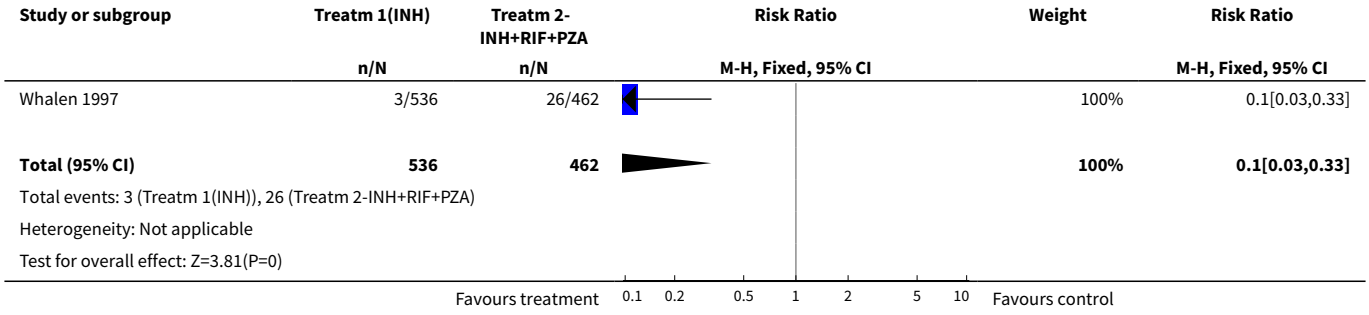
Analysis 9.3. Comparison 9 Isoniazid vs isoniazid + rifampicin + Pyrazinamide, Outcome 3 Incidence of death (all cause).

Study or subgroup	Treatm 1(INH) n/N	Treatm 2-INH+RIF+PZA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
9.3.1 PPD+					
Whalen 1997	58/536	58/462		100%	0.86[0.61,1.21]
Subtotal (95% CI)	**536**	**462**		**100%**	**0.86[0.61,1.21]**
Total events: 58 (Treatm 1(INH)), 58 (Treatm 2-INH+RIF+PZA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.85(P=0.39)					
9.3.2 PPD-					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatm 1(INH)), 0 (Treatm 2-INH+RIF+PZA)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
9.3.3 PPD unknown					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatm 1(INH)), 0 (Treatm 2-INH+RIF+PZA)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**536**	**462**		**100%**	**0.86[0.61,1.21]**
Total events: 58 (Treatm 1(INH)), 58 (Treatm 2-INH+RIF+PZA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.85(P=0.39)					





Analysis 9.5. Comparison 9 Isoniazid vs isoniazid + rifampicin + Pyrazinamide, Outcome 5 Incidence of adverse events leading to stopping treatment.



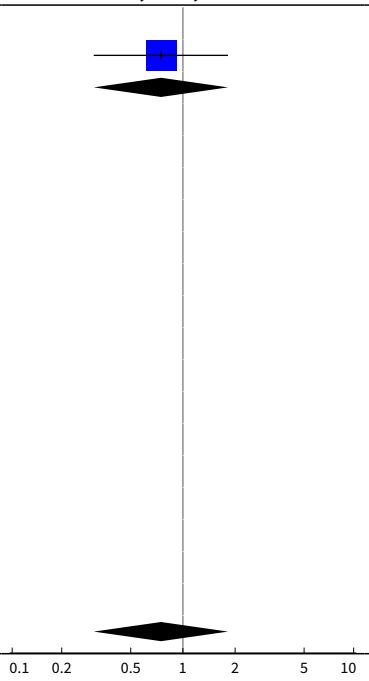
Comparison 10. Isoniazid + rifampicin vs isoniazid + rifampicin + Pyrazinamide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of active TB (confirmed, probable or possible)	1	1018	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.31, 1.82]
1.1 PPD+	1	1018	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.31, 1.82]
1.2 PPD-	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Incidence of confirmed TB	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.1 PPD+	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 PPD-	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Incidence of death (all cause)	1	1018	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.58, 1.15]
3.1 PPD+	1	1018	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.58, 1.15]
3.2 PPD-	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Incidence of AIDS	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 PPD+	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 PPD-	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 PPD unknown	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Incidence of adverse events leading to stopping treatment	1	1018	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.22, 0.80]
6 Mean CD4 count	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.1 PPD+	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 PPD-	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 PPD unknown	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Mean time to TB	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Mean time to death	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Mean time to AIDS	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 10.1. Comparison 10 Isoniazid + rifampicin vs isoniazid + rifampicin + Pyrazinamide, Outcome 1 Incidence of active TB (confirmed, probable or possible).

Study or subgroup	Treatm 1(INH+RIF) n/N	Treatm 2-INH+RIF+PZA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
10.1.1 PPD+					
Whalen 1997	9/556	10/462		100%	0.75[0.31,1.82]
Subtotal (95% CI)	**556**	**462**		**100%**	**0.75[0.31,1.82]**
Total events: 9 (Treatm 1(INH+RIF)), 10 (Treatm 2-INH+RIF+PZA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.64(P=0.52)					
10.1.2 PPD-					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatm 1(INH+RIF)), 0 (Treatm 2-INH+RIF+PZA)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
10.1.3 PPD unknown					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatm 1(INH+RIF)), 0 (Treatm 2-INH+RIF+PZA)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**556**	**462**		**100%**	**0.75[0.31,1.82]**



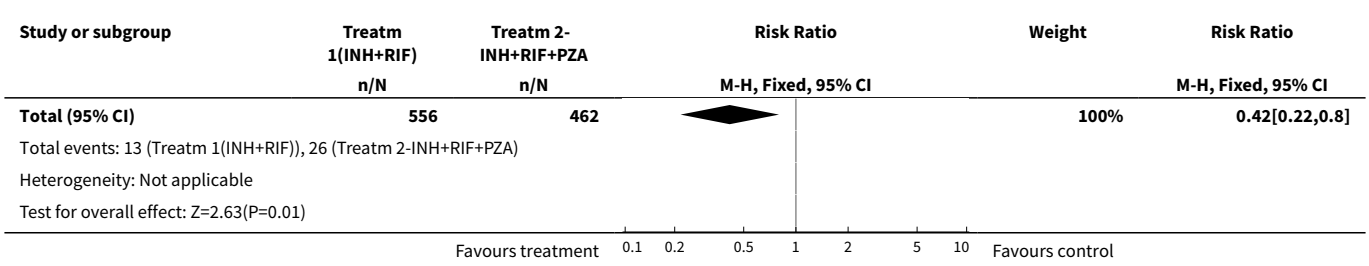
Study or subgroup	Treatm 1(INH+RIF) n/N	Treatm 2-INH+RIF+PZA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total events: 9 (Treatm 1(INH+RIF)), 10 (Treatm 2-INH+RIF+PZA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.64(P=0.52)					
Test for subgroup differences: Not applicable					

Analysis 10.3. Comparison 10 Isoniazid + rifampicin vs isoniazid + rifampicin + Pyrazinamide, Outcome 3 Incidence of death (all cause).

Study or subgroup	Treatm 1(INH+RIF) n/N	Treatm 2-INH+RIF+PZA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
10.3.1 PPD+					
Whalen 1997	57/556	58/462		100%	0.82[0.58,1.15]
Subtotal (95% CI)	**556**	**462**		**100%**	**0.82[0.58,1.15]**
Total events: 57 (Treatm 1(INH+RIF)), 58 (Treatm 2-INH+RIF+PZA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.15(P=0.25)					
10.3.2 PPD-					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatm 1(INH+RIF)), 0 (Treatm 2-INH+RIF+PZA)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
10.3.3 PPD unknown					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatm 1(INH+RIF)), 0 (Treatm 2-INH+RIF+PZA)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**556**	**462**		**100%**	**0.82[0.58,1.15]**
Total events: 57 (Treatm 1(INH+RIF)), 58 (Treatm 2-INH+RIF+PZA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.15(P=0.25)					
Test for subgroup differences: Not applicable					

Analysis 10.5. Comparison 10 Isoniazid + rifampicin vs isoniazid + rifampicin + Pyrazinamide, Outcome 5 Incidence of adverse events leading to stopping treatment.

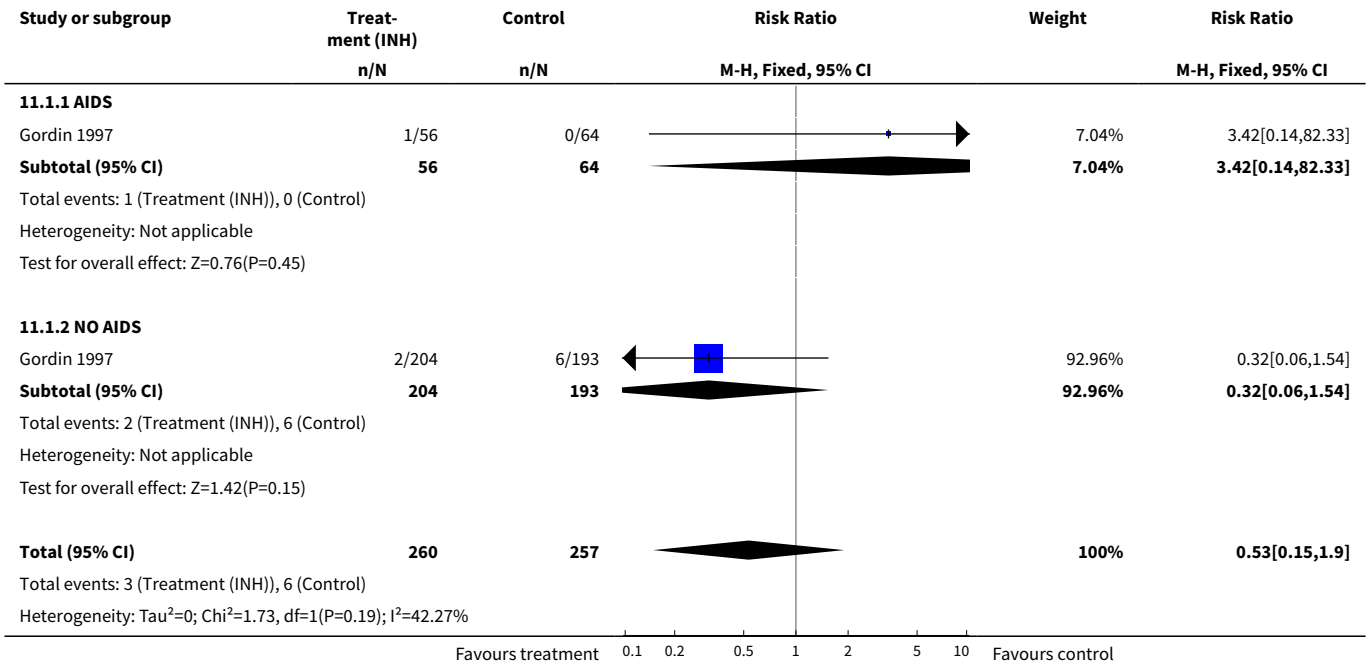
Study or subgroup	Treatm 1(INH+RIF) n/N	Treatm 2-INH+RIF+PZA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Whalen 1997	13/556	26/462		100%	0.42[0.22,0.8]

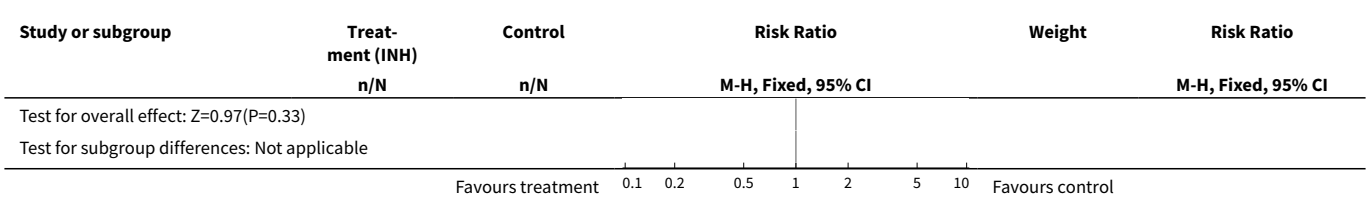


Comparison 11. Isoniazid vs placebo (stratified by AIDS status at baseline)

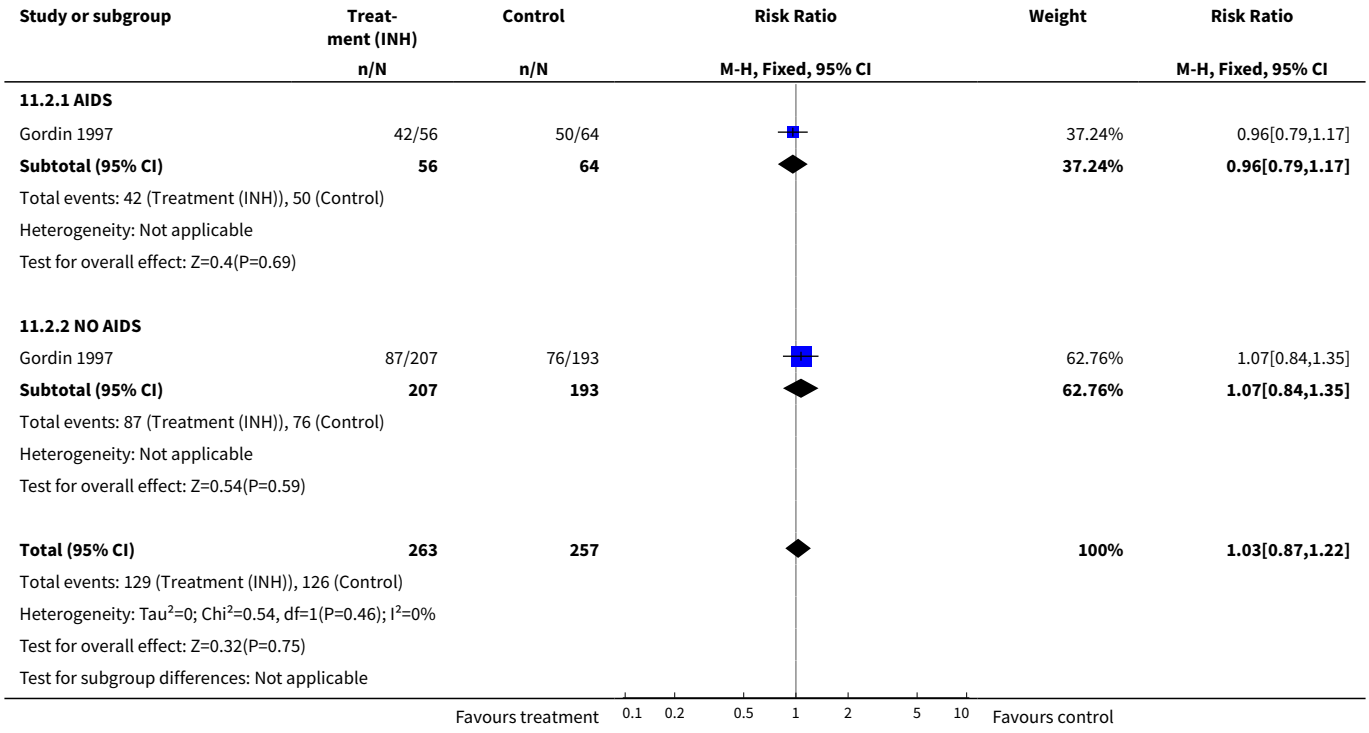
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of confirmed TB	1	517	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.15, 1.90]
1.1 AIDS	1	120	Risk Ratio (M-H, Fixed, 95% CI)	3.42 [0.14, 82.33]
1.2 NO AIDS	1	397	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.06, 1.54]
2 Incidence of death (all cause)	1	520	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.87, 1.22]
2.1 AIDS	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.79, 1.17]
2.2 NO AIDS	1	400	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.84, 1.35]

Analysis 11.1. Comparison 11 Isoniazid vs placebo (stratified by AIDS status at baseline), Outcome 1 Incidence of confirmed TB.





Analysis 11.2. Comparison 11 Isoniazid vs placebo (stratified by AIDS status at baseline), Outcome 2 Incidence of death (all cause).



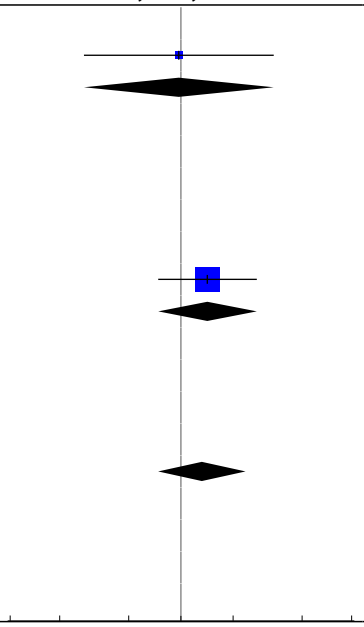
Comparison 12. Isoniazid vs rifampicin + pyrazinimide (stratified by AIDS status at baseline)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Incidence of confirmed TB	1	1583	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.74, 2.36]
1.1 AIDS	1	112	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.28, 3.43]
1.2 NO AIDS	1	1471	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.74, 2.74]
2 Incidence of death (all cause)	1	1583	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.90, 1.35]
2.1 AIDS	1	112	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.69, 1.41]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 NO AIDS	1	1471	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.90, 1.43]

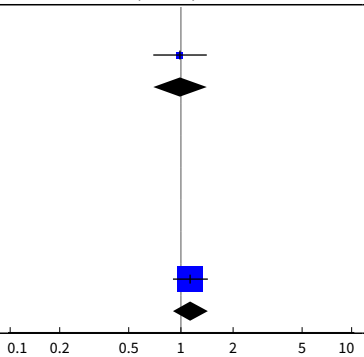
Analysis 12.1. Comparison 12 Isoniazid vs rifampicin + pyrazinimide (stratified by AIDS status at baseline), Outcome 1 Incidence of confirmed TB.

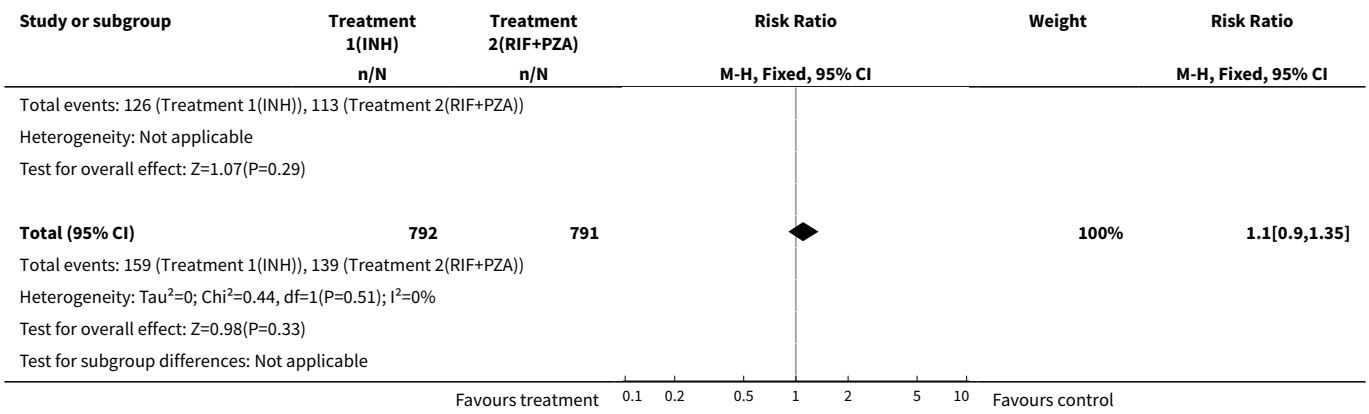
Study or subgroup	Treatment 1(INH) n/N	Treatment 2(RIF+PZA) n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
12.1.1 AIDS					
Gordin 2000	5/63	4/49		23.23%	0.97[0.28,3.43]
Subtotal (95% CI)	**63**	**49**		**23.23%**	**0.97[0.28,3.43]**
Total events: 5 (Treatment 1(INH)), 4 (Treatment 2(RIF+PZA))					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.04(P=0.97)					
12.1.2 NO AIDS					
Gordin 2000	21/729	15/742		76.77%	1.42[0.74,2.74]
Subtotal (95% CI)	**729**	**742**		**76.77%**	**1.42[0.74,2.74]**
Total events: 21 (Treatment 1(INH)), 15 (Treatment 2(RIF+PZA))					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.06(P=0.29)					
Total (95% CI)	**792**	**791**		**100%**	**1.32[0.74,2.36]**
Total events: 26 (Treatment 1(INH)), 19 (Treatment 2(RIF+PZA))					
Heterogeneity: Tau^2=0; Chi^2=0.28, df=1(P=0.6); I^2=0%					
Test for overall effect: Z=0.94(P=0.35)					
Test for subgroup differences: Not applicable					



Analysis 12.2. Comparison 12 Isoniazid vs rifampicin + pyrazinimide (stratified by AIDS status at baseline), Outcome 2 Incidence of death (all cause).

Study or subgroup	Treatment 1(INH) n/N	Treatment 2(RIF+PZA) n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
12.2.1 AIDS					
Gordin 2000	33/63	26/49		20.71%	0.99[0.69,1.41]
Subtotal (95% CI)	**63**	**49**		**20.71%**	**0.99[0.69,1.41]**
Total events: 33 (Treatment 1(INH)), 26 (Treatment 2(RIF+PZA))					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.07(P=0.94)					
12.2.2 NO AIDS					
Gordin 2000	126/729	113/742		79.29%	1.13[0.9,1.43]
Subtotal (95% CI)	**729**	**742**		**79.29%**	**1.13[0.9,1.43]**





APPENDICES

Appendix 1. Summary of current or planned TB preventive therapy

Study name and trial number	Sponsors	Country / Sample size	Criteria	Phase	Study arms Intervention	Con- trol	Duration / Primary outcome
Individually randomized controlled trials							
TBTC Study 26:Effectiveness and Tolerability of Weekly Rifapentine/Isoniazid for Three Months Versus Daily Isoniazid for Nine Months for the Treatment of Latent Tuberculosis Infection. NCT00023452	CDC Dept. of Veteran Affairs	USA Brazil Canada Spain N˜8000 (Enrolling)	?2 yrs Not pregnant TST+ at high risk of developing TB HIV+ close contacts of culture + TB patients	III	RPT/INH once weekly for 3 months	INH for 9 months	?18yrs: Culture+ TB <18yrs: Culture+ or probable (clinical) TB
Tuberculosis Prevention for HIV Infected Adults. NCT00057122	Johns Hopkins University and NIAID	South Africa N˜1148 (enrolment closed)	Age?18 yrs HIV-+ TST ?5mm CXR negative for TB	III	* RPT/INH for 3 months and observed weekly * RIF/INH for 3 months and observed twice weekly * Continuous INH self supervised	INH self super-vised for 6 months	1-4 yrs follow up Active TB
A Randomized, Placebo-Controlled Study of Limited Vs. Continuous Isoniazid Tuberculosis Preventive Therapy for HIV-Infected Persons in Botswana NCT00164281	CDC Botswana MOH USAID	Botswana N˜1800 (Enrolling)	?18yrs HIV+ TST + or not pregnant	IV	Continuous INH	INH for 6 months	Accrual 1yr, follow-up 24-36 months Active PTB or ETB
Randomized Controlled Trial of 4 Months Rifampin Versus 9 Months INH for the Treatment of Latent TB. NCT00170209	McGill University	Canada Number not specified	Age?15yrs TST + Not pregnant	IV	RIF for 4 months	INH for 9 months	April 2004 - July 2007

(Continued)

			HIV+ or other immune suppressed conditions				
An efficacy study of two preventive therapy studies in HIV-infected persons in India. NCT00351702	Tuberculosis Research Centre, India USAID	India N=650 (enrolment closed)	?15yrs HIV +	III	* ETH/IINH for 6 months	INH for 36 months	Follow up 5 yrs Active TB Mortality

Study name and trial number	Sponsors	Country / Sample size	Criteria	Phase	Study arms Intervention	Control	Duration / Primary outcome
Community level trials in settings with a high HIV prevalence							
The Zambia, South Africa, Tuberculosis and Acquired Immune Deficiency Syndrome-reduction Trial (ZAMSTAR). ISRCTN36729271	CREATE, Bill and Melinda Gates Foundation	Zambia South Africa	Those with symptoms and families with a member with TB [1]	Community randomised, factorial design	* Improved TB case finding * Integrated TB/HIV care delivered through the household: including TB preventive therapy (INH for 6 months)	Standard TB control	Prevalence of culture-positive TB, measured after 3 years of the interventions
Effect of community-wide isoniazid preventive therapy on tuberculosis among South African gold miners (Thibela TB). ISRCTN63327174	CREATE, Bill and Melinda Gates Foundation	South Africa	Employees at intervention clusters Age: ?18 years No active TB	Cluster randomized non-blinded controlled trial	* Standard TB control + INH for 9 months to all eligible employees (N~38000) regardless of HIV and silicosis status	Standard TB control N~30000	Start June 2006 End June 2010 Each arm followed for 2 yrs TB incidence in second year of follow up
Impact of TB Preventive Therapy for HIV/TB Co-Infected Patients With Access to Highly Active Antiretroviral Therapy in Rio De Janeiro, Brazil. NCT00107887	CREATE, Bill and Melinda Gates Foundation	Brazil N~15000 (Enrolling)	Age?16yrs HIV+ Attending a participating HIV clinic	A Phased Implementation Trial.	ARVs and implementation of IPT policy	ARVs alone	4 yr duration Incidence of active TB before and following implementation of IPT policy
Nation wide TB preventive therapy program	Botswana Government CDC	Botswana N>30000	HIV+ No active TB	Routine implementation	INH for 6 months	NA	TB incidence

MOH = Ministry of Health, PTB = pulmonary TB, ETB=extra pulmonary TB, CREATE= Consortium to respond effectively to the AIDS/TB epidemic, NA = not applicable, TST = tuberculin skin testing, wks = weeks, yrs = years, ARV = antriretrovirals, INH = isoniazid, RIF = rifampicin, RPT = rifapentine, + = positive, - = negative, neuron exam = neurological examination

[1] http://www.tbhiv-create.org/about/studies/ZAMSTAR

WHAT'S NEW

Date	Event	Description
11 November 2009	New search has been performed	Update of review (last was Issue 1, 2004).
11 November 2009	New citation required but conclusions have not changed	Substantive update with new author team.

HISTORY

Review first published: Issue 2, 1996

Date	Event	Description
11 November 2009	Feedback has been incorporated	Minor revision following peer review
24 April 2009	New citation required but conclusions have not changed	slight amendment
7 January 2009	New citation required but conclusions have not changed	Conclusion similar to previous version of this review.
6 October 2008	New search has been performed	Two new trials were added in this update
15 May 2008	Amended	Converted to new review format

CONTRIBUTIONS OF AUTHORS

All the authors contributed to the update of this review.

DECLARATIONS OF INTEREST

We certify that we have no affiliations with or involvement in any organization or entity with a direct financial interest in the subject matter of the review (e.g. employment, consultancy, stock ownership, honoraria, expert testimony).

SOURCES OF SUPPORT

Internal sources

- Department of Public Health, University of Oxford, UK.

External sources

- AIDS Treatment Care Unit, Department of HIV/AIDS, World Health Organisation, Geneva, Switzerland.
- Sasha Shepperd is funded by an NIHR Research Scientist in Evidence Synthesis Award, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol we specified that participants had to be HIV infected individuals (at least 13 years of age) who did not have active TB at the start of trial or in the past. We have changed this to participants had to be HIV infected individuals (at least 13 years of age) who did not have active TB at the start of trial.

INDEX TERMS

Medical Subject Headings (MeSH)

AIDS-Related Opportunistic Infections [prevention & control]; Antitubercular Agents [*therapeutic use]; HIV Infections [*complications]; Isoniazid [therapeutic use]; Latent Tuberculosis [*drug therapy]; Randomized Controlled Trials as Topic; Tuberculin Test; Tuberculosis, Pulmonary [*prevention & control]

MeSH check words

Adult; Humans