ClinicalEvidence

# Tuberculosis (HIV-negative people)

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## ABSTRACT

INTRODUCTION: About a third of the world's population has latent tuberculosis. In 2004, over 14 million people had active tuberculosis. Approximately 1.7 million people died from the infection. Over 80% of new cases diagnosed in 2004 were in people in Africa, South-East Asia, and Western Pacific regions. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of interventions to prevent tuberculosis in people without HIV infection at high risk of developing tuberculosis? What are the effects of interventions to prevent tuberculosis in people without HIV infection at high risk of developing multidrug-resistant tuberculosis? What are the effects of different drug regimens in people with newly diagnosed pulmonary tuberculosis without HIV infection? What are the effects of different drug regimens in people with multidrug-resistant tuberculosis without HIV infection? What are the effects of low-level laser therapy in people with tuberculosis without HIV infection? Which interventions improve adherence to treatment in people with tuberculosis without HIV infection? We searched: Medline, Embase, The Cochrane Library, and other important databases up to July 2008 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 31 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: adding pyrazinamide in chemotherapy regimens lasting up to 6 months; adding rifampicin to isoniazid regimens; benefits of different regimens; chemotherapy for less than 6 months; daily chemotherapy; direct observation treatment; intermittent chemotherapy for 6 months or longer; isoniazid; low-level laser therapy for pulmonary tuberculosis; regimens containing quinolones; rifampicin plus isoniazid; substituting rifampicin with ethambutol in the continuous phase; and support mechanisms for directly observed treatment.


## QUESTIONS



## INTERVENTIONS

### PREVENTING TUBERCULOSIS IN HIGH-RISK PEOPLE WITHOUT HIV INFECTION

#### Trade off between benefits and harms



### PREVENTING TUBERCULOSIS IN PEOPLE WITHOUT HIV INFECTION WITH HIGH RISK OF MULTIDRUG-RESISTANT TUBERCULOSIS

#### Unknown effectiveness



### DRUGS FOR PULMONARY TUBERCULOSIS IN PEOPLE WITHOUT HIV INFECTION

#### Beneficial



#### Likely to be beneficial



#### Unknown effectiveness



#### Unlikely to be beneficial



#### Likely to be ineffective or harmful



### DIFFERENT REGIMENS FOR DRUG-RESISTANT TUBERCULOSIS IN PEOPLE WITHOUT HIV INFECTION

#### Unknown effectiveness

## Key points

- About a third of the world's population has latent tuberculosis.

  Over 14 million people had active tuberculosis in 2004, many of whom also had HIV. Approximately 1.7 million people died from the infection.

  Over 80% of new cases diagnosed in 2004 were in people in Africa, South-East Asia, and Western Pacific regions.
- Most people who inhale *Mycobacterium tuberculosis* clear the infection and become skin-test positive.

  Active infection is more likely in people affected by social factors, such as poverty, overcrowding, homelessness, and inadequate health care, or with reduced immune function — such as with HIV infection.

  Some people develop latent infection — persistent bacterial presence which is asymptomatic and not infectious.
- Drug treatments can reduce the risk of active tuberculosis in people at high risk of infection.

  Prophylactic isoniazid for 6 months can reduce the risk of tuberculosis infection in high-risk people without HIV, but increases the risk of hepatotoxicity.

  Rifampicin plus isoniazid for 3–4 months, or isoniazid for 6–12 months, may be equally effective at reducing active infection rates in people with latent tuberculosis.
- Treatment requires chemotherapy with combination regimens.

  Adding rifampicin to isoniazid is more effective than isoniazid treatment alone, and more effective than ethambutol plus isoniazid regimens.

  Regimens including pyrazinamide improve short-term sputum clearance, but long-term effects are unclear.

  Quinolones, such as ciprofloxacin, ofloxacin, and moxifloxacin, have not been shown to improve outcomes compared with ethambutol, isoniazid, and pyrazinamide regimens, but the evidence is sparse.
- The optimal length of treatment seems to be 6 months, but evidence is not robust.

  Relapse rates are the same after 6 months' treatment compared with longer regimens.

  Intermittent chemotherapy, taken 2−3 times a week, may be as effective as daily treatment for 6 months or more, but the evidence is weak.
- Current practice in multidrug-resistant tuberculosis is to use at least three drugs to which the particular strain is sensitive.
- Direct observation of treatment (DOT) does not seem to increase cure rates compared with self-administered treatment.

  We don't know how different types of support mechanisms for DOT compare with each other.

**DEFINITION**

Tuberculosis is caused by *Mycobacterium tuberculosis* and can affect many organs. Specific symptoms relate to site of infection, and are generally accompanied by fever, sweats, and weight loss. This review focuses on tuberculosis in people who do not have HIV. For tuberculosis in people with HIV, see separate review on tuberculosis in people with HIV.

**INCIDENCE/ PREVALENCE**

The *M tuberculosis* organism kills more people than any other infectious agent. The number of cases of tuberculosis was stable or falling in five of six WHO regions in 2004, but growing at 0.6% a year globally. [1] Incidence is rising in Africa, where the tuberculosis epidemic is still driven by the spread of HIV. According to WHO data, there were 8.9 million new cases of tuberculosis worldwide in 2004 (140/100,000 population), of which 3.9 million (62/100,000) were smear positive, and 741,000 were in adults infected with HIV. There were 14.6 million prevalent cases (229/100,000), of which 6.1 million were smear positive (95/100,000). More than 80% of people newly diagnosed

with tuberculosis in 2004 were in the African, South-East Asian, and Western Pacific regions. [1] About a third of the world's population has latent tuberculosis (see aetiology). [2]

**AETIOLOGY/ RISK FACTORS** The chief route of infection is through inhalation of airborne bacteria released by people with active respiratory tuberculosis by cough, sneeze, or speech. Inhaled mycobacteria reach the lung, and grow slowly over several weeks. The immune systems of most healthy exposed people (80–90%) kill the bacteria, and they are removed from the body, with only a positive skin test left as a marker of exposure. In a small proportion of people infected, a defensive barrier is built around the infection, but the tuberculosis bacteria are not killed and lie dormant. [2] This is known as latent tuberculosis, where the person is asymptomatic and not infectious. In the rest of those infected, active tuberculosis develops immediately. **Risk factors:** Social factors include poverty, overcrowding, homelessness, and inadequate health services. Medical factors include HIV and immunosuppression.

**PROGNOSIS** Prognosis varies widely and depends on treatment. [3] An estimated 1.7 million people (27/100,000) died from tuberculosis in 2004, including those co-infected with HIV (248,000). [1] Directly observed treatment, short course (DOTS), has been implemented for more than 10 years and millions of people treated for tuberculosis. However, recurrence after successful treatment ranged from 0% to 14% in one systematic review (search date 2006), [4] which identified RCT and observational studies assessing recurrence after successful treatment; little is known about the long-term efficacy of this strategy.

**AIMS OF INTERVENTION** Prevention: to prevent the development of active tuberculosis. Treatment: to cure tuberculosis; eliminate risk of relapse; reduce infectivity; avoid emergence of drug resistance; and prevent death, with minimal adverse effects of treatment.

**OUTCOMES** *M tuberculosis* in sputum (smear examination and culture); symptoms; weight; cure; relapse rates; attendance; completion of treatment; adverse effects of treatment.

**METHODS** *Clinical Evidence* search and appraisal July 2008. The following databases were used to identify studies for this review: Medline 1966 to July 2008, Embase 1980 to July 2008, and The Cochrane Library (all databases) 2008, Issue 2. An additional search was carried out on the NHS Centre for Reviews and Dissemination (CRD) website across all databases. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for evaluation in this review were: published systematic reviews and RCTs in any language, at least single blinded (if possible), and containing 20 or more individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as “open”, “open label”, or not blinded unless blinding was impossible. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the review as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). For GRADE evaluation of interventions for tuberculosis in HIV-negative people, see table, p 16 .

## QUESTION What are the effects of interventions to prevent tuberculosis in people without HIV infection at high risk of developing tuberculosis?

## OPTION ISONIAZID

**Development of active tuberculosis**

*Isoniazid compared with placebo* Prophylaxis with isoniazid for 6–12 months is more effective at reducing the risk of developing active tuberculosis or extrapulmonary tuberculosis in HIV-negative people at increased risk of tuberculosis (high-quality evidence).

*Isoniazid compared with no isoniazid in people undergoing renal transplantation* Prophylaxis with isoniazid may be more effective than no prophylaxis at reducing the risk of developing active tuberculosis in renal transplant patients at increased risk of tuberculosis, although evidence was inconsistent (very low-quality evidence).

**Adverse effects**

*Isoniazid compared with placebo* Isoniazid increases the risk of hepatotoxicity (high-quality evidence).

**For GRADE evaluation of interventions for tuberculosis in HIV-negative people, see table, p 16 .**

**Benefits:**

**Isoniazid versus placebo:**
We found one systematic review (search date 2003; 11 RCTs, 73,375 people) [5] comparing isoniazid for 6–12 months versus placebo in HIV-negative people at increased risk of developing tuberculosis (people with previous pulmonary tuberculosis or positive skin tests, people with recent or remote contact with an active case of pulmonary tuberculosis, or people living in an area with a high incidence and prevalence of disease). It found that, between 2 and 10 years' follow-up, isoniazid significantly reduced the risk of active tuberculosis (defined as symptoms, positive microscopy or culture, or change in chest x ray), or extrapulmonary tuberculosis compared with placebo (AR for active tuberculosis; 11 RCTs: 239/40,262 [0.6%] with isoniazid *v* 557/33,113 [1.7%] with placebo; RR 0.40, 95% CI 0.31 to 0.52; AR for extrapulmonary tuberculosis; 4 RCTs: 9/22,379 [0.04%] with isoniazid *v* 28/22,257 [1.3%] with placebo; RR 0.34, 95% CI 0.16 to 0.71). The review found no significant difference in active tuberculosis or extrapulmonary tuberculosis between a 6-month and a 12-month course of isoniazid (AR for active tuberculosis; 1 RCT: 34/6965 [0.5%] with 6 months of isoniazid *v* 24/6919 [0.3%] with 12 months of isoniazid; RR 1.41, 95% CI 0.84 to 2.37). Isoniazid did not significantly reduce deaths from tuberculosis compared with placebo (2 RCTs: 3/16,318 [0.02%] with isoniazid *v* 10/9396 [0.1%] with placebo; RR 0.29, 95% CI 0.07 to 1.18).

**Isoniazid versus no isoniazid in people undergoing renal transplantation:**
We found two small RCTs, conducted in a hospital in India comparing isoniazid prophylaxis (300 mg or 200 mg in people with body weight less than 50 kg, plus pyridoxine 20 mg daily) versus no prophylaxis for 1 year or until the development of tuberculosis — whichever occurred first. [6] [7] The first RCT (90 renal transplant recipients) compared isoniazid versus no treatment from the day of renal transplantation. It found that fewer people developed tuberculosis after isoniazid prophylaxis compared with no treatment, although this difference was not significant (3/27 [11%] with isoniazid *v* 15/58 [26%] with no treatment; RR 0.36, 95% CI 0.10 to 1.32). [6] The second RCT (109 people with end-stage renal disease) compared isoniazid prophylaxis versus no treatment from the start of maintenance dialysis in people who later had renal transplantation. It found that significantly fewer people developed tuberculosis after isoniazid prophylaxis than after no treatment (9/54 [17%] with isoniazid *v* 18/55 [33%] with no treatment; RR 0.40, 95% CI 0.17 to 0.92; P = 0.032). [7] Because of the weak methods of the RCTs, these results should be interpreted with caution — the RCTs gave no information about allocation concealment or HIV status, and the first RCT did not report the method of randomisation. [6] [7]

**Harms:**

**Isoniazid versus placebo:**
The review found that hepatotoxicity was significantly more common in people receiving isoniazid compared with placebo (AR for hepatitis; 1 RCT: 77/13,884 [0.6%] with isoniazid *v* 7/6990 [0.1%] with placebo; RR 5.54, 95% CI 2.56 to 12.00). [5] Other reported adverse effects of isoniazid include: mild and transient headache, nausea, and dizziness.

**Isoniazid versus no isoniazid in people undergoing renal transplantation:**
The first RCT reported that 1/27 (4%) people developed isoniazid-induced hepatitis that required discontinuation of treatment. [6] The second RCT reported that a higher proportion of people in the isoniazid group had serious hepatitis requiring discontinuation of treatment, or liver dysfunction compared with the no-treatment group (serious hepatitis: 9/54 [17%] with isoniazid *v* 6/55 [11%] with no treatment; liver dysfunction: 27/54 [50%] with isoniazid *v* 17/54 [31%] with no treatment; P values not reported; results reported as not significant). The majority of people in both groups were positive for hepatitis B or C or both. [7]

**Comment:**

Even in the isoniazid group, the absolute risk of hepatotoxicity was small (0.6%). [5]

**Isoniazid resistance:**
We found one systematic review (12 RCTs and 1 cohort study; 18,095 people in isoniazid groups and 17,985 people in control groups) comparing isoniazid prophylaxis treatment versus control in HIV-positive and HIV-negative people using data published since 1951. [8] It suggested there was no significant difference in rates of isoniazid resistance between treatment and control groups (RR 1.45, 95% CI: 0.85 to 2.47). The review reported similar results when studies of HIV-negative and HIV-positive people were analysed separately. [8] The review reported that five of the 12 RCTs reported methods of randomisation (2 RCTs used computer-generated random numbers, 2 used random number tables, and 1 assigned using odd or even hospital numbers), three reported that treatment allocation was concealed, and eight were double blinded.

**Clinical guide:**
Active tuberculosis should be excluded prior to initiation of isoniazid prophylaxis.

## OPTION RIFAMPICIN PLUS ISONIAZID

**Development of active tuberculosis**

*Compared with isoniazid* We don't know whether rifampicin plus isoniazid for 3 months is more effective than isoniazid alone for 6–12 months at reducing the development of active tuberculosis at 1–3 years in HIV-negative people with latent tuberculosis, or whether rifampicin plus isoniazid for 4 months is more effective than isoniazid alone for 9 months at reducing clinical tuberculosis at the end of treatment or during follow-up in children with latent tuberculosis (HIV status not reported) (very low-quality evidence).

**Note**
Isoniazid may increase the risk of hepatotoxicity compared with placebo.

**For GRADE evaluation of interventions for tuberculosis in HIV-negative people,** **see table, p 16 .**

**Benefits:**

**Rifampicin plus isoniazid versus isoniazid alone:**
We found one systematic review (search date 2005) [9] and two subsequent RCTs. [10] [11] The systematic review identified one RCT (196 adults from Spain with latent tuberculosis infection determined by positive skin test, and without HIV) comparing rifampicin plus isoniazid daily for 3 months versus isoniazid daily for 6–12 months. [9] The mean duration of follow-up varied from 13 to 37 months. The RCT found no significant difference between groups in the proportion of people who developed culture-confirmed active tuberculosis (1/98 [1%] with rifampicin plus isoniazid *v* 0/98 [0%] with isoniazid; ARR +1%, 95% CI –2% to +4%). The RCT did not assess mortality. Results from this RCT were supported by a meta-analysis of trials including people with HIV. The review found no significant difference in mortality between rifampicin plus isoniazid and isoniazid alone in people with HIV (3 RCTs: 67/707 [9%] with rifampicin plus isoniazid *v* 71/683 [10%] with isoniazid alone; ARR –1%, 95% CI –4% to +2%). [9] The first subsequent quasi-randomised RCT compared rifampicin plus isoniazid daily for 4 months versus isoniazid daily for 9 months, and also compared a 3-month rifampicin plus isoniazid versus a 4-month rifampicin plus isoniazid regimen in Greece. [10] We have only reported the rifampicin plus isoniazid versus isoniazid alone analysis here. The RCT included children under 15 years of age with latent tuberculosis infection (232 participants having 9-months' isoniazid therapy, 238 participants having 4-months' isoniazid and rifampicin therapy, study period 1995–1998). However, the RCT was quasi-randomised as allocation was based on the children's number in the clinic (odd or even). Hence, any conclusions drawn should be made with caution. A significantly higher proportion of children had recent infection in the isoniazid alone group (64%) than in the isoniazid plus rifampicin group (53%) at baseline (P = 0.013). The RCT found that, compared with isoniazid alone, rifampicin plus isoniazid significantly reduced the proportion of children who developed new radiographic findings suggestive of possible active tuberculosis at 4 months after the initiation of treatment (48/200 [24%] with isoniazid alone *v* 26/220 [12%] with rifampicin plus isoniazid; P = 0.001). [10] However, these results were based on 420/470 (89%) people initially randomised who had excellent or moderate compliance with treatment. The RCT reported that in those with poor compliance (50/470 [11%]), treatment outcomes could not be evaluated, and these people were not included in the analysis of treatment outcome. All participants with radiographic findings were subsequently treated for active tuberculosis with isoniazid and rifampicin for a total of 9 months. The RCT did not assess mortality as an outcome. It found no cases of clinical tuberculosis at the end of treatment or during follow-up (7–11 years), with less than 10% of participants lost to follow-up. The RCT found that, compared with isoniazid alone, rifampicin plus isoniazid significantly reduced the proportion of participants with poor compliance (32/232 [14%] with isoniazid alone *v* 18/238 [8%] with isoniazid plus rifampicin; P = 0.029). Compliance was considered to be poor if: no medication was detected in more than two urine strips in the 9-month isoniazid alone group; in more than one urine strip in rifampicin plus isoniazid group; and if participants did not return to follow-up visits or if they were lost to follow-up. The RCT did not provide data either on resistance patterns or on the HIV status of participants. [10]

The second small subsequent RCT compared rifampicin plus isoniazid daily for 3 months versus isoniazid alone daily for 6 months. [11] The RCT included 105 HIV-negative people with positive tuberculin skin test meeting the 1990 Centers for Disease Control and Prevention (CDC) criteria for latent tuberculosis infection. In total, 51 people received rifampicin plus isoniazid, 45 people received isoniazid alone, and nine people refused treatment. Results were based on the 96/105 (91%) people who received treatment. Participants were enrolled between 1996 and 2003 in a high-prevalence area (prevalence of tuberculosis 16.22/100,000 population). The RCT did not provide data on resistance patterns, and the duration of follow-up was 5 years. The RCT found significantly higher treatment completion rates with rifampicin plus isoniazid compared with isoniazid alone, although results were of borderline significance (46/51 [90%] with rifampicin plus isoniazid *v* 34/45 [76%] with isoniazid alone; P = 0.05). One participant in the isoniazid group who developed active tuberculosis in the second month of treatment was subsequently successfully treated with standard tuberculosis treatment (tuberculosis development: 1/45 [2%] with isoniazid alone *v* 0/51 [0%] with rifampicin plus isoniazid; P = 0.1). [11]

**Harms:** **Rifampicin plus isoniazid versus isoniazid alone:**
The review found similar rates of adverse effects (e.g. hepatotoxicity, rash, gastrointestinal intolerance) requiring withdrawal from treatment between rifampicin plus isoniazid for 3 months and isoniazid alone for 6–12 months (10% with rifampicin plus isoniazid *v* 13% with isoniazid alone; CI and absolute numbers not reported). [9] The first subsequent quasi-randomised RCT reported no serious adverse effects. [10] The second small RCT found a significantly higher rate of minor adverse events with isoniazid alone compared with rifampicin plus isoniazid (23/45 [55%] with isoniazid alone *v* 17/51 [33%] with rifampicin plus isoniazid; P = 0.04). [11] It found no significant difference between groups in the proportion of people with hepatotoxicity requiring treatment interruption, although rates were higher with isoniazid alone (2/45 [4%] with isoniazid alone *v* 1/51 [2%] with rifampicin plus isoniazid; P = 0.5). [11]

**Comment:** None.

**QUESTION** **What are the effects of interventions to prevent tuberculosis in people without HIV infection at high risk of developing multidrug-resistant tuberculosis?**

**OPTION** **DIFFERENT REGIMENS VERSUS EACH OTHER FOR PREVENTING MULTIDRUG-RESISTANT TUBERCULOSIS IN HIGH-RISK PEOPLE WITHOUT HIV INFECTION**

**We found no clinically important results from RCTs comparing different drug regimens for preventing multidrug-resistant tuberculosis in people without HIV infection at high risk of multidrug-resistant tuberculosis.**

**For GRADE evaluation of interventions for tuberculosis in HIV-negative people,** **see table, p 16 .**

**Benefits:** We found one systematic review (search date 2006) comparing different drug regimens for preventing multidrug-resistant tuberculosis in people at high risk of multidrug-resistant tuberculosis, which identified no RCTs in people without HIV infection. [12]

**Harms:** We found one systematic review (search date 2006) comparing different drug regimens for preventing multidrug-resistant tuberculosis in people at high risk of multidrug-resistant tuberculosis, which identified no RCTs in people without HIV infection. [12]

**Comment:** **Clinical guide:**
The balance of benefits and harms associated with treatment for latent tuberculosis infection in people exposed to multidrug-resistant tuberculosis is unknown. Antituberculous drugs should only be offered within the context of a well-designed RCT, or when people are given the details of the current evidence on benefits and harms, along with the uncertainties.

**QUESTION** **What are the effects of different drug regimens in people with newly diagnosed pulmonary tuberculosis without HIV infection?**

**OPTION** **SHORTER (6 MONTHS) VERSUS LONGER (8–9 MONTHS) CHEMOTHERAPY REGIMENS**

**Relapse rates**
*Shorter (6 months) regimens compared with longer (8–9 months) regimens* Shorter chemotherapy regimens for 6 months seem to be as effective as longer course regimens for 8–9 months at reducing relapse rates (moderate-quality evidence).

**For GRADE evaluation of interventions for tuberculosis in HIV-negative people,** **see table, p 16 .**

**Benefits:** **Shorter (6 months) versus longer (8–9 months) chemotherapy regimens**:
We found two RCTs (1295 people with untreated, culture- or smear-positive pulmonary tuberculosis), comparing 6 versus 8–9 months of chemotherapy. [13] [14] Participants were followed up for at least 1 year after treatment was completed. The trials were performed in the UK and in east and central Africa, using different combinations of isoniazid, rifampicin, ethambutol, streptomycin, and pyrazinamide for initial treatment (first 2 months) and continuation treatment (lasting 4–7 months). Both RCTs found no significant difference in relapse rates between 6-month and longer-course chemotherapy regimens (P greater than 0.1). The first RCT (851 people) found no significant difference in relapse rates between 6–8 months' continuation with isoniazid alone (9% with isoniazid alone for 6 months *v* 3% with isoniazid alone for 8 months; P greater than 0.1). [13] The second RCT (444 people) compared a 6-month regimen (isoniazid plus rifampicin supplemented in initial 2 months with ethambutol plus pyrazinamide or with streptomycin plus pyrazinamide) versus a 9-month regimen (isoniazid plus rifampicin, supplemented in initial 2 months with ethambutol). [14] It found similar relapse rates between 6 and 9 months' treatment (2/119 [2%] with 6 months *v* 4/127 [3%] with 9 months; significance assessment not reported).

**Harms:** **Shorter (6 months) versus longer (8–9 months) chemotherapy regimens:**
In the first RCT, possible adverse reactions were reported in 24/851 (3%) people, with six people equiring modification of treatment. [13] Two people in the trial developed jaundice, one of whom died. The second RCT gave no information on adverse effects. [14]

**Comment:** None.

## OPTION PYRAZINAMIDE IN CHEMOTHERAPY REGIMENS LASTING UP TO 6 MONTHS

**Cure rate**
*Pyrazinamide-containing regimens compared with regimens not containing pyrazinamide* Chemotherapy regimens containing pyrazinamide seem to be more effective at improving sputum clearance at 2 months compared with regimens without pyrazinamide (moderate-quality evidence).

**Relapse rates**
*Pyrazinamide-containing regimens compared with regimens not containing pyrazinamide* Chemotherapy regimens containing pyrazinamide may be more effective at reducing relapse rates at 12 months compared with regimens without pyrazinamide, but we don't know whether they are more effective at 18 months (low-quality evidence).

**For GRADE evaluation of interventions for tuberculosis in HIV-negative people, see table, p 16 .**

**Benefits:** **Pyrazinamide-containing regimens versus regimens not containing pyrazinamide:**
We found three RCTs comparing chemotherapy regimens with or without pyrazinamide for initial and continuation treatment. [14] [15] [16] The first RCT (444 people) found that sputum conversion was faster at 2 months with regimens containing pyrazinamide (AR for negative cultures: 77% with pyrazinamide *v* 64% without pyrazinamide; P less than 0.01). [14] The second RCT (833 people) compared four different 6-month regimens, and found that bacterial relapse was significantly lower in people receiving pyrazinamide for 12 months after chemotherapy compared with people receiving no pyrazinamide (bacterial relapse: 8/625 [1%] with pyrazinamide *v* 12/160 [8%] without pyrazinamide; P less than 0.001). [15] The third RCT (497 people) compared ongoing pyrazinamide versus no treatment. [16] It found that relapse at 18 months was more likely in those not receiving pyrazinamide, but the difference was not significant (P = 0.49).

**Harms:** **Pyrazinamide-containing regimens versus regimens not containing pyrazinamide:**
The first RCT found that adding pyrazinamide did not increase the risk of hepatitis (4% with pyrazinamide *v* 4% without pyrazinamide). [14] However, mild adverse effects — including arthralgia, skin rashes, influenza-like symptoms, mild gastrointestinal disturbance, vestibular disturbance, peripheral neuropathy, and confusion — were more common. Arthralgia was the most common adverse effect — reported in about 1% of people on pyrazinamide — but was mild and never required modification to treatment. [14] [15]

**Comment:** None.

## OPTION RIFAMPICIN IN CONTINUATION PHASE OF CHEMOTHERAPY REGIMENS FOR 6 MONTHS OR LONGER

**Relapse rates**
*Rifampicin plus isoniazid compared with isoniazid* Rifampicin plus isoniazid chemotherapy regimens in the continuation phase seem to be more effective than isoniazid alone in the continuation phase at reducing relapse rates at 6 months (moderate-quality evidence).

**For GRADE evaluation of interventions for tuberculosis in HIV-negative people, see table, p 16 .**

**Benefits:** We found one RCT (851 people) comparing four daily chemotherapy regimens (3 of 6 months' and 1 of 8 months' duration). [13] All four treatment arms had the same initial 2-month phase of streptomycin, isoniazid, rifampicin, and pyrazinamide. The continuation phases of the 6-month regimens were: isoniazid plus rifampicin; isoniazid plus pyrazinamide; or isoniazid alone. The continuation phase of the 8-month regimen was isoniazid alone. It found that bacteriological relapse at 6 months was significantly reduced with isoniazid plus rifampicin compared with isoniazid alone (2% with rifampicin plus isoniazid *v* 9% with isoniazid alone; P less than 0.01).

**Harms:** In the RCT, possible adverse reactions were reported in 24/851 (3%) people, with six requiring modification of treatment. [13] Two people in the trial developed jaundice, one of whom died.

**Comment:** None.

## OPTION INTERMITTENT CHEMOTHERAPY FOR 6 MONTHS OR LONGER

**Cure rates**

*Intermittent chemotherapy for 6 months or longer compared with daily therapy* We don't know whether intermittent chemotherapy (2 or 3 times a week) is more effective than daily therapy at increasing cure rates in people with newly diagnosed tuberculosis (low-quality evidence).

**Relapse rates**

*Intermittent chemotherapy for 6 months or longer compared with daily therapy* We don't know whether intermittent chemotherapy (3 times a week) is more effective than daily therapy at decreasing relapse rates in people with newly diagnosed pulmonary tuberculosis (low-quality evidence).

**For GRADE evaluation of interventions for tuberculosis in HIV-negative people,** **see table, p 16 .**

**Benefits:**

**Intermittent chemotherapy for 6 months or longer versus daily chemotherapy:**
We found one systematic review (search date 2003) [17] and one additional RCT. [18] The review identified one RCT (399 people) comparing three-times-weekly versus daily chemotherapy for 6 months in people with newly diagnosed pulmonary tuberculosis. [17] It found no significant difference in bacteriological cure rates (defined as negative sputum culture: 99.9% with three times weekly *v* 100% with daily) or relapse rates (5/186 [3%] with three times weekly *v* 1/192 [1%] with daily; RR 4.0, 95% CI 0.7 to 24.1) between three-times-weekly and daily chemotherapy 1 month after treatment was completed. The additional RCT (206 children with all forms of intrathoracic tuberculosis, tuberculosis confirmed in 4%, probable in 94%, and suspected in 2%) compared twice-weekly versus daily chemotherapy. [18] It found no significant difference in cure rates between the two regimens (85/89 [95%] people with twice-weekly *v* 114/117 [97%] people with daily; RR 0.98, 95% CI 0.84 to 1.02).

**Harms:**

**Intermittent chemotherapy for 6 months or longer versus daily chemotherapy:**
It has been documented that drug resistance is associated with previous treatment, but this was not found in the RCTs. [17] [18]

**Comment:**

The RCTs had low event rates and were too small to detect a clinically important effect difference between the dosing regimens. At least 12 cohort studies have found cure rates of 80–100% with three-times-weekly regimens taken over 6–9 months. [17]

## OPTION REGIMENS CONTAINING QUINOLONES

**Cure rates**

*Ciprofloxacin-substituted regimens compared with standard regimens* We don't know whether ciprofloxacin-substituted regimens are more effective than standard regimens (including ethambutol plus pyrazinamide or rifampicin) at reducing treatment failure at 12 months in people with tuberculosis with or without HIV (low-quality evidence).

*Quinolone-substituted regimens compared with standard regimens* We don't know whether quinolone-substituted regimens (ciprofloxacin and moxifloxacin) are more effective than standard regimens (including ethambutol plus pyrazinamide, ethambutol, or rifampicin) at improving cure at 8 weeks in people with tuberculosis with or without HIV (low-quality evidence).

*Levofloxacin plus standard-drug regimen compared with standard-drug regimen alone* We don't know whether levofloxacin plus standard-drug regimens is more effective than standard drug regimens alone at increasing cure rates at 8 weeks in drug-resistant areas (low-quality evidence).

*Levofloxacin plus standard-drug regimen compared with ofloxacin plus standard-drug regimen* We don't know whether levofloxacin plus standard-drug regimens is more effective than ofloxacin plus standard-drug regimens at increasing cure rates at 2 weeks (low-quality evidence).

**Relapse rates**

*Quinolone-substituted regimens compared with standard regimens* Quinolone-substituted regimens (ciprofloxacin and ofloxacin) may be less effective than standard regimens (including ethambutol plus pyrazinamide, ethambutol, or rifampicin) at reducing relapse rates (low-quality evidence).

**Note**

A drug safety alert has been issued on serious hepatic and bullous skin reactions associated with moxifloxacin.

**For GRADE evaluation of interventions for tuberculosis in HIV-negative people,** **see table, p 16 .**

**Benefits:**

We found three systematic reviews. [19] [20] [21] The first systematic review (search date 2007, 11 RCTs, 1514 people with bacterially confirmed pulmonary tuberculosis with or without HIV infection)

assessed fluoroquinolones (mainly ciprofloxacin) substituted for or added to standard-drug regimens (including ethambutol, rifampicin, or pyrazinamide) and pooled data. [19] The review did not report data for most outcomes separately for people with or without HIV. The second and third systematic reviews (search dates 2006) [20] [21] were general reviews including both RCT and non-RCT data, were narrative in character, and did not pool data. They found similar studies to the first review. We have therefore reported the first systematic review [19] in detail, and have not reported the second and third reviews further. The first review reported that, of the 11 included RCTs: allocation concealment was adequate in one RCT and unclear in the remaining 10 RCTs; randomisation was adequate in four RCTs and unclear in the rest; and two included RCTs were unblinded and blinding was unclear in five further RCTs.

**Ciprofloxacin substitution for existing drugs:**
The first review found no significant difference between substituting ciprofloxacin for one or two agents in existing drug regimens (ethambutol plus pyrazinamide, or rifampicin) compared with standard drugs in treatment failure at 12 months (3 RCTs: 9/193 [5%] with ciprofloxacin *v* 4/195 [2%] with standard drugs; RR 2.14, 95% CI 0.71 to 6.42) in people with tuberculosis with or without HIV. [19] It found that substituting ciprofloxacin for ethambutol plus pyrazinamide significantly increased the time to sputum culture conversion (1 RCT, 168 people: WMD 0.50 months, 95% CI 0.18 months to 0.82 months), although this was in both HIV-negative and HIV-positive participants. In subgroup analysis, it found no significant increase in time to sputum culture conversion in HIV-negative participants alone (1 RCT, 101 people: WMD +0.20 months, 95% CI –0.10 months to +0.50 months). [19]

**Quinolone substitution for existing drugs:**
The first review found no significant difference in cure at 8 weeks between substituting ciprofloxacin or moxifloxacin for one or two agents in existing drug regimens (ethambutol plus pyrazinamide, ethambutol, or rifampicin) compared with standard drugs (3 RCTs: 132/208 [63%] with quinolone *v* 134/206 [65%] with standard drugs; RR 0.98, 95% CI 0.81 to 1.18) in people with tuberculosis with or without HIV. [19] It found that ciprofloxacin or ofloxacin significantly increased relapse rates over the duration of the trials (unspecified) compared with standard-drug regimens (3 RCTs: 10/191 [5%] with quinolone *v* 1/193 [1%] with ethambutol plus pyrazinamide, ethambutol, or rifampicin; RR 7.17, 95% CI 1.33 to 38.58). [19]

**Adding levofloxacin to standard-drug regimen versus standard-drug regimen alone:**
The first review found that adding levofloxacin to basic-drug regimens in drug-resistant areas increased cure rates at 8 weeks, but this difference was not significant (1 RCT, cure: 46/87 [53%] with added levofloxacin *v* 36/87 [42%] with standard-drug regimen alone; RR 1.28, 95% CI 0.93 to 1.76). [19] This RCT had unclear allocation concealment, and blinding was in assessors only.

**Adding levofloxacin versus adding ofloxacin to standard-drug regimen:**
The first review found no significant difference in cure at 2 weeks between levofloxacin and ofloxacin substituted into basic regimens for rifampicin (1 RCT, 59/75 [79%] with substituting levofloxacin *v* 56/69 [81%] with substituting ofloxacin; RR 0.97, 95% CI 0.82 to 1.14). [19] This RCT had unclear allocation concealment, and it was unclear whether assessors were blinded. [19]

**Harms:**

The review found no significant difference between regimens with and without quinolones, substituting for ethambutol, ethambutol plus pyrazinamide, or rifampicin, in the total number of adverse events (4 RCTs, 712 people, RR 1.17, 95% CI 0.96 to 1.43) or the number of serious adverse events (5 RCTs, 743 people, RR 0.98, 95% CI 0.56 to 1.72). [19] The review also subgrouped the results by quinolone substitutions for ethambutol, and found that the substitution with moxifloxacin and ofloxacin resulted in a significantly greater total number of adverse events compared with ethambutol (2 RCTs, 91/248 [37%] with quinolone *v* 67/244 [27%] with ethambutol; RR 1.34, 95% CI 1.05 to 1.72). These adverse events included fever, rash, gastrointestinal disturbance, hepatotoxicity, arthralgia, vision change, giddiness, and serious adverse events. It found no significant difference in total number of adverse effects between levofloxacin and ofloxacin (1 RCT: 11/65 [17%] with levofloxacin *v* 13/69 [19%] with ofloxacin; RR 0.78, 95% CI 0.37 to 1.62). [19] **Drug safety alert:** A drug safety alert has been issued on serious hepatic and bullous skin reactions associated with moxifloxacin (http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON014103&RevisionSelectionMethod=Latest).

**Comment:**

Quinolones are potentially important, and some of the newer quinolones have greater *in vitro* activity against *Mycobacteria tuberculosis* than ciprofloxacin; no difference in cure was demonstrated between moxifloxacin and ethambutol used in a four-drug regimen, and a greater total number of adverse events were found with moxifloxacin or ofloxacin substitution into standard regimen. Larger trials are awaited.

## OPTION ETHAMBUTOL IN PLACE OF RIFAMPICIN IN CONTINUATION PHASE IN CHEMOTHERAPY REGIMENS FOR 6 MONTHS OR MORE

**Cure rates**

*Ethambutol plus isoniazid regimens in the continuation phase compared with rifampicin plus isoniazid regimens*
Ethambutol plus isoniazid regimens in the continuation phase of chemotherapy regimens may be less effective than rifampicin plus isoniazid regimens in the continuation phase of chemotherapy regimens at reducing the proportion of people with bacteriological failure or relapse 12 months after treatment (low-quality evidence).

**For GRADE evaluation of interventions for tuberculosis in HIV-negative people, see table, p 16 .**

**Benefits:** One RCT (1355 people from 8 centres in Africa and Asia with newly diagnosed pulmonary tuberculosis, 10% with HIV infection) compared three short-course regimens. [22] One group received an initial 2 months of ethambutol plus isoniazid plus rifampicin plus pyrazinamide daily, followed by ethambutol plus isoniazid daily in a 6-month continuation phase. A second group received the same initial 2 months' treatment, followed by daily rifampicin plus isoniazid in a 4-month continuation phase. A third group received the same treatments as the first group, but were given initial drugs three-times weekly. The RCT found that the regimen containing ethambutol in the continuation phase was significantly less effective than the regimen containing rifampicin in reducing the proportion of people with bacteriological failure or relapse at 12 months after treatment (14% with ethambutol *v* 5% with rifampicin; adjusted OR 2.25, 95% CI 1.22 to 4.15).

**Harms:** Possible adverse effects were reported in 28/1355 (2%) people requiring modification or interruption of treatment for 7 days or more. [22] There were no deaths attributable to adverse effects.

**Comment:** None.

## OPTION CHEMOTHERAPY FOR LESS THAN 6 MONTHS

**Relapse rates**

*Short-course chemotherapy regimens (less than 6 months) compared with longer-course regimens* A short-course chemotherapy regimen of 3 months seems less effective than a longer 12 month course regimen at reducing relapse rates (moderate-quality evidence).

**For GRADE evaluation of interventions for tuberculosis in HIV-negative people, see table, p 16 .**

**Benefits:** We found one systematic review (search date 2004, 7 RCTs, 4100 people with newly diagnosed pulmonary tuberculosis) comparing a variety of shorter (minimum 2 months) and longer (maximum 12 months) drug regimens. [23] The RCTs included people in India, Hong Kong, Singapore, and Germany. The review found that a 3-month regimen significantly increased relapse rates compared with a 12-month regimen (5 RCTs: 71/1290 [6%] with 3 months *v* 39/1298 [3%] with 12 months; RR 3.03, 95% CI 2.08 to 4.40). However, one RCT found that people given a 2-month regimen were significantly less likely to change or discontinue drugs than those given a 12-month regimen (6/299 [2%] with 2 months *v* 17/299 [6%] with 12 months; RR 0.35, 95% CI 0.14 to 0.88). We found one subsequent small RCT (100 HIV-negative people, newly diagnosed with pulmonary tuberculosis bacteriologically confirmed, living in South-East Iran) comparing 4 months versus 6 months of treatment. All participants received isoniazid, rifampicin, pyrazinamide, and ethambutol daily for 2 months, followed by isoniazid plus rifampicin daily for 2 or 4 months. [24] All drugs were administered under direct supervision as a single dose. No drug resistance was reported in the area. The RCT found no significant difference in rates of treatment failure (defined as positive sputum smear at end of treatment: 0/33 [0%] with 4 months *v* 3/67 [5%] with 6 months; P greater than 0.05) or relapse at 5 years (defined as positive sputum smear during follow-up: 3/33 [9.1%] with 4 months *v* 6/67 [8.9%] with 6 months; P greater than 0.05). [24]

**Harms:** The review [23] found similar rates of adverse effects or toxicity requiring interruption, alteration, or complete cessation of treatment with both shorter and longer regimens with the exception of one RCT, [25] in which significantly fewer participants changed or discontinued treatment in the 2-month regimen than in the 12-month regimen. However, numbers were small (6/299 [2%] with 2 months *v* 17/299 [6%] with 12 months; RR 0.35, 95% CI 0.14 to 0.88). The subsequent RCT gave no information about harms. [24]

**Comment:** The treatments were given under optimal conditions. In clinical practice, adherence is likely to be lower, and so relapse rates associated with shorter regimens are likely to be higher than those in clinical trials. The authors of the subsequent RCT suggested that larger RCTs are needed to confirm these results. [24]

**QUESTION** **What are the effects of different drug regimens in people with multidrug-resistant tuberculosis without HIV infection?**

**OPTION** **DIFFERENT DRUG REGIMENS VERSUS EACH OTHER IN MULTIDRUG-RESISTANT TUBERCULOSIS**

**Cure rates**

*Sparfloxacin plus standard-drug regimens compared with ofloxacin plus standard-drug regimens* We don't know whether sparfloxacin added to standard-drug regimens is more effective than ofloxacin added to standard-drug regimens at increasing cure rates or reducing treatment failure in people with drug-resistant tuberculosis (low-quality evidence).

*High-dose isoniazid added to second-line therapy compared with normal-dose isoniazid or placebo added to second-line therapy* Adding high-dose isoniazid to second-line therapy may be more effective than adding normal-dose isoniazid or placebo to second-line therapy (results for both groups combined in analysis) at increasing sputum culture conversion at 6 months after initiation of treatment in people with multidrug resistant tuberculosis. We don't know whether adding high-dose isoniazid is more effective than adding normal-dose isoniazid to second-line therapy as the RCT did not compare these groups directly (low-quality evidence).

**Adverse effects**

*High-dose isoniazid added to second-line therapy compared with normal-dose isoniazid or placebo added to second-line therapy* Adding high-dose isoniazid to second-line therapy may increase the proportion of people with peripheral neuropathy compared with adding normal-dose isoniazid or placebo to second-line therapy (results for both groups combined in analysis) in people with multidrug-resistant tuberculosis. We don't know about hepatotoxicity or overall toxicity (low-quality evidence).

**For GRADE evaluation of interventions for tuberculosis in HIV-negative people, see table, p 16 .**

**Benefits:**

We found one systematic review (search date 2007) [19] and one subsequent RCT. [26] The review did not report data for most outcomes separately for people with or without HIV.

**Adding sparfloxacin versus adding ofloxacin to standard-drug regimens:**
The review, which included three RCTs, found no significant difference in cure or treatment-failure outcomes in people with drug-resistant tuberculosis between sparfloxacin and ofloxacin added to standard-drug regimens (cure: 2 RCTs, 184 people; 42/92 [46%] with sparfloxacin *v* 19/92 [21%] with ofloxacin; RR 2.10, 95% CI 0.77 to 5.71; treatment failure: 2 RCTs, 149 people; 7/71 [10%] with sparfloxacin *v* 12/78 [15%] with ofloxacin; RR 0.61, 95% CI 0.26 to 1.47). [19] The three included RCTs had weak methods (unclear details of randomisation, allocation concealment, and blinding).

**Adding high-dose isoniazid versus adding normal-dose isoniazid or placebo to second-line therapy:**
The subsequent RCT (134 HIV-negative people, with documented multidrug-resistant tuberculosis in India) compared high-dose adjuvant isoniazid (16–18 mg/kg) versus normal-dose isoniazid (5 mg/kg) or placebo added to otherwise the same second-line multidrug regimen consisting of kanamycin (15 mg/kg), levofloxacin (7.5–15 mg/kg), prothionamide (10–20 mg/kg), cycloserine (10–20 mg/kg) and para-aminosalicylic acid (150 mg/kg). Eleven people (8%) were lost to follow-up, and results were based on 123 people (92%) who completed the trial. [26] The RCT found higher cure rates (defined as culture negative at 6 months after initiation of treatment with 2 consecutive culture-negative reports repeated at 1-month intervals) in the high-dose isoniazid group (31/42 [74%] with high-dose isoniazid *v* 18/40 [45%] with normal-dose isoniazid *v* 20/41 [49%] with placebo). The RCT performed a regression analysis adjusting for possible confounders, such as age, sex, smoking, duration of disease, and drug resistance, among others. It found that adding high-dose isoniazid to second-line therapy significantly increased sputum culture conversion at 6 months compared with adding placebo to second-line therapy (RR 2.31, 95% CI 1.31 to 4.08; P = 0.004; regression analysis). It found that adding high-dose isoniazid significantly increased sputum culture conversion at 6 months compared with adding normal-dose isoniazid or placebo (results for normal-dose isoniazid and placebo combined in analysis: RR 2.37, 95% CI 1.46 to 3.84; P less than 0.001; regression analysis). However, it did not present a separate analysis of adding high-dose isoniazid versus adding normal-dose isoniazid alone, or adding normal-dose isoniazid versus adding placebo. [26] The RCT reported that it had no data on baseline grade of sputum positivity, although it suggested baseline differences between groups were likely to be minimal.

**Harms:**

**Adding sparfloxacin versus adding ofloxacin to standard-drug regimens:**
The review found no significant difference in total number of adverse effects between sparfloxacin and ofloxacin (3 RCTs: 23/123 [19%] with sparfloxacin *v* 24/130 [18%] with ofloxacin; RR 0.98, 95% CI 0.59 to 1.64). [19]

**Adding high-dose isoniazid versus adding normal-dose isoniazid or placebo to second-line therapy:**
The RCT found a significantly higher incidence of peripheral neuropathy in people treated with high-dose isoniazid added to second-line therapy compared with adding normal-dose isoniazid or placebo (results for normal-dose isoniazid and placebo combined in analysis: RR 9.64, 95% CI 1.13 to 82.5; P = 0.039; absolute numbers not reported, results presented graphically). [26] It found no significant difference between groups in hepatotoxicity (normal-dose isoniazid and placebo combined in analysis: RR 0.96, 95% CI 0.54 to 1.70; P = 0.904; absolute numbers not reported, results presented graphically) or in overall toxicity (normal-dose isoniazid and placebo combined in analysis: RR 1.71, 95% CI 0.66 to 4.44; P = 0.267; further details not reported). [26]

**Comment:** **Clinical guide:**
Current clinical practice in people with multidrug-resistant tuberculosis is to include at least three drugs to which the particular strain of tuberculosis is sensitive, using as many bactericidal agents as possible. People are observed directly and managed by a specialised clinician.

## QUESTION What are the effects of low-level laser therapy in people with tuberculosis without HIV infection?

### OPTION LASER THERAPY

**We found no direct information from RCTs about the effects of low-level laser therapy in the treatment of people with tuberculosis without HIV infection.**

**For GRADE evaluation of interventions for tuberculosis in HIV-negative people,** **see table, p 16** **.**

**Benefits:** **Low-level laser therapy:**
We found one systematic review (search date 2005, 1 RCT; [27] see comment below). [28] The RCT included in the review (130 people in India) was poorly reported, with no information on the generation of allocation sequence or concealment exclusion, or relevant outcomes. [27]

**Harms:** **Low-level laser therapy:**
The review provided no reliable data on harms. [28]

**Comment:** The review found 29 observational studies, mainly from Russia and India. [28] It found no reliable evidence for a beneficial effect of low-level laser therapy in people with tuberculosis, although a "range of positive effects" was reported.

## QUESTION Which interventions improve adherence to treatment in people with tuberculosis without HIV infection?

### OPTION DIRECT OBSERVATION TREATMENT (DOT) VERSUS SELF-ADMINISTERED TREATMENT

**Cure rates**
*Direct observation treatment compared with self-administered treatment* Direct observation treatment seems to be no more effective than self-administered treatment at increasing the proportion of people who are cured or at increasing the proportion of people who are cured or completed treatment (moderate quality evidence).

**For GRADE evaluation of interventions for tuberculosis in HIV-negative people,** **see table, p 16** **.**

**Benefits:** **Direct observation treatment versus self-administered treatment:**
We found one systematic review (search date 2007, 11 trials, 5609 people requiring treatment for clinically active tuberculosis or medication for preventing active disease — prophylaxis or preventive therapy — with positive smear tests with or without HIV). [29] It compared direct observation treatment (DOT) of people as they took their drugs (by a health worker, family member, or community volunteer) versus self-administered treatment. The systematic review found no significant difference between DOT and self-administration of treatment in the number of people cured (4 RCTs, 587/914 [64%] with DOT *v* 432/689 [62%] with self-administration; RR 1.02, 95% CI 0.86 to 1.21, random-effects model, P = 0.8; significant heterogeneity between RCTs in analysis), or who were cured or completed treatment (4 RCTs, 663/914 [73%] with DOT *v* 488/689 [71%] with self-administration; RR 1.06, 95% CI 1.00 to 1.13, P = 0.07). Stratifying the location of DOT by home or clinic suggests a possible small effect with home-based DOT on the number of people cured (at home: 3 RCTs, 507/737 [68%] with DOT *v* 401/628 [64%] with self-administration; RR 1.10, 95% CI 1.02 to 1.18, P = 0.01). [29] The review found no significant difference in preventive treatment completion rates for intravenous drug users between twice-weekly clinic-based DOT and daily self-administration

(1 RCT, 80/99 [80%] with DOT *v* 79/100 [79%] with self-administration; RR 1.02, 95% CI 0.89 to 1.18).

**Harms:** The review did not report on harms. [29] Potential harms include reduced cooperation between person and doctor, removal of individual responsibility, detriment to long-term sustainability of antituberculosis programmes, and increased burden on health services to the detriment of care for other diseases. None of these has been adequately investigated in RCTs.

**Comment:** Numerous observational studies have evaluated interventions described as DOT, but all were packages of interventions that included specific investment in antituberculosis programmes, such as strengthened drug supplies, improved microscopy services, and numerous incentives, sanctions, and other co-interventions that were likely to influence adherence. [29] [30] [31]

## OPTION SUPPORT MECHANISMS FOR DIRECTLY OBSERVED TREATMENT

**Cure rates**

*Clinic-based support compared with family-member-based support* We don't know whether directly observed treatment (DOT) at a clinic by a health worker is more effective than DOT at home by a family member or community-health volunteer at improving cure or sputum conversion at 2 months (low-quality evidence).

*Community-based health-worker support compared with family-member support* We don't know whether DOT provided by a family member is more effective than DOT provided by a community health worker at improving the combined outcome of cure and treatment completion (low-quality evidence).

*Complex support interventions compared with usual treatment* A complex intervention (including: counselling through improved communication between health personnel, such as a nurse and patients; decentralisation of treatment; choice of DOT supporter by patient; and reinforcement of supervision activities) may be more effective than the usual DOT programme at increasing treatment success (defined as the sum of those cured or completing the 8-month treatment course, but missing sputum smear results) (low-quality evidence).

**Treatment compliance rates**

*Participant-chosen site compared with designated site* We don't know whether a participant-chosen site for DOT is more effective than a designated site for DOT at increasing treatment compliance rates in drug users with positive tuberculin skin tests (low-quality evidence).

**For GRADE evaluation of interventions for tuberculosis in HIV-negative people, see table, p 16 .**

**Benefits:**

**Participant-chosen site versus designated site:**
We found one systematic review (search date 2007), [29] which included one RCT (163 drug users with positive tuberculin skin test) [32] in people receiving prophylaxis. The review found no significant difference in the proportion of people completing treatment between those allowed to choose their directly observed treatment (DOT) location and those receiving DOT at a community clinic (1 RCT, 28/53 [53%] with own location *v* 33/55 [60%] with treatment centre; RR 0.88, 95% CI 0.63 to 1.23). [29]

**Clinic-based support versus family-member support:**
We found one systematic review (search date 2007), [29] which included two RCTs. It found no significant difference in clinical outcomes between DOT at a clinic by a health worker versus DOT by a family member at home (cure or completion of treatment: 1 RCT, 587 people; RR 1.03, 95% CI 0.96 to 1.10) or between clinic-based DOT and home-based DOT by a community health volunteer (1 cluster-randomised trial, 18 clusters, 522 people: sputum conversion at 2 months; OR 0.62, 95% CI 0.23 to 1.71; cure at the end of treatment; OR 1.58, 95% CI 0.32 to 7.88; original trial authors adjusted for design [cluster] effects).

**Community-based health worker support versus family-member support:**
We found one systematic review (search date 2007), [29] which included two RCTs. The review found no significant difference between DOT provided by a family member versus DOT provided by a community health worker in cure or treatment completion (1 RCT, 440/662 [66%] with family member *v* 453/664 [68%] with health worker; RR 0.97, 95% CI 0.90 to 1.05; 1 cluster-randomised trial,10 clusters, 907 people; 85% with community health worker *v* 89% with family member; OR 0.67, 95% CI 0.41 to 1.10; original trial authors [33] adjusted for design [cluster] effects). [29]

**Complex support interventions versus usual treatment:**
We found two RCTs. [34] [35] The first cluster RCT (16 clusters, 1522 people in Senegal) compared a complex intervention consisting of: counselling through improved communication between health personnel and patients; decentralisation of treatment; choice of DOT supporter by patient; and reinforcement of supervision activities, involving a nurse, versus the usual DOT programme. [34] The

RCT found a significantly larger proportion of people had treatment success in the intervention group compared with the control group (treatment success defined as sum of people cured or who completed the 8-month treatment course, but missing sputum smear results: 682/778 [88%] with intervention *v* 563/744 [76%] with control; adjusted RR 1.18, 95% CI 1.03 to 1.34). It also found a significantly smaller proportion of people defaulted from treatment in the intervention group (43/778 [6%] with intervention *v* 125/744 [17%] with control; adjusted RR 0.43, 95% CI 0.21 to 0.89). [34] The second small RCT (96 adults with open tuberculosis in Taiwan) compared DOT case management (in-hospital education, DOT in the first 2 months and 1 home visit/week) versus self-administration with traditional case management (in-hospital education and 1 home visit/month) versus a control group (self-administration without case management). [35] The RCT found that, compared with self-administration plus traditional case management and conventional management, DOT plus nurse case management had higher rates of treatment completion (31/32 [97%] with DOT plus case management *v* 22/32 [69%] with traditional case management *v* 22/32 [69%] with control; P = 0.007), sputum smear conversion at 2 months (28/32 [88%] with DOT plus case management *v* 24/32 [75%] with traditional case management *v* 17/32 [53%] with control; P = 0.008), and sputum smear conversion at completion at 6 months (30/32 [94%] *with DOT plus case management v* 22/32 [69%] with traditional case management *v* 22/32 [69%] with control; P = 0.023). [35] The RCT only reported between-group comparisons, and did not compare one group directly with another statistically. [35]

**Harms:** The review [29] and RCTs [34] [35] did not report harms. Potential harms include: reduced cooperation between person and doctor; removal of individual responsibility; detriment to long-term sustainability of antituberculosis programmes; and increased burden on health services to the detriment of care for other diseases. None of these has been adequately investigated in RCTs.

**Comment:** Numerous observational studies have evaluated interventions described as DOT, but all were packages of interventions that included specific investment in antituberculosis programmes, such as strengthened drug supplies, improved microscopy services, and numerous incentives, sanctions, and other co-interventions that were likely to influence adherence. [30] [36]

## GLOSSARY

**High-quality evidence** Further research is very unlikely to change our confidence in the estimate of effect.
**Low-quality evidence** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Moderate-quality evidence** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Very low-quality evidence** Any estimate of effect is very uncertain.

## SUBSTANTIVE CHANGES

**Different drug regimens versus each other in multidrug-resistant tuberculosis** Search date of one already included systematic review updated (to 2007). [19] The systematic review still included the same pooled analysis of three included RCTs that was previously reported in this review. No new data added from the review. One subsequent RCT (134 people) added comparing adding high-dose isoniazid versus adding normal-dose isoniazid or placebo to second-line therapy. [26] Categorisation unchanged (Unknown effectiveness).
**Direct observation treatment (DOT) versus self-administered treatment** One already reported systematic review updated (search date 2007). [29] New data added to benefits and harms sections, but overall conclusions of the updated review remain the same. Categorisation unchanged (Unlikely to be beneficial).
**Regimens containing quinolones** One already reported systematic review updated (search date 2007) [19] to now include one further RCT, which was already reported in this review. Reporting in benefits and harms enhanced. Two other systematic reviews added (search dates 2006), which were narrative in character, and did not pool data. [20] [21] No further data added from these two reviews. Overall conclusions similar to before. Categorisation unchanged (Unknown effectiveness).
**Rifampicin plus isoniazid** Two subsequent RCTs added [10] [11] to the existing reporting of one systematic review. One of the subsequent RCTs (470 people) was quasi-randomised, and the other RCT was small (105 people). Categorisation unchanged (Trade-off between benefits and harms).
**Support mechanisms for directly observed treatment** One systematic review (search date 2007) [29] and two RCTs added [34] [35] including a variety of support mechanisms for DOT such as different sites, different support personnel (health workers or family members), or complex support interventions. Overall conclusions unchanged, with no clear differences in effectiveness between different support mechanisms. Categorisation unchanged (Unknown effectiveness).

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## Disclaimer

**TABLE** **GRADE evaluation of interventions for tuberculosis**

| Important outcomes | Develpment of active tuberculosis, cure rates, relapse, treatment compliance rates, adverse effects | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Number of studies (participants)** | **Outcome** | **Comparison** | **Type of evidence** | **Quality** | **Consistency** | **Directness** | **Effect size** | **GRADE** | **Comment** |
| What are the effects of interventions to prevent tuberculosis in people without HIV infection at high risk of developing tuberculosis? | | | | | | | | | |
| 11 (73,375) [5] | Development of active TB | Isoniazid *v* placebo | 4 | 0 | 0 | 0 | 0 | High | |
| 2 (199) [6] [7] | Development of active TB | Isoniazid *v* no isoniazid in people undergoing renal transplant | 4 | –3 | 0 | 0 | 0 | Very low | Quality points deducted for sparse data and methodological flaws (uncertainty about allocation concealment, unclear randomisation) |
| 1 (20,874) [5] | Adverse effects | Isoniazid *v* placebo | 4 | 0 | 0 | 0 | +1 | High | Effect-size point added for odds ratio greater than 5 |
| 1 (630) [9] [10] | Development of active TB | Rifampicin plus isoniazid *v* isoniazid alone | 4 | –2 | 0 | –1 | 0 | Very low | Quality points deducted for quasi-randomised RCT, and baseline differences. Directness point deducted for unclear population (HIV status) |
| What are the effects of different drug regimens in people with newly diagnosed pulmonary tuberculosis without HIV infection? | | | | | | | | | |
| 2 (1295) [13] [14] | Relapse rates | Shorter (6 months) *v* longer regimens (8–9 months) | 4 | –1 | 0 | 0 | 0 | Moderate | Quality point deducted for incomplete reporting of results |
| 1 (444) [14] | Cure rates | Pyrazinamide-containing regimens *v* regimens not containing pyrazinamide | 4 | –1 | 0 | 0 | 0 | Moderate | Quality point deducted for incomplete reporting of results |
| 2 (1330) [15] [16] | Relapse rates | Pyrazinamide-containing regimens *v* regimens not containing pyrazinamide | 4 | –1 | 0 | –1 | 0 | Low | Quality point deducted for incomplete reporting of results. Directness point deducted for inconsistent results at different lengths of follow-up |
| 1 (851) [13] | Relapse rates | Rifampicin plus isoniazid *v* isoniazid | 4 | –1 | 0 | 0 | 0 | Moderate | Quality point deducted for incomplete reporting of results |
| 2 (605) [17] [18] | Cure rates | Intermittent chemotherapy for 6 months or longer *v* daily therapy | 4 | –1 | 0 | –1 | 0 | Low | Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of different disease states |
| 1 (378) [17] | Relapse rates | Intermittent chemotherapy for 6 months or longer *v* daily therapy | 4 | 0 | 0 | 0 | –2 | Low | Directness points deducted for short follow-up and small number of events (6 in total), suggesting it may have been too small to detect a clinically important difference |
| 4 (489) [19] | Cure rates | Ciprofloxacin-substituted regimens *v* standard regimens | 4 | –1 | 0 | –1 | 0 | Low | Quality point deducted for weak methods. Directness point deducted for inclusion of HIV-positive people in analysis |
| 3 (412) [19] | Cure rates | Quinolone-substituted regimens *v* standard regimens | 4 | –1 | 0 | –1 | 0 | Low | Quality point deducted for weak methods. Directness point deducted for inclusion of HIV-positive people in analysis |

| Important outcomes | Develpment of active tuberculosis, cure rates, relapse, treatment compliance rates, adverse effects | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Number of studies (participants) | Outcome | Comparison | Type of evidence | Quality | Consistency | Directness | Effect size | GRADE | Comment |
| 3 (384) [19] | Relapse rates | Quinolone-substituted regimens *v* standard regimens | 4 | –2 | 0 | –2 | +2 | Low | Quality points deducted for weak methods and unclear treatment duration. Directness points deducted for inclusion of HIV-positive people in analysis and small number of events (11 in total). Effect-size points added for RR above 5 |
| 1 (144) [19] | Cure rates | Levofoxacin plus standard-drug regimen *v* standard-drug regimen alone | 4 | –2 | 0 | 0 | 0 | Low | Quality points deducted for sparse data and weak methods |
| 1 (144) [19] | Cure rates | Levofoxacin plus standard-drug regimen *v* ofloxacin plus standard-drug regimen | 4 | –2 | 0 | 0 | 0 | Low | Quality points deducted for sparse data and weak methods |
| 1 (1355) [22] | Cure rates | Ethambutol-containing regimens *v* rifampicin-containing regimens | 4 | –1 | 0 | –1 | 0 | Low | Quality point deducted for incomplete reporting of results. Directness point deducted for composite outcome |
| 5 (2588) [23] | Relapse rates | Short-course chemotherapy regimens (less than 6 months) *v* longer-course regimens | 4 | 0 | 0 | –1 | 0 | Moderate | Directness point deducted as treatments given under optimal conditions affecting generalisability (adherence likely to be lower in clinical practice) |
| What are the effects of different drug regimens in people with multidrug-resistant tuberculosis without HIV infection? | | | | | | | | | |
| 2 (unclear, at least 184 people) [19] | Cure rates | Sparfloxacin plus standard-drug regimens *v* ofloxacin plus standard-drug regimens | 4 | –2 | 0 | 0 | 0 | Low | Quality points deducted for weak methods (unclear allocation concealment, unclear blinding) |
| 1 (134) [26] | Cure rates | Adding high-dose isoniazid *v* adding normal-dose isoniazid or placebo to second-line therapy | 4 | –1 | 0 | –1 | 0 | Low | Quality point deducted for sparse data, and lack of baseline data on sputum positivity. Directness point deducted for combined comparison group (normal-dose isoniazid and placebo groups combined in analysis) |
| 1 (134) [26] | Adverse effects | Adding high-dose isoniazid *v* adding normal-dose isoniazid or placebo to second-line therapy | 4 | –1 | 0 | –1 | 0 | Low | Quality point deducted for sparse data. Directness point deducted for combined comparison group (normal-dose isoniazid and placebo groups combined in analysis) |
| Which interventions improve adherence to treatment in people with tuberculosis without HIV infection? | | | | | | | | | |
| 4 (1603) [29] | Cure rates | Direct observation treatment *v* self-administered treatment | 4 | 0 | 0 | –1 | 0 | Moderate | Directness point deducted for heterogeneity among RCTs |
| 1 (163) [29] | Treatment compliance rates | Participant-chosen site *v* designated site | 4 | –1 | 0 | –1 | 0 | Low | Quality point deducted for sparse data. Directness point deducted for restricted population (drug users) |
| 2 (1109) [29] | Cure rates | Clinic-based support *v* family-member support | 4 | –1 | 0 | –1 | 0 | Low | Quality point deducted for cluster randomised trial. Directness point deducted for composite outcome in 1 RCT |
| 2 (2233) [29] | Cure rates | Community-based health-worker support *v* family-member-based support | 4 | –1 | 0 | –1 | 0 | Low | Quality point deducted for cluster randomised trial. Directness point deducted for composite outcome (cure or completion of treatment) |

| Important out-comes | Develpment of active tuberculosis, cure rates, relapse, treatment compliance rates, adverse effects | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Number of studies (participants)** | **Outcome** | **Comparison** | **Type of evi-dence** | **Quality** | **Consis-tency** | **Direct-ness** | **Effect size** | **GRADE** | **Comment** |
| 2 (1628) [34] [35] | Cure rates | Complex support interventions *v* usual treatment | 4 | –1 | 0 | –1 | 0 | Low | Quality point deducted for cluster randomised trial. Directness point deducted for composite outcome |

Type of evidence: 4 = RCT.
Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.