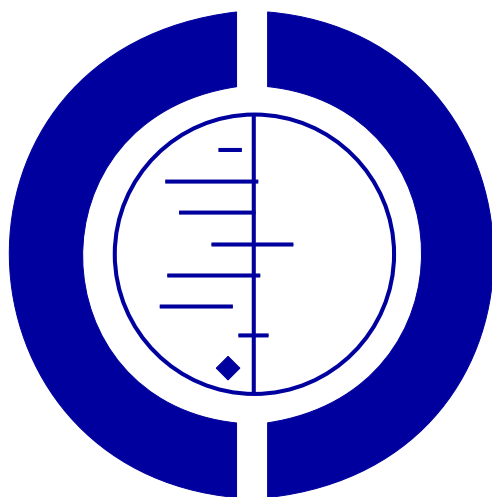


Treatment of latent tuberculosis infection in HIV infected persons (Review)

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ABSTRACT

Background

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

Objectives

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

Search strategy

We searched the Cochrane Controlled Trials Register (CCTR), MEDLINE, EMBASE, AIDSLINE, AIDSTRIALS and AIDSDRUGS. We also scanned reference lists of articles and contacted authors and other researchers in the field.

Selection criteria

We included studies in which HIV positive individuals were randomly allocated to preventive therapy for TB and 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

Two reviewers independently applied study selection criteria, assessed study quality and extracted data. Effects were assessed using relative risk for dichotomous data and weighted mean difference for continuous data.

Main results

11 trials were included with a total of 8,130 randomized participants. Preventive therapy (any anti-TB drug) versus placebo was associated with a lower incidence of active tuberculosis (RR 0.64, 95% CI 0.51 to 0.81). 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 0.83, 95% CI 0.58 to 1.18.). Limited data suggest that the initial protective effect against tuberculosis may decline over the short to medium term. 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. Overall, there was no evidence that preventive therapy versus placebo reduced all-cause mortality (RR 0.95, 95% CI 0.85 to 1.06), although a favourable trend was found in people with a positive tuberculin test (RR 0.80, 95% CI 0.63 to 1.02).

Authors' conclusions

Treatment of latent tuberculosis infection (LTBI) reduces the risk of active tuberculosis in HIV positive individuals with a positive tuberculin skin test. The choice of regimen will depend on factors such as 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 and the influence of level of immunocompromise on effectiveness are needed.

SYNOPSIS

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

People infected with HIV/AIDS are at increased risk of getting tuberculosis (TB), which can lead to an earlier death. Most people infected with TB never get TB symptoms. This is called latent TB. However, about 30% of people with HIV who have latent TB will eventually get active TB. The review of 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 needed to show the best treatment regime for people with HIV.

BACKGROUND

One third of the world's population is believed to be infected with *Mycobacterium tuberculosis* (MTb) but most infected people will never have symptoms (Dye 1999). Infection with the human immunodeficiency virus (HIV) has, however, changed the natural history of tuberculosis (TB). In HIV negative populations, only 5-10% will ever develop active tuberculosis (Enarson 1994). However, HIV positive persons who are infected with MTb have a 5-8% annual risk and a 30% lifetime risk of developing active tuberculosis (Selwyn 1989). It is estimated that close to 70% of the world's 10.7 million population dually infected with HIV and MTb live in Africa (Dye 1999). In this group, tuberculosis is the leading cause of morbidity and mortality.

The primary screening test for tuberculosis infection is the tuberculin skin test, where material derived from MTb is introduced into the skin. People infected with MTb typically have a strong reaction to this skin test, and are termed positive for the tuberculin skin test (PPD positive). They are at greater risk of subsequently developing active disease than are people who are not infected with MTb (Watkins 2000). While the risk factors for developing clinical tuberculosis are not completely understood, age (highest risk for children under 4 years old), dosage of infection, and a compromised immune system may all increase the risk of disease (Comsock 2000). Reactivation of dormant tuberculosis infection due to a weakened immune system appears to be the main mechanism for the development of HIV-related tuberculosis but HIV positive patients may also be at higher risk of acquiring new TB infection (Cobo 2002). With the progression of HIV disease, tuberculosis tends to occur at higher CD4 lymphocytes levels than other opportunistic infections (Harries 1994).

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 infected (Harries 1994).

It is worth noting that tuberculosis also impacts the progression and manifestation of HIV/AIDS. Active tuberculosis has been shown to accelerate the progression of HIV disease (Bocchino 2000; CDC 1998; Daniel 2000). Current research indicates that MTb increases viral replication both in vitro and in HIV patients with active TB (Goletti 1996). In addition, it has also been shown that patients co-infected with TB and HIV are at increased risk for other opportunistic infections (Cohn 2000).

Traditional tuberculosis control strategies consist of case-finding and treatment (considered the most important short-term strategy), preventive therapy (PT), also referred to as chemoprophylaxis, and BCG vaccination of children with the knowledge that better socio-economic conditions lead to a decline in incidence of the disease. The rationale behind preventive therapy is to eradicate latent infection in PPD positive individuals before it develops into active disease.

Several placebo-controlled trials in HIV negative people infected with MTb have shown that daily isoniazid given for 6-12 months substantially reduces the subsequent risk of active tuberculosis (O'Brien 1994; Smieja 2003). However, in the context of HIV infection, a variety of factors may impact the effectiveness of TB preventive therapy. There is some evidence that absorption of anti-tuberculous drugs may be suboptimal in patients with AIDS (Peloquin 1996). Secondly, since HIV patients may be taking anti-retroviral therapy, as well as other drugs for the treatment of AIDS-related diseases, drug interactions can arise (Kovacs 2000; Piscitelli 2001). Furthermore, adherence to treatment may be a problem in dually infected patients for reasons including serious morbidity, poly-pharmacy and adverse effects thus increasing the likelihood of multidrug-resistant tuberculosis. Assumptions about the protective potential of TB preventive therapy in HIV positive people may therefore not be warranted.

In the light of the above concerns a systematic review of the ev-

idence concerning the effectiveness of preventive therapy for tuberculosis in HIV infected persons was conducted.

OBJECTIVES

The objective of this review was to determine the effectiveness of tuberculosis preventive therapy (PT)/chemoprophylaxis in reducing the risk of active tuberculosis 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 tuberculosis 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 tuberculin skin test 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 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

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

We included randomized controlled studies in which individuals were randomly allocated to preventive therapy for TB and placebo, or to alternative TB preventive therapy regimens.

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

Types of participants

Participants had to be HIV infected adults who did not have active TB currently or in the past. Participants could be of either gender and from any setting. They could be either tuberculin skin test positive (PPD - purified protein derivative) or negative. Anergic patients were considered tuberculin skin test negative.

Types of intervention

Experimental group: Any tuberculosis drug or drug combination
Control group: Inactive placebo or an alternative tuberculosis drug or drug combination

Types of outcome measures

Primary outcomes:

1. Active tuberculosis 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-tuberculosis treatment) (ATS 1990)
2. Interval to active tuberculosis 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 STRATEGY FOR IDENTIFICATION OF STUDIES

See: search strategy

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 through July 2002:

- The Cochrane Controlled Trials Register (CCTR)
- MEDLINE
- EMBASE
- AIDSLINE
- AIDSTRIALS
- AIDS DRUGS

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 review.

METHODS OF THE REVIEW

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 labeled as adequate if more than 90% of the randomized participants were included.

We did not assign quality scores to studies.

We independently extracted the following information using a standardized data collection form: 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 (SW & JV) 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 trials results at the 0.1 level. For continuous data such as time to AIDS, we used the weighted mean difference (WMD).

DESCRIPTION OF STUDIES

17 trials were initially included because they were thought to meet our inclusion criteria. Four of these studies were later excluded for the following reasons: one evaluated preventive therapy to reduce recurrence of TB in individuals who had previously had the disease (Fitzgerald 2000); two primarily assessed drug tolerability rather than prevention of active TB (Garcia 1993; Matteelli 1998); and one study was assumed to be non-randomized as it was described only as "prospective, comparative" (Saenghirunvatta 1996).

A further two studies are awaiting assessment for inclusion in the review because data on active TB are yet to be reported (Sanchez 2002) or the results originally presented at a conference remain unpublished and we are attempting to obtain the data (Wadhawan 1993).

The current review thus includes 11 trials with a total of 8130 randomized participants. Study size varied from 118 to 2018. The study by Whalen et al was counted as two distinct trials as randomisation was carried out separately for PPD+ persons (Whalen 1997) and those who were anergic (Whalen 1997-anergy). Follow-up data for these two trials were reported in Johnson 2001 and Johnson 2001 -anergy, respectively. Long-term follow-up results of Mwinga 1998 were in Quigley 1998. We have included one unpublished trial based using data from a conference poster presentation (Rivero 2002).

Full details of the studies included in this review are provided in the table of included studies.

Summary of included studies:

Trials were conducted in several countries: Haiti (Fitzgerald 2001; Halsey 1998; Pape 1993), Uganda (Whalen 1997), Kenya (Hawken 1997), Zambia (Mwinga 1998), Spain (Martinez 2001; Rivero 2002) 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 32). 52% were female, with a range of 23% to 77% 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) and others involved only those known to be anergic (Gordin 1997; Rivero 2002) Two articles included both PPD+ and anergic individuals either as separately randomized groups (Whalen 1997) or as one group with stratification by PPD status in the analysis (Martinez 2001). 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, 4495 individuals were PPD+, 1932 were PPD- (of which 1640 were known to be anergic) and in 1737 individuals the PPD status was unknown.

All 11 trials evaluated isoniazid (INH) either compared with placebo (8 trials) or to a combination anti-TB regimen (3 trials): INH plus rifampicin (RIF) (3 trials), RIF plus pyrazinamide (PZA) (4 trials) and INH plus RIF plus PZA (1 trial).

Treatment dosage varied among the trials: INH 300 mg or 600mg for daily regimens; 600mg or 900 mg 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 2001; Pape 1993) and 6 months (Gordin 1997; Halsey 1998; Hawken 1997; Mwinga 1998; Rivero 2002; Whalen 1997). All the remaining trials evaluated short-course, rifampicin-containing combination drug therapies typically offered for 2 or 3 months.

We collected data for active TB diagnosed either by culture or other methods of diagnosis as defined by the study authors (con-

firmed, probable and possible). Active TB data were available for all participants. Culture -confirmed TB was available for 5039 participants (62%).

METHODOLOGICAL QUALITY

Generation of randomization sequence was adequate in 5 studies and unclear in 6. Allocation concealment was adequate in 5 studies and unclear in the rest. There were only 3 trials where both sequence generation and allocation concealment were adequate. In 3 trials both providers and participants were blinded, in 7 trials both were unblinded and in 1 blinding was unclear. Assessors were blinded in 7 trials. It should be noted that although the majority of the trials were placebo-controlled this did not ensure blinding as anti-tuberculosis drugs produce distinguishable adverse effects. The inclusion of randomized participants was adequate in all the included trials. All randomized participants were included in analysis in 8 of the trials. The remaining studies excluded 2% (2 trials) or 4% (1 trial) of randomized participants. Participant loss to follow-up ranged from 0 to 31% (mean 11% across all studies). (See Table of Included Studies for details of individual studies.)

RESULTS

ACTIVE TUBERCULOSIS

Preventive therapy (any anti-TB drug) versus placebo reduced the risk of active TB by 36% (13 trials; 5664 participants; RR 0.64, 95% CI 0.51 to 0.81). We found no statistical heterogeneity among the trials. For confirmed (culture-proven) TB, the result was similar (6 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: 13 trials; RR 0.67, 95% CI 0.51 to 0.87
- INH+RIF: 2 trials; RR 0.41, 95% CI 0.21 to 0.81
- RIF+PZA: 4 trials; RR 0.54, 95% CI 0.34 to 0.86
- INH+RIF+PZA: 1 trial; RR 0.48, 95% CI 0.23 to 1.00

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

- INH vs. RIF+PZA: 6 trials; RR 1.00, 95% CI 0.73 to 1.38
- INH vs. INH+RIF: 4 trials; RR 1.05, 95% CI 0.51 to 2.17
- INH + RIF vs. RIF+PZA: 1 trial; RR 2.82, 95% CI 0.30 to 26.51
- INH vs. INH+RIF+PZA: 1 trial; RR 0.60, 95% CI 0.23 to 1.57
- INH + RIF vs. INH+RIF+PZA: 1 trial; RR 0.75, 95% CI 0.31 to 1.82

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). Although a similar trend was found for individuals with a negative tuberculin test (7 trials; 2822 participants; RR 0.83, 95% CI 0.58 to 1.18) and those with confirmed anergy (3 trials; 1554 participants; RR 0.67, 95% CI 0.36 to 1.24) these results were not statistically significant.

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 (13 trials; 5664 participants; RR 0.95, 95% CI 0.85 to 1.06). Among those who were PPD positive the trend was towards a benefit (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)

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.

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).

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 (5 trials; 5427 participants; RR 2.49, 95% CI 1.64 to 3.77).

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: 5 trials; RR 1.66, 95% CI 1.09 to 2.51
 - INH+RIF: 2 trials; RR 16.72, 95% CI 3.29 to 84.90
 - RIF+PZA: 2 trials; RR 7.84, 95% CI 2.60 to 23.67
 - INH+RIF+PZA: 1 trial; RR 26.11, 95% CI 3.56 to 191.64
- Direct comparisons:
- INH vs RIF+PZA: 3 trials; RR 0.64, 95% CI 0.48 to 0.86
 - INH vs INH+RIF: 3 trials; RR 0.75, 95% CI 0.46 to 1.24
 - INH+RIF vs RIF+PZA: 1 trial; RR 1.08, 95% CI 0.55 to 2.13
 - INH vs INH+RIF+PZA: 1 trial; RR 0.10, 95% CI 0.03 to 0.33
 - INH+RIF vs INH+ RIF+PZA: 1 trial; RR 0.42, 95% CI 0.22 to 0.80

ADHERENCE

Less than half of the studies reported on adherence to therapy (Halsey 1998; Hawken 1997; Martinez 2001; Mwinga 1998; 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 2001 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. We did not have sufficient data to assess adherence as an effect modifier in the studies included in the review.

DISCUSSION

In countries where antiretroviral treatment is not yet widely available, measures to control opportunistic infections, including tuberculosis, are especially important. This systematic review which updates a previous Cochrane review (Wilkinson 1998) confirms that chemoprophylaxis with anti-tuberculosis drugs reduces the risk of clinical tuberculosis in HIV infected populations. For INH monotherapy the short-term reduction in the relative risk compared to placebo 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 two studies with limited follow-up, it seems that the initial protection conferred by chemoprophylaxis may diminish over time. 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 mycobacterium 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.

Potential limitations of the review

We used a comprehensive search strategy to identify studies and contacted authors for clarification of reported findings or for additional data. A funnel plot of the treatment effects with active TB as the outcome was symmetrical suggesting a reduced likelihood of publication bias. We also used methods to minimize systematic error in the extraction of data and assessment of methodological quality of included studies. Trials seemed to be of good quality although key components of quality, such as allocation concealment, were not reported in many of the studies. Although the trial characteristics varied it is reassuring that we found no statistical heterogeneity for the primary outcomes assessed in this review. 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 recommending preventive therapy in HIV infected individuals who are tuberculin skin test positive are supported by the results of this review (CDC 1998; WHO 1998). 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 chemoprophylaxis may be substantial. Care should be taken that a programme of preventive therapy does not divert resources from treating active tuberculosis or from offering antiretroviral therapy to the large numbers of people who may need HIV/AIDS treatment. In addition, poor adherence and drug resistant TB disease potentially associated with the use of long courses of isoniazid monotherapy should be considered. Multi-drug regimens

containing rifampicin may help overcome these problems, but may be unaffordable in low- and middle-income countries. Policy makers should take all these factors into consideration when designing broad public health interventions.

Implications for research

Trials assessing the long-term effects of anti-tuberculosis 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. 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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POTENTIAL CONFLICT 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).

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* Indicates the major publication for the study

T A B L E S

Characteristics of included studies

Study	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.
Allocation concealment	B
Study	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.

Characteristics of included studies (Continued)

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.

Allocation concealment A

Study 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.

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.”

Allocation concealment B

Study 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 .

Allocation concealment B

Study 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.

Characteristics of included studies (Continued)

Outcomes	1) TB: symptoms plus either a) \geq 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).
Allocation concealment	A

Study *Johnson 2001*

Methods	2018 individuals “randomized” in blocks of 6; sequentially numbered, sealed opaque envelopes; blinding: providers no, participants no, assessors yes. 427 (21%) lost to follow up; intention to treat analysis.
Participants	As in Whalen97.
Interventions	As in Whalen97.
Outcomes	1) Definite TB: Culture confirmed (from 3 sputum specimens for suspected cases). 2) Probable TB: Clinical illness consistent with TB based on at least 2 of the following: a) results of chest X ray; b) smear positive for AFB c) response to anti-TB therapy. 3) Possible TB. Not defined. 4) Drug resistance: Isolates tested for drug susceptibility against INH, RIF, PZA ethambutol and streptomycin using standard BACTEC radiometric methods. 5) Death. – Mean duration of follow-up 2 years.
Notes	Long-term follow up of Whalen97 study. Following the interim analysis, INH was offered to all participants in the placebo arm. Relative risks were adjusted for haemoglobin, body mass index and period of enrolment in a Cox proportional hazards model
Allocation concealment	A

Study *Johnson 2001 -anergy*

Methods	718 individuals “randomized” in blocks of 6. Sequentially numbered, sealed opaque envelopes; blinding: providers no, participants no, assessors blind. 103 (14.3%) lost to follow-up; intention to treat analysis.
Participants	As in Whalen97anergy.
Interventions	As in Whalen97anergy.
Outcomes	As in Johnson01. – Mean duration of follow-up= 1.6 years.
Notes	Long-term follow up of Whalen97anergy study. After interim analysis, INH was offered to participants in placebo arm. Relative risks were adjusted for haemoglobin, body mass index and period of enrolment in a Cox proportional hazards model
Allocation concealment	A

Study *Martinez 2001*

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 \geq 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	
Allocation concealment	B

Study *Mwinga 1998*

Characteristics of included studies (Continued)

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.
Interventions	1) Placebo twice a week for 6 months or 3 months.
Outcomes	2) INH 900 mg, twice a week, for 6 months. 3) RIF 600mg plus PZA 3500 mg twice a week for 3 months. 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
Allocation concealment	A

Study 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, trichophyton and candida. The % of PPD+ in the INH plus pyridoxine group was significantly higher than the placebo group (66% vs. 38%).
Allocation concealment	B

Study 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.
Allocation concealment	A

Study Rivero 2002

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 chemoprophylaxis for TB; history of hypersensitivity to study drugs; Aspartate aminotransferase (ALT) > 4x normal values; Bilirubin > 2 mg/ml; Creatinine > 2 mg/ml; pregnancy.

Characteristics of included studies (Continued)

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	Unpublished data derived from conference poster.
Allocation concealment	B

Study 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 \geq 5mm, Karnofsky 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.
Allocation concealment	A

Study 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.
Allocation concealment	A

Characteristics of excluded studies

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
Matteelli 1998	Assessed drug tolerability rather than prevention of active TB
Saenghirunvatta 1996	Described only as “prospective, comparative”

GRAPHS

Comparison 01 Any TB drug vs placebo

<i>Outcome title</i>	<i>No. of studies</i>	<i>No. of participants</i>	<i>Statistical method</i>	<i>Effect size</i>
01 Incidence of active TB (confirmed, probable or possible)	13	5664	Relative Risk (Fixed) 95% CI	0.64 [0.51, 0.81]
02 Incidence of confirmed TB	6	2573	Relative Risk (Fixed) 95% CI	0.73 [0.49, 1.08]
03 Incidence of death (all cause)	13	5664	Relative Risk (Fixed) 95% CI	0.95 [0.85, 1.06]
04 Incidence of AIDS	3	355	Relative Risk (Fixed) 95% CI	0.88 [0.60, 1.28]
05 Incidence of adverse events leading to stopping treatment	7	5427	Relative Risk (Fixed) 95% CI	2.49 [1.64, 3.77]
07 Mean CD4 count	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
08 Mean time to TB	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
09 Mean time to death	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
10 Mean time to AIDS	1	118	Weighted Mean Difference (Fixed) 95% CI	7.80 [1.71, 13.89]

Comparison 02 Isoniazid vs placebo

<i>Outcome title</i>	<i>No. of studies</i>	<i>No. of participants</i>	<i>Statistical method</i>	<i>Effect size</i>
01 Incidence of active TB (confirmed, probable or possible)	13	4136	Relative Risk (Fixed) 95% CI	0.67 [0.51, 0.87]
02 Incidence of confirmed TB	6	2063	Relative Risk (Fixed) 95% CI	0.72 [0.47, 1.11]
03 Incidence of death (all cause)	13	4136	Relative Risk (Fixed) 95% CI	0.95 [0.85, 1.06]
04 Incidence of AIDS	3	355	Relative Risk (Fixed) 95% CI	0.88 [0.60, 1.28]
05 Incidence of adverse events leading to stopping treatment	7	3899	Relative Risk (Fixed) 95% CI	1.66 [1.09, 2.51]
07 Mean CD4 count	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
08 Mean time to TB	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
09 Mean time to death	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
10 Mean time to AIDS	1	118	Weighted Mean Difference (Fixed) 95% CI	7.80 [1.71, 13.89]

Comparison 03 Isoniazid + rifampicin vs placebo

<i>Outcome title</i>	<i>No. of studies</i>	<i>No. of participants</i>	<i>Statistical method</i>	<i>Effect size</i>
01 Incidence of active TB (confirmed, probable or possible)	2	1179	Relative Risk (Fixed) 95% CI	0.41 [0.21, 0.81]
02 Incidence of confirmed TB	1	159	Relative Risk (Fixed) 95% CI	0.70 [0.16, 3.05]
03 Incidence of death (all cause)	2	1179	Relative Risk (Fixed) 95% CI	0.69 [0.50, 0.95]
04 Incidence of AIDS	0	0	Relative Risk (Fixed) 95% CI	Not estimable
05 Incidence of adverse events leading to stopping treatment	2	1179	Relative Risk (Fixed) 95% CI	16.72 [3.29, 84.90]

07 Mean CD4 count	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
08 Mean time to TB	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
09 Mean time to death	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
10 Mean time to AIDS	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable

Comparison 04 Rifampicin + pyrazinimide vs placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Incidence of active TB (confirmed, probable or possible)	4	855	Relative Risk (Fixed) 95% CI	0.54 [0.34, 0.86]
02 Incidence of confirmed TB	4	855	Relative Risk (Fixed) 95% CI	0.69 [0.34, 1.38]
03 Incidence of death (all cause)	4	855	Relative Risk (Fixed) 95% CI	1.04 [0.77, 1.41]
04 Incidence of AIDS	0	0	Relative Risk (Fixed) 95% CI	Not estimable
05 Incidence of adverse events leading to stopping treatment	2	855	Relative Risk (Fixed) 95% CI	7.84 [2.60, 23.67]
07 Mean CD4 count	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
08 Mean time to TB	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
09 Mean time to death	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
10 Mean time to AIDS	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable

Comparison 05 Isoniazid + rifampicin + pyrazinamid vs placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Incidence of active TB (confirmed, probable or possible)	1	926	Relative Risk (Fixed) 95% CI	0.48 [0.23, 1.00]
02 Incidence of confirmed TB	0	0	Relative Risk (Fixed) 95% CI	Not estimable
03 Incidence of death (all cause)	1	926	Relative Risk (Fixed) 95% CI	0.91 [0.65, 1.27]
04 Incidence of AIDS	0	0	Relative Risk (Fixed) 95% CI	Not estimable
05 Incidence of adverse events leading to stopping treatment	1	926	Relative Risk (Fixed) 95% CI	26.11 [3.56, 191.64]
07 Mean CD4 count	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
08 Mean time to TB	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
09 Mean time to death	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
10 Mean time to AIDS	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable

Comparison 06 Isoniazid vs rifampicin + pyrazinimide

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Incidence of active TB (confirmed, probable or possible)	6	3196	Relative Risk (Fixed) 95% CI	1.00 [0.73, 1.38]
02 Incidence of confirmed TB	6	3196	Relative Risk (Fixed) 95% CI	1.02 [0.67, 1.55]
03 Incidence of death (all cause)	6	3137	Relative Risk (Fixed) 95% CI	1.03 [0.89, 1.19]

04 Incidence of AIDS	0	0	Relative Risk (Fixed) 95% CI	Not estimable
05 Incidence of adverse events leading to stopping treatment	4	3196	Relative Risk (Fixed) 95% CI	0.64 [0.48, 0.86]
07 Mean CD4 count	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
08 Mean time to TB	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
09 Mean time to death	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
10 Mean time to AIDS	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable

Comparison 07 Isoniazid vs isoniazid + rifampicin

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Incidence of active TB (confirmed, probable or possible)	4	1390	Relative Risk (Fixed) 95% CI	1.05 [0.51, 2.17]
02 Incidence of confirmed TB	3	298	Relative Risk (Fixed) 95% CI	1.49 [0.49, 4.50]
03 Incidence of death (all cause)	4	1385	Relative Risk (Fixed) 95% CI	1.09 [0.80, 1.50]
04 Incidence of AIDS	0	0	Relative Risk (Fixed) 95% CI	Not estimable
05 Incidence of adverse events leading to stopping treatment	3	1390	Relative Risk (Fixed) 95% CI	0.75 [0.46, 1.24]
07 Mean CD4 count	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
08 Mean time to TB	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
09 Mean time to death	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
10 Mean time to AIDS	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable

Comparison 08 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Incidence of active TB (confirmed, probable or possible)	1	159	Relative Risk (Fixed) 95% CI	2.82 [0.30, 26.51]
02 Incidence of confirmed TB	1	159	Relative Risk (Fixed) 95% CI	2.82 [0.30, 26.51]
03 Incidence of death (all cause)	1	159	Relative Risk (Fixed) 95% CI	0.75 [0.21, 2.70]
04 Incidence of AIDS	0	0	Relative Risk (Fixed) 95% CI	Not estimable
05 Incidence of adverse events leading to stopping treatment	1	159	Relative Risk (Fixed) 95% CI	1.08 [0.55, 2.13]
07 Mean CD4 count	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
08 Mean time to TB	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
09 Mean time to death	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
10 Mean time to AIDS	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable

Comparison 09 Isoniazid vs isoniazid + rifampicin + Pyrazinamide

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Incidence of active TB (confirmed, probable or possible)	1	998	Relative Risk (Fixed) 95% CI	0.60 [0.23, 1.57]

02 Incidence of confirmed TB	0	0	Relative Risk (Fixed) 95% CI	Not estimable
03 Incidence of death (all cause)	1	998	Relative Risk (Fixed) 95% CI	0.86 [0.61, 1.21]
04 Incidence of AIDS	0	0	Relative Risk (Fixed) 95% CI	Not estimable
05 Incidence of adverse events leading to stopping treatment	1	998	Relative Risk (Fixed) 95% CI	0.10 [0.03, 0.33]
07 Mean CD4 count	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
08 Mean time to TB	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
09 Mean time to death	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
10 Mean time to AIDS	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable

Comparison 10 Isoniazid + rifampicin vs isoniazid + rifampicin + Pyrazinamide

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Incidence of active TB (confirmed, probable or possible)	1	1018	Relative Risk (Fixed) 95% CI	0.75 [0.31, 1.82]
02 Incidence of confirmed TB	0	0	Relative Risk (Fixed) 95% CI	Not estimable
03 Incidence of death (all cause)	1	1018	Relative Risk (Fixed) 95% CI	0.82 [0.58, 1.15]
04 Incidence of AIDS	0	0	Relative Risk (Fixed) 95% CI	Not estimable
05 Incidence of adverse events leading to stopping treatment	1	1018	Relative Risk (Fixed) 95% CI	0.42 [0.22, 0.80]
07 Mean CD4 count	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
08 Mean time to TB	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
09 Mean time to death	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
10 Mean time to AIDS	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable

Comparison 22 Isoniazid vs placebo (stratified by AIDS status at baseline)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
02 Incidence of confirmed TB	2	517	Relative Risk (Fixed) 95% CI	0.53 [0.15, 1.90]
03 Incidence of death (all cause)	2	520	Relative Risk (Fixed) 95% CI	1.03 [0.87, 1.22]

Comparison 26 Isoniazid vs rifampicin + pyrazinimide (stratified by AIDS status at baseline)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
02 Incidence of confirmed TB	2	1583	Relative Risk (Fixed) 95% CI	1.32 [0.74, 2.36]
03 Incidence of death (all cause)	2	1583	Relative Risk (Fixed) 95% CI	1.10 [0.90, 1.35]

COVER SHEET

Title	Treatment of latent tuberculosis infection in HIV infected persons
Authors	Woldehanna S, Volmink J
Contribution of author(s)	SW and JV both contributed to the update of this review
Issue protocol first published	/

Review first published	/
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Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
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GRAPHS AND OTHER TABLES

Fig. 1. Comparison 01 Any TB drug vs placebo

01.01 Incidence of active TB (confirmed, probable or possible)

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 01 Any TB drug vs placebo

Outcome: 01 Incidence of active TB (confirmed, probable or possible)

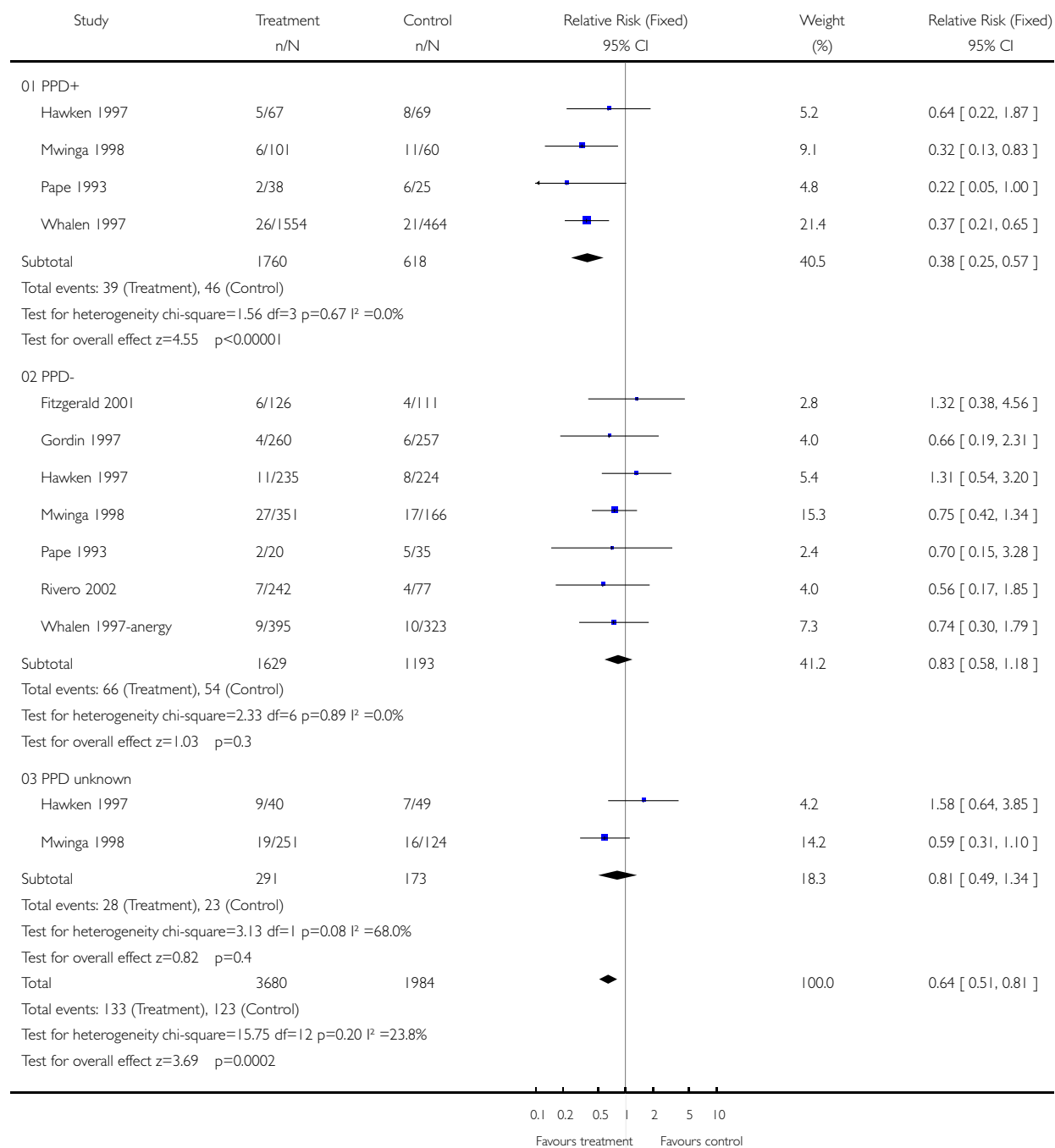


Fig. 2. Comparison 01 Any TB drug vs placebo

01.02 Incidence of confirmed TB

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 01 Any TB drug vs placebo

Outcome: 02 Incidence of confirmed TB

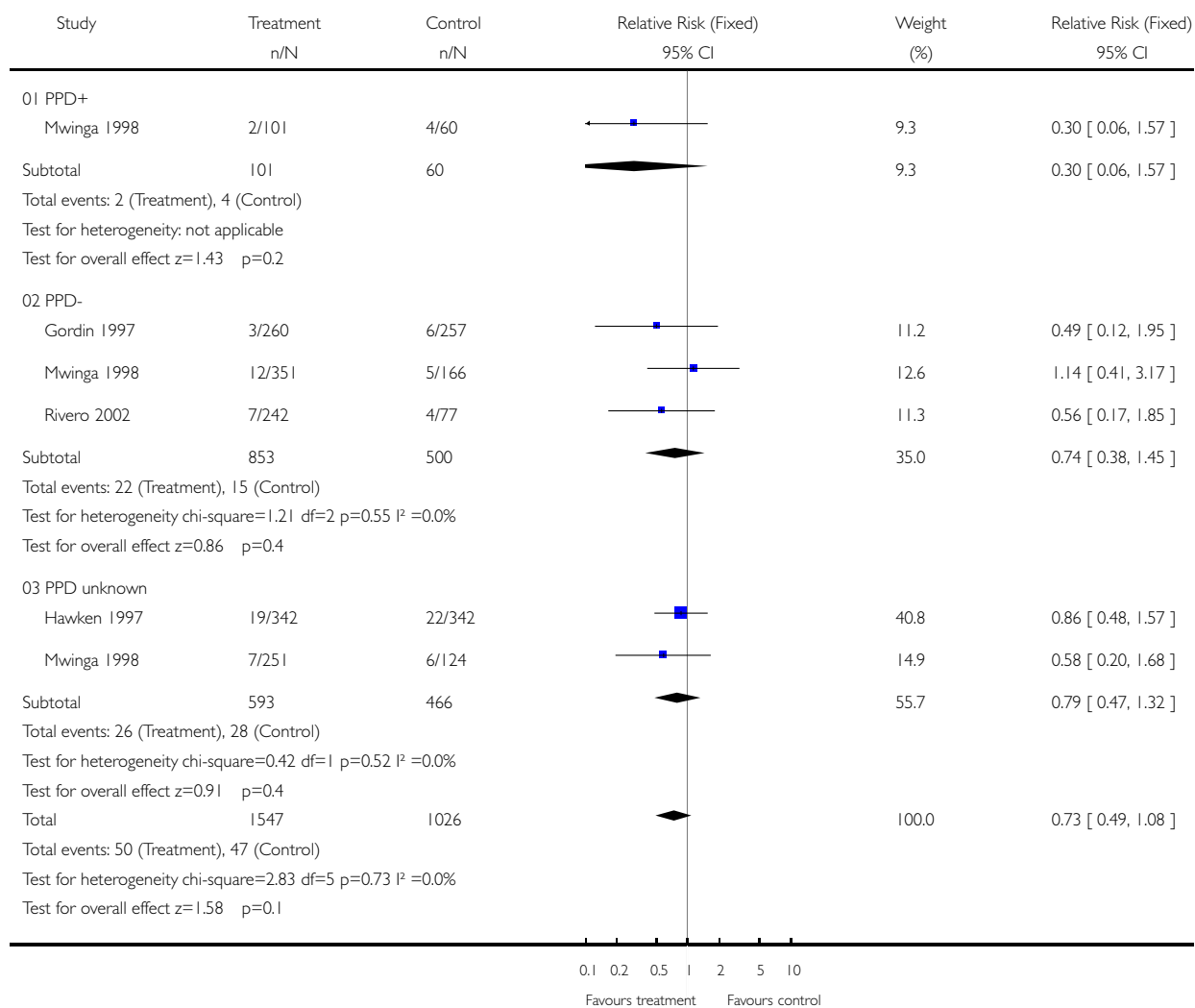


Fig. 3. Comparison 01 Any TB drug vs placebo

01.03 Incidence of death (all cause)

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 01 Any TB drug vs placebo

Outcome: 03 Incidence of death (all cause)

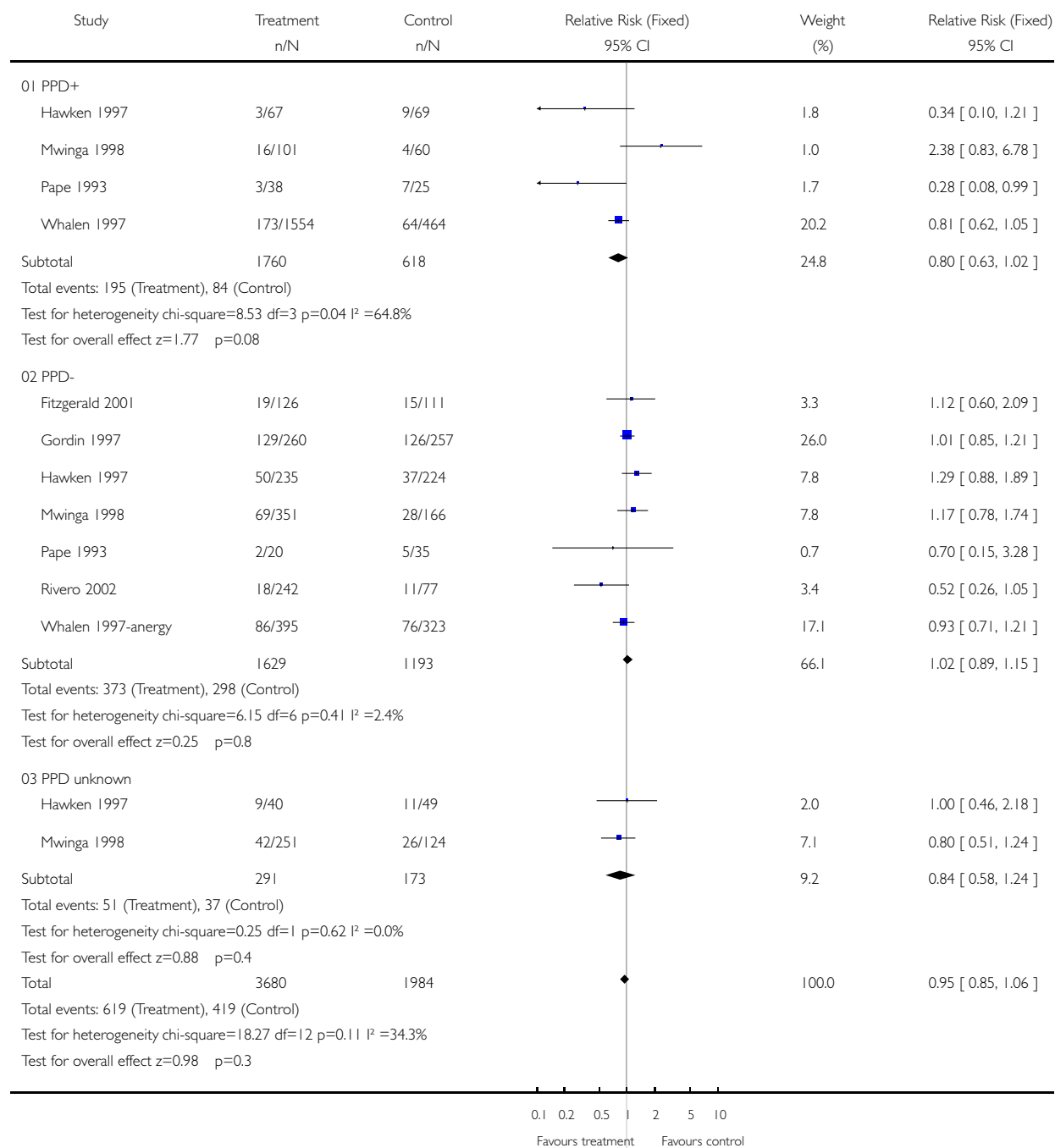


Fig. 4. Comparison 01 Any TB drug vs placebo

01.04 Incidence of AIDS

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 01 Any TB drug vs placebo

Outcome: 04 Incidence of AIDS

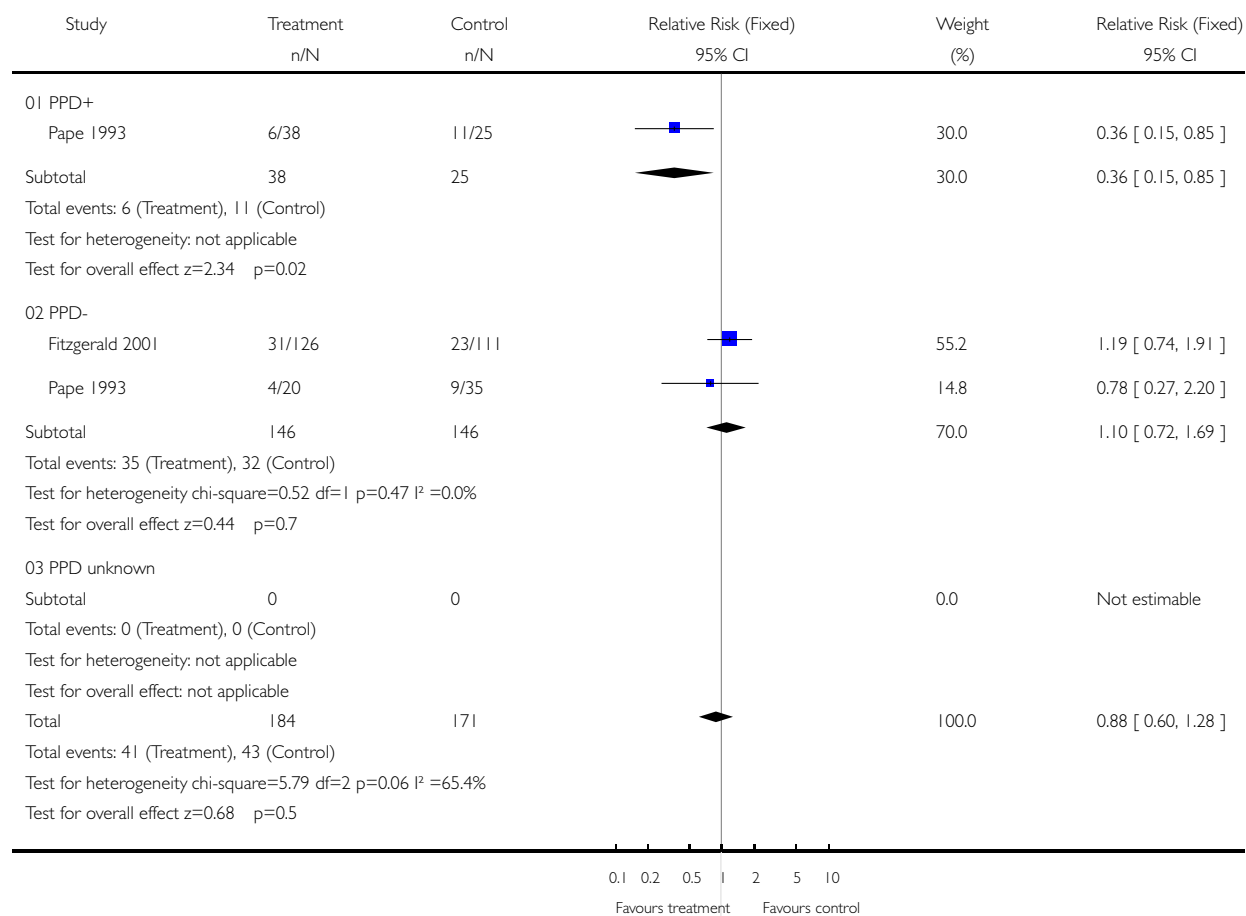


Fig. 5. Comparison 01 Any TB drug vs placebo

01.05 Incidence of adverse events leading to stopping treatment

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 01 Any TB drug vs placebo

Outcome: 05 Incidence of adverse events leading to stopping treatment

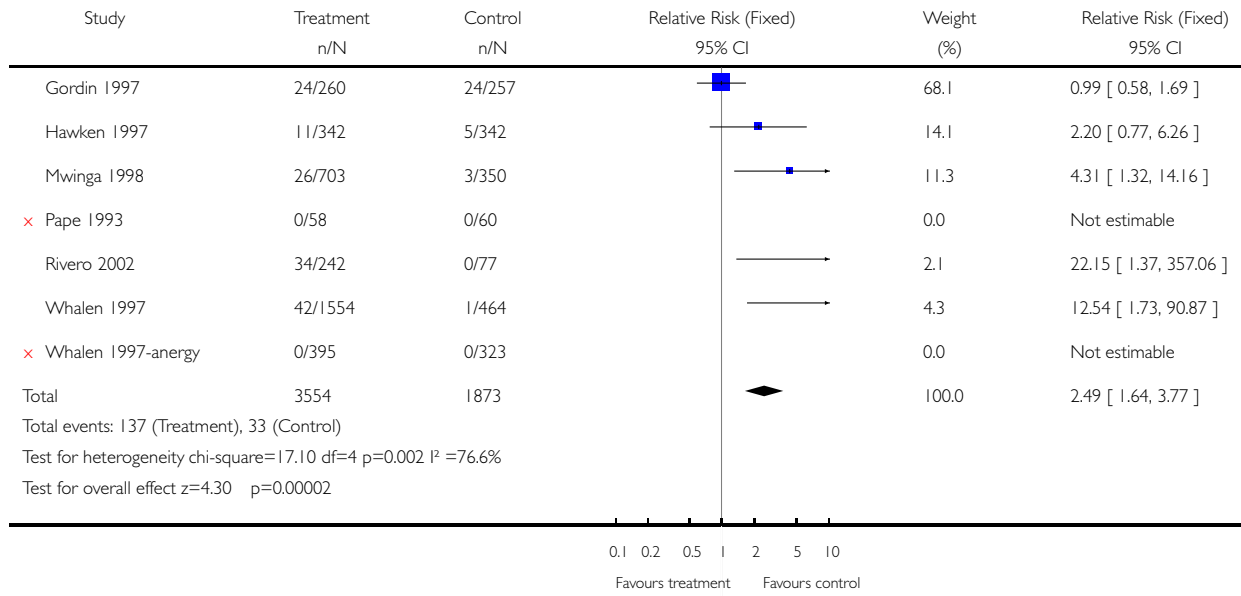


Fig. 6. Comparison 01 Any TB drug vs placebo

01.07 Mean CD4 count

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 01 Any TB drug vs placebo

Outcome: 07 Mean CD4 count

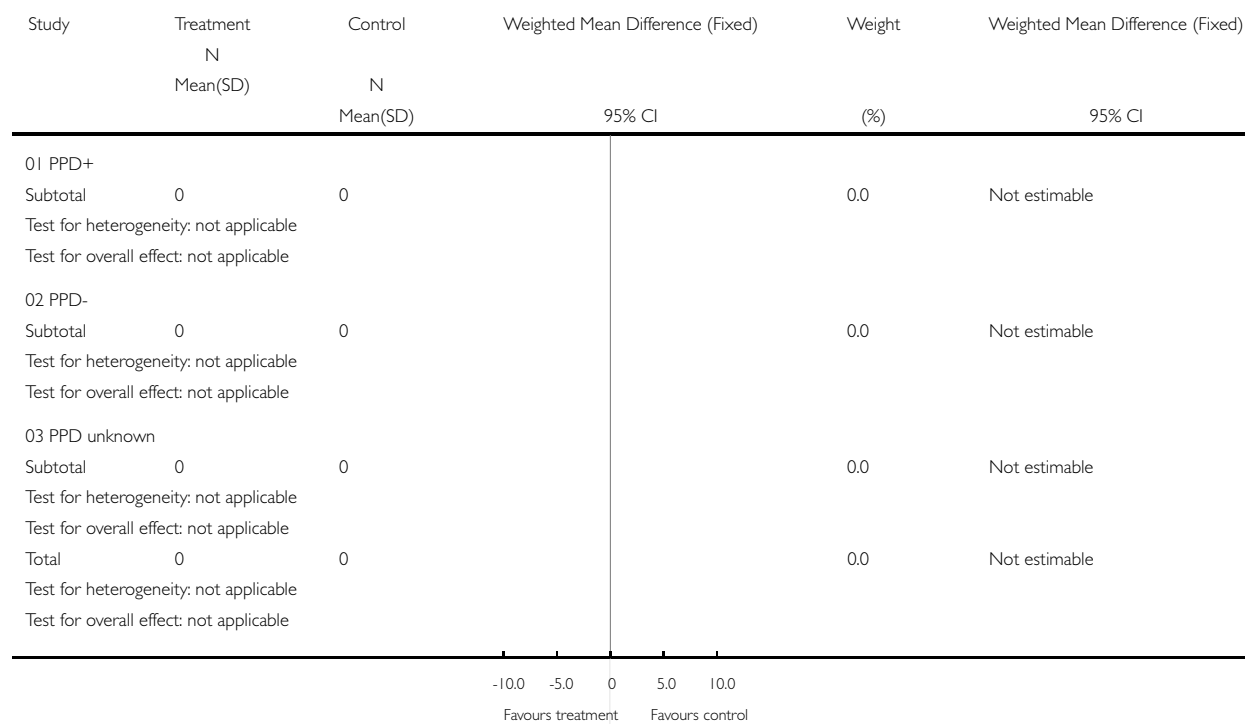


Fig. 7. Comparison 01 Any TB drug vs placebo

01.08 Mean time to TB

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 01 Any TB drug vs placebo

Outcome: 08 Mean time to TB

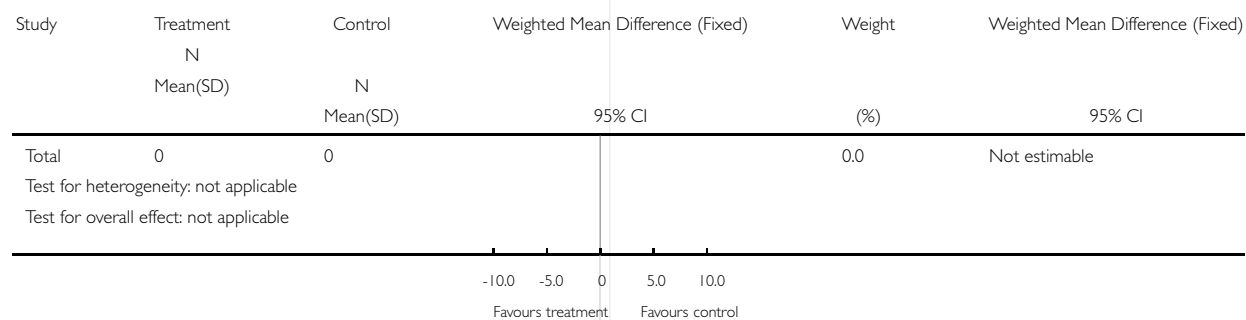


Fig. 8. Comparison 01 Any TB drug vs placebo

01.09 Mean time to death

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 01 Any TB drug vs placebo

Outcome: 09 Mean time to death

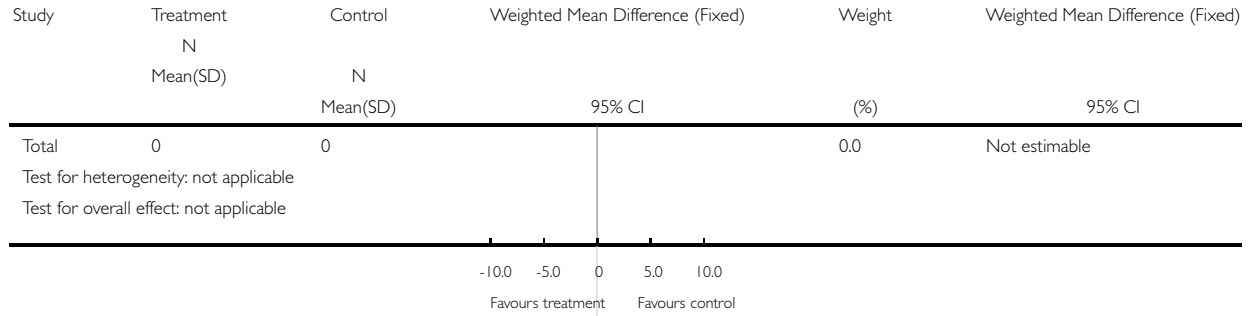


Fig. 9. Comparison 01 Any TB drug vs placebo

01.10 Mean time to AIDS

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 01 Any TB drug vs placebo

Outcome: 10 Mean time to AIDS

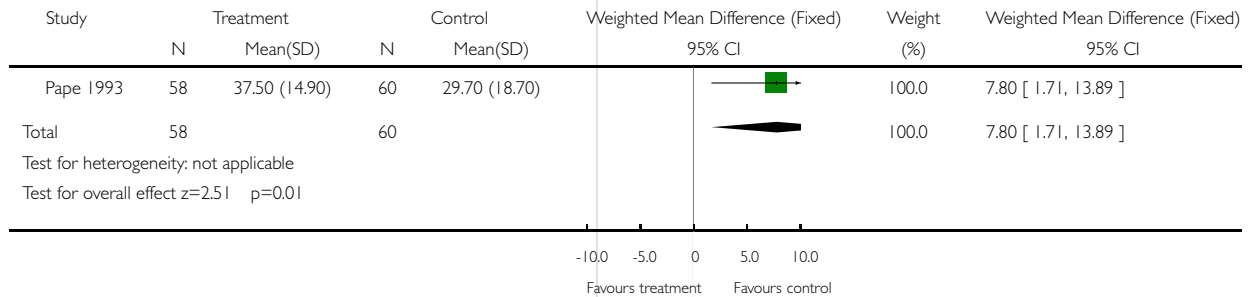


Fig. 10. Comparison 02 Isoniazid vs placebo

02.01 Incidence of active TB (confirmed, probable or possible)

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 02 Isoniazid vs placebo

Outcome: 01 Incidence of active TB (confirmed, probable or possible)

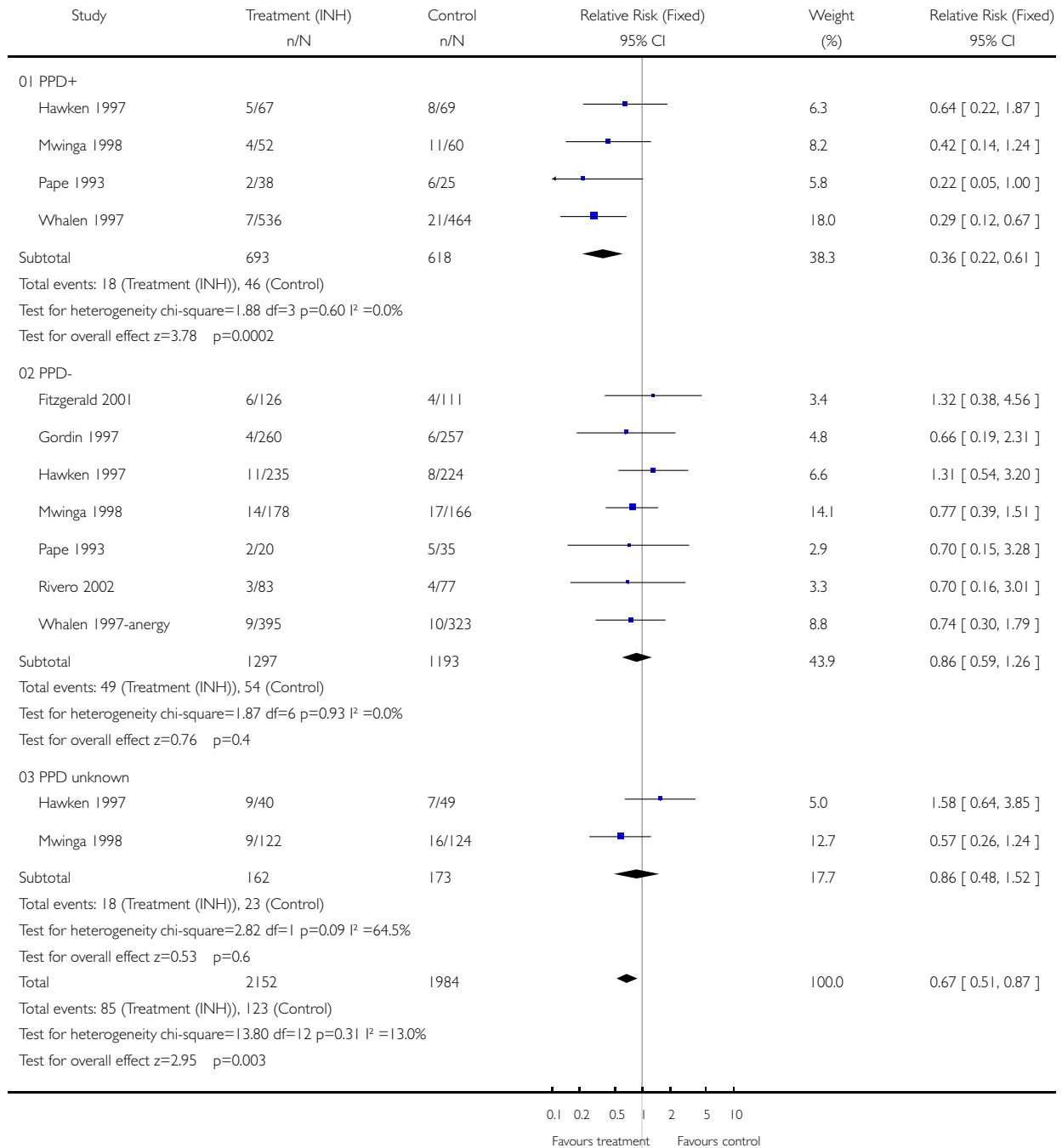


Fig. 11. Comparison 02 Isoniazid vs placebo

02.02 Incidence of confirmed TB

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 02 Isoniazid vs placebo

Outcome: 02 Incidence of confirmed TB

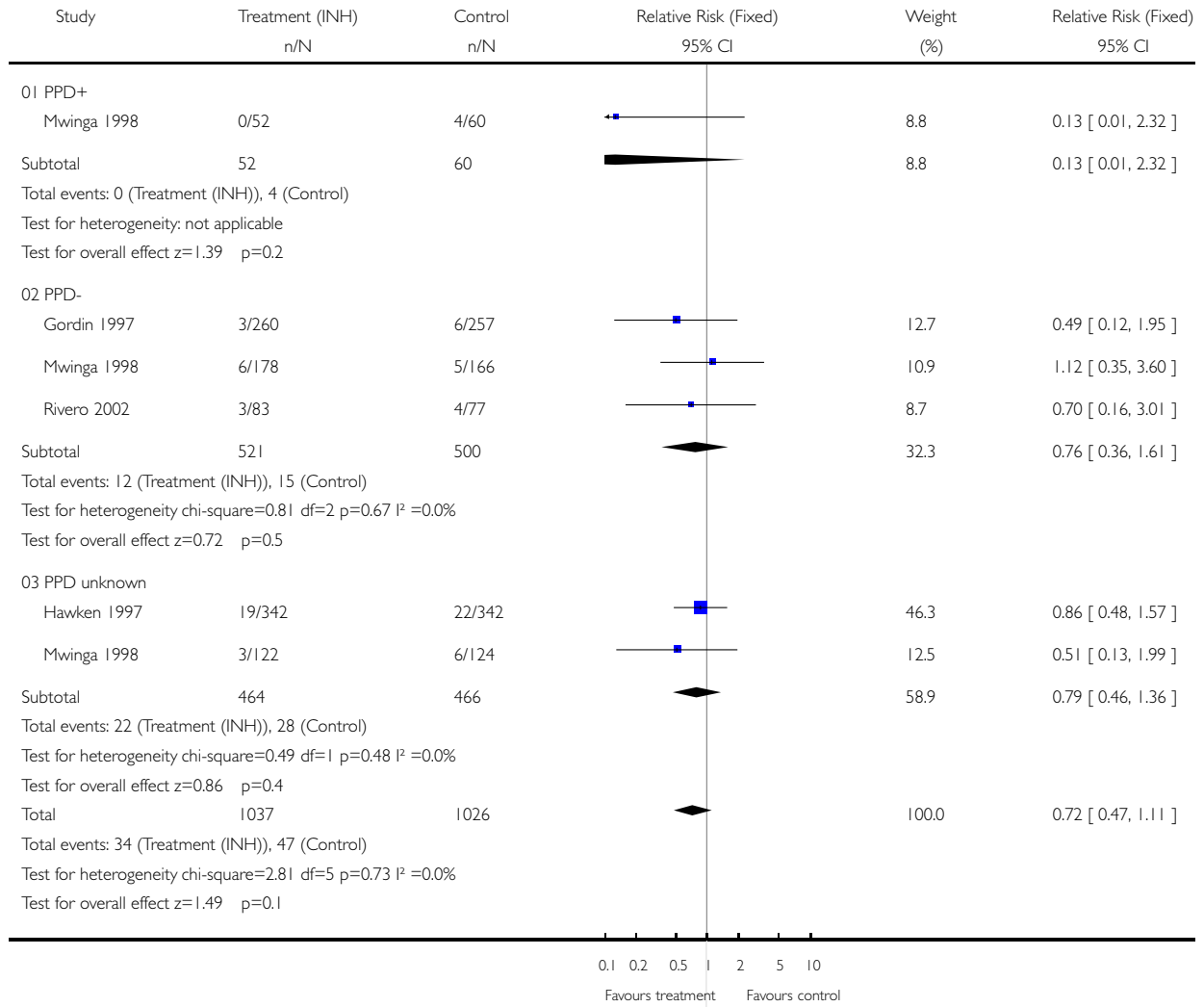


Fig. 12. Comparison 02 Isoniazid vs placebo

02.03 Incidence of death (all cause)

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 02 Isoniazid vs placebo

Outcome: 03 Incidence of death (all cause)

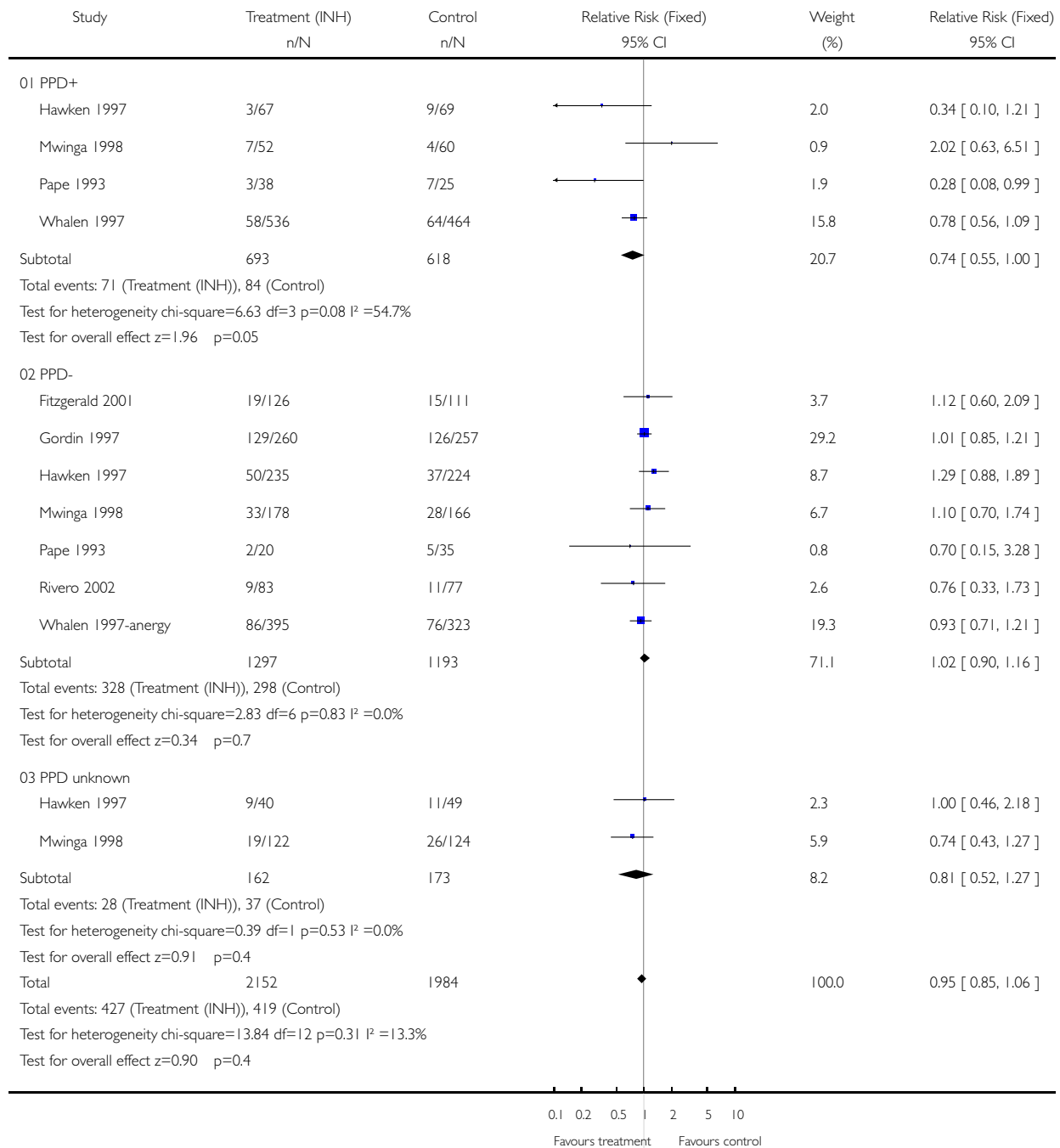


Fig. 13. Comparison 02 Isoniazid vs placebo

02.04 Incidence of AIDS

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 02 Isoniazid vs placebo

Outcome: 04 Incidence of AIDS

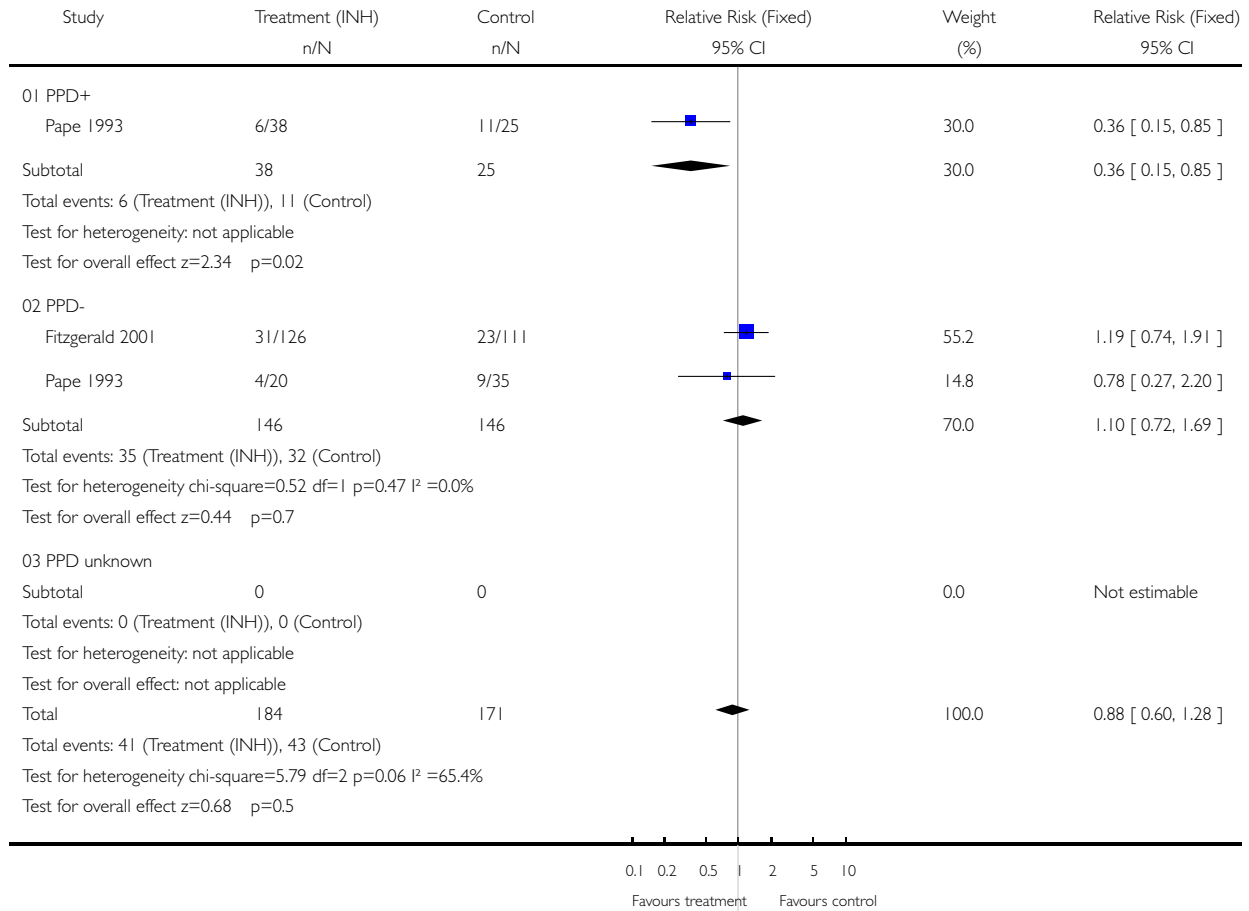


Fig. 14. Comparison 02 Isoniazid vs placebo

02.05 Incidence of adverse events leading to stopping treatment

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 02 Isoniazid vs placebo

Outcome: 05 Incidence of adverse events leading to stopping treatment

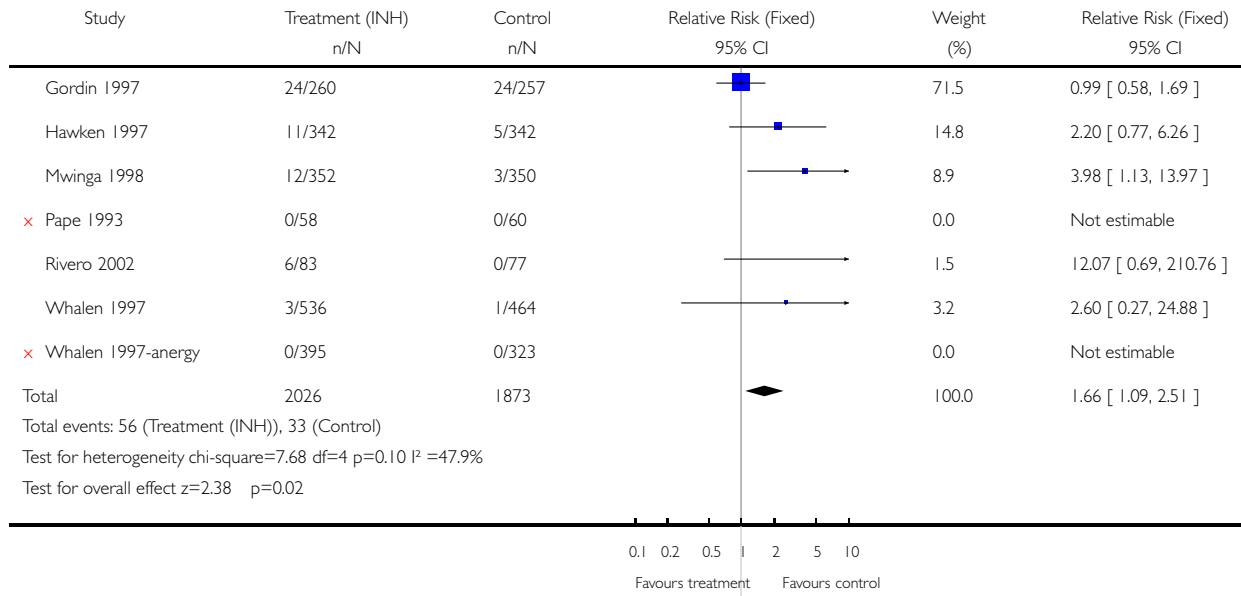


Fig. 15. Comparison 02 Isoniazid vs placebo

02.07 Mean CD4 count

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 02 Isoniazid vs placebo

Outcome: 07 Mean CD4 count

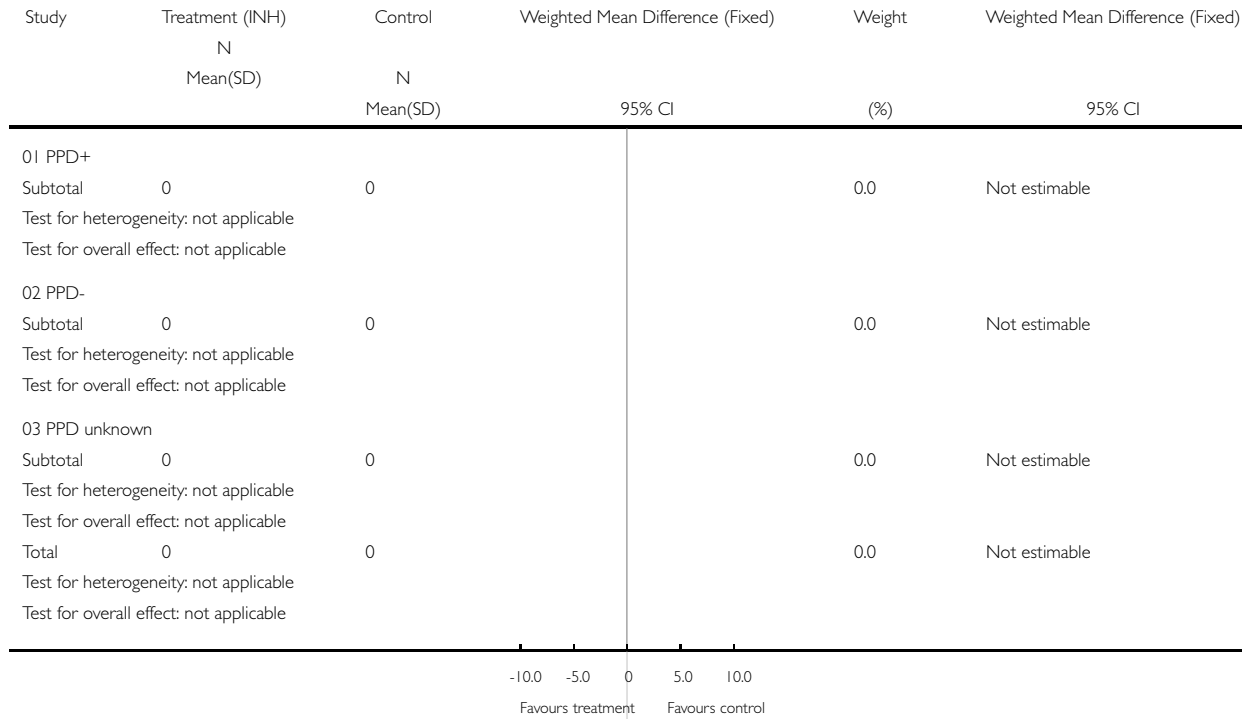


Fig. 16. Comparison 02 Isoniazid vs placebo

02.08 Mean time to TB

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 02 Isoniazid vs placebo

Outcome: 08 Mean time to TB

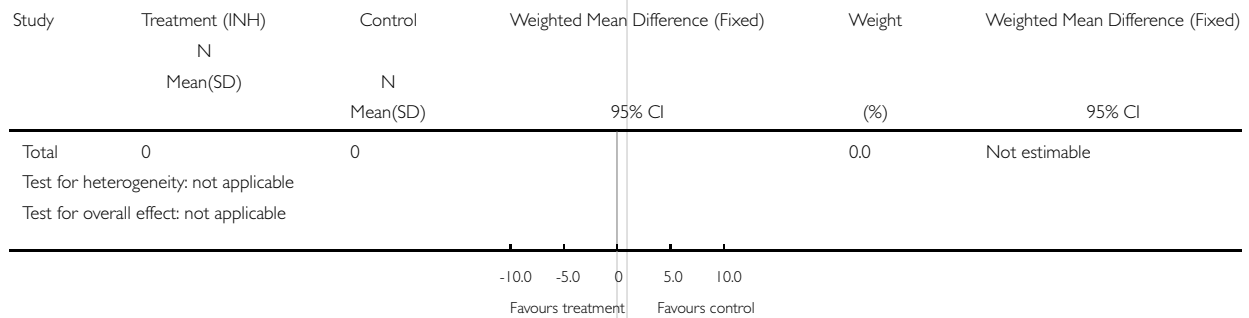


Fig. 17. Comparison 02 Isoniazid vs placebo

02.09 Mean time to death

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 02 Isoniazid vs placebo

Outcome: 09 Mean time to death

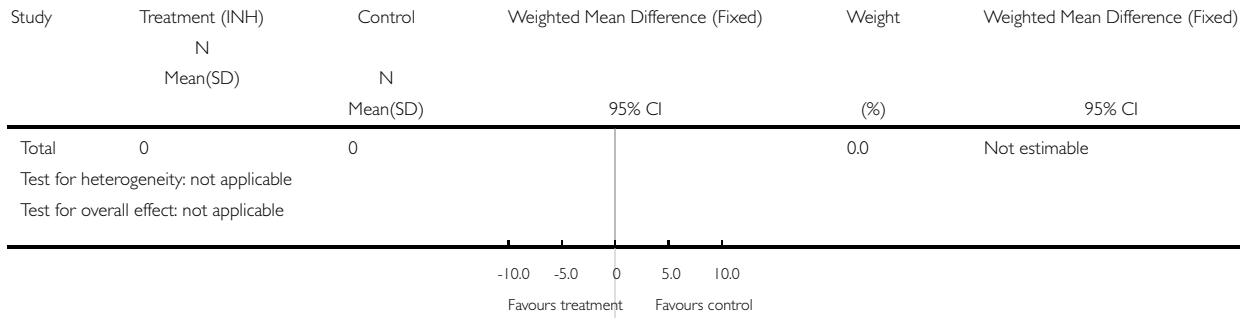


Fig. 18. Comparison 02 Isoniazid vs placebo

02.10 Mean time to AIDS

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 02 Isoniazid vs placebo

Outcome: 10 Mean time to AIDS

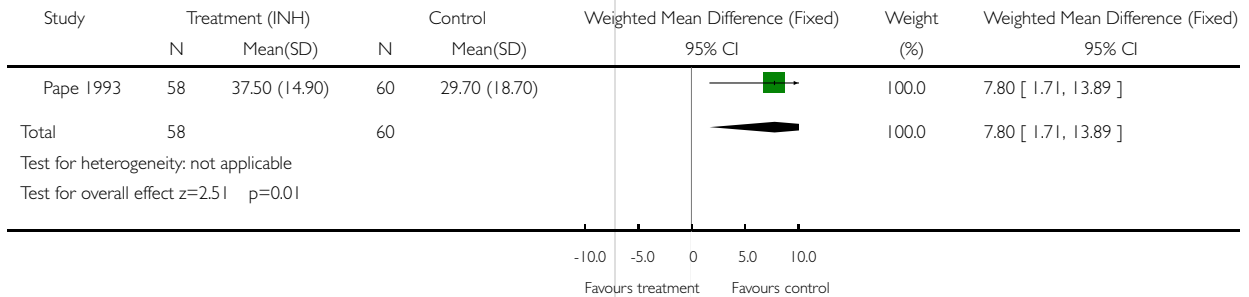


Fig. 19. Comparison 03 Isoniazid + rifampicin vs placebo

03.01 Incidence of active TB (confirmed, probable or possible)

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 03 Isoniazid + rifampicin vs placebo

Outcome: 01 Incidence of active TB (confirmed, probable or possible)

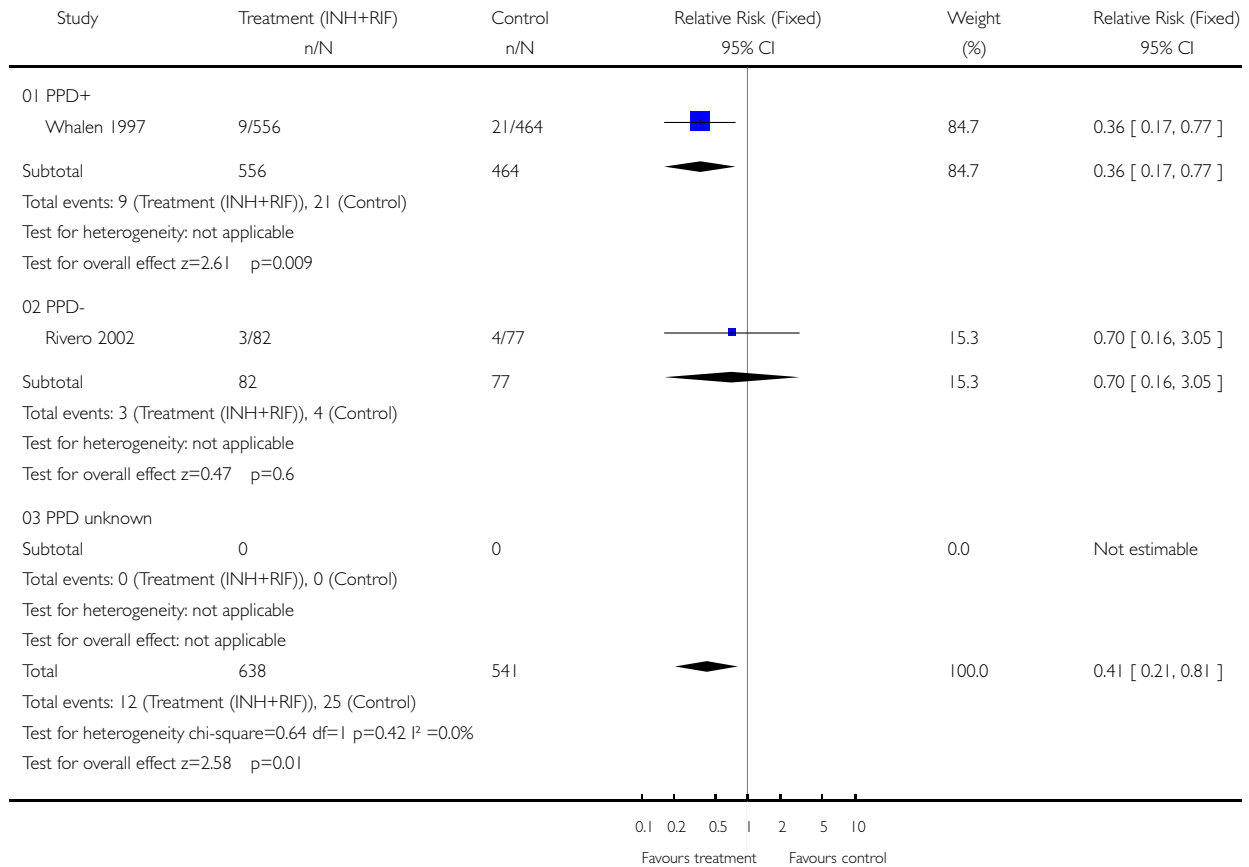


Fig. 20. Comparison 03 Isoniazid + rifampicin vs placebo

03.02 Incidence of confirmed TB

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 03 Isoniazid + rifampicin vs placebo

Outcome: 02 Incidence of confirmed TB

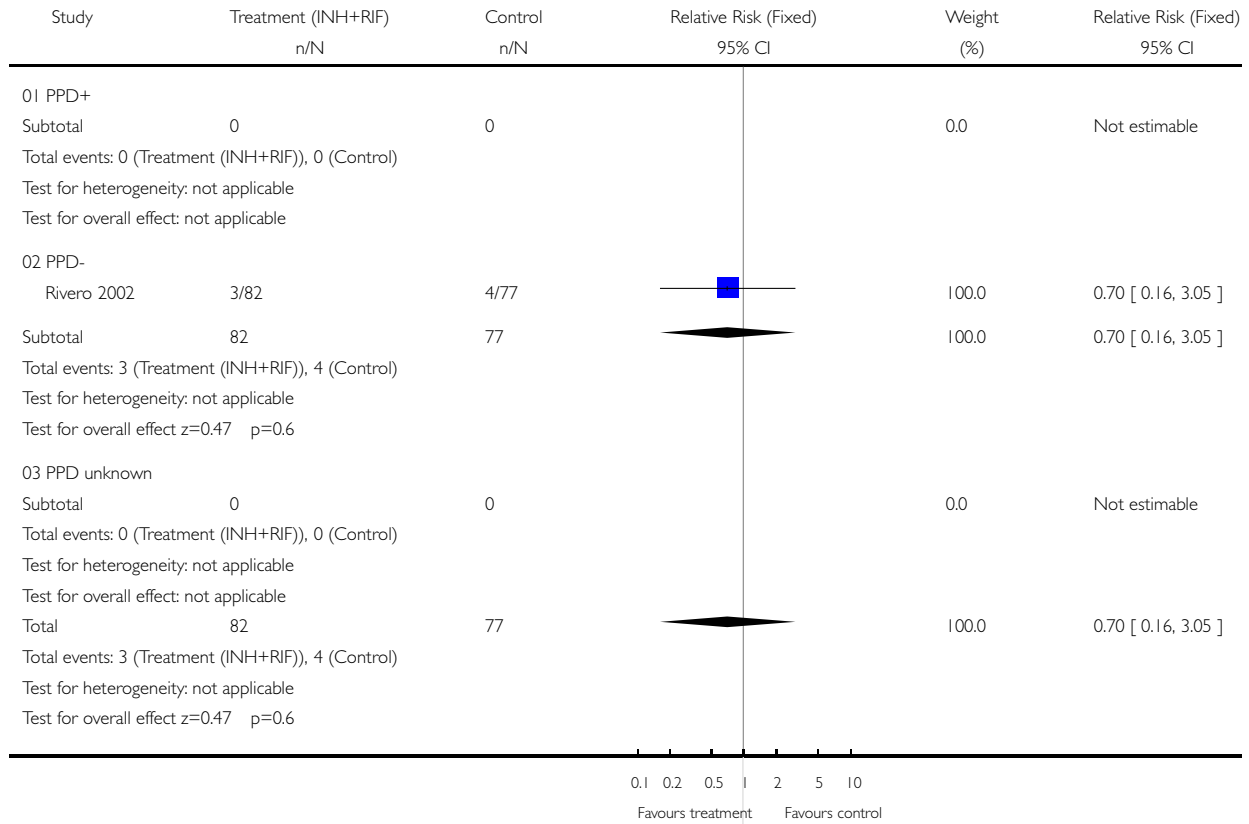


Fig. 21. Comparison 03 Isoniazid + rifampicin vs placebo

03.03 Incidence of death (all cause)

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 03 Isoniazid + rifampicin vs placebo

Outcome: 03 Incidence of death (all cause)

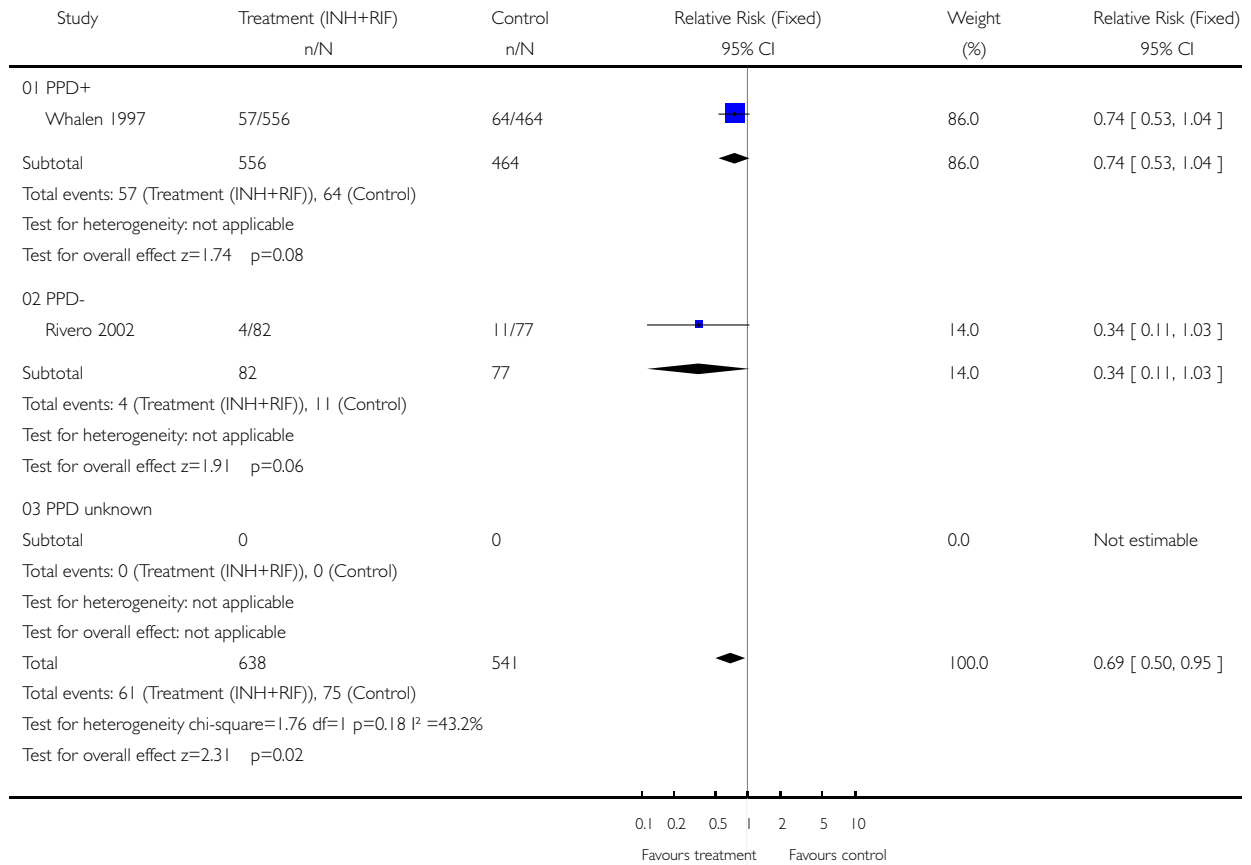


Fig. 22. Comparison 03 Isoniazid + rifampicin vs placebo

03.04 Incidence of AIDS

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 03 Isoniazid + rifampicin vs placebo

Outcome: 04 Incidence of AIDS

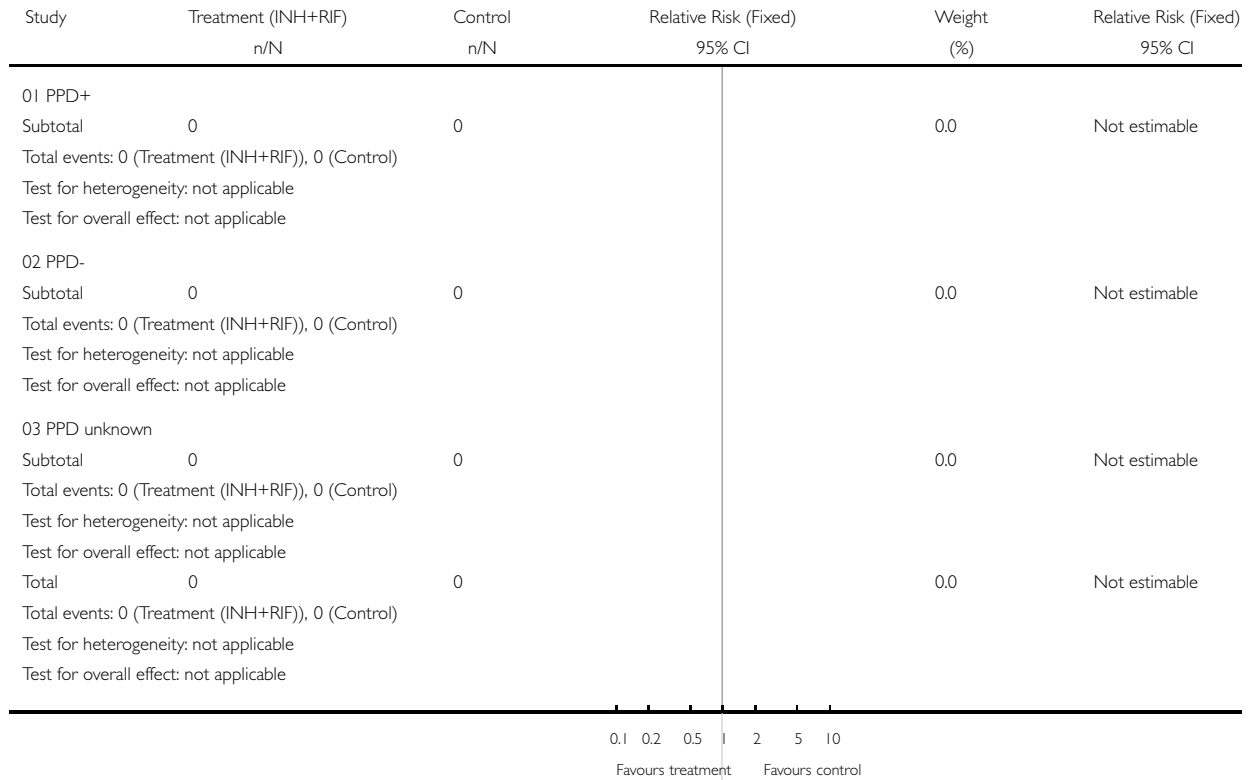


Fig. 23. Comparison 03 Isoniazid + rifampicin vs placebo

03.05 Incidence of adverse events leading to stopping treatment

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 03 Isoniazid + rifampicin vs placebo

Outcome: 05 Incidence of adverse events leading to stopping treatment

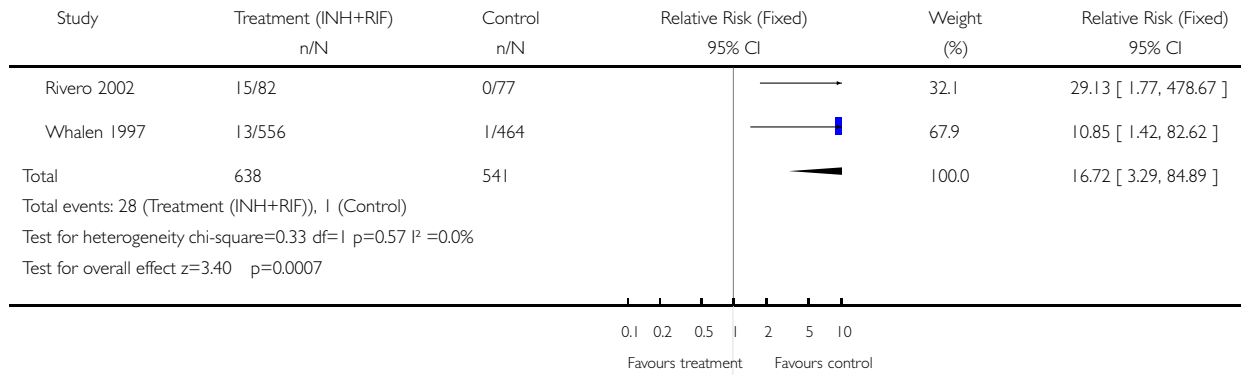


Fig. 24. Comparison 03 Isoniazid + rifampicin vs placebo

03.07 Mean CD4 count

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 03 Isoniazid + rifampicin vs placebo

Outcome: 07 Mean CD4 count

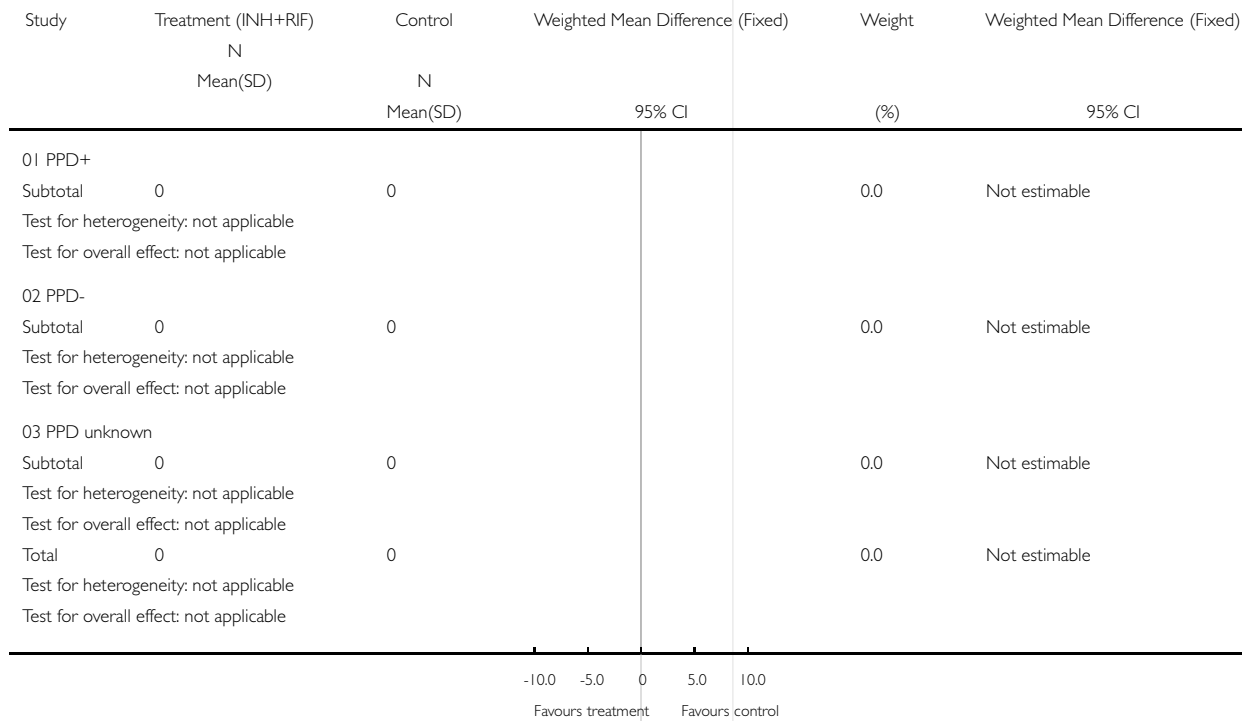


Fig. 25. Comparison 03 Isoniazid + rifampicin vs placebo

03.08 Mean time to TB

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 03 Isoniazid + rifampicin vs placebo

Outcome: 08 Mean time to TB

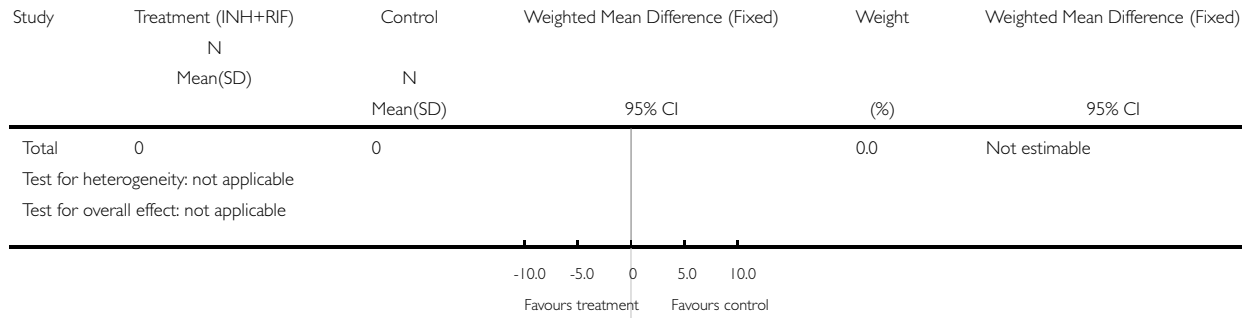


Fig. 26. Comparison 03 Isoniazid + rifampicin vs placebo

03.09 Mean time to death

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 03 Isoniazid + rifampicin vs placebo

Outcome: 09 Mean time to death

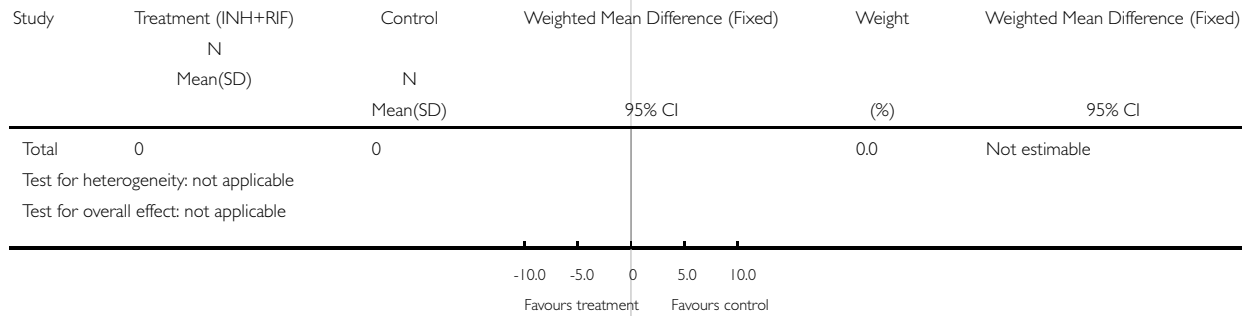


Fig. 27. Comparison 03 Isoniazid + rifampicin vs placebo

03.10 Mean time to AIDS

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 03 Isoniazid + rifampicin vs placebo

Outcome: 10 Mean time to AIDS

Study	Treatment (INH+RIF)	Control	Weighted Mean Difference (Fixed)		Weight	Weighted Mean Difference (Fixed)	
	N Mean(SD)	N Mean(SD)	95% CI			(%)	95% CI
Total	0	0			0.0	Not estimable	
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
			-10.0	-5.0	0	5.0	10.0
			Favours treatment			Favours control	

Fig. 28. Comparison 04 Rifampicin + pyrazinimide vs placebo

04.01 Incidence of active TB (confirmed, probable or possible)

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 04 Rifampicin + pyrazinimide vs placebo

Outcome: 01 Incidence of active TB (confirmed, probable or possible)

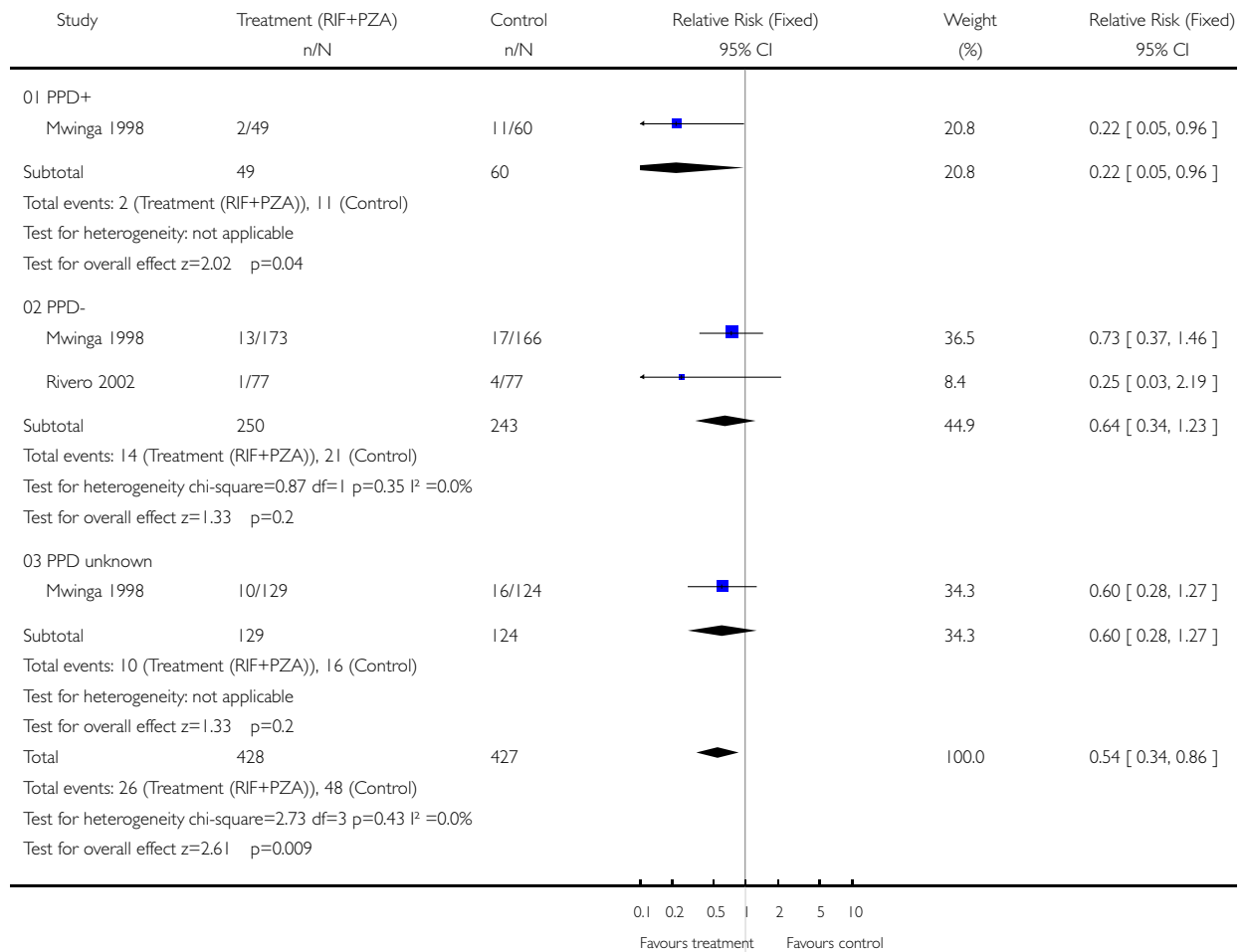


Fig. 29. Comparison 04 Rifampicin + pyrazinimide vs placebo

04.02 Incidence of confirmed TB

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 04 Rifampicin + pyrazinimide vs placebo

Outcome: 02 Incidence of confirmed TB

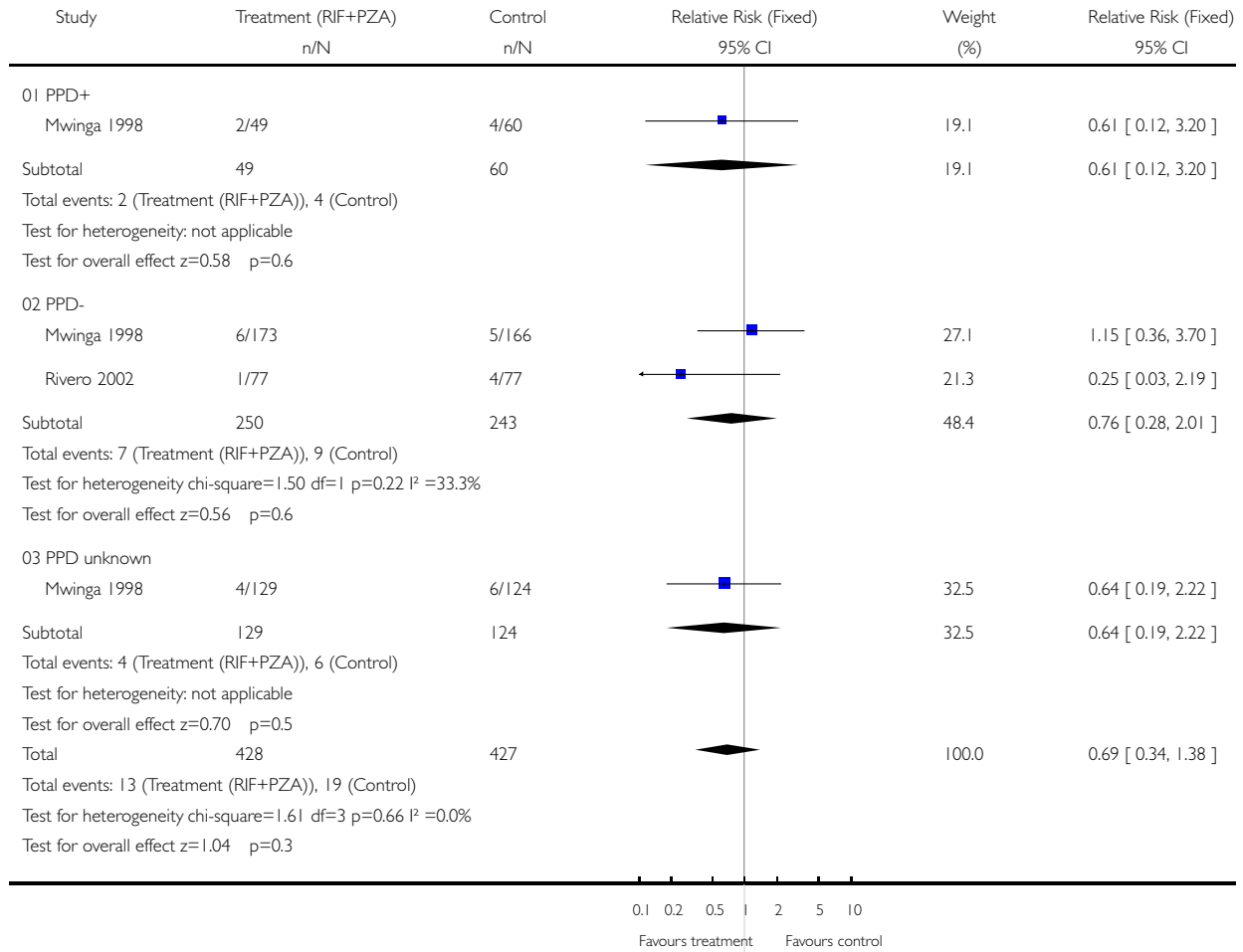


Fig. 30. Comparison 04 Rifampicin + pyrazinimide vs placebo

04.03 Incidence of death (all cause)

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 04 Rifampicin + pyrazinimide vs placebo

Outcome: 03 Incidence of death (all cause)

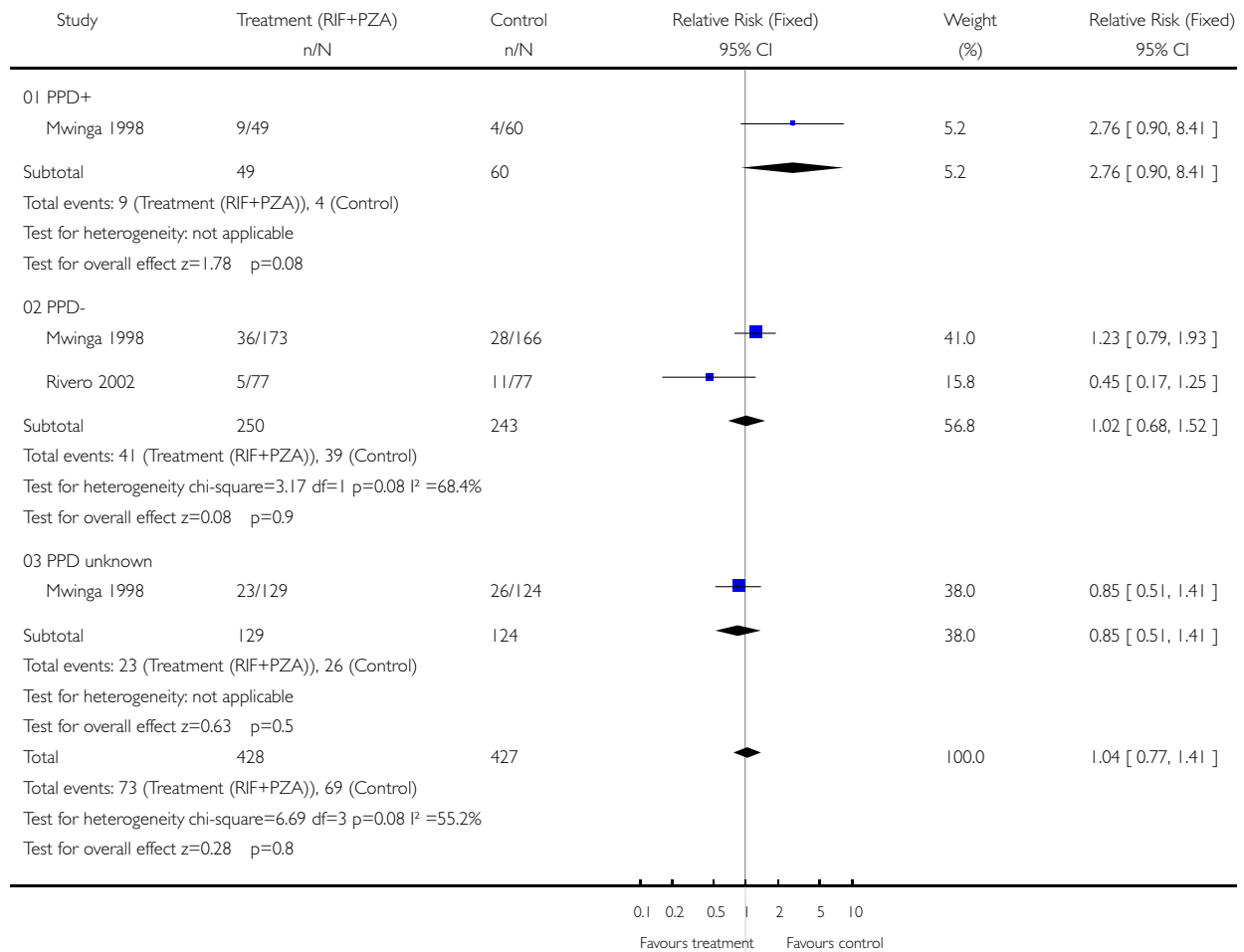


Fig. 31. Comparison 04 Rifampicin + pyrazinimide vs placebo

04.04 Incidence of AIDS

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 04 Rifampicin + pyrazinimide vs placebo

Outcome: 04 Incidence of AIDS

Study	Treatment (RIF+PZA) n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 PPD+					
Subtotal	0	0		0.0	Not estimable
Total events: 0 (Treatment (RIF+PZA)), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
02 PPD-					
Subtotal	0	0		0.0	Not estimable
Total events: 0 (Treatment (RIF+PZA)), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 PPD unknown					
Subtotal	0	0		0.0	Not estimable
Total events: 0 (Treatment (RIF+PZA)), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
Total	0	0		0.0	Not estimable
Total events: 0 (Treatment (RIF+PZA)), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

0.1 0.2 0.5 1 2 5 10
Favours treatment Favours control

Fig. 32. Comparison 04 Rifampicin + pyrazinimide vs placebo

04.05 Incidence of adverse events leading to stopping treatment

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 04 Rifampicin + pyrazinimide vs placebo

Outcome: 05 Incidence of adverse events leading to stopping treatment

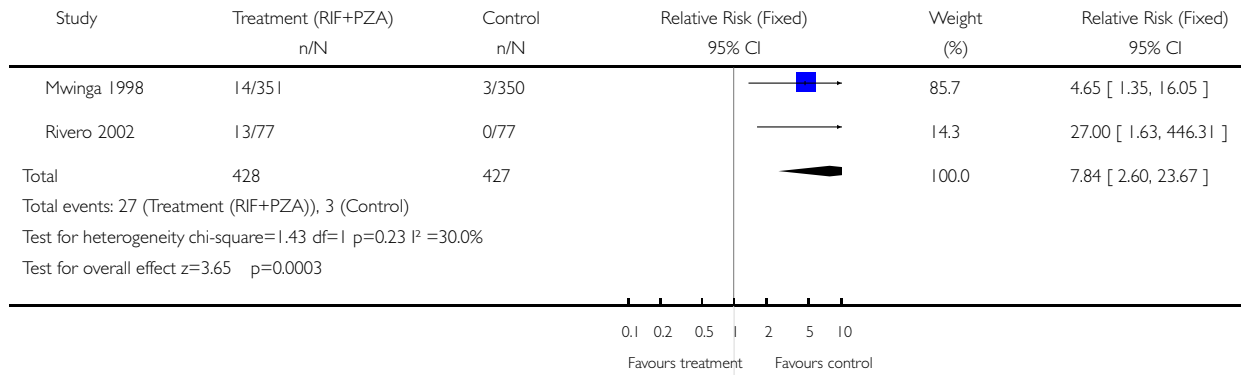


Fig. 33. Comparison 04 Rifampicin + pyrazinimide vs placebo

04.07 Mean CD4 count

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 04 Rifampicin + pyrazinimide vs placebo

Outcome: 07 Mean CD4 count

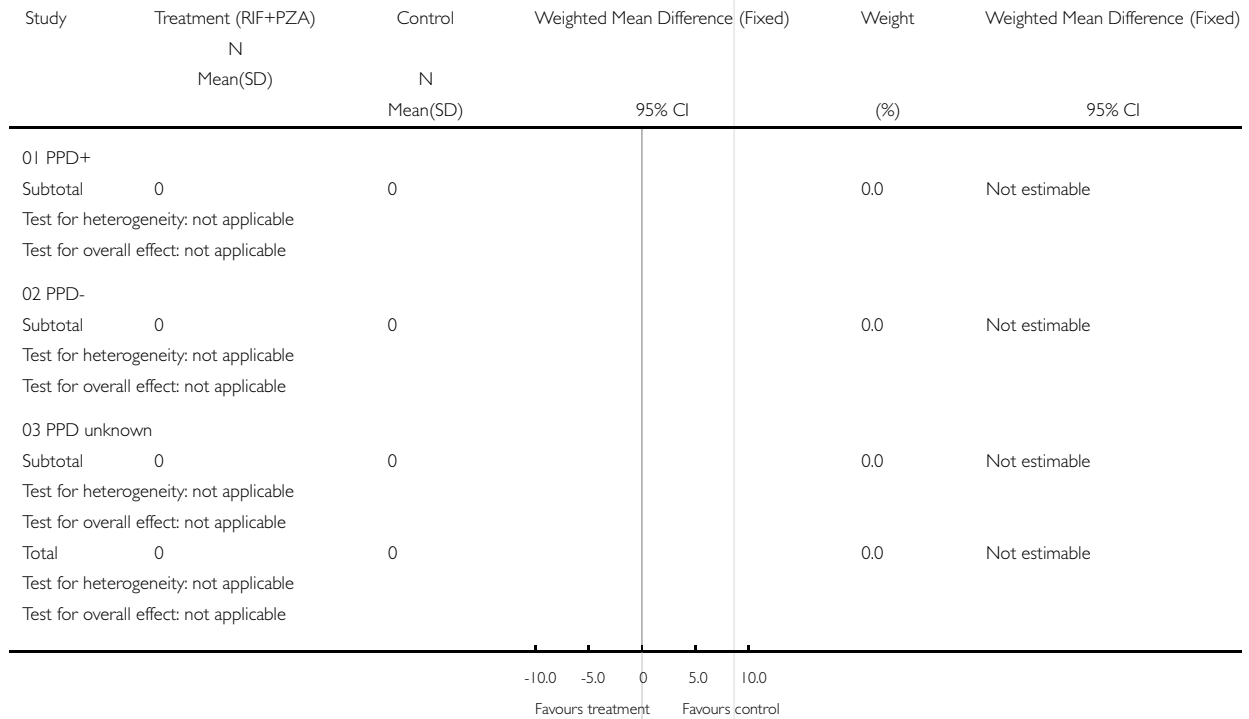


Fig. 34. Comparison 04 Rifampicin + pyrazinimide vs placebo

04.08 Mean time to TB

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 04 Rifampicin + pyrazinimide vs placebo

Outcome: 08 Mean time to TB

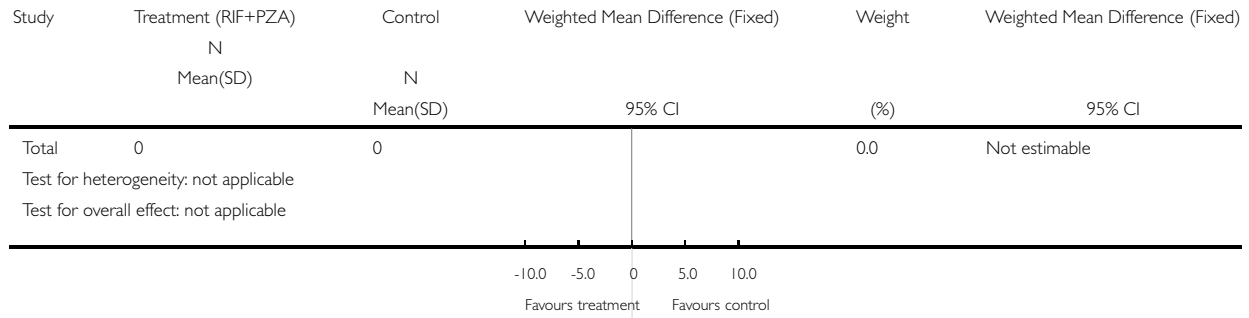


Fig. 35. Comparison 04 Rifampicin + pyrazinimide vs placebo

04.09 Mean time to death

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 04 Rifampicin + pyrazinimide vs placebo

Outcome: 09 Mean time to death

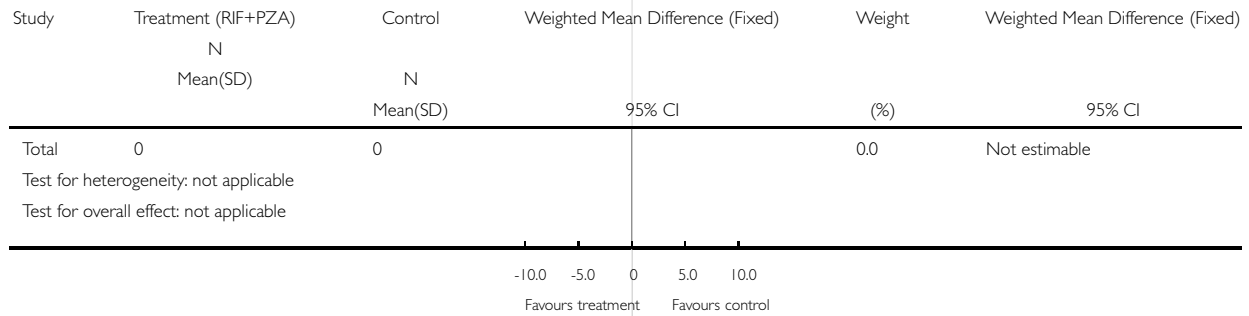


Fig. 36. Comparison 04 Rifampicin + pyrazinimide vs placebo

04.10 Mean time to AIDS

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 04 Rifampicin + pyrazinimide vs placebo

Outcome: 10 Mean time to AIDS

Study	Treatment (RIF+PZA) N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Fig. 37. Comparison 05 Isoniazid + rifampicin + pyrazinamid vs placebo

05.01 Incidence of active TB (confirmed, probable or possible)

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 05 Isoniazid + rifampicin + pyrazinamid vs placebo

Outcome: 01 Incidence of active TB (confirmed, probable or possible)

Study	Treatm (INH+RIF+PZA) n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 PPD+					
Whalen 1997	10/462	21/464		100.0	0.48 [0.23, 1.00]
Subtotal	462	464		100.0	0.48 [0.23, 1.00]
Total events: 10 (Treatm (INH+RIF+PZA)), 21 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.95 p=0.05					
02 PPD-					
Subtotal	0	0		0.0	Not estimable
Total events: 0 (Treatm (INH+RIF+PZA)), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 PPD unknown					
Subtotal	0	0		0.0	Not estimable
Total events: 0 (Treatm (INH+RIF+PZA)), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
Total	462	464		100.0	0.48 [0.23, 1.00]
Total events: 10 (Treatm (INH+RIF+PZA)), 21 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.95 p=0.05					

Fig. 38. Comparison 05 Isoniazid + rifampicin + pyrazinamid vs placebo

05.02 Incidence of confirmed TB

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 05 Isoniazid + rifampicin + pyrazinamid vs placebo

Outcome: 02 Incidence of confirmed TB

Study	Treatm (INH+RIF+PZA) n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 PPD+					
Subtotal	0	0		0.0	Not estimable
Total events: 0 (Treatm (INH+RIF+PZA)), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
02 PPD-					
Subtotal	0	0		0.0	Not estimable
Total events: 0 (Treatm (INH+RIF+PZA)), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 PPD unknown					
Subtotal	0	0		0.0	Not estimable
Total events: 0 (Treatm (INH+RIF+PZA)), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
Total	0	0		0.0	Not estimable
Total events: 0 (Treatm (INH+RIF+PZA)), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Fig. 39. Comparison 05 Isoniazid + rifampicin + pyrazinamid vs placebo

05.03 Incidence of death (all cause)

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 05 Isoniazid + rifampicin + pyrazinamid vs placebo

Outcome: 03 Incidence of death (all cause)

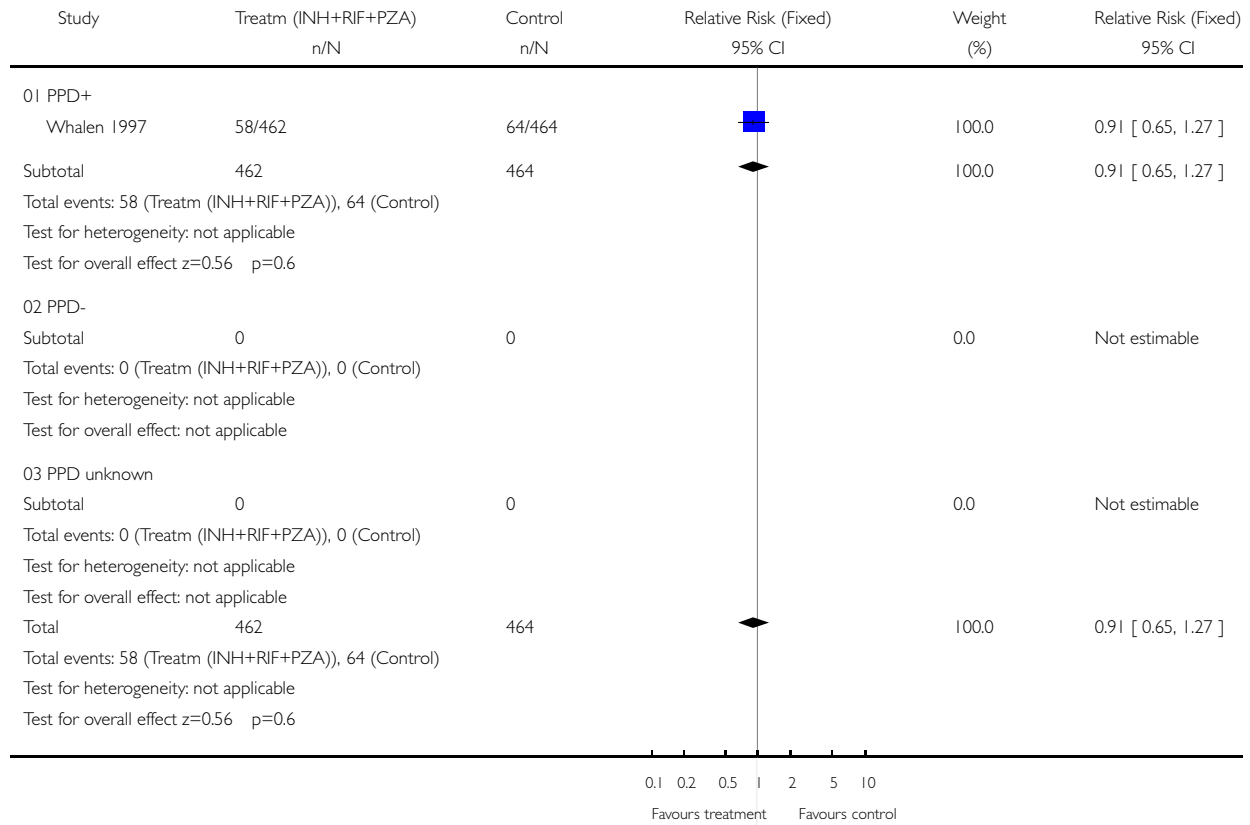


Fig. 40. Comparison 05 Isoniazid + rifampicin + pyrazinamid vs placebo

05.04 Incidence of AIDS

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 05 Isoniazid + rifampicin + pyrazinamid vs placebo

Outcome: 04 Incidence of AIDS

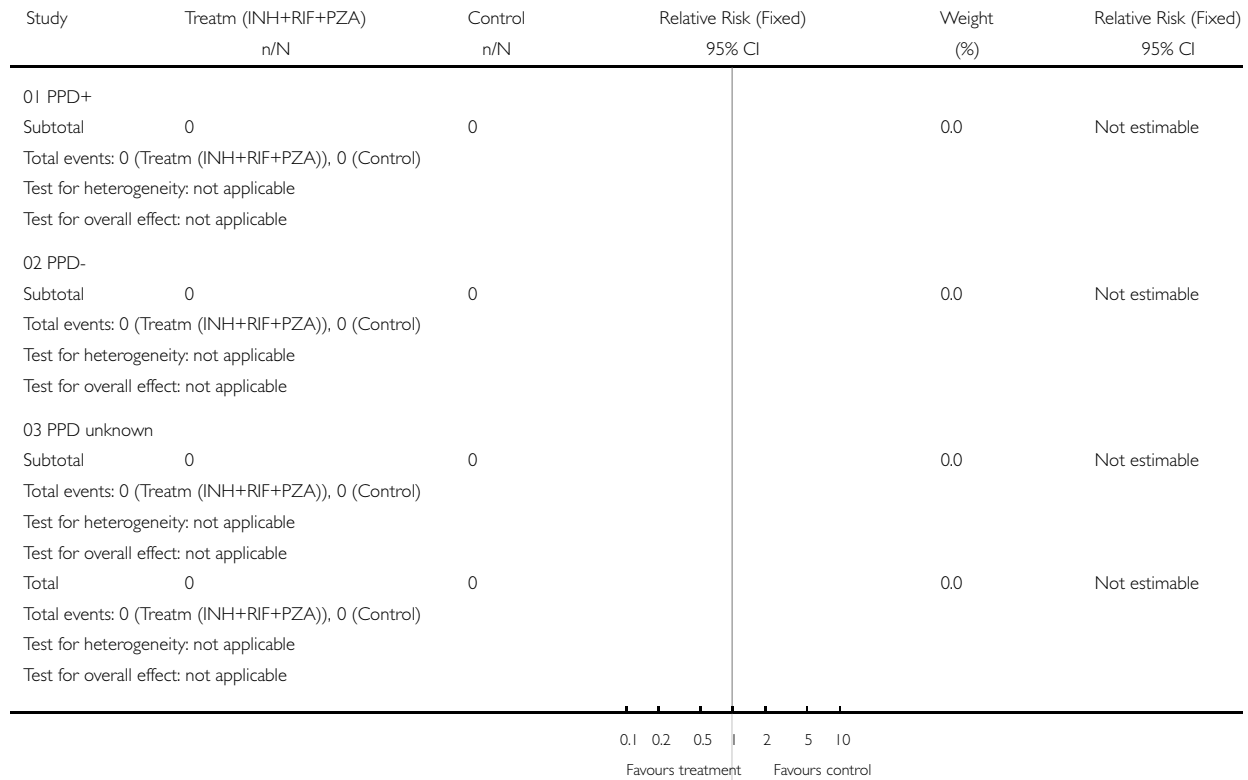


Fig. 41. Comparison 05 Isoniazid + rifampicin + pyrazinamid vs placebo

05.05 Incidence of adverse events leading to stopping treatment

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 05 Isoniazid + rifampicin + pyrazinamid vs placebo

Outcome: 05 Incidence of adverse events leading to stopping treatment

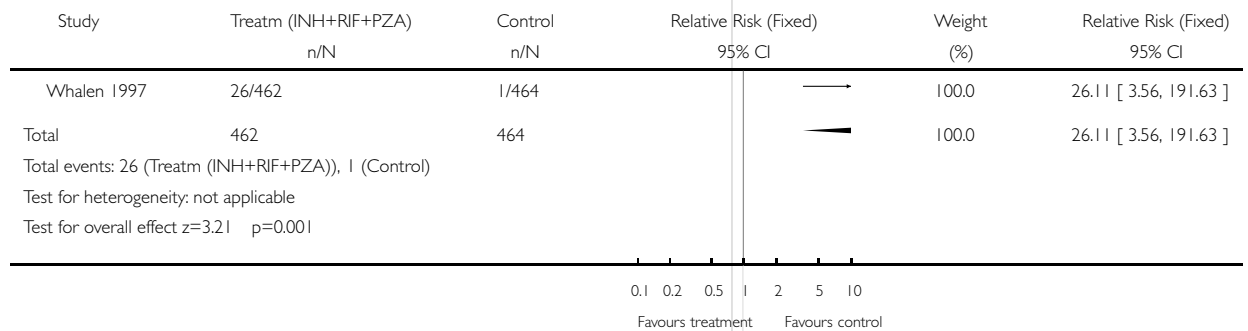


Fig. 42. Comparison 05 Isoniazid + rifampicin + pyrazinamid vs placebo

05.07 Mean CD4 count

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 05 Isoniazid + rifampicin + pyrazinamid vs placebo

Outcome: 07 Mean CD4 count

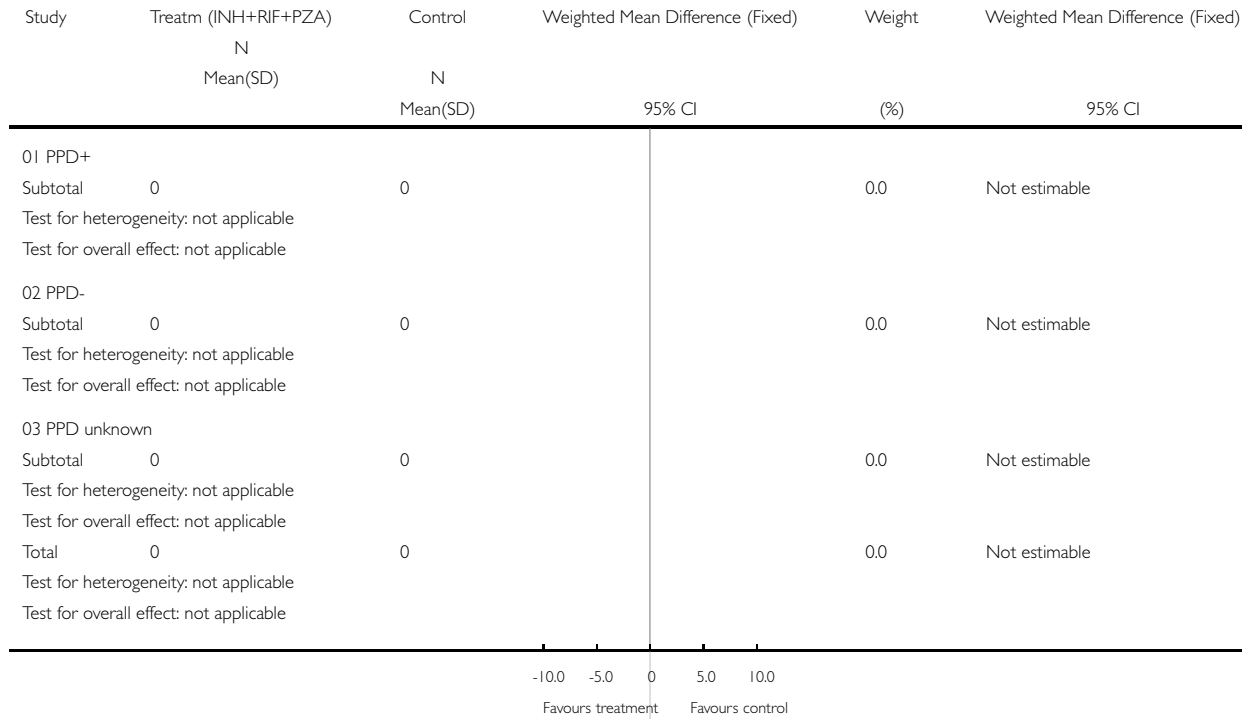


Fig. 43. Comparison 05 Isoniazid + rifampicin + pyrazinamid vs placebo

05.08 Mean time to TB

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 05 Isoniazid + rifampicin + pyrazinamid vs placebo

Outcome: 08 Mean time to TB

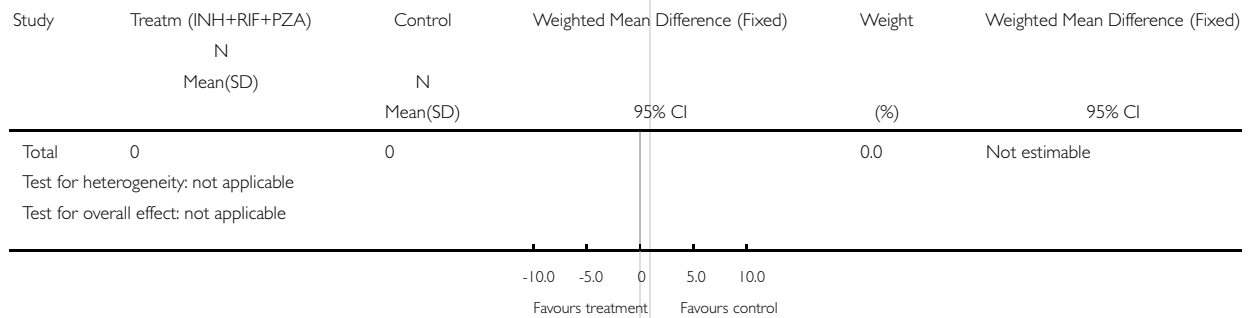


Fig. 44. Comparison 05 Isoniazid + rifampicin + pyrazinamid vs placebo

05.09 Mean time to death

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 05 Isoniazid + rifampicin + pyrazinamid vs placebo

Outcome: 09 Mean time to death

Study	Treatm (INH+RIF+PZA) N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Fig. 45. Comparison 05 Isoniazid + rifampicin + pyrazinamid vs placebo

05.10 Mean time to AIDS

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 05 Isoniazid + rifampicin + pyrazinamid vs placebo

Outcome: 10 Mean time to AIDS

Study	Treatm (INH+RIF+PZA) N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Fig. 46. Comparison 06 Isoniazid vs rifampicin + pyrazinimide

06.01 Incidence of active TB (confirmed, probable or possible)

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 06 Isoniazid vs rifampicin + pyrazinimide

Outcome: 01 Incidence of active TB (confirmed, probable or possible)

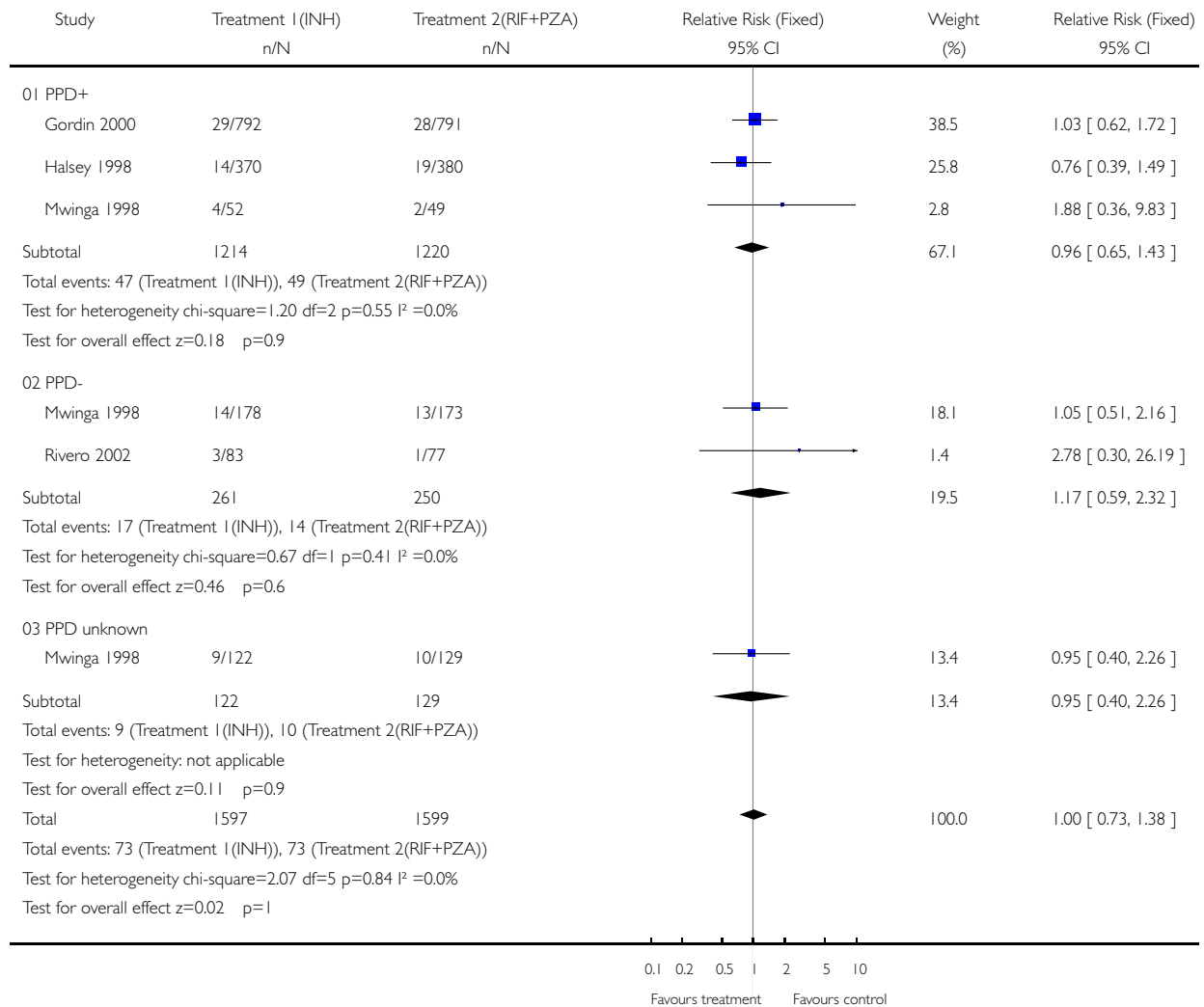


Fig. 47. Comparison 06 Isoniazid vs rifampicin + pyrazinimide

06.02 Incidence of confirmed TB

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 06 Isoniazid vs rifampicin + pyrazinimide

Outcome: 02 Incidence of confirmed TB

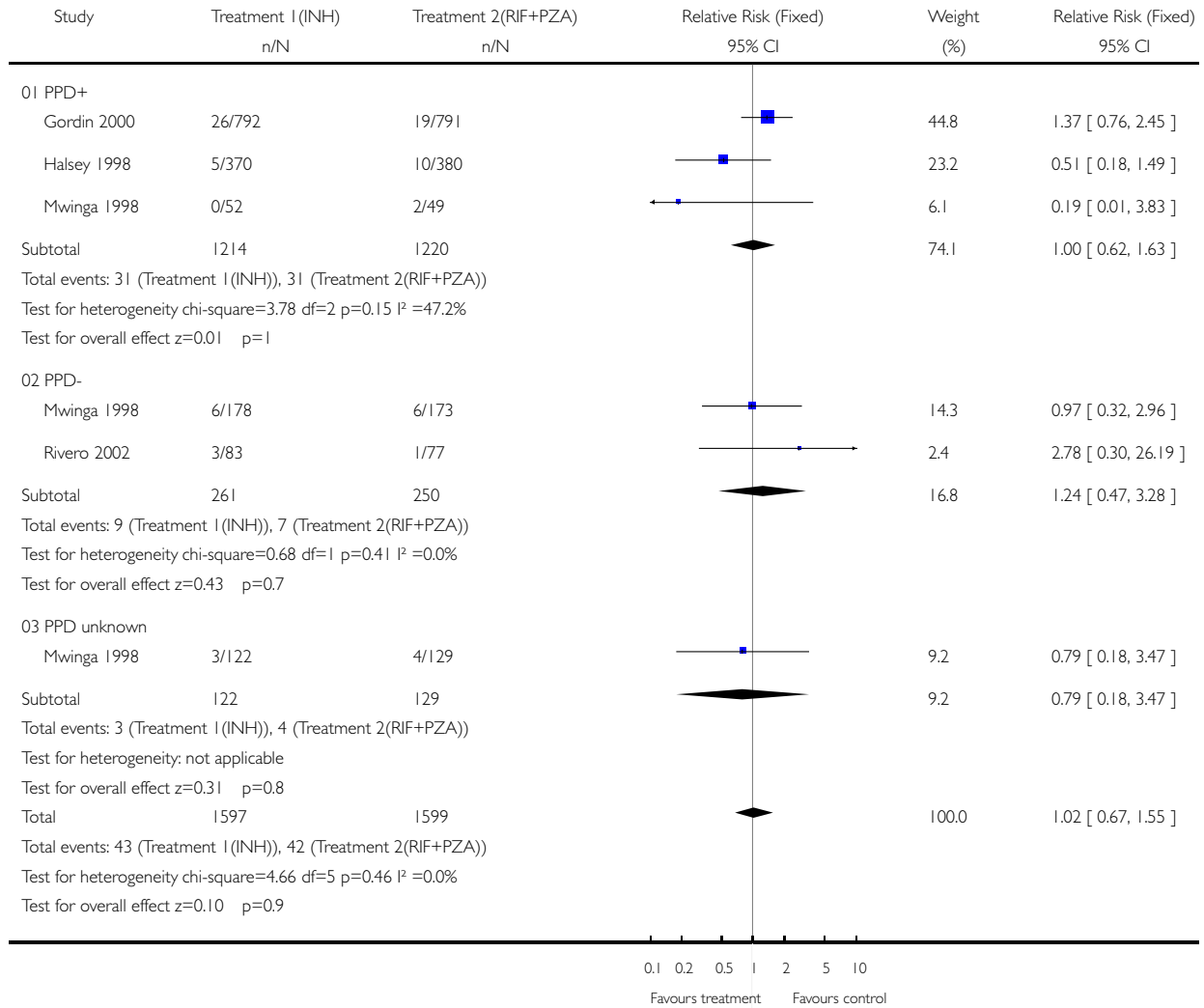


Fig. 48. Comparison 06 Isoniazid vs rifampicin + pyrazinimide

06.03 Incidence of death (all cause)

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 06 Isoniazid vs rifampicin + pyrazinimide

Outcome: 03 Incidence of death (all cause)

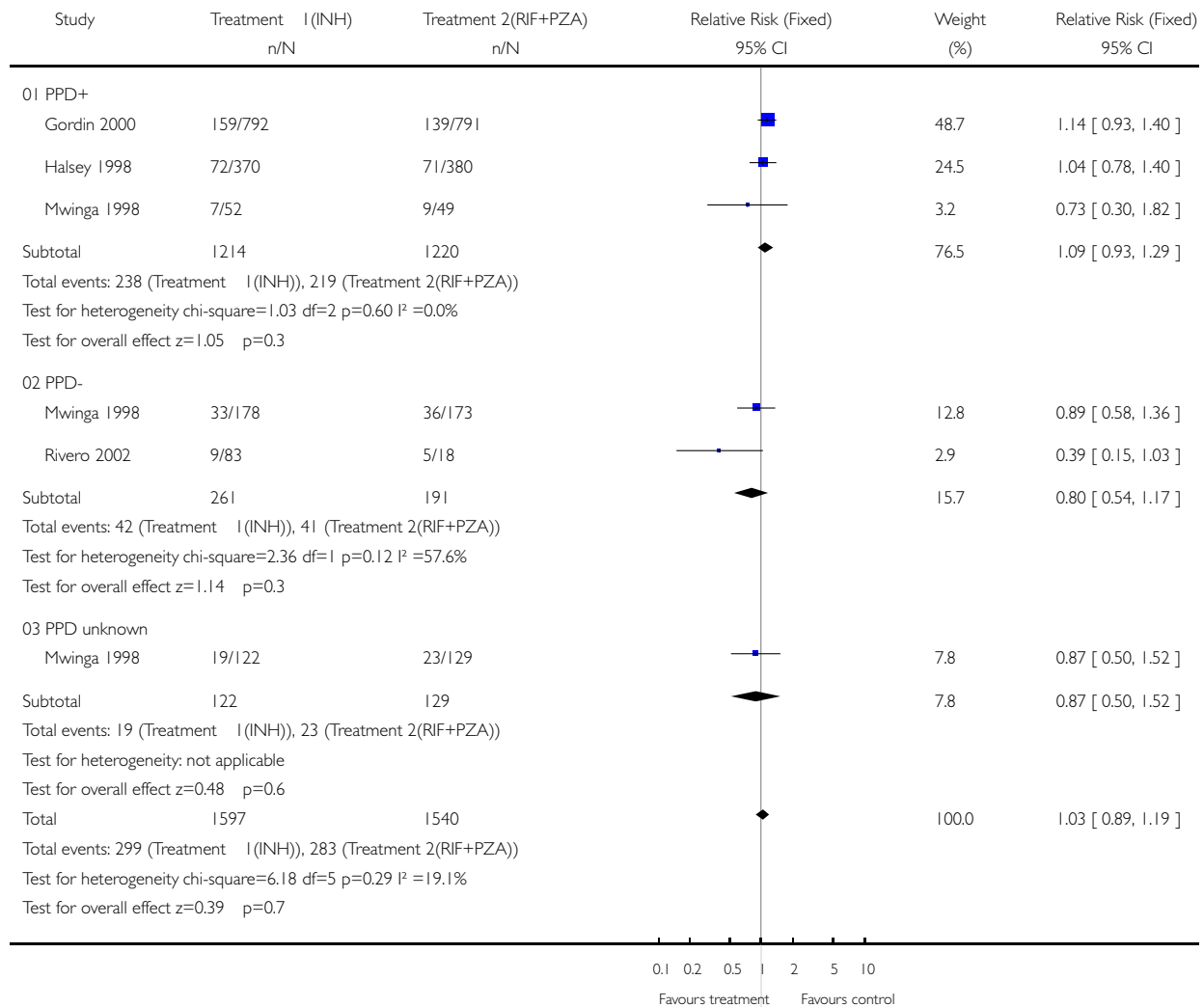


Fig. 49. Comparison 06 Isoniazid vs rifampicin + pyrazinimide

06.04 Incidence of AIDS

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 06 Isoniazid vs rifampicin + pyrazinimide

Outcome: 04 Incidence of AIDS

Study	Treatment 1 (INH) n/N	Treatment 2 (RIF+PZA) n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 PPD+					
Subtotal	0	0		0.0	Not estimable
Total events: 0 (Treatment 1 (INH)), 0 (Treatment 2 (RIF+PZA))					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
02 PPD-					
Subtotal	0	0		0.0	Not estimable
Total events: 0 (Treatment 1 (INH)), 0 (Treatment 2 (RIF+PZA))					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 PPD unknown					
Subtotal	0	0		0.0	Not estimable
Total events: 0 (Treatment 1 (INH)), 0 (Treatment 2 (RIF+PZA))					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
Total	0	0		0.0	Not estimable
Total events: 0 (Treatment 1 (INH)), 0 (Treatment 2 (RIF+PZA))					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

0.1 0.2 0.5 1 2 5 10

Favours treatment Favours control

Fig. 50. Comparison 06 Isoniazid vs rifampicin + pyrazinimide

06.05 Incidence of adverse events leading to stopping treatment

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 06 Isoniazid vs rifampicin + pyrazinimide

Outcome: 05 Incidence of adverse events leading to stopping treatment

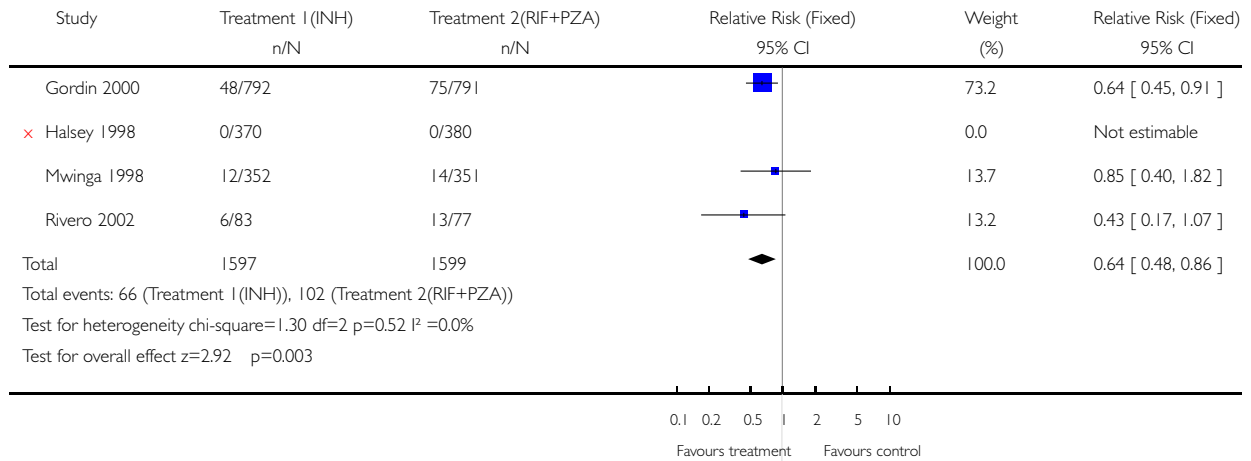


Fig. 51. Comparison 06 Isoniazid vs rifampicin + pyrazinimide

06.07 Mean CD4 count

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 06 Isoniazid vs rifampicin + pyrazinimide

Outcome: 07 Mean CD4 count

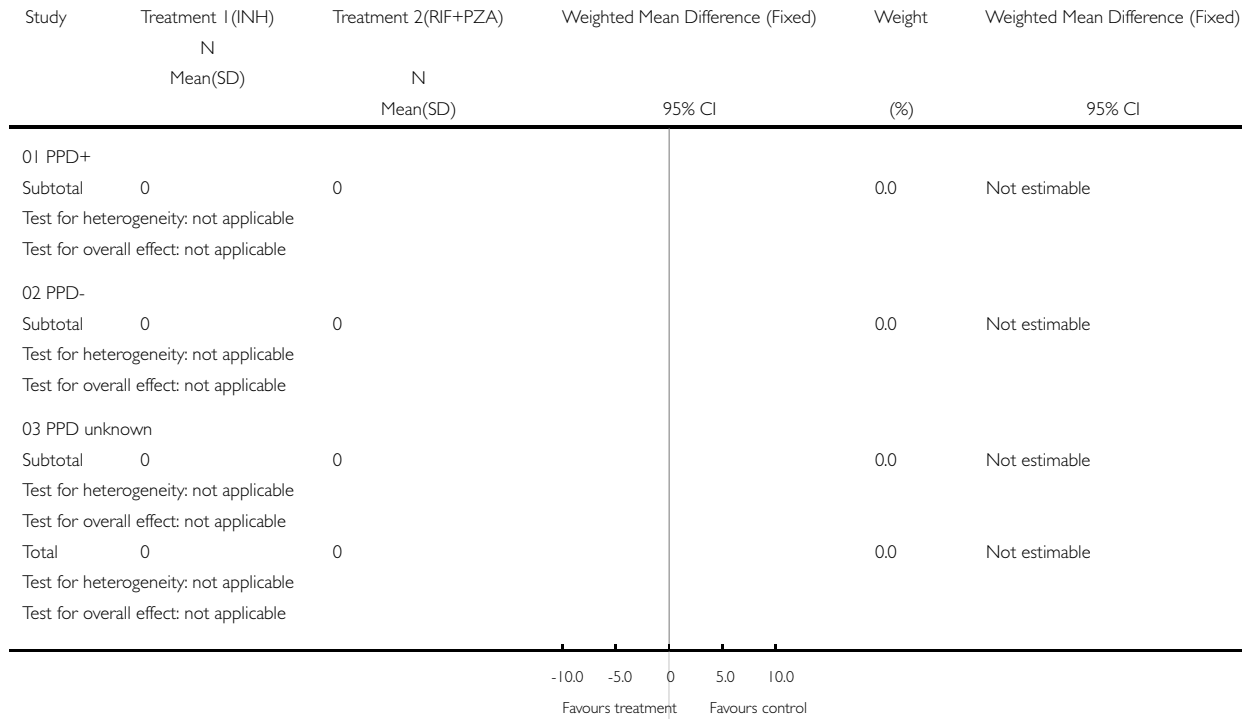


Fig. 52. Comparison 06 Isoniazid vs rifampicin + pyrazinimide

06.08 Mean time to TB

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 06 Isoniazid vs rifampicin + pyrazinimide

Outcome: 08 Mean time to TB

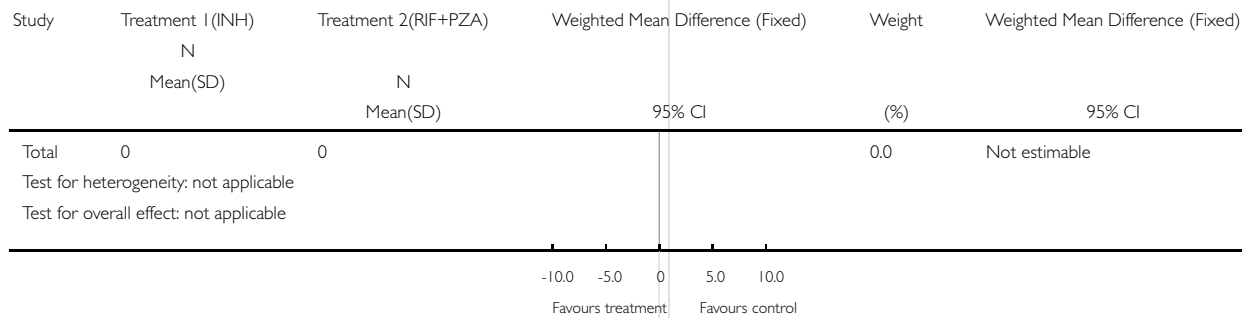


Fig. 53. Comparison 06 Isoniazid vs rifampicin + pyrazinimide

06.09 Mean time to death

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 06 Isoniazid vs rifampicin + pyrazinimide

Outcome: 09 Mean time to death

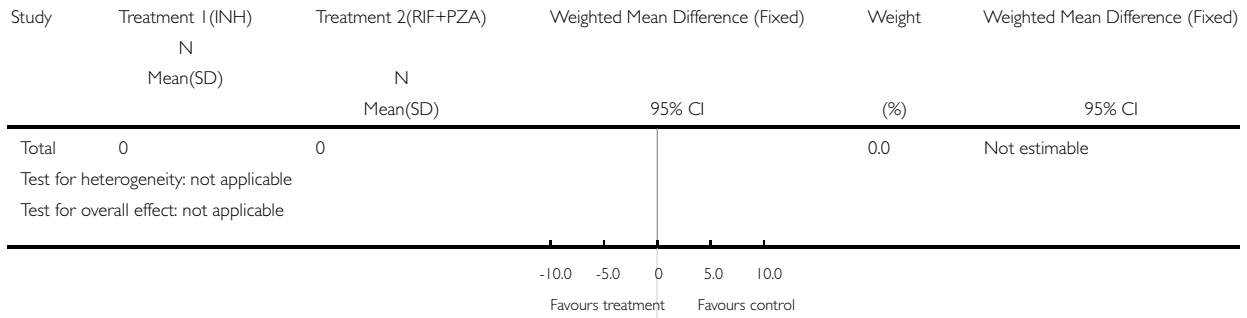


Fig. 54. Comparison 06 Isoniazid vs rifampicin + pyrazinimide

06.10 Mean time to AIDS

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 06 Isoniazid vs rifampicin + pyrazinimide

Outcome: 10 Mean time to AIDS

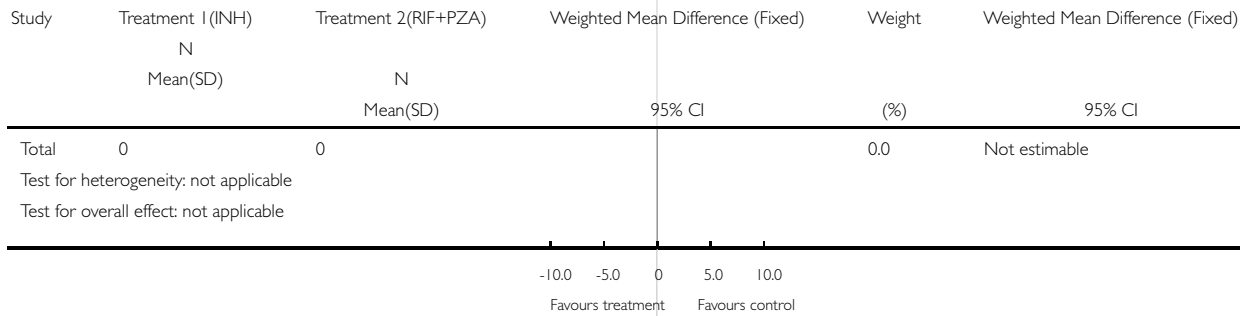


Fig. 55. Comparison 07 Isoniazid vs isoniazid + rifampicin

07.01 Incidence of active TB (confirmed, probable or possible)

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 07 Isoniazid vs isoniazid + rifampicin

Outcome: 01 Incidence of active TB (confirmed, probable or possible)

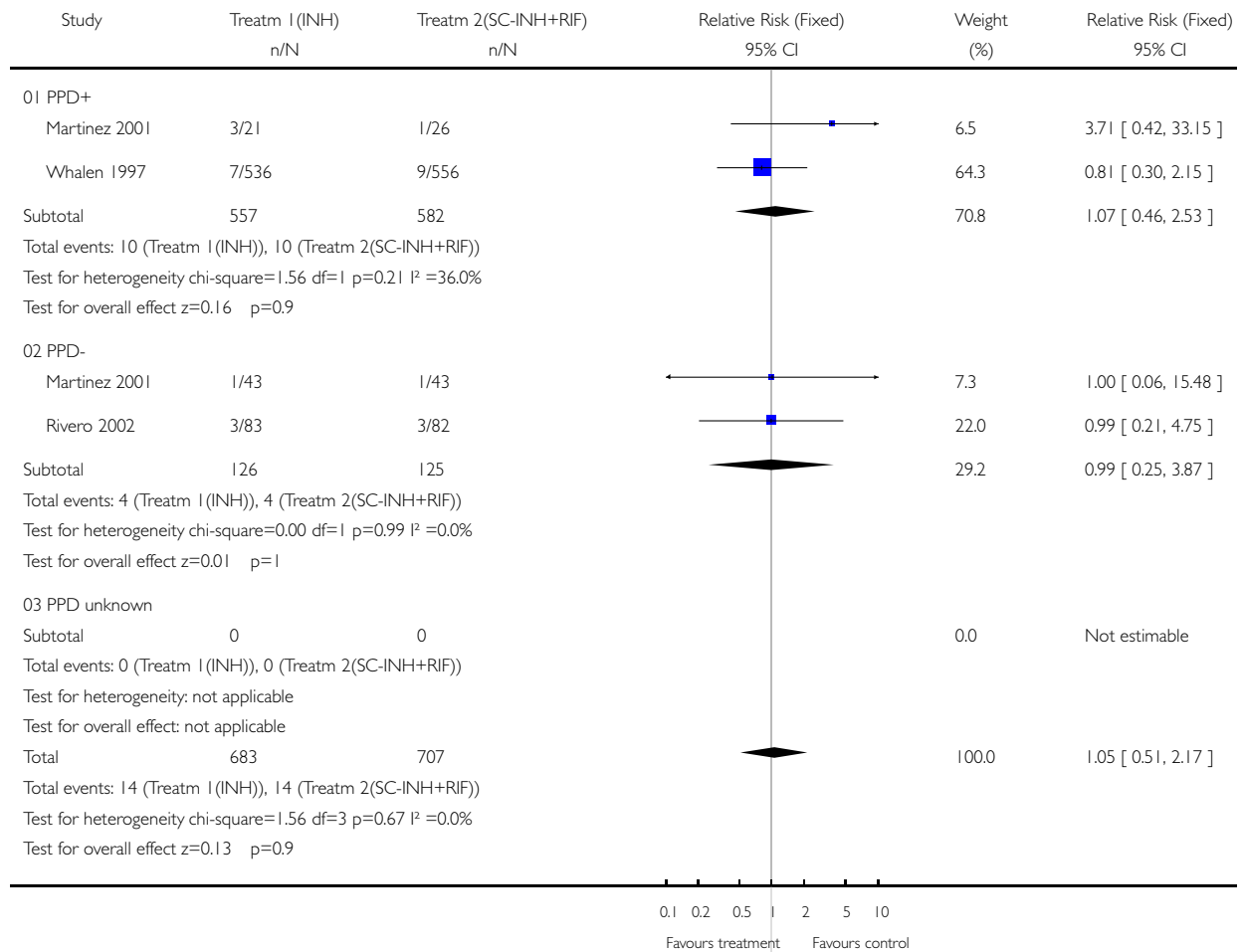


Fig. 56. Comparison 07 Isoniazid vs isoniazid + rifampicin

07.02 Incidence of confirmed TB

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 07 Isoniazid vs isoniazid + rifampicin

Outcome: 02 Incidence of confirmed TB

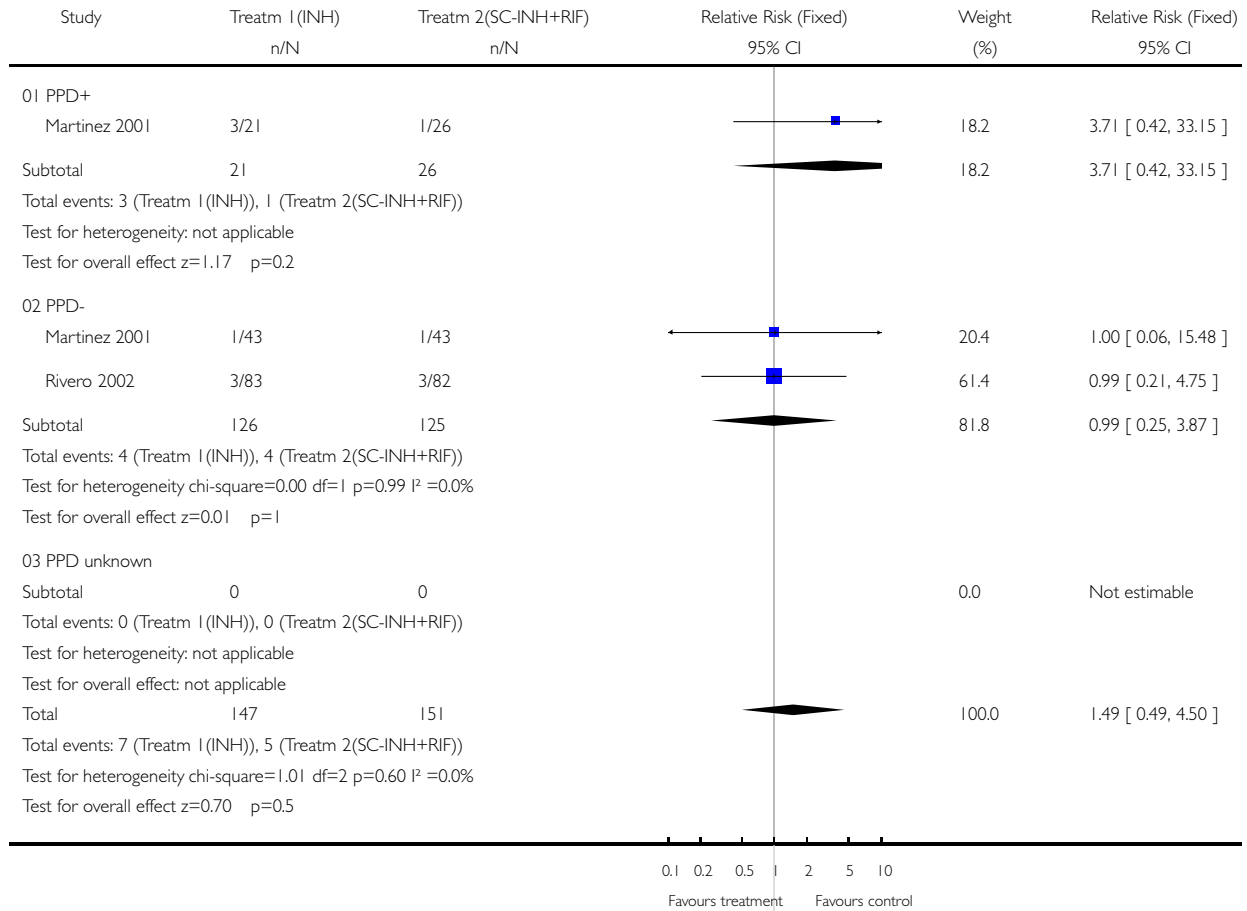


Fig. 57. Comparison 07 Isoniazid vs isoniazid + rifampicin

07.03 Incidence of death (all cause)

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 07 Isoniazid vs isoniazid + rifampicin

Outcome: 03 Incidence of death (all cause)

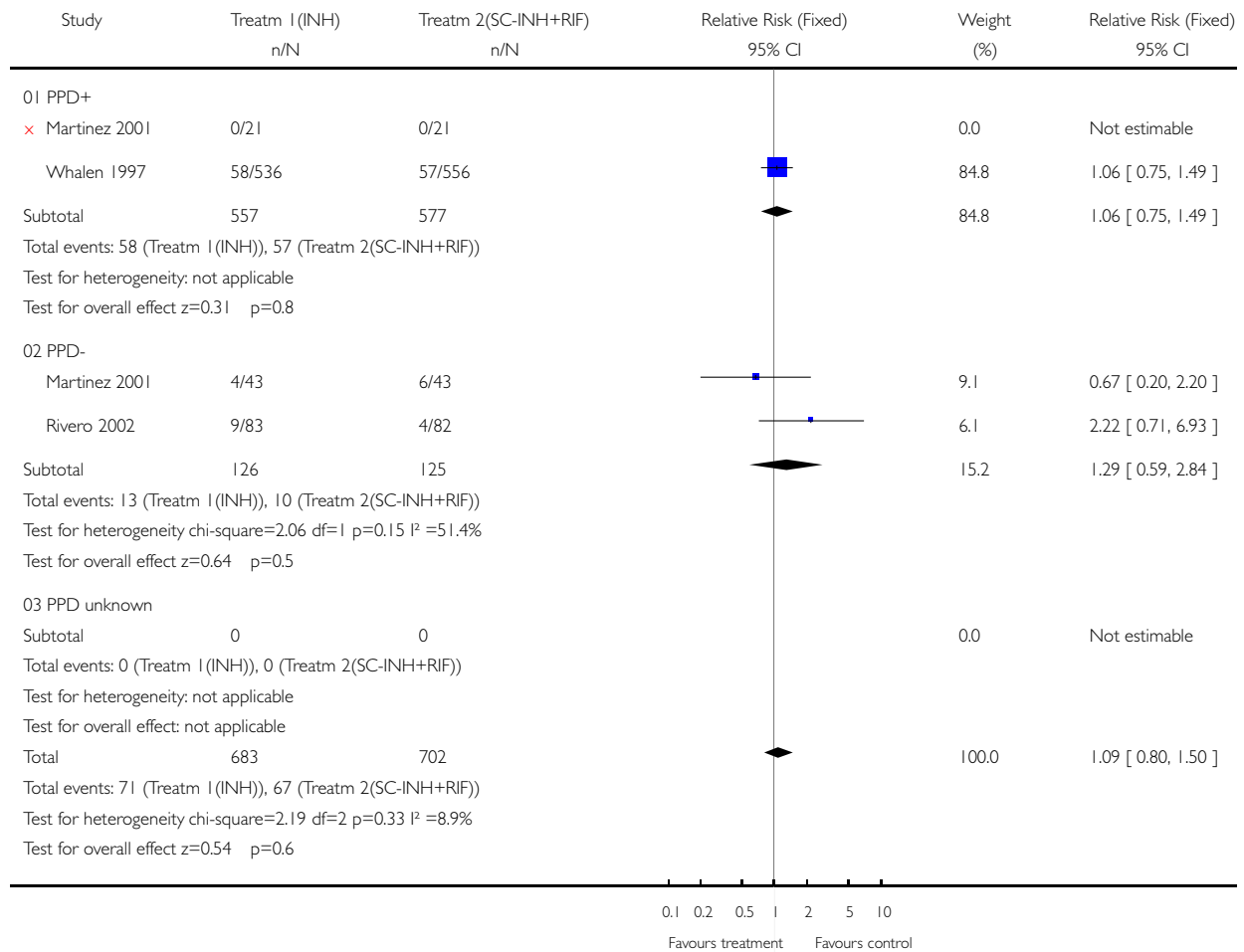


Fig. 58. Comparison 07 Isoniazid vs isoniazid + rifampicin

07.04 Incidence of AIDS

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 07 Isoniazid vs isoniazid + rifampicin

Outcome: 04 Incidence of AIDS

Study	Treatm 1 (INH) n/N	Treatm 2(SC-INH+RIF) n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 PPD+					
Subtotal	0	0		0.0	Not estimable
Total events: 0 (Treatm 1 (INH)), 0 (Treatm 2(SC-INH+RIF))					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
02 PPD-					
Subtotal	0	0		0.0	Not estimable
Total events: 0 (Treatm 1 (INH)), 0 (Treatm 2(SC-INH+RIF))					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 PPD unknown					
Subtotal	0	0		0.0	Not estimable
Total events: 0 (Treatm 1 (INH)), 0 (Treatm 2(SC-INH+RIF))					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
Total	0	0		0.0	Not estimable
Total events: 0 (Treatm 1 (INH)), 0 (Treatm 2(SC-INH+RIF))					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

0.1 0.2 0.5 1 2 5 10

Favours treatment Favours control

Fig. 59. Comparison 07 Isoniazid vs isoniazid + rifampicin

07.05 Incidence of adverse events leading to stopping treatment

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 07 Isoniazid vs isoniazid + rifampicin

Outcome: 05 Incidence of adverse events leading to stopping treatment

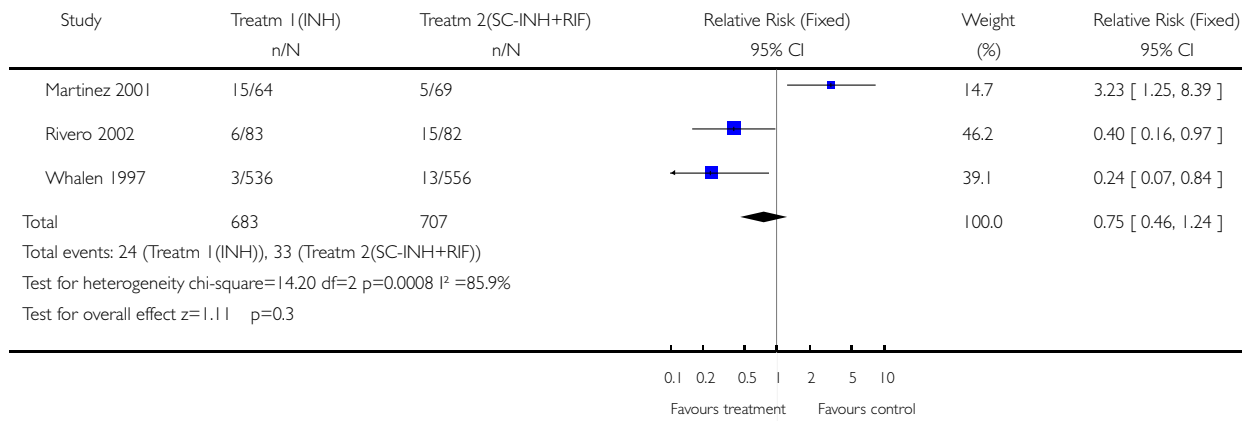


Fig. 60. Comparison 07 Isoniazid vs isoniazid + rifampicin

07.07 Mean CD4 count

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 07 Isoniazid vs isoniazid + rifampicin

Outcome: 07 Mean CD4 count

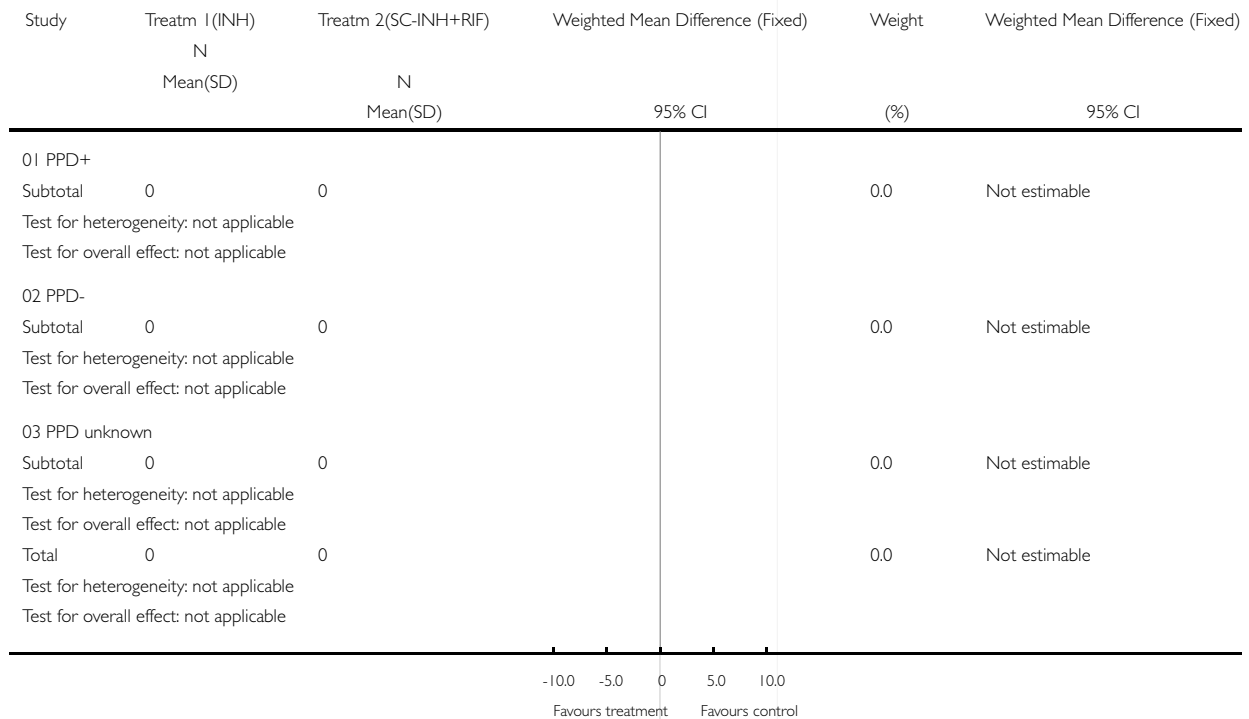


Fig. 61. Comparison 07 Isoniazid vs isoniazid + rifampicin

07.08 Mean time to TB

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 07 Isoniazid vs isoniazid + rifampicin

Outcome: 08 Mean time to TB

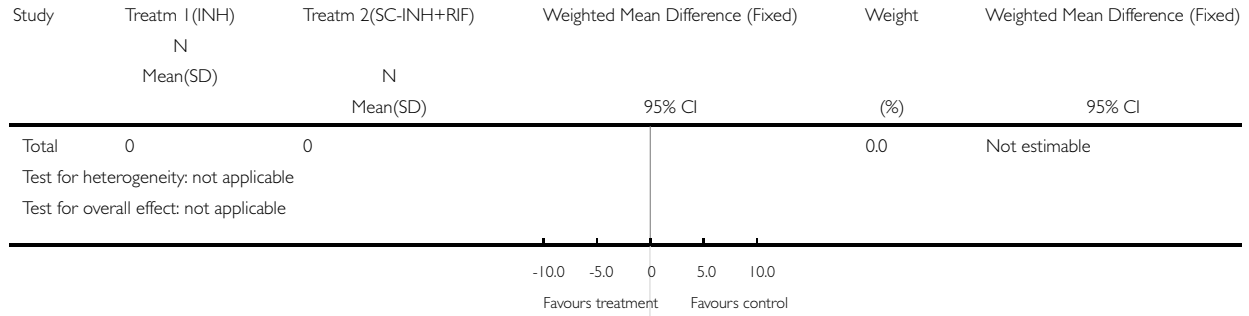


Fig. 62. Comparison 07 Isoniazid vs isoniazid + rifampicin

07.09 Mean time to death

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 07 Isoniazid vs isoniazid + rifampicin

Outcome: 09 Mean time to death

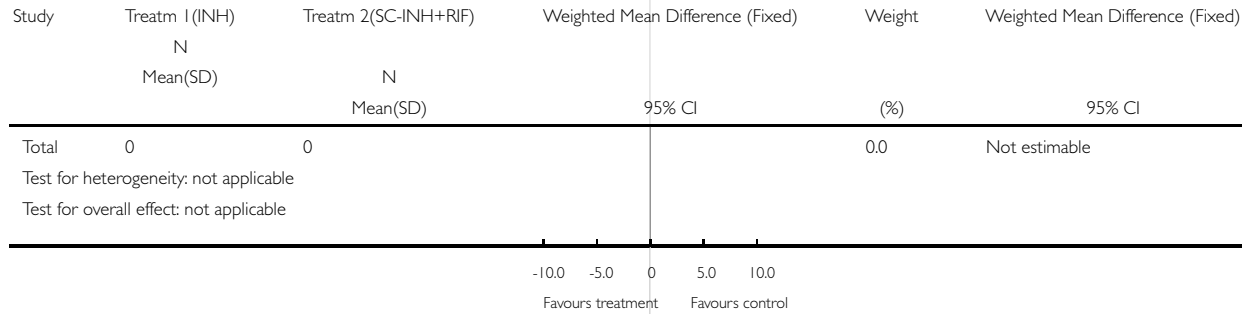


Fig. 63. Comparison 07 Isoniazid vs isoniazid + rifampicin

07.10 Mean time to AIDS

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 07 Isoniazid vs isoniazid + rifampicin

Outcome: 10 Mean time to AIDS

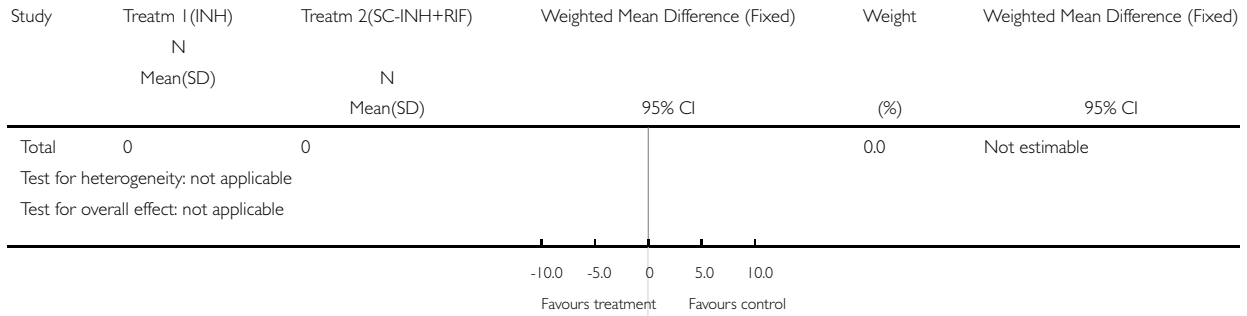


Fig. 64. Comparison 08 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide

08.01 Incidence of active TB (confirmed, probable or possible)

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 08 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide

Outcome: 01 Incidence of active TB (confirmed, probable or possible)

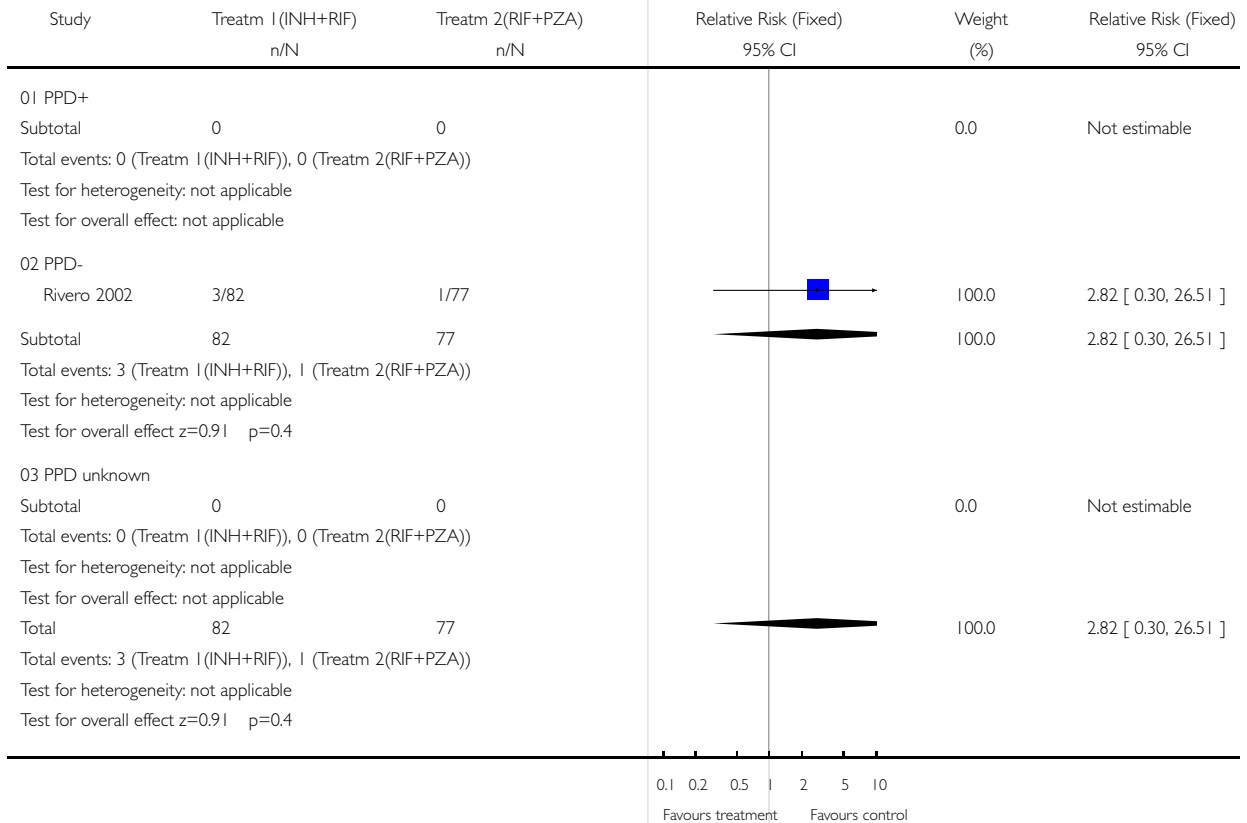


Fig. 65. Comparison 08 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide

08.02 Incidence of confirmed TB

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 08 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide

Outcome: 02 Incidence of confirmed TB

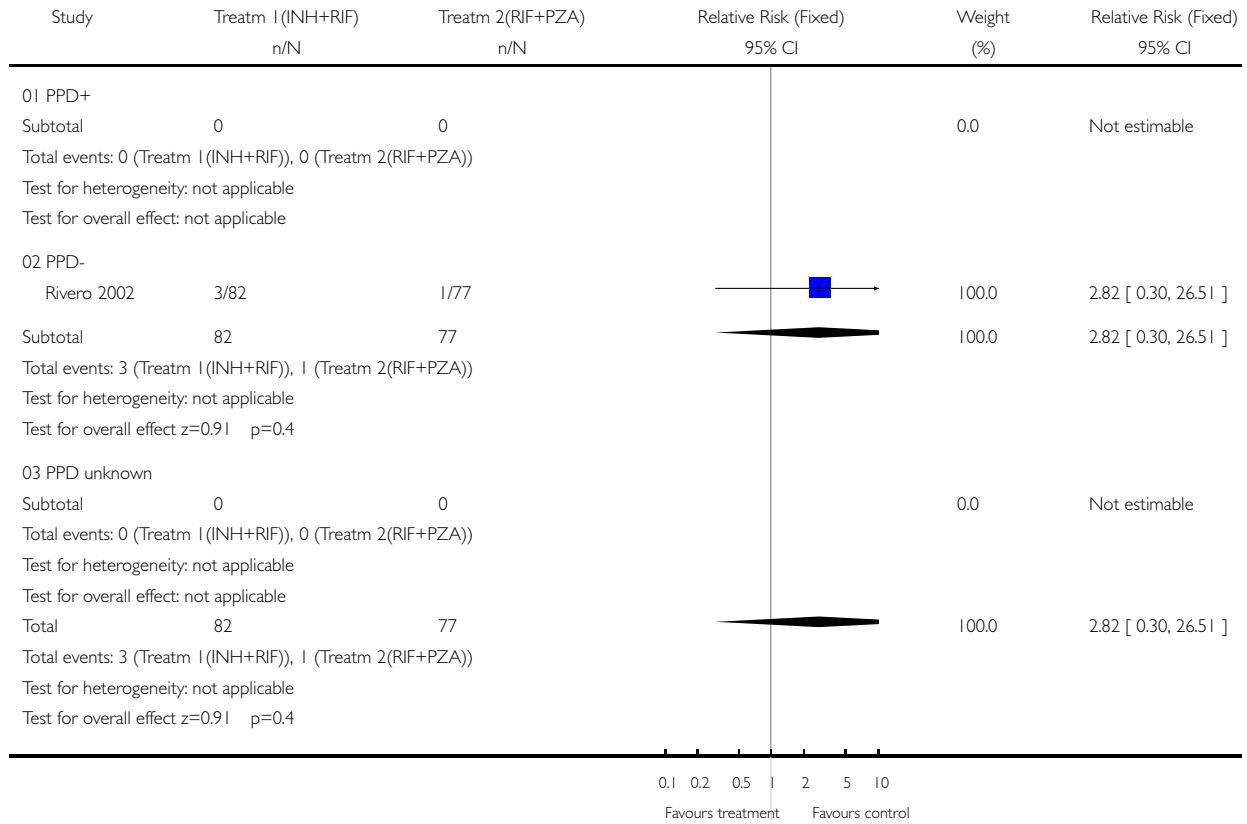


Fig. 66. Comparison 08 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide

08.03 Incidence of death (all cause)

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 08 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide

Outcome: 03 Incidence of death (all cause)

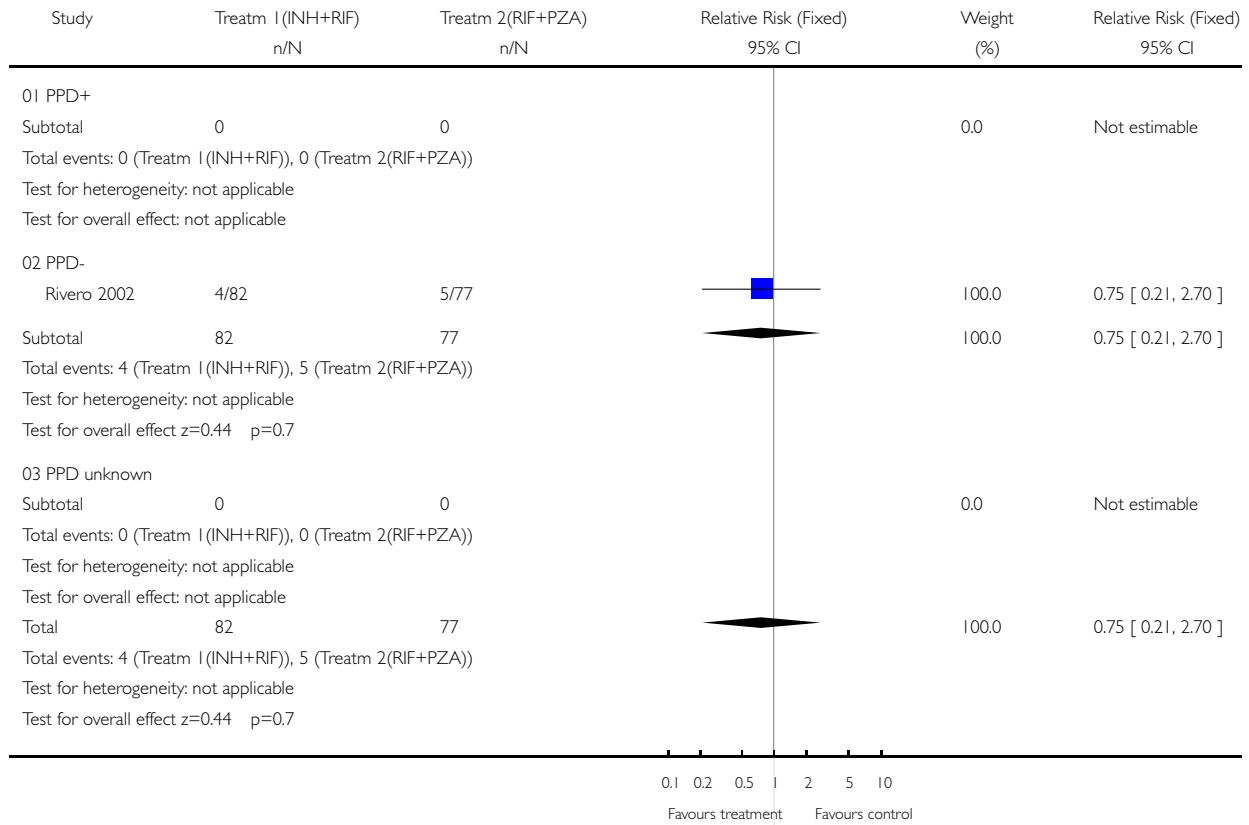


Fig. 67. Comparison 08 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide

08.04 Incidence of AIDS

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 08 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide

Outcome: 04 Incidence of AIDS

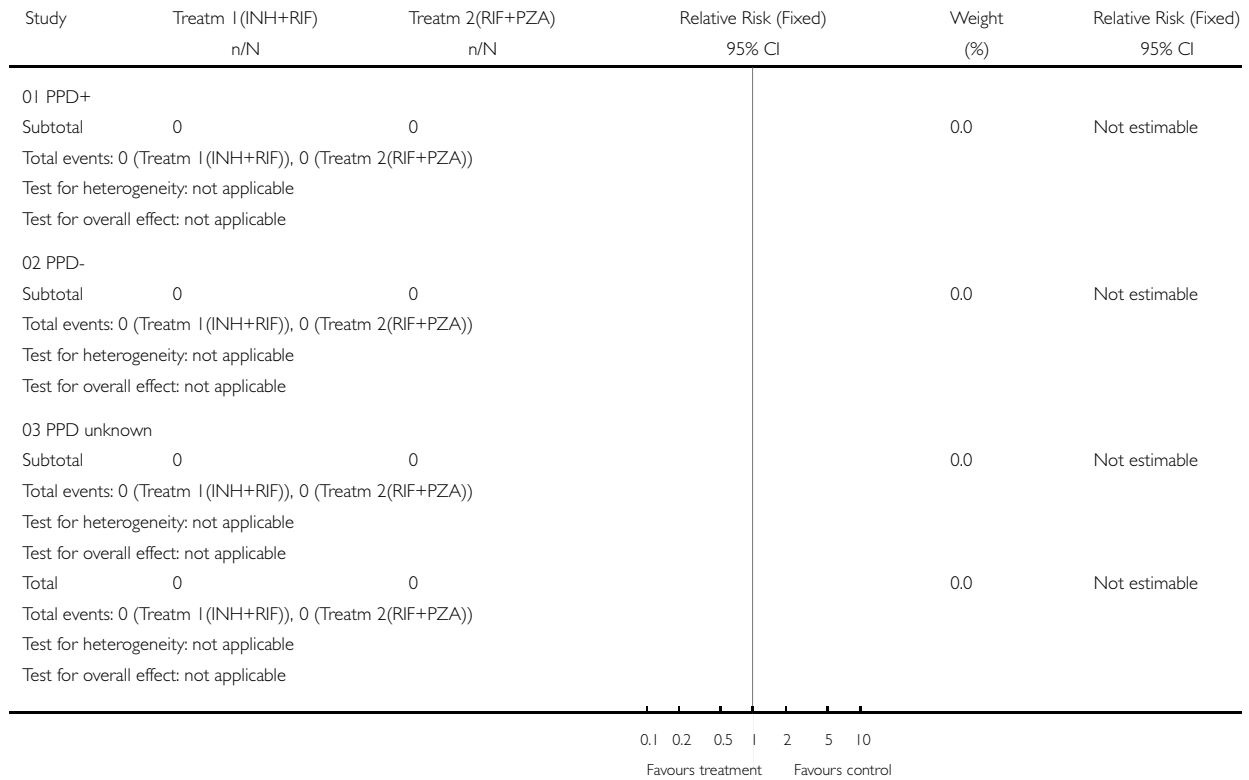


Fig. 68. Comparison 08 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide

08.05 Incidence of adverse events leading to stopping treatment

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 08 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide

Outcome: 05 Incidence of adverse events leading to stopping treatment

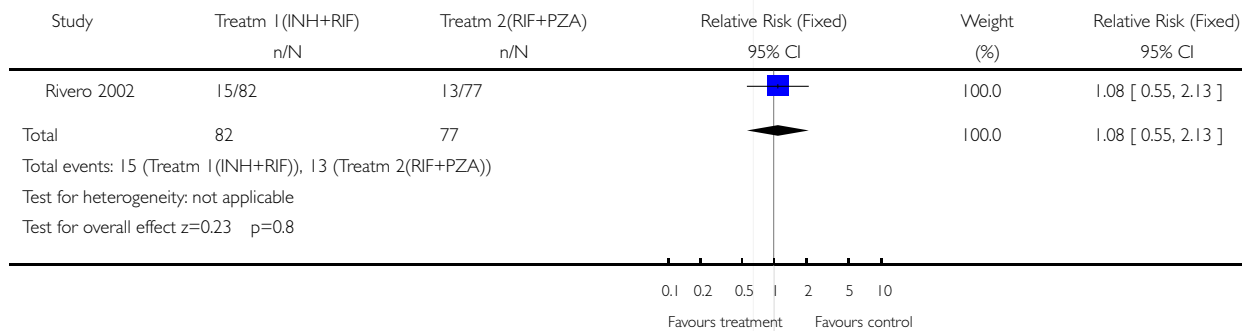


Fig. 69. Comparison 08 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide

08.07 Mean CD4 count

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 08 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide

Outcome: 07 Mean CD4 count

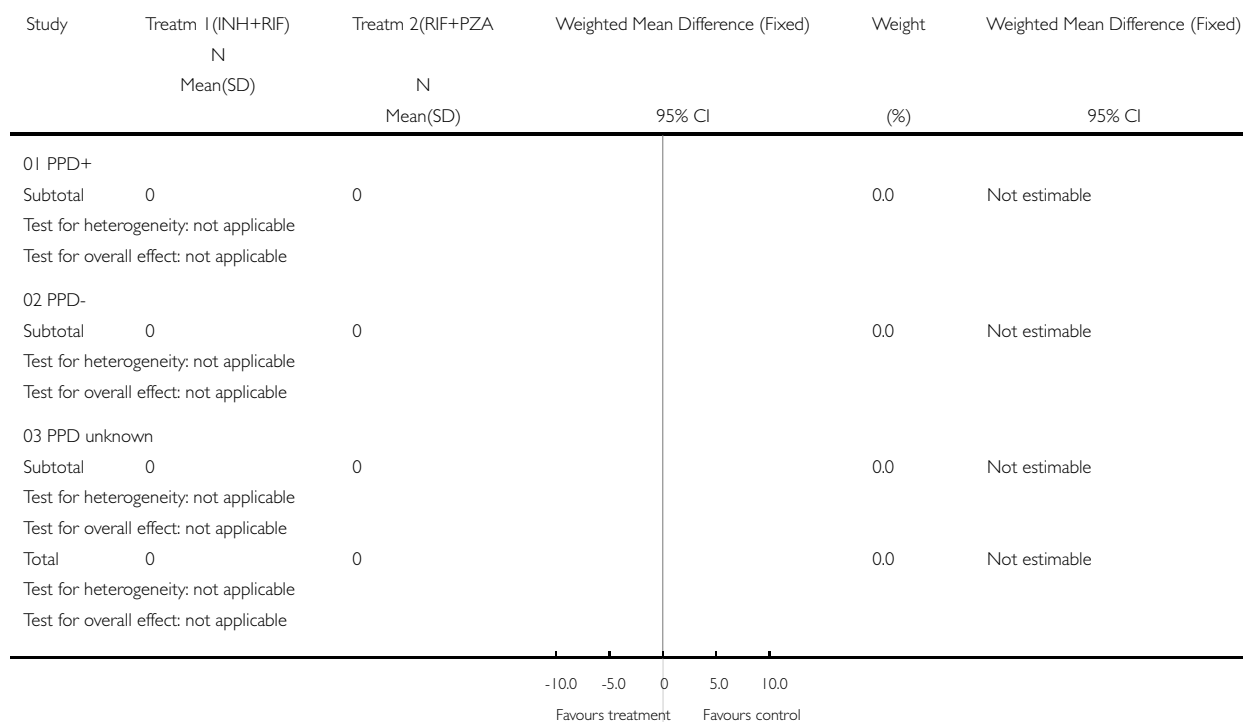


Fig. 70. Comparison 08 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide

08.08 Mean time to TB

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 08 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide

Outcome: 08 Mean time to TB

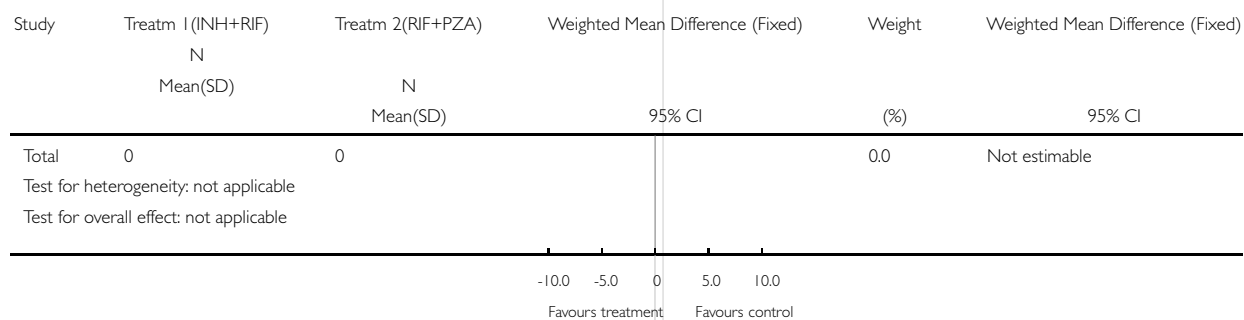


Fig. 71. Comparison 08 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide

08.09 Mean time to death

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 08 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide

Outcome: 09 Mean time to death

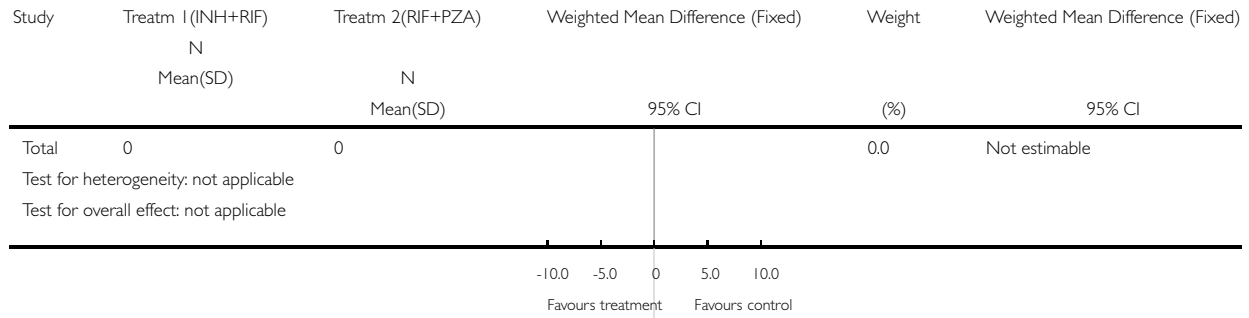


Fig. 72. Comparison 08 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide

08.10 Mean time to AIDS

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 08 Isoniazid + rifampicine vs Rifampicin + Pyrazinimide

Outcome: 10 Mean time to AIDS

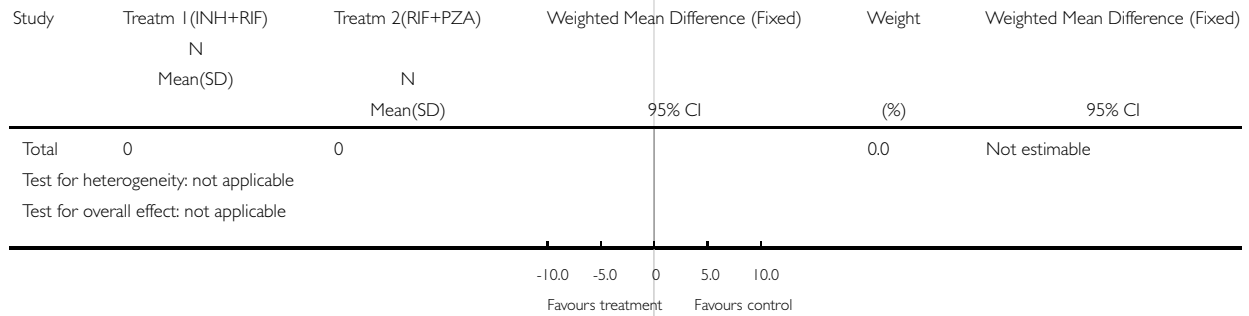


Fig. 73. Comparison 09 Isoniazid vs isoniazid + rifampicin + Pyrazinamide

09.01 Incidence of active TB (confirmed, probable or possible)

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 09 Isoniazid vs isoniazid + rifampicin + Pyrazinamide

Outcome: 01 Incidence of active TB (confirmed, probable or possible)

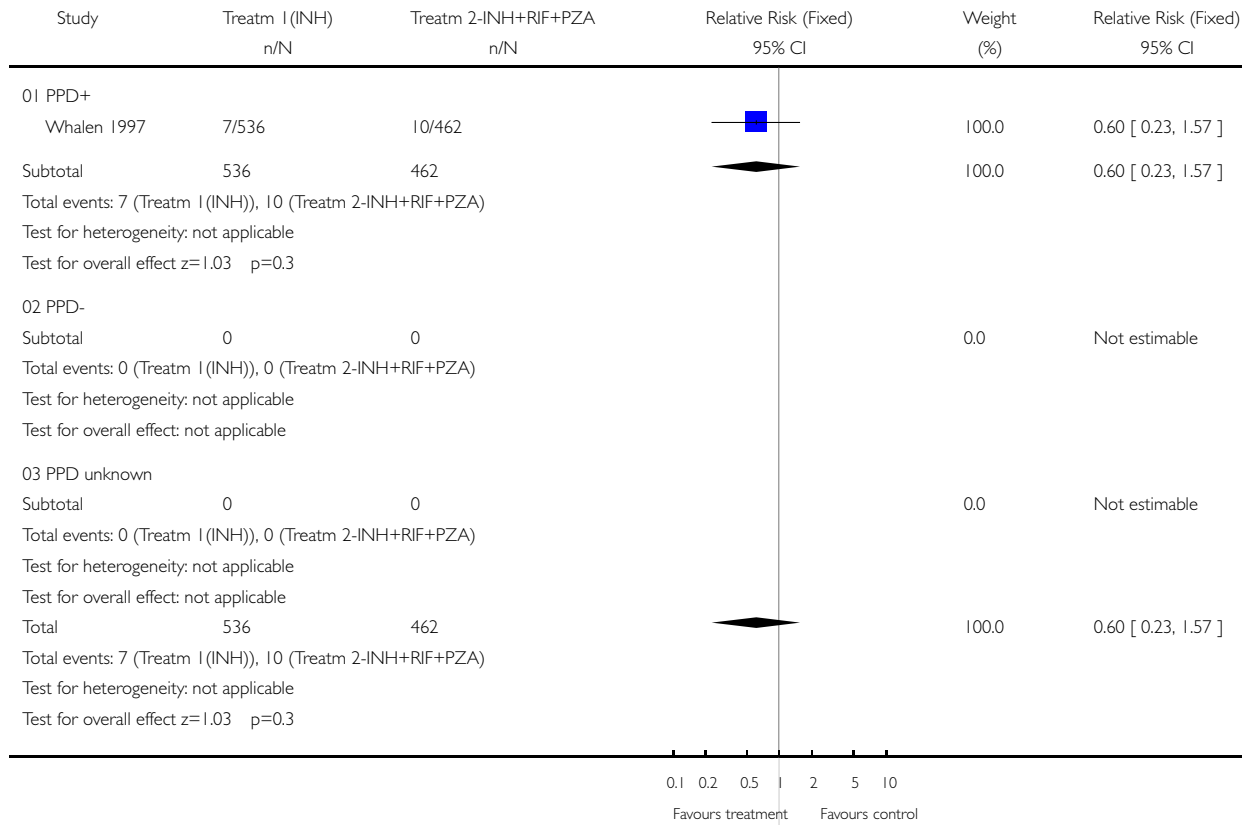


Fig. 74. Comparison 09 Isoniazid vs isoniazid + rifampicin + Pyrazinamide

09.02 Incidence of confirmed TB

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 09 Isoniazid vs isoniazid + rifampicin + Pyrazinamide

Outcome: 02 Incidence of confirmed TB

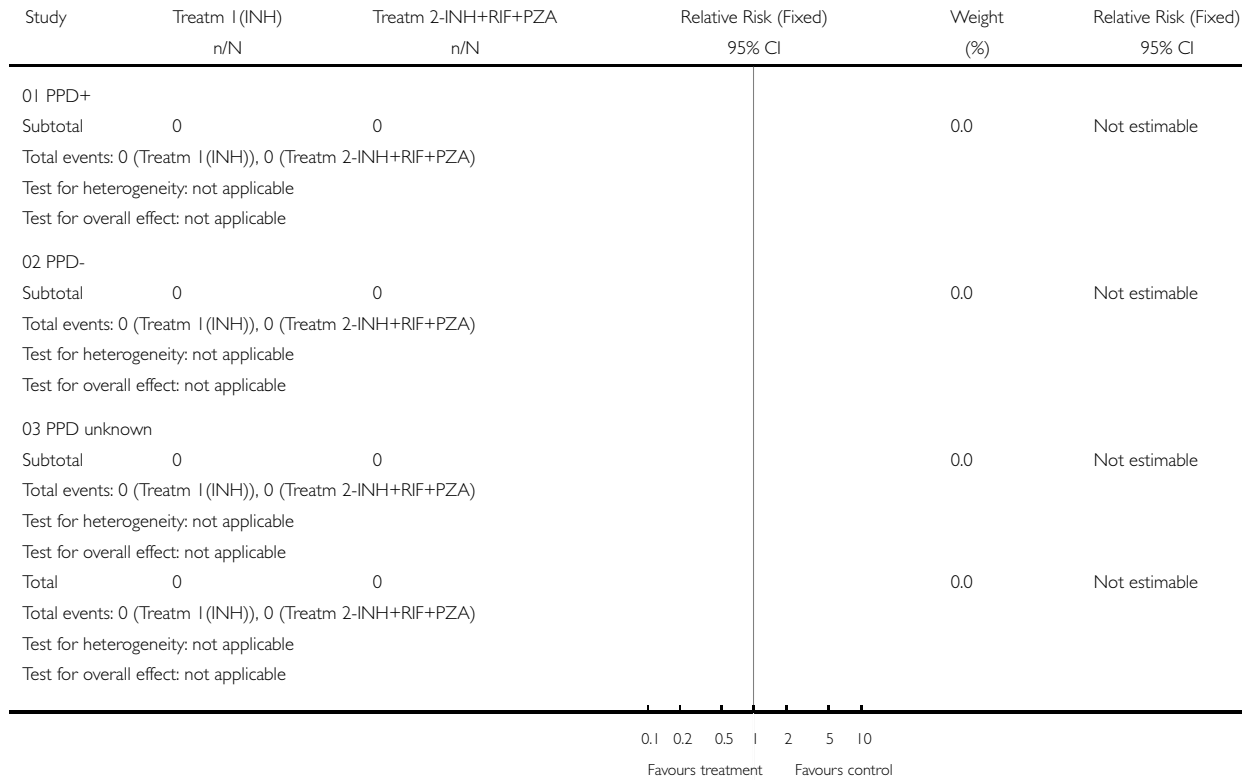


Fig. 75. Comparison 09 Isoniazid vs isoniazid + rifampicin + Pyrazinamide

09.03 Incidence of death (all cause)

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 09 Isoniazid vs isoniazid + rifampicin + Pyrazinamide

Outcome: 03 Incidence of death (all cause)

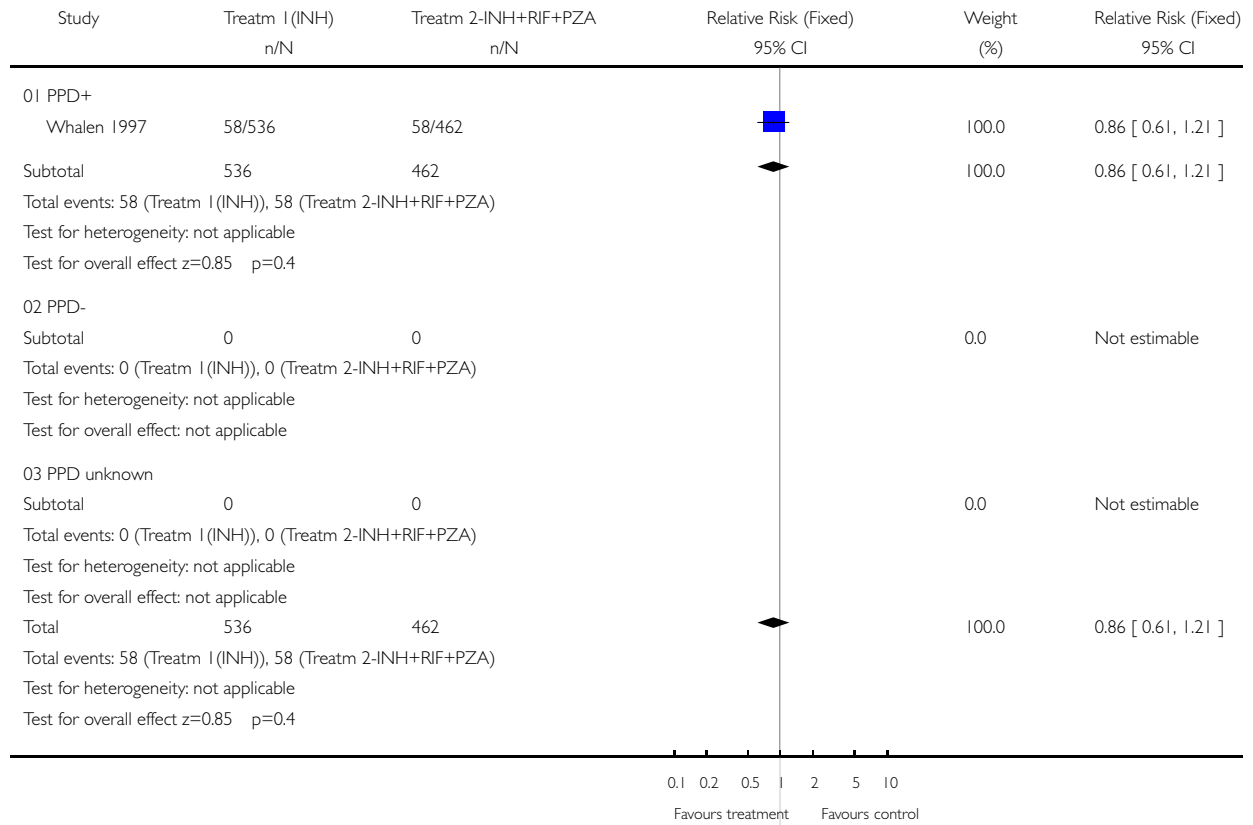


Fig. 76. Comparison 09 Isoniazid vs isoniazid + rifampicin + Pyrazinamide

09.04 Incidence of AIDS

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 09 Isoniazid vs isoniazid + rifampicin + Pyrazinamide

Outcome: 04 Incidence of AIDS

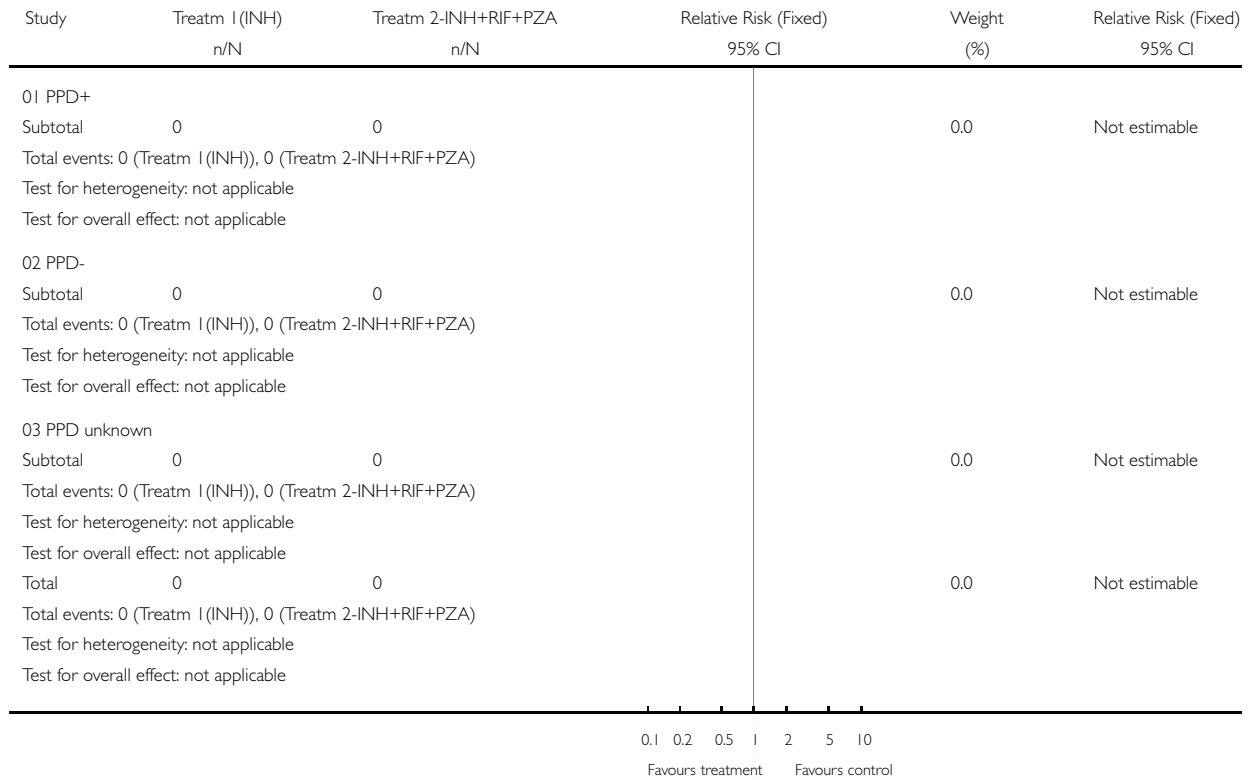


Fig. 77. Comparison 09 Isoniazid vs isoniazid + rifampicin + Pyrazinamide

09.05 Incidence of adverse events leading to stopping treatment

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 09 Isoniazid vs isoniazid + rifampicin + Pyrazinamide

Outcome: 05 Incidence of adverse events leading to stopping treatment

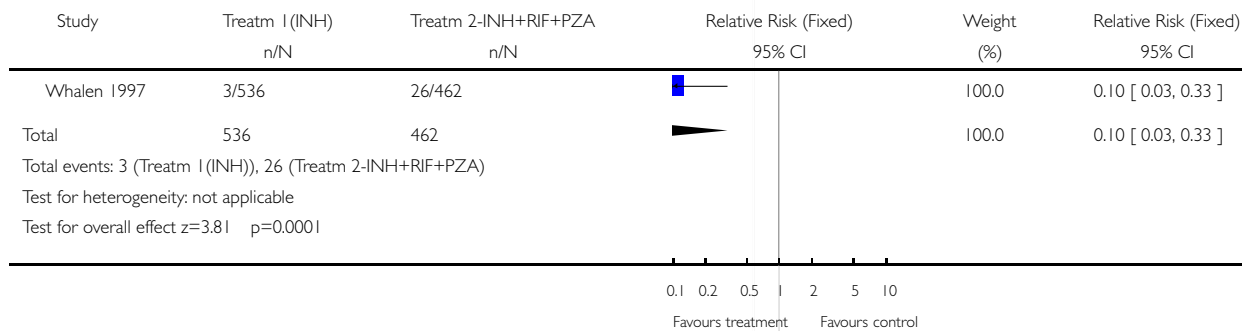


Fig. 78. Comparison 09 Isoniazid vs isoniazid + rifampicin + Pyrazinamide

09.07 Mean CD4 count

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 09 Isoniazid vs isoniazid + rifampicin + Pyrazinamide

Outcome: 07 Mean CD4 count

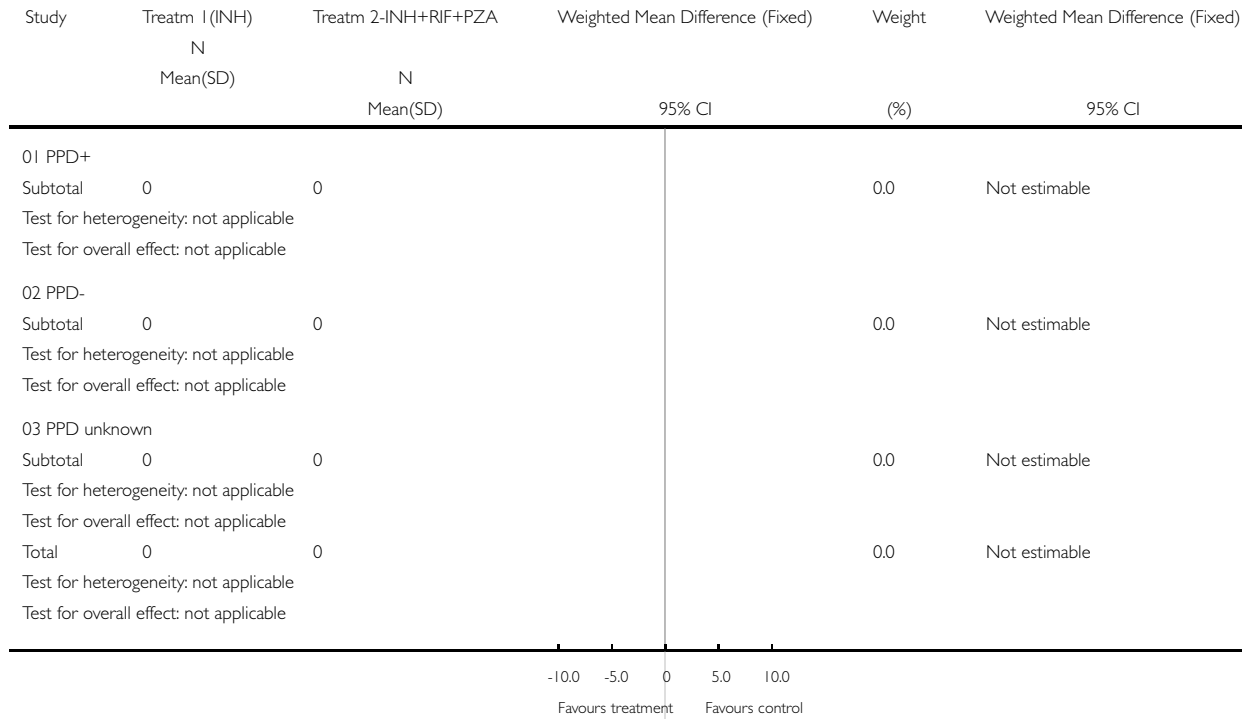


Fig. 79. Comparison 09 Isoniazid vs isoniazid + rifampicin + Pyrazinamide

09.08 Mean time to TB

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 09 Isoniazid vs isoniazid + rifampicin + Pyrazinamide

Outcome: 08 Mean time to TB

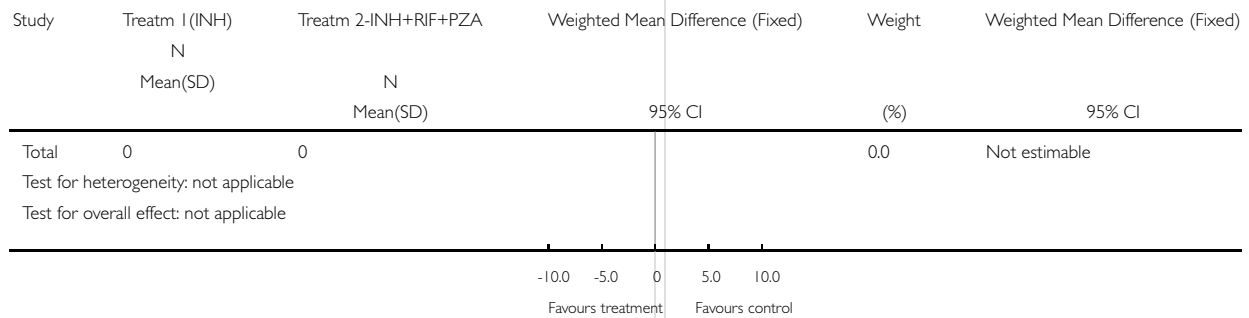


Fig. 80. Comparison 09 Isoniazid vs isoniazid + rifampicin + Pyrazinamide

09.09 Mean time to death

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 09 Isoniazid vs isoniazid + rifampicin + Pyrazinamide

Outcome: 09 Mean time to death

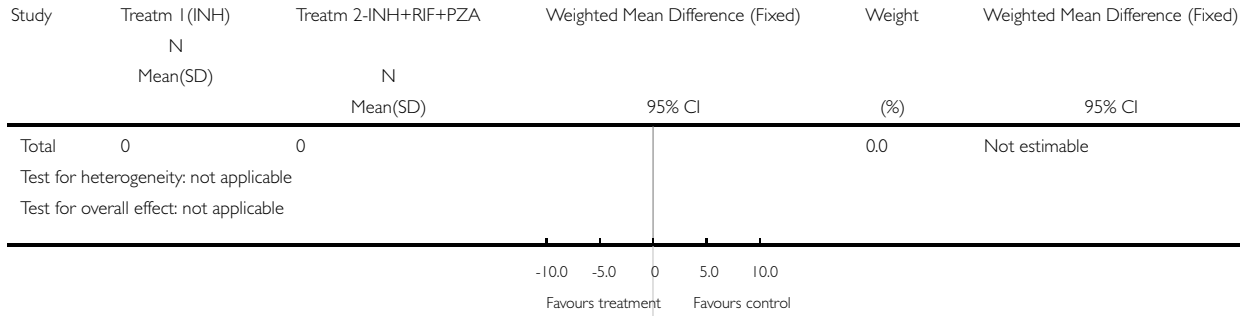


Fig. 81. Comparison 09 Isoniazid vs isoniazid + rifampicin + Pyrazinamide

09.10 Mean time to AIDS

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 09 Isoniazid vs isoniazid + rifampicin + Pyrazinamide

Outcome: 10 Mean time to AIDS

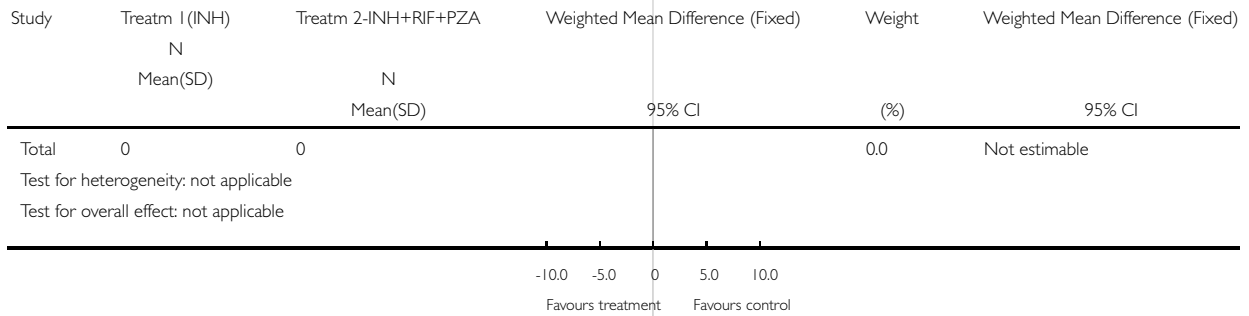


Fig. 82. Comparison 10 Isoniazid + rifampicin vs isoniazid + rifampicin + Pyrazinamide

10.01 Incidence of active TB (confirmed, probable or possible)

Review: Treatment of latent tuberculosis infection in HIV infected persons

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

Outcome: 01 Incidence of active TB (confirmed, probable or possible)

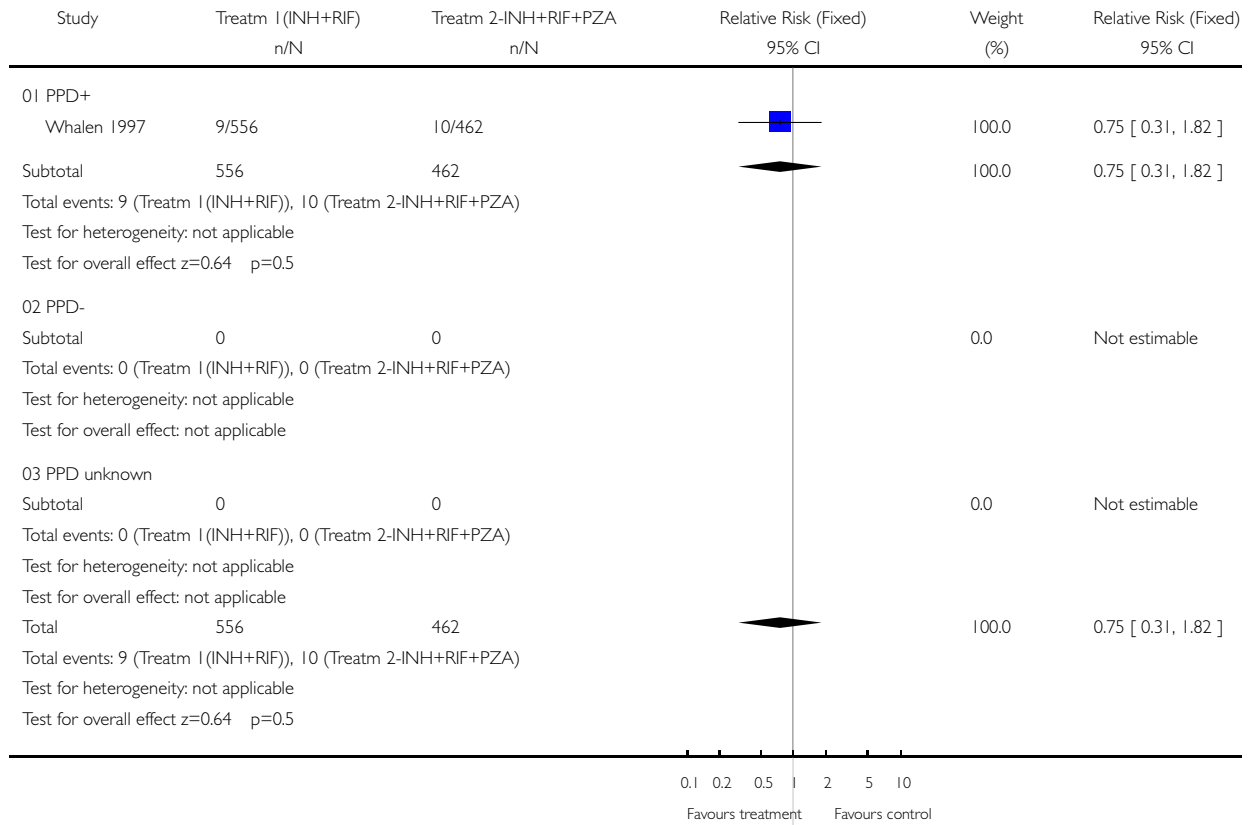


Fig. 83. Comparison 10 Isoniazid + rifampicin vs isoniazid + rifampicin + Pyrazinamide

10.02 Incidence of confirmed TB

Review: Treatment of latent tuberculosis infection in HIV infected persons

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

Outcome: 02 Incidence of confirmed TB

Study	Treatm 1 (INH+RIF) n/N	Treatm 2-INH+RIF+PZA n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 PPD+					
Subtotal	0	0		0.0	Not estimable
Total events: 0 (Treatm 1 (INH+RIF)), 0 (Treatm 2-INH+RIF+PZA)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
02 PPD-					
Subtotal	0	0		0.0	Not estimable
Total events: 0 (Treatm 1 (INH+RIF)), 0 (Treatm 2-INH+RIF+PZA)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 PPD unknown					
Subtotal	0	0		0.0	Not estimable
Total events: 0 (Treatm 1 (INH+RIF)), 0 (Treatm 2-INH+RIF+PZA)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
Total	0	0		0.0	Not estimable
Total events: 0 (Treatm 1 (INH+RIF)), 0 (Treatm 2-INH+RIF+PZA)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Fig. 84. Comparison 10 Isoniazid + rifampicin vs isoniazid + rifampicin + Pyrazinamide

10.03 Incidence of death (all cause)

Review: Treatment of latent tuberculosis infection in HIV infected persons

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

Outcome: 03 Incidence of death (all cause)

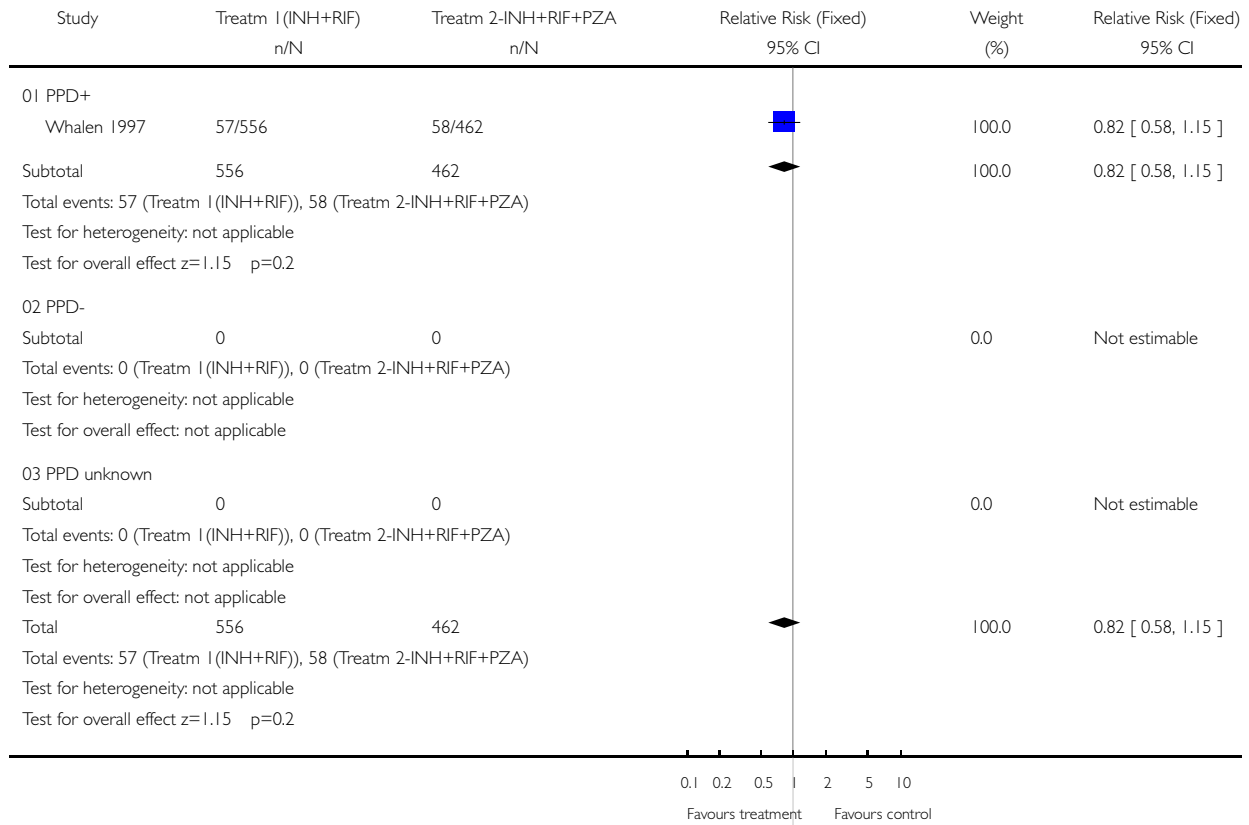


Fig. 85. Comparison 10 Isoniazid + rifampicin vs isoniazid + rifampicin + Pyrazinamide

10.04 Incidence of AIDS

Review: Treatment of latent tuberculosis infection in HIV infected persons
 Comparison: 10 Isoniazid + rifampicin vs isoniazid + rifampicin + Pyrazinamide
 Outcome: 04 Incidence of AIDS

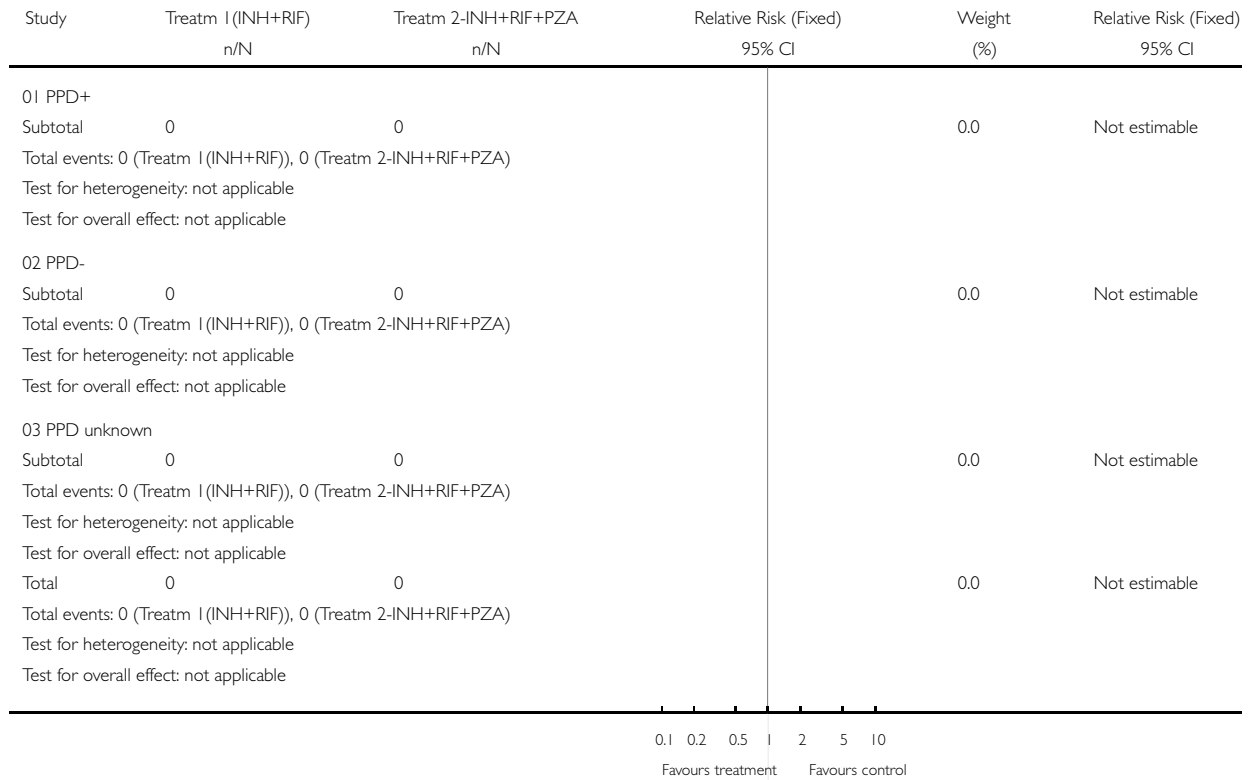


Fig. 86. Comparison 10 Isoniazid + rifampicin vs isoniazid + rifampicin + Pyrazinamide

10.05 Incidence of adverse events leading to stopping treatment

Review: Treatment of latent tuberculosis infection in HIV infected persons
 Comparison: 10 Isoniazid + rifampicin vs isoniazid + rifampicin + Pyrazinamide
 Outcome: 05 Incidence of adverse events leading to stopping treatment

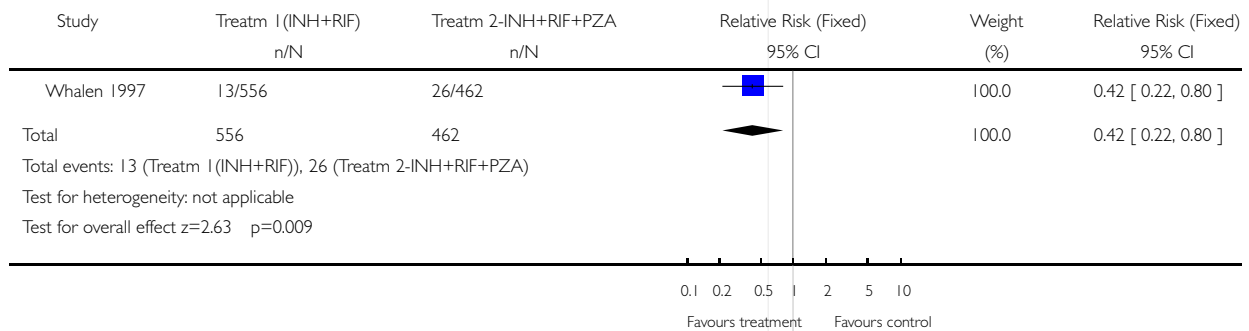


Fig. 87. Comparison 10 Isoniazid + rifampicin vs isoniazid + rifampicin + Pyrazinamide

10.07 Mean CD4 count

Review: Treatment of latent tuberculosis infection in HIV infected persons

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

Outcome: 07 Mean CD4 count

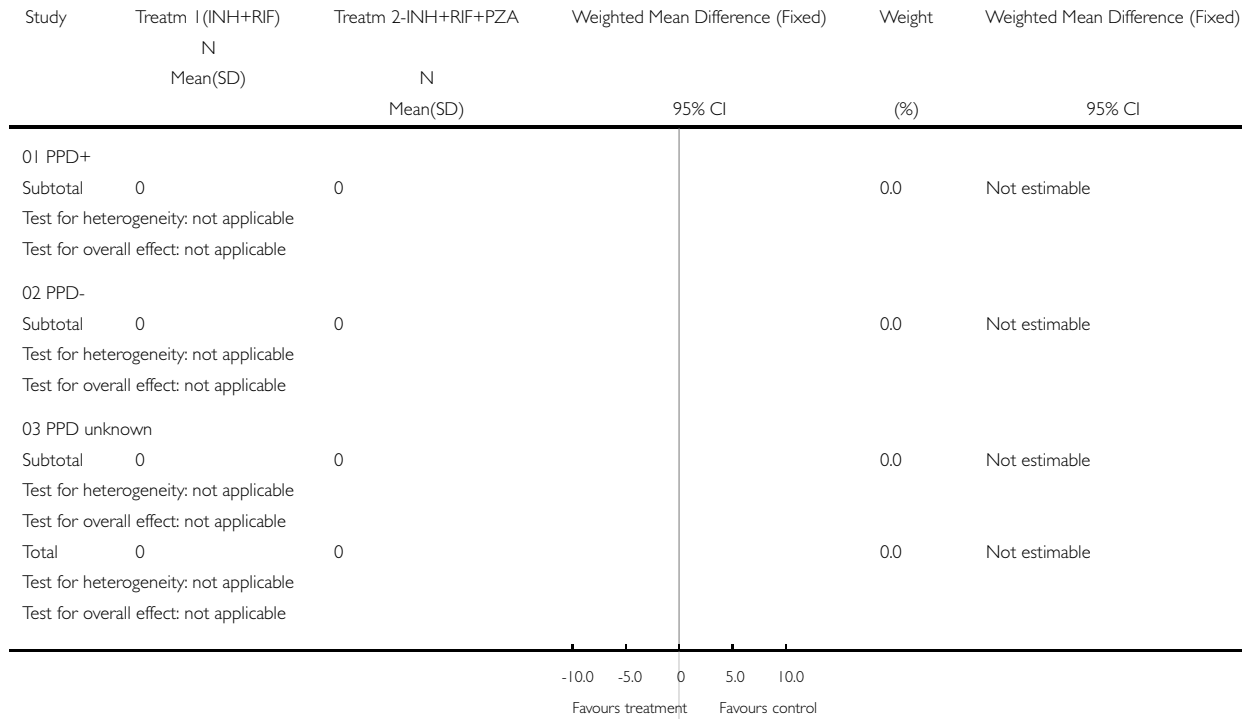


Fig. 88. Comparison 10 Isoniazid + rifampicin vs isoniazid + rifampicin + Pyrazinamide

10.08 Mean time to TB

Review: Treatment of latent tuberculosis infection in HIV infected persons

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

Outcome: 08 Mean time to TB

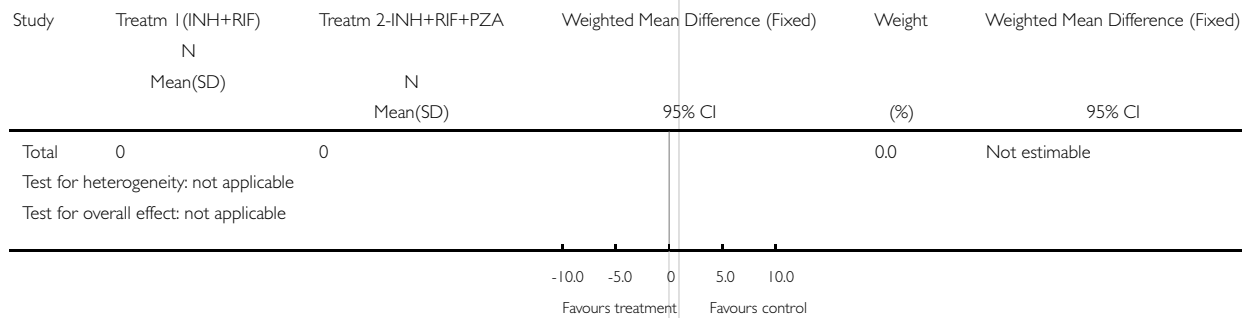


Fig. 89. Comparison 10 Isoniazid + rifampicin vs isoniazid + rifampicin + Pyrazinamide

10.09 Mean time to death

Review: Treatment of latent tuberculosis infection in HIV infected persons

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

Outcome: 09 Mean time to death

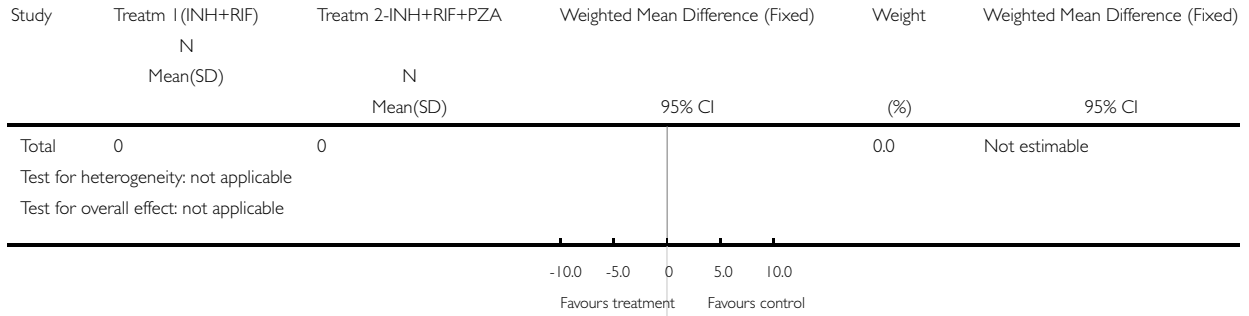


Fig. 90. Comparison 10 Isoniazid + rifampicin vs isoniazid + rifampicin + Pyrazinamide

10.10 Mean time to AIDS

Review: Treatment of latent tuberculosis infection in HIV infected persons

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

Outcome: 10 Mean time to AIDS

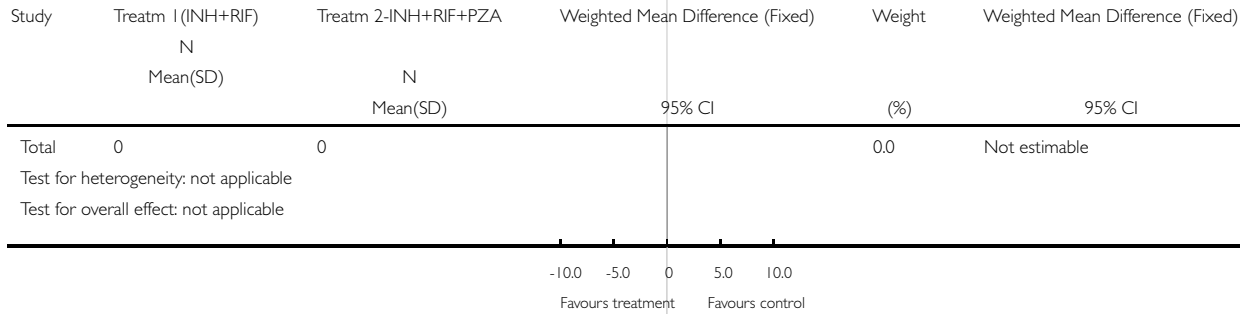


Fig. 91. Comparison 22 Isoniazid vs placebo (stratified by AIDS status at baseline)

22.02 Incidence of confirmed TB

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 22 Isoniazid vs placebo (stratified by AIDS status at baseline)

Outcome: 02 Incidence of confirmed TB

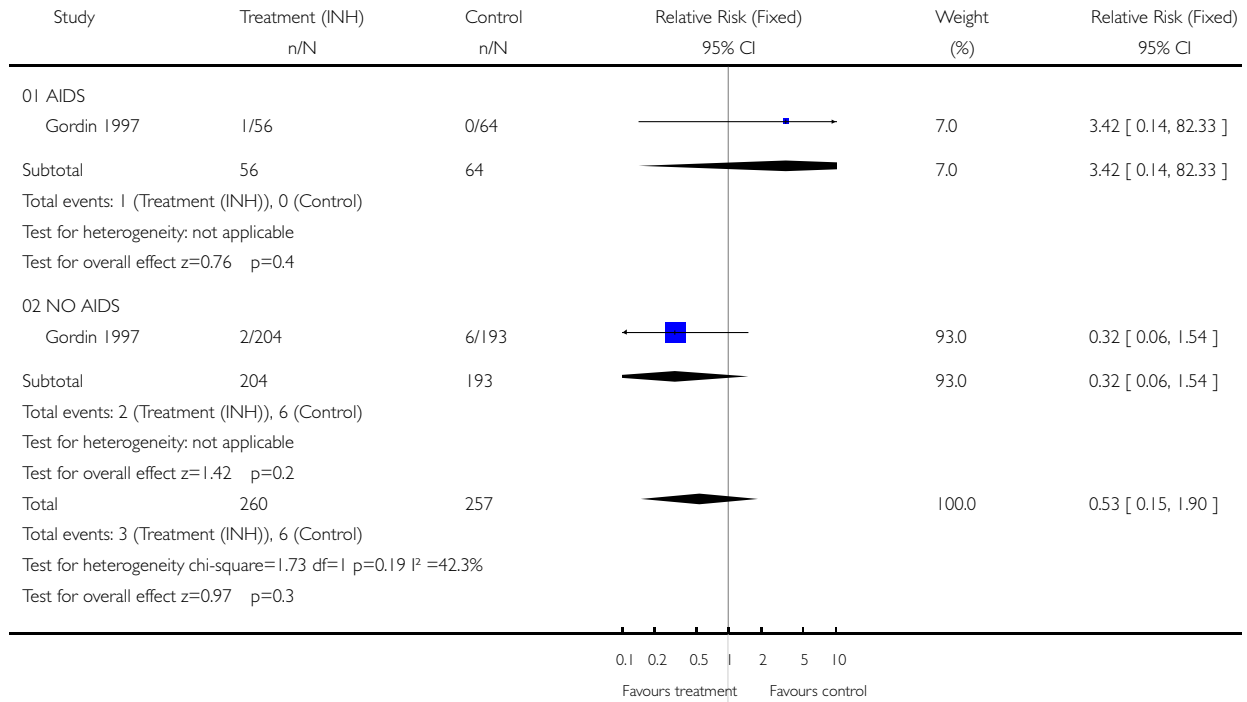


Fig. 92. Comparison 22 Isoniazid vs placebo (stratified by AIDS status at baseline)

22.03 Incidence of death (all cause)

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 22 Isoniazid vs placebo (stratified by AIDS status at baseline)

Outcome: 03 Incidence of death (all cause)

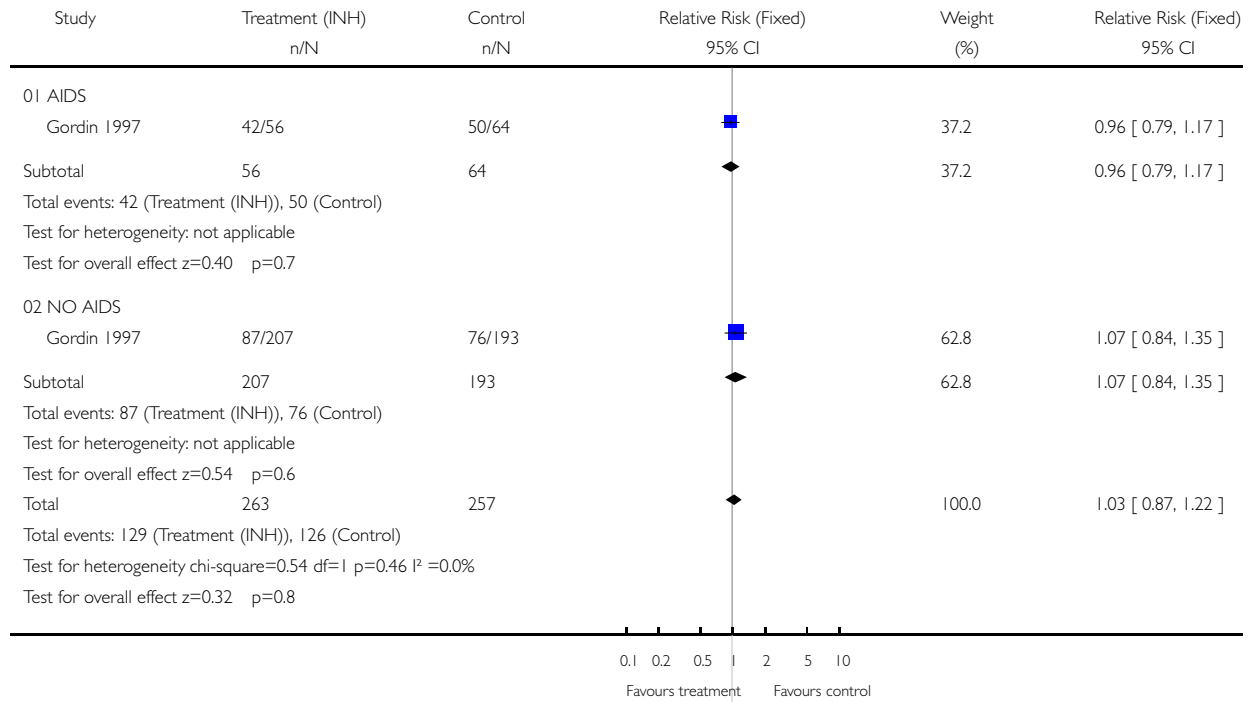


Fig. 93. Comparison 26 Isoniazid vs rifampicin + pyrazinimide (stratified by AIDS status at baseline)

26.02 Incidence of confirmed TB

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 26 Isoniazid vs rifampicin + pyrazinimide (stratified by AIDS status at baseline)

Outcome: 02 Incidence of confirmed TB

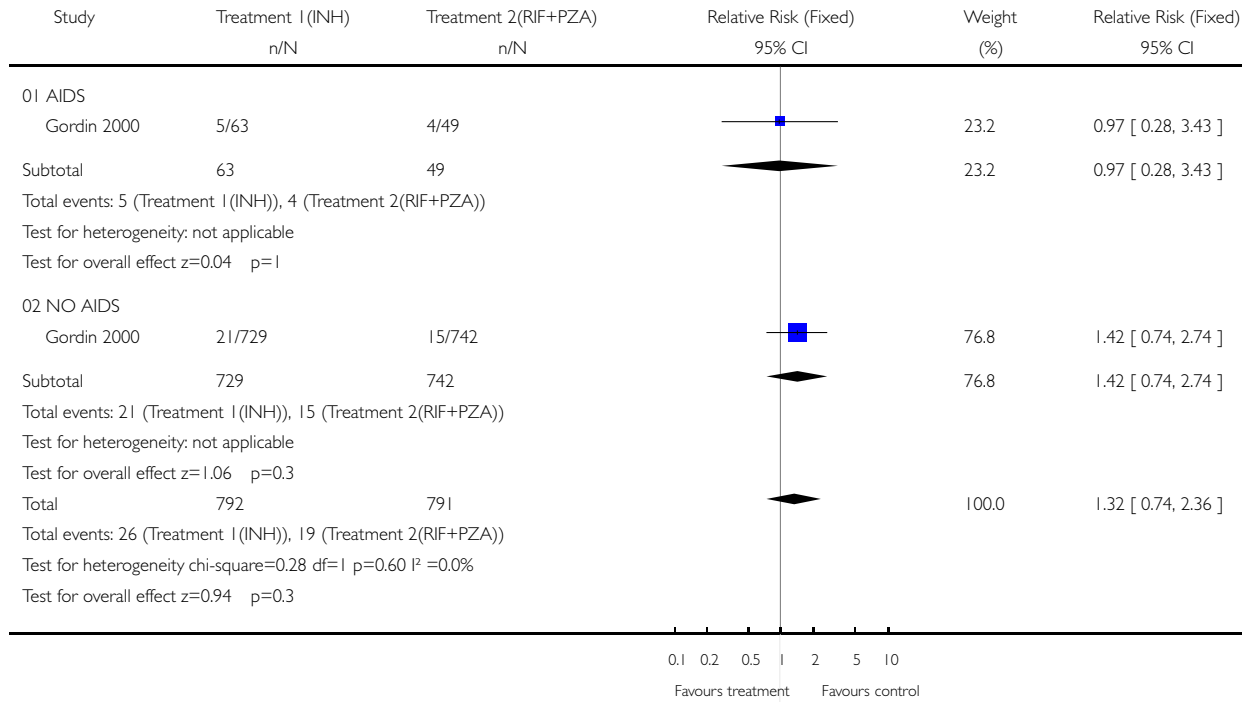


Fig. 94. Comparison 26 Isoniazid vs rifampicin + pyrazinimide (stratified by AIDS status at baseline)

26.03 Incidence of death (all cause)

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 26 Isoniazid vs rifampicin + pyrazinimide (stratified by AIDS status at baseline)

Outcome: 03 Incidence of death (all cause)

