ABSTRACT

INTRODUCTION: In people infected with both HIV and Mycobacterium tuberculosis, the annual risk of developing active tuberculosis is 5% to 10%—more than 10 times the rate for HIV-negative people with M tuberculosis infection. Untreated, mortality from tuberculosis in people with HIV is likely to be high, and over 5% of people relapse after successful treatment.

METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of first-line treatments for tuberculosis in HIV-positive people? What are the effects of second-line treatments for tuberculosis in HIV-positive people? We searched: Medline, Embase, The Cochrane Library, and other important databases up to July 2009 (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 23 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: adjuvant immunotherapy (with corticosteroids, or Mycobacterium vaccae); antimycobacterial treatment combinations; conventional antituberculous treatment (short course, long course, including rifabutin [3 or 5 months], quinolones, or thiacetazone); directly observed therapy (short course); highly active antiretroviral treatment (early initiation or delayed initiation); rifampicin (3 months or less); secondary prophylaxis with antituberculous treatment; and unsupervised treatment.

QUESTIONS

What are the effects of first-line treatments for tuberculosis in HIV-positive people? .......................... 4
What are the effects of second-line treatments for tuberculosis in HIV-positive people? ..................... 15

INTERVENTIONS

FIRST-LINE TREATMENTS

Beneficial

Conventional antituberculous treatment* .............. 4

Unknown effectiveness

Adjuvant immunotherapy with corticosteroids .... 5
Antituberculous treatment containing quinolones (compared with alternative regimens) ................. 8
Antituberculous treatment containing rifabutin (compared with alternative regimens) ................. 9
Directly observed therapy, short course (compared with unsupervised treatment) ......................... 10
Early initiation of highly active antiretroviral treatment (compared with delayed initiation of highly active antiretroviral treatment) ......................... 11
Longer courses of antituberculous treatment (compared with conventional short-course treatment) .... 11

Unlikely to be beneficial

Adjuvant immunotherapy with Mycobacterium vaccae ............................................................. 12

Likely to be ineffective or harmful

Antituberculous treatment containing 3 months or less of rifampicin (compared with rifampicin for 5 months or more) .................................................... 13

SECOND-LINE TREATMENTS

Unknown effectiveness

Antimycobacterial treatment combinations (comparative benefits of different regimens unclear) ........ 15
Secondary prophylaxis with antituberculous drugs versus placebo after successful completion of conventional antituberculous treatment ................................. 15

Covered elsewhere in Clinical Evidence

Prevention of tuberculosis in people with HIV (see HIV: prevention of opportunistic infections)
Treatment of HIV infection (see HIV infection)
Tuberculosis in people who are not infected with HIV (see Tuberculosis)

To be covered in future updates

Daily antituberculous treatment compared with less-frequent antituberculous treatment

Footnote

*Categorisation based on consensus.

Key points

- Tuberculosis is a major opportunistic infection and cause of death in people with HIV, and often presents as non-pulmonary disease.

In people infected with both HIV and Mycobacterium tuberculosis, the annual risk of developing active tuberculosis is 5% to 10%, more than 10 times the rate for people with Mycobacterium tuberculosis infection but without HIV.

Untreated, mortality from tuberculosis in people with HIV is likely to be very high, and over 5% of people relapse after successful treatment.
HIV: treating tuberculosis

- Conventional antituberculous treatment (2 months of rifampicin plus isoniazid plus pyrazinamide, with or without ethambutol, followed by 4–7 months of rifampicin plus isoniazid) is considered beneficial in people with HIV and is standard treatment. Placebo-controlled RCTs of active tuberculosis would therefore be considered unethical and are unlikely to be performed.

  We don’t know whether antituberculous treatment regimens containing rifabutin or quinolones are more effective compared with conventional regimens.

  Regimens containing thiacetazone may be less effective at producing negative sputum cultures compared with conventional regimens and may have more adverse effects, including fatal mucocutaneous reactions.

  We don’t know whether regimens lasting longer than 6 months are more effective than shorter regimens, but regimens that use rifampicin for at least 5 months are less likely to lead to recurrence compared with regimens that use 3 months or less of rifampicin.

- Adjuvant immunotherapy with Mycobacterium vaccae does not increase cure rates or survival compared with placebo vaccination.

- Adjuvant immunotherapy with corticosteroids may not increase survival or decrease tuberculosis recurrence in HIV-positive people with pulmonary or pleural tuberculosis compared with placebo. RCTs found that corticosteroids caused an increased risk of high blood glucose and high blood pressure.

  We don’t know whether adjuvant immunotherapy with corticosteroids increases survival in HIV-positive people with tuberculous meningitis or tuberculous pericarditis compared with placebo.

  We don’t know whether early initiation of highly active antiretroviral treatment (HAART) improves tuberculosis cure rates compared with delayed initiation of HAART, and there is a risk of interaction with antituberculous drugs.

  We don’t know whether directly observed therapy improves cure rates compared with unsupervised treatment in people with HIV.

- We don’t know which antimycobacterial treatment combinations are most effective in people with HIV who have failed first-line treatment.

- Secondary prophylaxis with antituberculous drugs after successful completion of conventional antituberculous treatment reduces the risk of tuberculosis recurrence in people with HIV, who are not receiving HAART, compared with placebo.

  We don’t know whether secondary prophylaxis with antituberculous drugs reduces mortality.

### Clinical context

**DEFINITION**

HIV infection kills more people than any other infectious disease.\(^1\) Infection with Mycobacterium tuberculosis is among the most important HIV-related opportunistic infections, in both resource-rich and resource-poor countries. The WHO estimates that tuberculosis is the cause of death in 13% of people who die from AIDS.\(^1\) HIV infection compromises the host's immune defences and can lead to failure to control latent M tuberculosis infection, with the subsequent development of active (i.e., symptomatic) tuberculosis. The HIV pandemic has been a major contributing factor in the spread of tuberculosis in many countries. Tuberculosis most commonly affects the lungs, but can also affect many other organs, such as lymph nodes, kidneys, liver, GI tract, and the central nervous system. In a study of 132 HIV-positive people with tuberculosis in San Francisco, 50 (38%) had solely pulmonary disease, 40 (30%) had solely extrapulmonary disease, and 42 (32%) had both pulmonary and extrapulmonary disease.\(^2\) In Africa and South America, 40% to 80% of HIV-positive people presenting with tuberculosis have pulmonary disease.\(^3\) The specific symptoms of tuberculosis depend on the site of infection. Pulmonary disease characteristically presents with cough, haemoptysis, chest pain, and systemic symptoms, such as weight loss and night sweats.

This review deals with the treatment of active tuberculosis (both pulmonary and extrapulmonary) in people with HIV. Prevention of tuberculosis in people with HIV is covered in a separate review (see review on HIV: prevention of opportunistic infections).

**INCIDENCE/PREVALENCE**

About one third of the world's population has latent Mycobacterium tuberculosis infection.\(^4\) Each year about 741,000 cases of active tuberculosis occur in people who are HIV positive, resulting in 248,000 deaths.\(^4\) HIV infection has been a major factor in the increase in the number of cases of tuberculosis occurring worldwide.\(^5\) \(^6\) Most people infected with HIV live in sub-Saharan Africa. In several countries of this region, over 40% of people who develop tuberculosis are infected with HIV.\(^5\) \(^7\) \(^8\) \(^9\) Tuberculosis is the most frequent cause of death in people infected with HIV in the Democratic Republic of Congo.\(^10\) Reliable data on cause of death in people in other sub-Saharan African countries are rare, but tuberculosis is probably a frequent cause of death among people with HIV.

**AETIOLOGY/RISK FACTORS**

Risk factors for tuberculosis include social factors such as poverty, overcrowding, and homelessness, and medical factors such as corticosteroid treatment. In people co-infected with HIV and Mycobac-
**METHODS**

Without treatment, active tuberculosis would probably be fatal in a person infected with HIV. For ethical reasons, no studies have examined the prognosis of active tuberculosis without treatment in people infected with HIV. In one study in the era before highly active antiretroviral treatment in the USA, the median survival of HIV-positive people treated for tuberculosis was 16 months. However, only 13/99 (13%) of the deaths were attributed to tuberculosis. The other common causes of death were *Pneumocystis carinii* pneumonia (24%), bacterial pneumonia (14%), wasting syndrome (9%), and Kaposi's sarcoma (9%). In Malawi, 47% of HIV-positive people with tuberculosis died during 32 months' follow-up. The most common causes of death among people with HIV in sub-Saharan Africa are wasting syndrome, chronic diarrhoea, cryptococcal meningitis, and chest infection. The differences in cause of death between sub-Saharan Africa and the USA may be attributable to the availability of diagnostic tests as much as to genuine differences in the underlying causes. Recurrence of tuberculosis after completion of treatment is more common among people with HIV than among HIV-negative people. In one study in New York, 83/1530 (5.4%) people with HIV who completed tuberculosis treatment had a recurrence of disease, compared with 21/1413 (1.5%) HIV-negative people who completed tuberculosis treatment. One cohort study in 326 South African mineworkers successfully treated for tuberculosis found a higher recurrence rate of tuberculosis in HIV-positive people, with 16.0 cases per 100 person-years of follow-up compared with 6.4 cases per 100 person-years of follow-up among HIV-negative people. In a randomised trial in Haiti, the tuberculosis recurrence rate among HIV-positive people not receiving post-treatment isoniazid was 7.8 cases per 100 person-years of follow-up compared with 0.4 per 100 person-years of follow-up in HIV-negative people.

**PROGNOSIS**

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**AIMS OF INTERVENTION**

To cure tuberculosis; prevent relapse; and to minimise adverse effects of treatment.

**OUTCOMES**

**Primary outcomes:** Mortality; quality of life; and adverse effects of treatment. **Secondary outcomes:** Presence of *Mycobacterium tuberculosis* in sputum during treatment or at the end of treatment (culture or smear test); recurrence of tuberculosis; and respiratory failure.

**METHODS**

Clinical Evidence search and appraisal July 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to July 2009, Embase 1980 to July 2009, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2009, Issue 3 (1966 to date of issue). An additional search was carried out of the NHS Centre for Reviews and Dissemination (CRD) — for the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews, RCTs, and prospective comparative cohort studies in any language. Minimum population size was 20 for RCTs and 50 for prospective cohort studies. Studies could be open or blinded, and there was no minimum length of follow-up, or maximum loss to follow-up required to include studies. We included systematic reviews and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. We also searched for prospective or retrospective comparative cohort studies or case control studies of any size for adverse effects of treatments. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. We placed emphasis on systematic reviews of RCTs and large RCTs. Placebo-controlled trials of treatment of active tuberculosis would be considered unethical and have therefore not been performed. We considered smaller RCTs and systematic reviews of non-controlled studies if large RCTs were not available. Prospective cohort studies were only included in the review when there were no adequately sized RCTs available. Some of the studies of the treatment of tuberculosis in people with HIV were difficult to interpret because many participants

**REFERENCES**

1. Ziehl–Neelsen staining of sputum or other specimens is used to detect acid-fast bacilli (the smear test). Acid-fast bacilli are most likely to be *Mycobacterium tuberculosis*, but in a person with HIV they could be other species of mycobacteria. Culture of *M tuberculosis* from sputum or other specimens is the definitive test to confirm active tuberculosis. However, *M tuberculosis* culture is frequently not available in resource-poor settings.

2. Without treatment, active tuberculosis would probably be fatal in a person infected with HIV. For ethical reasons, no studies have examined the prognosis of active tuberculosis without treatment in people infected with HIV. In one study in the era before highly active antiretroviral treatment in the USA, the median survival of HIV-positive people treated for tuberculosis was 16 months. However, only 13/99 (13%) of the deaths were attributed to tuberculosis. The other common causes of death were *Pneumocystis carinii* pneumonia (24%), bacterial pneumonia (14%), wasting syndrome (9%), and Kaposi's sarcoma (9%). In Malawi, 47% of HIV-positive people with tuberculosis died during 32 months' follow-up. The most common causes of death among people with HIV in sub-Saharan Africa are wasting syndrome, chronic diarrhoea, cryptococcal meningitis, and chest infection. The differences in cause of death between sub-Saharan Africa and the USA may be attributable to the availability of diagnostic tests as much as to genuine differences in the underlying causes. Recurrence of tuberculosis after completion of treatment is more common among people with HIV than among HIV-negative people. In one study in New York, 83/1530 (5.4%) people with HIV who completed tuberculosis treatment had a recurrence of disease, compared with 21/1413 (1.5%) HIV-negative people who completed tuberculosis treatment. One cohort study in 326 South African mineworkers successfully treated for tuberculosis found a higher recurrence rate of tuberculosis in HIV-positive people, with 16.0 cases per 100 person-years of follow-up compared with 6.4 cases per 100 person-years of follow-up among HIV-negative people. In a randomised trial in Haiti, the tuberculosis recurrence rate among HIV-positive people not receiving post-treatment isoniazid was 7.8 cases per 100 person-years of follow-up compared with 0.4 per 100 person-years of follow-up in HIV-negative people.
were lost to follow-up or did not have sputum examined for *M tuberculosis*. Some authors presented true cure rates based on the proportion of all people randomised who had negative sputum examinations at the end of treatment, whereas other authors presented negative sputum rates based only on those participants who were available for sputum examination at the end of treatment. This may introduce bias, as people who were available for sputum examination may not be comparable to people who were not available. This review describes the treatment of tuberculosis in HIV-positive people only. Where studies included both HIV-positive and HIV-negative people, results for HIV-positive people are presented if subgroup analysis was pre-specified. Studies performing post hoc subgroup analyses are described in the comments sections where appropriate. Although some studies included teenagers, there were few data from this group, and most studies excluded pregnant women and children; it was therefore hard to draw conclusions about the effects of treatment in these groups. In most studies, people were not receiving highly active antiretroviral treatment (HAART) (or there is no comment on this); it was therefore hard to draw conclusions about the effects of treatment in people who were receiving HAART. The conventional treatment for tuberculosis is generally regarded as 2 months of rifampicin plus isoniazid plus pyrazinamide (plus ethambutol in areas where drug-resistant tuberculosis is likely) followed by 4 to 7 months of rifampicin plus isoniazid. Most studies used this regimen as their comparator. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 19). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com). 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).

**QUESTION**

What are the effects of first-line treatments for tuberculosis in HIV-positive people?

**OPTION**

**CONVENTIONAL ANTITUBERCULOUS TREATMENT**

**Mortality**

*Compared with regimens containing rifabutin*  
We don’t know whether conventional antituberculous regimens are more effective than regimens containing rifabutin at reducing mortality in people with HIV and pulmonary tuberculosis (low-quality evidence).

*Compared with regimens containing thiacetazone*  
We don’t know whether conventional regimens are more effective than regimens containing thiacetazone at improving survival at 1 year in people with HIV and pulmonary tuberculosis (low-quality evidence).

*Compared with regimens containing quinolones*  
We don’t know whether conventional antituberculous regimens are more effective than regimens containing quinolones at reducing mortality during 8 weeks’ treatment in people with pulmonary tuberculosis and HIV-associated immunosuppression (very low-quality evidence).

**Presence of Mycobacterium tuberculosis in sputum**

*Compared with regimens containing rifabutin*  
Conventional regimens may be less effective than regimens containing rifabutin at reducing time to sputum smear conversion in people with HIV and pulmonary tuberculosis, but we don’t know about negative sputum culture for *M tuberculosis* at 6 months (low-quality evidence).

*Compared with regimens containing thiacetazone*  
Conventional regimens may be more effective than regimens containing thiacetazone at increasing the proportion of people with negative sputum culture for *M tuberculosis* at 2 months in people with HIV and pulmonary tuberculosis (low-quality evidence).

*Compared with regimens containing quinolones*  
We don’t know whether conventional antituberculous regimens are more effective than regimens containing quinolones after 8 weeks’ initial treatment at increasing the proportion of people with negative cultures for *M tuberculosis* in people with pulmonary tuberculosis and HIV-associated immunosuppression (low-quality evidence).

**Adverse effects**

*Compared with regimens containing thiacetazone*  
Conventional antituberculous regimens are associated with decreased overall adverse effects (high-quality evidence).

**Note**

We found no direct information about whether conventional antituberculous treatment (2 months of rifampicin plus isoniazid plus pyrazinamide [plus ethambutol in areas where drug-resistant tuberculosis is likely] followed by 4 to 7 months of rifampicin plus isoniazid) was more effective than regimens containing rifampicin plus isoniazid at reducing mortality in people with HIV and pulmonary tuberculosis (low-quality evidence).
months of rifampicin plus isoniazid) is better than no active treatment for people with tuberculosis and HIV. However, there is consensus that this conventional regimen is effective for treatment in people with HIV.

For GRADE evaluation of interventions for tuberculosis in people with HIV, see table, p 19.

Benefits:  
Conventional antituberculous treatment versus regimens containing rifabutin:  
See benefits of antituberculous treatment containing rifabutin, p 9.

Conventional antituberculous treatment versus regimens containing thiacetazone:  
See benefits of antituberculous treatment containing thiacetazone, p 14.

Conventional antituberculous treatment versus regimens containing quinolones:  
See benefits of antituberculous treatment containing quinolones, p 8.

Harms:  
Many of the published RCTs did not report on the frequency of adverse effects of conventional antituberculous treatment in detail. Recognition of the adverse effects of treatment is dependent upon the method of follow-up, and there may be considerable under-reporting in some studies. One cohort study (265 HIV-positive and 26 HIV-negative adults with culture-confirmed pulmonary tuberculosis in Uganda) found that adverse effects occurred in over one third of HIV-positive people (98/265 [37%]) who received conventional antituberculous treatment (including ethambutol). The most common adverse effects were arthralgia, peripheral neuropathy, skin rash, hepatitis, and gastrointestinal intolerance (arthralgia: 59/265 [22.3%]; peripheral neuropathy: 18/265 [6.8%]; skin rash: 7/265 [2.6%]; hepatitis: 2/265 [0.8%]; gastrointestinal intolerance: 2/265 [0.8%]). Adverse effects requiring termination of treatment were rare (2/265 [0.8%]). Other RCTs have reported a higher rate of serious adverse effects. One RCT conducted in the USA found that 17.2% of people receiving conventional antituberculous treatment experienced an adverse effect that was potentially life threatening or that required termination of treatment (see harms of antituberculous treatment containing quinolones, p 8).

Conventional antituberculous treatment versus regimens containing rifabutin:  
See harms of antituberculous treatment containing rifabutin, p 9.

Conventional antituberculous treatment versus regimens containing thiacetazone:  
See harms of antituberculous treatment containing thiacetazone, p 14.

Conventional antituberculous treatment versus regimens containing quinolones:  
See harms of antituberculous treatment containing quinolones, p 8.

Comment:  
Clinical guide:  
Conventional treatment for tuberculosis is generally regarded as 2 months of rifampicin plus isoniazid plus pyrazinamide (plus ethambutol in areas where drug-resistant tuberculosis is likely) followed by 4 to 7 months of rifampicin plus isoniazid. There is consensus that this conventional regimen is effective for the treatment of tuberculosis in people with HIV. RCTs comparing conventional treatment for tuberculosis versus placebo would be considered unethical because of the high risk of mortality if tuberculosis is not treated in HIV-positive people.

OPTION ADJUVANT IMMUNOTHERAPY WITH CORTICOSTEROIDS

Mortality

Antituberculous treatment plus adjuvant corticosteroids compared with antituberculous treatment plus placebo in people with pulmonary tuberculosis  
We don't know whether antituberculous treatment plus adjuvant corticosteroids is more effective than antituberculous treatment plus placebo at reducing mortality at 36 months’ follow-up in people with HIV and pulmonary tuberculosis (low-quality evidence).

Antituberculous treatment plus adjuvant corticosteroids compared with antituberculous treatment plus placebo in people with pleural tuberculosis  
Antituberculous treatment plus adjuvant corticosteroids seems no more effective than antituberculous treatment plus placebo at reducing mortality in people with HIV and pleural tuberculosis (moderate-quality evidence).

Antituberculous treatment plus adjuvant corticosteroids compared with antituberculous treatment plus placebo in people with tuberculous meningitis  
We don't know whether antituberculous treatment plus adjuvant corticosteroids is more effective than antituberculous treatment plus placebo at reducing mortality or the composite outcome of death and disability at 9 months’ follow-up in people with HIV and clinically diagnosed tuberculous meningitis (very low-quality evidence).
Antituberculous treatment plus adjuvant corticosteroids compared with antituberculous treatment plus placebo in people with pericardial tuberculosis

Antituberculous treatment plus adjuvant corticosteroids may be more effective than antituberculous treatment plus placebo at reducing mortality at 18 months in people with HIV and presumed pericardial tuberculosis (very low-quality evidence).

Presence of Mycobacterium tuberculosis in sputum

Antituberculous treatment plus adjuvant corticosteroids compared with antituberculous treatment plus placebo in people with pulmonary tuberculosis

Antituberculous treatment plus adjuvant corticosteroids may be more effective than antituberculous treatment plus placebo at increasing the proportion of people with negative sputum culture for Mycobacterium tuberculosis at 1 month, but we don't know whether it is more effective at 2 months (low-quality evidence).

Recurrence of tuberculosis

Antituberculous treatment plus adjuvant corticosteroids compared with antituberculous treatment plus placebo in people with pulmonary tuberculosis

Antituberculous treatment plus adjuvant corticosteroids may be no more effective than antituberculous treatment plus placebo at reducing tuberculosis recurrence within 2 years in people with HIV and pulmonary tuberculosis (low-quality evidence).

Antituberculous treatment plus adjuvant corticosteroids compared with antituberculous treatment plus placebo in people with pleural tuberculosis

Antituberculous treatment plus adjuvant corticosteroids seems no more effective at reducing tuberculosis recurrence in people with HIV and pleural tuberculosis (moderate-quality evidence).

Note

Corticosteroids are associated with an increased risk of high blood glucose and high blood pressure.

For GRADE evaluation of interventions for tuberculosis in people with HIV, see table, p 19.

Benefits:

Antituberculous treatment plus adjuvant corticosteroids versus antituberculous treatment plus placebo in pulmonary tuberculosis:

We found one RCT (187 HIV-positive adults in Uganda with smear-positive pulmonary tuberculosis). It compared prednisolone 2.75 mg/kg daily for 4 weeks followed by a tapering dose over a further 4 weeks versus placebo. Everyone in the RCT also received conventional antituberculous treatment (isoniazid plus rifampicin plus pyrazinamide plus ethambutol [whether followed by 4 months of isoniazid plus rifampicin not reported]). It found that the addition of prednisolone to antituberculous treatment increased the proportion of people with negative sputum culture for Mycobacterium tuberculosis at 1 month compared with placebo (62% with prednisolone v 37% with placebo; P = 0.001). However, the proportion of people with negative sputum culture was similar at 2 months (86% with prednisolone v 85% with placebo; significance not reported). It found similar rates of treatment failure, mortality after 36 months’ follow-up, and tuberculosis recurrence within 2 years in both groups (treatment failure: 1/93 [1%] with prednisolone v 1/94 [1%] with placebo; mortality after 36 months’ follow-up: 17/93 [18%] died with prednisolone v 14/94 [15%] died with placebo; tuberculosis recurrence within 2 years: 9% with prednisolone v 12% with placebo; significance not reported for any outcome).

Antituberculous treatment plus adjuvant corticosteroids versus antituberculous treatment plus placebo in pleural tuberculosis:

We found one RCT (197 HIV-positive adults in Uganda with a large pleural effusion and clinical features suggesting tuberculosis of whom 180 had histological or microbiological confirmation of the diagnosis). It compared prednisolone (50 mg/day for 2 weeks, then 40 mg/day for 2 weeks, then 25 mg/day for 2 weeks, then 15 mg/day for 2 weeks) versus placebo. Everyone in the RCT also received a 6-month course of conventional antituberculous treatment (isoniazid plus rifampicin plus pyrazinamide plus ethambutol for 2 months followed by 4 months of isoniazid plus rifampicin). It found no significant difference between prednisolone and placebo in mortality or tuberculosis recurrence (mortality: 21 deaths/100 person-years of follow-up with prednisolone v 25 deaths/100 person-years of follow-up with placebo; RR 0.84, 95% CI 0.53 to 1.32; P = 0.44; tuberculosis recurrence: 4.5/100 person-years of follow-up with prednisolone v 6.8/100 person-years of follow-up with placebo; RR 0.67, 95% CI 0.40 to 1.12; P = 0.09). The RCT also found that pleural effusions resolved more rapidly in those receiving prednisolone (P <0.001).

Antituberculous treatment plus adjuvant corticosteroids versus antituberculous treatment plus placebo in tuberculous meningitis:

We found one RCT (545 people aged >14 years with a clinical diagnosis of tuberculous meningitis in Vietnam, of whom 98 [18%] were HIV positive). It compared a 6- to 8-week course of dexamethasone (initially 0.3–0.4 mg/kg/day iv followed by a progressively decreasing dose over 6–8 weeks; initial dose, duration of iv treatment, and duration of subsequent oral treatment was adjusted according to disease severity) versus placebo. All people with HIV received a 3-month course of oral isoniazid 5 mg/kg daily plus rifampicin 10 mg/kg daily plus pyrazinamide 25 mg/kg daily
HIV: treating tuberculosis

Harms: Antituberculous treatment plus adjuvant corticosteroids versus antituberculous treatment plus placebo in tuberculous pericarditis:

We found one RCT (58 HIV-positive people aged 18–55 years, with presumed tuberculous pericarditis characterised by an exudative pericarditis containing a high lymphocyte count and absence of an alternative explanation). [23] It compared 6 weeks of prednisolone (initially 60 mg/day for 7 days, then reduced by 10 mg/day each week over 6 weeks) versus placebo. Everyone in the RCT received a 6-month course of conventional antituberculous treatment (isoniazid plus rifampicin plus pyrazinamide plus ethambutol for 2 months followed by 4 months of isoniazid plus rifampicin). It found that mortality was significantly lower with prednisolone over 18 months compared with placebo (deaths: 5/29 [17%] with prednisolone v 10/29 [34%] with placebo; P = 0.004). Although the RCT did not report any other outcomes of interest, it did report on other outcomes of clinical improvement. The RCT found that raised venous pressure, hepatomegaly, ascites, and improvement in physical activity resolved faster with prednisolone compared with placebo (venous pressure: P = 0.017; hepatomegaly: P = 0.007; ascites: P = 0.015; physical activity: P = 0.02). It found no significant difference between treatments in clearance of pericardial effusion on chest x-ray or echocardiography (x-ray: P = 0.80; anterior view echocardiography: P = 0.19; posterior view: P = 0.80; subcostal view: P = 0.39). Only 38% of people had positive M tuberculosis cultures, therefore the initial diagnosis of tuberculosis may have been incorrect in some people. The results should therefore be interpreted with caution.

Antituberculous treatment plus adjuvant corticosteroids versus antituberculous treatment plus placebo in pulmonary tuberculosis:

The RCT found that significantly more people developed high blood pressure, high blood glucose, or fluid retention with prednisolone compared with placebo (high blood pressure: 11/93 [12%] with prednisolone v 3/94 [3%] with placebo; P = 0.039; high blood glucose: 9/93 [10%] with prednisolone v 3/94 [3%] with placebo; P = 0.036; fluid retention: 26/93 [28%] with prednisolone v 4/94 [4%] with placebo; P <0.001). [20] The RCT found no significant differences in the frequency of infectious complications (herpes simplex, herpes zoster, pneumonia, UTIs, and Kaposi's sarcoma) between groups.

Antituberculous treatment plus adjuvant corticosteroids versus antituberculous treatment plus placebo in pleural tuberculosis:

The RCT found that significantly more people developed Kaposi's sarcoma with prednisolone than with placebo (4.2 cases/100 person-years of follow-up with prednisolone v 0 cases/100 person-years of follow-up with placebo; P = 0.02). [21] However, the RCT found no significant difference between groups for other infections (herpes simplex, herpes zoster, oral or oesophageal candidiasis, and cryptococcal meningitis). It also found that the proportion of people with high blood glucose was greater with prednisolone than placebo (6/96 [6%] with prednisolone v 1/95 [1%] with placebo; P = 0.06). The RCT found that mean systolic blood pressure was significantly higher with prednisolone than with placebo (at 1 week: 111 mmHg with prednisolone v 104 mmHg with placebo; P = 0.002; at 1 month: 111 mmHg with prednisolone v 104 mmHg with placebo; P = 0.001).

Antituberculous treatment plus adjuvant corticosteroids versus antituberculous treatment plus placebo in tuberculous meningitis:

The RCT did not report adverse effects separately for people with HIV. [22]

Antituberculous treatment plus adjuvant corticosteroids versus antituberculous treatment plus placebo in tuberculous pericarditis:

The RCT found no significant difference in adverse effects (Kaposi's sarcoma, herpes zoster, herpes simplex, pneumonia, acne, and skin rash) between groups. [23]

Comment: Clinical guide:

Adjuvant immunotherapy with corticosteroids aims to dampen down the potentially harmful aspects of the host immune response that are believed to contribute to tissue damage in tuberculosis. It is hoped that this could improve the resolution of tuberculosis. There is no evidence that adjuvant...
immunotherapy with corticosteroids is useful for treatment of pulmonary or pleural tuberculosis in people with HIV. It is uncertain if adjuvant immunotherapy with corticosteroids is useful for treatment of tuberculous meningitis or tuberculous pericarditis in people with HIV.

**OPTION**  
**ANTITUBERCULOUS TREATMENT CONTAINING QUINOLONES**

**Mortality**  
**Compared with conventional regimens** We don't know whether regimens containing quinolones are more effective than conventional antituberculous regimens at reducing mortality during initial 8 weeks' treatment in people with pulmonary tuberculosis and HIV-associated immunosuppression (very low-quality evidence).

**Presence of Mycobacterium tuberculosis in sputum**  
**Compared with conventional regimens** We don't know whether regimens containing quinolones are more effective than conventional antituberculous regimens after initial 8 weeks' treatment at increasing the proportion of people with negative cultures for M tuberculosis in people with pulmonary tuberculosis and HIV-associated immunosuppression (very low-quality evidence).

**Note**  
We found no clinically important results from RCTs about the effect of antituberculous treatment containing quinolones compared with regimens containing rifabutin or thiacetazone as the first-line treatment for tuberculosis in HIV-positive people.

For GRADE evaluation of interventions for tuberculosis in people with HIV, see table, p 19.

**Benefits:**  
Antituberculous treatment containing quinolones versus conventional antituberculous treatment:  
We found one RCT (see comment below).\(^19\) The open-label RCT (174 people aged >13 years from the USA with suspected HIV and tuberculosis, of whom 101 had culture-confirmed, smear-positive pulmonary tuberculosis and HIV-associated immunosuppression) compared an initial 8-week regimen of conventional antituberculous treatment plus levofloxacin (a quinolone; 500 mg/day for 2 weeks, followed by 750 mg 3 times/week for 6 weeks) versus an initial 8-week regimen of conventional antituberculous treatment alone (see comment below).\(^19\) The conventional antituberculous treatment regimen in this study used daily dosing for 2 weeks, followed by a 6-week course of three times weekly rifampicin 600 mg plus isoniazid 900 mg (for people weighing 50 kg or more) or 600 mg (if <50 kg) plus ethambutol 20 mg/kg. Participants completing the initial 8-week phase were randomised to receive either 4 or 7 months of continued conventional treatment (the effects of the duration of treatment are discussed under longer courses of antituberculous treatment, p 11). The RCT found no significant difference between treatments in mortality during the initial 8 weeks of treatment (1/53 [2%] with levofloxacin-containing regimen v 3/48 [6%] with conventional treatment; P value reported as not significant). Similarly, it found no significant difference between treatments in the proportion of people with negative cultures for M tuberculosis after 8 weeks of treatment (46/48 [96%] with levofloxacin-containing regimen v 36/37 [97%] with conventional antituberculous treatment; P = 1.00).\(^19\) People in the RCT came from areas where at least 10% of people with tuberculosis were infected with an isoniazid-resistant strain of M tuberculosis.\(^19\) Everyone in this RCT received vitamin B6 supplementation. The RCT randomised some people who had suspected but not confirmed HIV and tuberculosis. However, analysis was only performed on the 101 people (58%) with culture-confirmed, smear-positive pulmonary tuberculosis and HIV-associated immunosuppression.

Antituberculous treatment containing quinolones versus regimens containing rifabutin or thiacetzone:  
We found no systematic review or RCTs.

**Harms:**  
Antituberculous treatment containing quinolones versus conventional antituberculous treatment:  
The RCT found no significant difference in serious adverse effects during the first 8 weeks of treatment between the levofloxacin-containing regimen and conventional antituberculous treatment (AR: 15/87 [17.2%] with levofloxacin-containing regimen v 15/87 [17.2%] with conventional treatment; P = 1.00).\(^19\)

Antituberculous treatment containing quinolones versus regimens containing rifabutin or thiacetzone:  
We found no RCTs.
Comment: Antituberculous treatment containing quinolones versus conventional antituberculous treatment:
We found one open-label RCT in 200 adults with smear-positive pulmonary tuberculosis in Tanzania, which conducted post hoc subgroup analysis in people who were HIV positive (58 people). It compared a 6-month course of rifampicin (600 mg daily) plus isoniazid (300 mg daily) plus ciprofloxacin (750 mg daily during the initial 4 months) versus a 6-month course of conventional antituberculous treatment (rifampicin 600 mg/day plus isoniazid 300 mg/day plus pyrazinamide 25 mg/kg/day during the initial 4 months plus ethambutol 15 mg/kg/day during the initial 2 months). It found that, among people with HIV, the ciprofloxacin-containing regimen significantly increased time to first negative sputum culture compared with conventional treatment (mean time: 2.9 months with ciprofloxacin-containing regimen v 1.7 months with conventional treatment; P <0.0004). It found no significant difference between treatments in recurrence of tuberculosis during the first 6 months after completion of treatment (AR: 3/25 [12%] with ciprofloxacin-containing regimen v 0/30 [0%] with conventional treatment; P = 0.09).

Clinical guide:
RCTs comparing antituberculous treatment containing quinolones versus placebo would be considered unethical because of high risk of mortality in HIV-positive people if tuberculosis is not treated. Antituberculous treatment containing quinolones would generally only be used for treatment of tuberculosis in HIV-positive people who were intolerant of conventional antituberculous drugs.

OPTION ANTITUBERCULOUS TREATMENT CONTAINING RIFABUTIN

Mortality
Compared with conventional regimens We don't know whether regimens containing rifabutin are more effective than conventional antituberculous regimens at reducing mortality in people with HIV and pulmonary tuberculosis (low-quality evidence).

Presence of Mycobacterium tuberculosis in sputum
Compared with conventional regimens Regimens containing rifabutin may be more effective than conventional regimens at reducing time to sputum smear conversion in people with HIV and pulmonary tuberculosis, but we don't know about negative sputum culture for M tuberculosis at 6 months (low-quality evidence).

Note
We found no clinically important results from RCTs about the effects of antituberculous treatment containing rifabutin compared with antituberculous treatment containing thiacetazone or quinolones as the first-line treatment for tuberculosis in HIV-positive people.

For GRADE evaluation of interventions for tuberculosis in people with HIV, see table, p 19.

Benefits: Antituberculous treatment containing rifabutin versus conventional antituberculous treatment:
We found one RCT (50 HIV-positive adults in Uganda, with sputum smear-positive pulmonary tuberculosis, see comment below). It compared rifabutin (150 mg/day for people weighing <50 kg and 300 mg/day if 50 kg or more) plus the conventional daily doses of isoniazid for 6 months plus ethambutol plus pyrazinamide for the first 2 months versus a 6-month course of conventional antituberculous treatment including ethambutol for the initial 2 months. It found that the rifabutin-containing regimen increased the proportion of people with negative sputum culture for M tuberculosis at 2 months compared with conventional treatment, but the difference between groups had decreased by the end of treatment (AR for negative sputum culture at 2 months: 18/24 [75%] with rifabutin-containing regimen v 11/25 [44%] with conventional treatment; AR for negative sputum culture at end of treatment: 22/24 [92%] with rifabutin-containing regimen v 22/25 [88%] with conventional treatment; significance of comparisons not reported). The rifabutin-containing regimen also significantly reduced time to sputum smear conversion (3 consecutive negative fortnightly smears) compared with conventional treatment (results presented graphically; log rank P <0.05). The study had insufficient power to detect clinically important differences in mortality between treatments (AR for mortality: 4/24 [17%] with rifabutin-containing regimen v 2/25 [8%] with conventional treatment; significance not reported).

Antituberculous treatment containing rifabutin versus regimens containing thiacetazone or quinolones:
We found no systematic review or RCTs.

Harms: Antituberculous treatment containing rifabutin versus conventional antituberculous treatment:
The RCT found no significant difference in reported adverse effects between people treated with the rifabutin-containing regimen and conventional antituberculous treatment (no further data report-
ed). Reported adverse events in both treatment groups included arthralgia (AR for mild arthralgia: 31%; moderate: 22%; severe: 4.4%), myalgia, nausea, vomiting, GI discomfort, and loss of appetite (no further data reported). There were no clinical episodes of jaundice and no participants experienced significant renal dysfunction with either treatment. However, people receiving the rifabutin-containing treatment had significant rises from baseline in serum creatinine concentration at week 6 (mean increase 0.3 mg/dL; no further data reported), and in serum alanine transaminase at week 24 (no further data or P values reported).

Antituberculous treatment containing rifabutin versus regimens containing thiacetazone or quinolones:
We found no RCTs.

Comment:
One person in the rifabutin group was excluded from analysis because of Mycobacterium fortuitum infection.

Clinical guide:
RCTs comparing antituberculous treatment containing rifabutin versus placebo would be considered unethical because of high risk of mortality in HIV-positive people if tuberculosis is not treated. Rifampicin can interact with antiretroviral drugs and needs to be avoided in people receiving some of these drugs. If rifampicin use needs to be avoided, in HIV-positive people with tuberculosis, clinicians might use rifabutin as part of first-line antituberculous treatment.

OPTION: DIRECTLY OBSERVED THERAPY (COMPARED WITH UNSUPERVISED TREATMENT)

Mortality
Controlled with unsupervised treatment We don't know whether directly observed therapy is more effective than unsupervised treatment at reducing mortality in people with HIV and tuberculosis (very low-quality evidence).

Presence of Mycobacterium tuberculosis in sputum
Controlled with conventional regimens We don't know whether directly observed therapy is more effective than unsupervised treatment at increasing the proportion of people with negative sputum smear for acid-fast bacilli at 2 months after starting treatment, but it may be more effective after 8 months' treatment (very low-quality evidence).

For GRADE evaluation of interventions for tuberculosis in people with HIV, see table, p 19.

Benefits:
We found no systematic review or RCTs comparing directly observed therapy (DOT) versus unsupervised treatment for tuberculosis in people with HIV. We found one review of cohort studies of DOT (Medline search limited to 1990–2000; 34 eligible studies including 78,253 analysable people from sub-Saharan Africa, the USA, and Asia). Although the review did not focus specifically on HIV-positive people, it was limited to the era in which HIV became highly prevalent, and a high proportion of the participants would have been HIV-positive. The review did not report on control groups, but did separate M tuberculosis culture-based data and acid-fast bacilli smear-based data. The mean treatment failure rates were 2.4% (standard deviation [SD] 2.2%) in 21 analysable M tuberculosis culture-based studies and 2.5% (SD 1.7%) in nine analysable acid-fast bacilli smear-based studies. If people who did not adhere to treatment, or who were lost to follow-up, were counted as treatment failures (conservative intention-to-treat analysis), mean treatment failure rates increased by 11.1% (SD 6.7%) in 20 culture-based studies and by 10.0% (SD 7.5%) in nine smear-based studies. The mean tuberculosis recurrence rates were 3.6% (SD 2.4%) in 21 analysable M tuberculosis culture-based studies and 3.2% in two analysable acid-fast bacilli smear-based studies. Although these recurrence rates were acceptably low, the authors could not discern whether DOT reduced case fatality compared with unsupervised treatment.

We found one subsequent non-randomised study in Zambia comparing a cohort receiving daily supervision of antituberculous treatment (DOT) versus a control population receiving 8 months of unsupervised antituberculous treatment (168 people with smear-positive pulmonary tuberculosis). All participants received 8 months of isoniazid plus ethambutol plus rifampicin plus pyrazinamide during the first 2 months. It was estimated that 70% to 80% of the people with tuberculosis in the study areas were likely to be HIV positive. The study found no significant difference between groups in mortality at the end of treatment (16/72 [22%] with DOT v 18/96 [19%] with unsupervised treatment; P value reported as not significant). It found that similar proportions of people in both groups had negative sputum smear for acid-fast bacilli 2 months after starting treatment (54/72 [75%] with DOT v 64/96 [67%] with unsupervised treatment; significance not reported). However, significantly more people receiving DOT had a negative sputum smear at the end of treatment (39/72 [54.2%] with DOT v 20/96 [21%] with unsupervised treatment; P <0.001).

Harms:
We found no RCTs. The review of cohort studies did not report on adverse effects.
Clinical guide:
DOT is strongly recommended by the WHO on the basis of evidence from successful tuberculosis treatment programmes. [1]

OPTION

EARLY INITIATION OF HIGHLY ACTIVE ANTIRETROVIRAL TREATMENT

Mortality

Early initiation compared with delayed initiation of highly active antiretroviral treatment
We don’t know whether early initiation of highly active antiretroviral treatment is more effective than delayed initiation of highly active antiretroviral treatment at reducing mortality in people with HIV and tuberculosis (very low-quality evidence).

For GRADE evaluation of interventions for tuberculosis in people with HIV, see table, p 19.

Benefits:

We found no systematic review or RCTs comparing antituberculous treatment plus early initiation of highly active antiretroviral treatment (HAART) versus antituberculous treatment plus delayed initiation of HAART. We found two cohort studies. [28] [29]

The first prospective study (667 HIV-positive adults with tuberculosis; 200 people started HAART at the beginning or during tuberculosis treatment) assessed the association between starting HAART (efavirenz- or nevirapine-containing regime) and mortality. It found that mortality was increased the longer HAART initiation was delayed after starting antituberculosis treatment (results presented graphically). People with bacteriologically confirmed tuberculosis who started HAART within the first 120 days of antituberculosis treatment had lower mortality compared with those who started after 120 days of antituberculosis treatment (127 people with bacteriologically confirmed tuberculosis who started HAART during tuberculosis treatment: HR 9.0, 95% CI 1.1 to 7.3; absolute numbers not reported). [28]

The second study (6934 HIV-positive adults) collected data retrospectively between 1984 and 2000 and prospectively from 2000 to 2004. [29] It included only people with tuberculosis diagnosed after 1996 (322 people) in the analysis of the effect of HAART on mortality, to avoid any bias due to different or lower potency antiretroviral treatments used in earlier years. It compared people who started HAART (combination therapy of at least 3 antiretroviral drugs, including a protease inhibitor or non-nucleoside reverse transcriptase inhibitor) within 2 months of starting antituberculosis treatment (simultaneous therapy) versus people who started HAART more than 3 months after antituberculosis treatment (delayed therapy). It found significantly better survival with simultaneous therapy compared with delayed therapy (mortality rate: 13/140 [9%] with simultaneous therapy v 34/173 [20%] with delayed therapy; P = 0.01; HR 0.37, 95% CI 0.17 to 0.66). [29] The results of this study should be interpreted with caution because the inclusion of retrospective data may have been a potential source of bias.

Harms:

We found no RCTs. The first cohort study found that adverse effects including rash occurred with similar frequency in those who did and did not receive HAART (rash: 12% with nevirapine v 11% with efavirenz v 18% with no HAART; absolute results not reported; among-group comparison: P = 0.09). [29] The second cohort study gave no information about adverse effects of treatments.

Clinical guide:

The use of HAART in people being treated for tuberculosis is complicated by the potential for drug interactions, compounding of adverse effects and HAART-associated immune reconstitution. There is a strong potential for pharmacokinetic interaction between antituberculous regimens including rifampicin and drugs used in HAART. The optimal timing for the initiation of HAART during treatment of tuberculosis is unknown. Early initiation of HAART may reduce the risk of HIV disease progression, but increase the risk of adverse effects, which could result in the need to discontinue both anti-HIV and antituberculosis drugs. US guidelines recommend that the timing of initiation of HAART should be determined by the baseline CD4 count. [30]

OPTION

LONGER COURSES OF ANTITUBERCULOUS TREATMENT (COMpared WITH CONVEnTIONAL SHORT-COURSE TREATMENT)

Mortality

Longer courses of antituberculous treatment compared with conventional short-course treatment
We don’t know whether longer courses of antituberculous treatment (regimens lasting longer than 6 months) are more effective than conventional treatment (lasting 6 months) at reducing mortality in people with HIV and pulmonary tuberculosis (low-quality evidence).

Recurrence of tuberculosis
Larger courses of antituberculous treatment compared with conventional short-course treatment

We don’t know whether antituberculous regimens lasting longer than 6 months are more effective than conventional treatment (lasting 6 months) at reducing recurrence of tuberculosis in people with HIV and pulmonary tuberculosis (low-quality evidence).

For GRADE evaluation of interventions for tuberculosis in people with HIV, see table, p 19.

Benefits:

- Longer courses of antituberculous treatment versus conventional short-course treatment: We found two RCTs.\(^{19,31}\) The first RCT enrolled 335 HIV-positive people in the Democratic Republic of Congo with smear-positive pulmonary tuberculosis, all of whom received 6 months of conventional antituberculous treatment (including ethambutol).\(^{31}\) At the end of 6 months, the 247 people who had negative sputum smears or cultures were randomised to receive another 6 months of further conventional treatment (twice-weekly rifampicin [600 mg for people weighing 50 kg or more, or 450 mg if <50 kg] plus isoniazid [15 mg/kg]) or placebo (see comment below). The RCT found no significant difference between treatments in survival at 12 months after randomisation (102/121 [84.3%] with 12 months’ treatment vs 100/119 [84.0%] with 6 months’ treatment; P = 0.95).\(^{31}\) However, the extended 12-month course of treatment significantly reduced tuberculosis recurrence during the first 18 months after treatment completion compared with the 6-month course of treatment (estimated AR for relapse: 1.9% with 12 months’ treatment vs 9% with 6 months’ treatment; P <0.01). The results of this study may not be generalisable to all HIV-positive people commencing antituberculous treatment, as people who remained culture- or smear-positive after 6 months of treatment were excluded from randomisation.\(^{31}\)

The second RCT included 101 HIV-positive people aged over 13 years from the USA with culture-confirmed pulmonary tuberculosis who had completed 2 months of treatment with either conventional treatment (including ethambutol) alone or conventional treatment plus levofloxacin (see benefits of antituberculous treatment containing quinolones, p 6).\(^{19}\) Participants were then randomised to either an additional 4-month course (i.e., a total of 6 months’ treatment), or an additional 7-month course (i.e., a total of 9 months’ treatment), of twice-weekly rifampicin 600 mg plus isoniazid (900 mg for people weighing 50 kg or more, or 600 mg if <50 kg). The RCT found no significant difference between treatments in the combined outcome of treatment failure or recurrence during a minimum of 2 years of follow-up (1/50 [2.0%; 1.0 events/100 person-years] with 9 months’ treatment vs 2/51 [3.9%; 2.1 events/100 person-years] with 6 months’ treatment; P reported as not significant). Similarly, it found no significant difference between treatments in mortality during a minimum of 2 years of follow-up (26/50 [52.0%; 27.1 events/100 person-years] with 9 months’ treatment vs 21/51 [41.2%; 21.1 events/100 person-years] with 6 months’ treatment; RR 1.3, CI not reported; P = 0.38).

Harms:

- Longer courses of antituberculous treatment versus conventional short-course treatment: The first RCT did not report the frequency of adverse effects by treatment group.\(^{91}\) Overall, common adverse effects of treatment were arthralgia, paraesthesia, and skin rash (arthralgia: 78% of people; paraesthesia: 21%; skin rash: 11%).\(^{91}\) The second RCT found no significant difference in the rate of serious adverse effects between 9 months’ and 6 months’ treatment (8/50 [16%] with 9 months’ treatment vs 4/51 [8%] with 6 months’ treatment; P = 0.23).\(^{19}\) Most of the adverse effects in this study were reportedly hepatic toxicities (no further data reported).\(^{19}\)

Comment:

- Clinical guide: Most clinicians would use conventional short-course treatment for first-line treatment of tuberculosis in people with HIV. However, these studies were largely conducted on pulmonary tuberculosis and are not directly applicable to central nervous system disease, where 12 months’ treatment is generally recommended (irrespective of HIV status).

OPTION

ADJUVANT IMMUNOTHERAPY WITH MYCOBACTERIUM VACCÆ

Mortality

Antituberculous treatment plus Mycobacterium vaccae vaccination compared with antituberculous treatment plus placebo vaccination

Antituberculous treatment plus Mycobacterium vaccae vaccination seems no more effective than antituberculous treatment plus placebo vaccination at reducing mortality at 2 years’ follow-up in people with HIV and tuberculosis (moderate-quality evidence).

Presence of Mycobacterium tuberculosis in sputum

Antituberculous treatment plus Mycobacterium vaccae vaccination compared with antituberculous treatment plus placebo vaccination

Antituberculous treatment plus Mycobacterium vaccae vaccination seems no more effective than antituberculous treatment plus placebo vaccination at increasing the proportion of people with negative Mycobacterium tuberculosis sputum culture at 6 or 12 months (moderate-quality evidence)

For GRADE evaluation of interventions for tuberculosis in people with HIV, see table, p 19.
HIV: treating tuberculosis

Benefits: We found two RCTs. The first RCT randomised 374 South African adults with smear-positive pulmonary tuberculosis, 119 of whom were HIV positive. Participants in both arms received 6 months of conventional antituberculous treatment (including ethambutol). The RCT compared Mycobacterium vaccae vaccination versus placebo vaccination on day 8 of conventional treatment. Pre-specified subgroup analysis in HIV-positive participants found no significant difference between treatments in the proportion of people with negative M tuberculosis sputum culture at 6 months (46/48 [96%] with M vaccae immunotherapy vs 48/48 [100%] with placebo; P = 0.48). The HIV-positive treatment groups may not have been balanced for potentially confounding factors, because of the small number of participants with HIV, and because randomisation was not stratified by HIV status. Therefore the results of this RCT should be interpreted with caution.

The second RCT randomised 1229 adults from Zambia and Malawi, 760 of whom were HIV positive. In Zambia, participants in both arms received 8 months of isoniazid plus ethambutol plus rifampicin plus pyrazinamide during the first 2 months. In Malawi, participants in both treatment arms received 2 months of streptomycin plus isoniazid plus rifampicin plus pyrazinamide, followed by a further 6 months of isoniazid plus ethambutol. The RCT compared M vaccae vaccination during the first 2 weeks of treatment with placebo vaccination. Pre-specified subgroup analysis in HIV-positive people found no significant difference between treatments in mortality over 2 years of follow-up (AR: 109/374 [29%] with M vaccae immunotherapy vs 107/386 [28%] with placebo; HR 1.03, 95% CI 0.79 to 1.35; P = 0.8). Similarly, it found no significant difference between treatments in the proportion of people with negative M tuberculosis sputum culture at 12 months (187/374 [50%] with M vaccae immunotherapy vs 201/386 [52%] with placebo; P reported as not significant).

Harms: The first RCT did not report adverse effects for HIV-positive people separately. Overall, erythema, vesiculation, and ulceration at the injection site occurred more frequently with M vaccae vaccination than with placebo (erythema: 98.4% with M vaccae immunotherapy vs 9.2% with placebo; vesiculation: 50.3% with M vaccae immunotherapy vs 1.1% with placebo; ulceration: 22.2% with M vaccae immunotherapy vs 1.1% with placebo; significance not reported). However, the frequency of serious adverse events was similar between groups (37/189 [20%] with M vaccae immunotherapy vs 34/185 [18%] with placebo; significance not reported). In the second RCT, the only reported adverse effects of M vaccae vaccination were pain at the injection site in two HIV-positive participants (2/374 [0.53%]), and pus oozing from the injection site in one HIV-negative participant (1/385 [0.26%]). There were no adverse effects reported in the placebo group.

Comment: Clinical guide: Adjuvant immunotherapy with M vaccae aims to stimulate the host immune system to produce a more effective response against M tuberculosis. Most clinicians would not use adjuvant immunotherapy with M vaccae for first-line treatment of tuberculosis in people with HIV.

TABLE

<table>
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<tr>
<th>OPTION</th>
<th>ANTITUBERCULOUS TREATMENT CONTAINING 3 MONTHS OR LESS OF RIFAMPICIN (COMPARSED WITH RIFAMPICIN FOR 5 MONTHS OR MORE)</th>
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Recurrence of tuberculosis

Shorter (3 months or less) compared with longer courses (5 months or more) of rifampicin Regimens containing 2 to 3 months of rifampicin may be less effective than regimens containing 5 to 6 months, or 7 months or more, of rifampicin at reducing tuberculosis recurrence in people with HIV (very low-quality evidence).

For GRADE evaluation of interventions for tuberculosis in people with HIV, see table , p 19 .

Benefits: Antituberculous treatment containing 5 months or more of rifampicin versus rifampicin for 3 months or less:

We found no RCTs assessing shorter compared with longer courses of rifampicin. We found one systematic review of prospective cohort studies (search date 2002; 47 studies; 21 studies including people with HIV) of rifampicin-based treatment regimens for tuberculosis. Studies were included comparing treatment regimens that differed by constituent drugs as well as by treatment duration. The review concluded that, in people with HIV, there is a significantly higher rate of tuberculosis recurrence with regimens containing 2 to 3 months of rifampicin compared with regimens containing 5 to 6 months of rifampicin or 7 months or more of rifampicin (2–3 months v 5–6 months: RR 3.2, 95% CI 1.6 to 4.7; 2–3 months v 7 months or more: RR 4.6, 95% CI 1.7 to 7.4). Overall (i.e., in both HIV-positive and HIV-negative people), there was no significant difference in tuberculosis recurrence between regimens containing 5 to 6 months of rifampicin and regimens of 7 months or longer (P = 0.17).

Harms: Antituberculous treatment containing 5 months or more of rifampicin versus rifampicin for 3 months or less:

The systematic review gave no information on adverse effects.
Comment: Clinical guide:
Most clinicians would not use antituberculous treatment containing rifampicin for 3 months or less for first-line treatment of tuberculosis in people with HIV.

OPTION

ANTITUBERCULOUS TREATMENT CONTAINING THIACETAZONE

Mortality

Compared with conventional regimens We don’t know whether regimens containing thiacezone are more effective than conventional regimens at improving survival at 1 year in people with HIV and pulmonary tuberculosis (low-quality evidence).

Presence of Mycobacterium tuberculosis in sputum

Compared with conventional regimens Regimens containing thiacezone may be less effective than conventional regimens at increasing the proportion of people with negative sputum culture for M tuberculosis at 2 months in people with HIV and pulmonary tuberculosis (low-quality evidence).

Adverse effects

Compared with conventional regimens Regimens containing thiacezone increase overall adverse effects including skin rash compared with conventional treatment (high-quality evidence).

Note

Regimens containing thiacezone have been associated with fatal mucocutaneous reactions. We found no clinically important results from RCTs about the effects of antituberculous treatment containing thiacezone compared with regimens containing rifabutin or quinolones as first-line treatment for tuberculosis in HIV-positive people. We found no direct information about whether thiacezone-based regimens are better than no active treatment.

For GRADE evaluation of interventions for tuberculosis in people with HIV, see table, p 19.

Benefits: Antituberculous treatment containing thiacezone versus conventional antituberculous treatment:
We found one RCT (191 HIV-positive adults in Uganda with smear-positive pulmonary tuberculosis) comparing a 12-month course of thiacezone (150 mg/day) plus isoniazid (300 mg/day) plus streptomycin (0.75 g/day for people weighing <50 kg or 1 g/day if 50 kg or more for the first 2 months) with a 9-month course of conventional antituberculous treatment (not including ethambutol). It found no significant difference in survival between groups at 1 year (AR: 65% with thiacezone-containing regimen v 72% with conventional treatment; log rank P >0.2). At 2 months, significantly fewer people had negative sputum culture for Mycobacterium tuberculosis with the thiacezone-containing regimen compared with conventional treatment (21/57 [36.8%] with thiacezone-containing regimen v 55/74 [74.3%] with conventional treatment; P <0.001). However, the sputum culture results should be interpreted with caution because the analysis was not conducted according to intention-to-treat principles (i.e., did not take account of the 60 people who could not provide sputum for culture or had died). This may have adversely affected the reliability of these results.

Antituberculous treatment containing thiacezone versus regimens containing rifabutin or quinolones:
We found no systematic review or RCTs.

Harms:
Skin rash has been reported as a common problem among HIV-positive people receiving thiacezone. In a retrospective survey, 24/79 (30.4%) Zambian HIV-positive adults who were treated with a thiacezone-containing antituberculous regimen were found to have developed a skin rash that required a change of treatment. A cohort study of Zambian children aged between 1 month and 15 years also reported a high rate of adverse effects among HIV-positive children treated with thiacezone (19/88 [22%]). Twelve children (14%) developed a severe mucocutaneous reaction (Stevens-Johnson syndrome) and 11 (13%) of these children died.

Antituberculous treatment containing thiacezone versus conventional antituberculous treatment:
The RCT found significantly more adverse effects with the thiacezone-containing regimen compared with conventional treatment (12 events [18.2/100 person-years of observation] with thiacezone-containing regimen v 1 event [1.6/100 person-years of observation] with conventional treatment; RR 11.7, 95% CI 1.52 to 90.0). The most common adverse effect was skin rash, which was also significantly more common with the thiacezone-containing regimen compared with conventional treatment (10 events [15.2/100 person-years of observation] with thiacezone-containing regimen v 1 event [1.6/100 person-years of observation] with conventional treatment; RR 9.7, 95% CI 1.24 to 75.8).
Antituberculous treatment containing thiacetazone versus regimens containing rifabutin or quinolones:
We found no RCTs.

Comment: Clinical guide:
RCTs comparing antituberculous treatment containing thiacetazone versus placebo would be considered unethical because of high risk of mortality if tuberculosis is not treated in HIV-positive people. Many countries no longer use thiacetazone because of the high frequency of adverse events associated with this drug.

QUESTION What are the effects of second-line treatments for tuberculosis in HIV-positive people?

OPTION ANTIMYCOBACTERIAL TREATMENT COMBINATIONS

We found no clinically important results from RCTs about the effects of different regimens of antituberculous treatment after failure of first-line treatment for tuberculosis in people with HIV.

For GRADE evaluation of interventions for tuberculosis in people with HIV, see table, p 19.

Benefits: We found no systematic review or RCTs comparing different regimens of antituberculous treatment after failure of first-line treatment in people with HIV.

Harms: We found no RCTs.

Comment: Clinical guide:
Most clinicians would base decisions on antituberculous treatment after failure of first-line treatment in people with HIV on in vitro sensitivity tests. For multi-drug-resistant tuberculosis, at least five drugs (to which the M. tuberculosis strain isolated is sensitive) would be used. If in vitro sensitivity tests are not available, we can make no recommendation on which drugs should be incorporated into antituberculous treatment after failure of first-line treatment due to lack of evidence.

OPTION SECONDARY PROPHYLAXIS WITH ANTITUBERCULOUS DRUGS AFTER SUCCESSFUL COMPLETION OF CONVENTIONAL ANTITUBERCULOUS TREATMENT

Mortality
Compared with placebo We don't know whether secondary prophylaxis with antituberculous drugs after successful completion of conventional antituberculous treatment is more effective than placebo at reducing mortality in HIV-positive people (very low-quality evidence).

Recurrence of tuberculosis
Compared with placebo/no treatment Secondary prophylaxis with antituberculous drugs after successful completion of conventional antituberculous treatment may be more effective than placebo at reducing tuberculosis recurrence; however, evidence is weak and may not be generalisable to all people with HIV (very low-quality evidence).

For GRADE evaluation of interventions for tuberculosis in people with HIV, see table, p 19.

Benefits: We found two RCTs. The first RCT (233 adults in Haiti; 142 were HIV positive, who had successfully completed 6 months of 3-drug antituberculous treatment for pulmonary tuberculosis) comparing 12 months' isoniazid 300 mg daily plus vitamin B6 40 mg daily versus placebo plus vitamin B6 40 mg daily. The RCT found that tuberculosis recurrence was significantly lower with isoniazid compared with placebo over a mean of 25 months in people with HIV (1.4 cases/100 person-years of follow-up with isoniazid vs 7.8 cases/100 person-years of follow-up with placebo; RR 0.18, 95% CI 0.04 to 0.83; P <0.001). However, it found no significant difference between groups in mortality in people with HIV over the same time period (deaths: 17 with isoniazid vs 17 with placebo; RR 0.93, 95% CI 0.51 to 1.65). The RCT may have been underpowered to detect a clinically important difference. Among HIV-positive people, all cases of recurrent tuberculosis occurred among those who had HIV-related symptoms before the initial diagnosis of tuberculosis. Therefore, any potential benefit from secondary prophylaxis with isoniazid may be limited to people with symptomatic HIV (a marker of advanced HIV). The criteria for diagnosis of recurrence of tuberculosis and for diagnosis of the initial episode were based on the case definition of the American Thoracic Society. Only 43% of people had positive M. tuberculosis cultures, therefore the initial diagnosis of tuberculosis or the diagnosis of recurrence may have been incorrect in some people. The results should therefore be interpreted with caution. In addition, as the 233 people included in the study had all successfully completed a 6-month course of antituberculous treatment, they are a select group. Therefore the results may not be applicable to all HIV-positive people with tuberculosis. Furthermore, the participants in this study were not receiving highly active antiretroviral...
treatment (HAART), therefore the results may not be applicable to people who were receiving HAART.

The second RCT (open-label, 263 HIV-positive people in Côte d'Ivoire who had completed treatment for tuberculosis) comparing isoniazid 300 mg once daily plus sulfadoxine–pyrimethamine (a drug that is active against toxoplasma, pneumocystis, and malaria, and which is not active against M tuberculosis) versus no intervention. It found that significantly fewer people had recurrent tuberculosis with isoniazid plus sulfadoxine–pyrimethamine compared with no treatment (2.1/100 person-years of follow-up with isoniazid plus sulfadoxine–pyrimethamine vs 7.0/100 person-years of follow-up with no treatment; RR 0.30, 95% CI 0.09 to 0.94; P = 0.023). [38] Fewer deaths were reported in the intervention group, although the difference was not statistically significant (10.4/100 person-years of follow-up with isoniazid plus sulfadoxine–pyrimethamine vs 16.2/100 person-years of follow-up with no treatment; RR 0.64, 95% CI 0.35 to 1.17; P = 0.17). However, the mortality results must be interpreted with caution because the intervention also included sulfadoxine–pyrimethamine, which was used to reduce the risk of infections other than tuberculosis.

**Harms:**
The first RCT did not report on the frequency of adverse effects among people receiving isoniazid compared with those receiving placebo. [17] As people in the RCT had already received 6 months' antituberculous treatment, they may be a select group who have been proved to tolerate isoniazid. The second RCT found significantly fewer adverse effects with isoniazid sulfadoxine–pyrimethamine compared with placebo (RR 0.35, 95% CI 0.31 to 0.4). [38] The main reported adverse effects were coughing, fatigue, headache, anorexia, fever, arthralgia, diarrhoea, rhinitis, pruritus, dizziness and confusion, and nausea and vomiting.

**Comment:**
People with HIV who have completed antituberculous treatment should receive HAART. At present, most clinicians probably do not give secondary prophylaxis with isoniazid. Further research is required to determine if secondary prophylaxis with isoniazid is beneficial in those who receive HAART.

**GLOSSARY**

**Directly observed therapy, short course (DOT)** Supervised administration of a combination antituberculous treatment regimen.

**Highly active antiretroviral treatment (HAART)** Combination drug treatment used to achieve maximal suppression of HIV replication.

**Conventional treatment** Two months of rifampicin plus isoniazid plus pyrazinamide (plus ethambutol in areas where drug-resistant tuberculosis is likely) followed by 4 to 7 months of rifampicin plus isoniazid. The conventional daily doses recommended by WHO are: rifampicin 600 mg daily (for people weighing 50 kg or more) or 450 mg daily (<50 kg); isoniazid 300 mg daily; ethambutol 15 mg/kg daily; and pyrazinamide 2000 mg daily (50 kg or over) or 1500 mg daily (<50 kg). [40] These are the dosages used in the studies described in this review except where stated otherwise in the text.

**Culture test** Laboratory test to detect Mycobacterium tuberculosis by culture of sputum or other specimen. This provides definitive proof of active tuberculosis, but is not always available in a resource-poor setting.

**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.

**Smear test** Direct Ziehl–Nielsen staining of sputum or other specimen to detect acid-fast bacilli (fluorescent microscopy of auramine-stained sputum is often preferred in resource-rich countries). These organisms are most likely to be Mycobacterium tuberculosis but, in a person with HIV, could represent atypical mycobacteria. HIV-positive people with tuberculosis have been found to have a higher probability than HIV-negative people of being smear negative, because a lower mycobacterial load is required to produce an active (i.e., symptomatic) infection. [9]

**Very low-quality evidence** Any estimate of effect is very uncertain.

**SUBSTANTIVE CHANGES**

**Early initiation of highly active antiretroviral treatment** Two cohort studies added. [28] [29] One prospective study found mortality was increased the longer HAART initiation was delayed after starting antituberculosis treatment, and found decreased mortality in people with bacteriologically confirmed tuberculosis, who started HAART within the first 120 days of antituberculosis treatment versus people who started HAART later than this. [38] Another study (retrospective from 1996 to 2000; prospective from 2000 to 2004) found better survival in people who started HAART...
HIV: treating tuberculosis within 2 months of starting antituberculous treatment versus people who started HAART more than 3 months after antituberculous treatment. [29] Categorisation unchanged (unknown effectiveness).

REFERENCES


### TABLE 1  Grade evaluation of interventions for tuberculosis in people with HIV

<table>
<thead>
<tr>
<th>Important outcomes</th>
<th>Mortality, quality of life, adverse effects, presence of mycobacterium tuberculosis in sputum, recurrence of tuberculosis, respiratory failure</th>
<th>Number of studies (participants)</th>
<th>Outcome</th>
<th>Comparison</th>
<th>Type of evidence</th>
<th>Quality</th>
<th>Consistency</th>
<th>Directness</th>
<th>Effect size</th>
<th>GRADE</th>
<th>Comment</th>
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<td>What are the effects of first-line treatments for tuberculosis in HIV-positive people?</td>
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<td>Mortality</td>
<td>Conventional treatment v regimen containing rifabutin</td>
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<td></td>
<td>Recurrence of tuberculosis</td>
<td>Adjuvant corticosteroids v placebo (pleural tuberculosis)</td>
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<td>1 (168) [27]</td>
<td>Presence of mycobacterium tuberculosis in sputum (acid-fast bacilli test)</td>
<td>Directly observed therapy v unsupervised treatment</td>
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<td>2 (341) [19] [31]</td>
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<td>Longer-course antituberculous treatment v conventional course</td>
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<td>Directness point deducted for exclusion of non-responders from one RCT, and use of a composite outcome in 1 RCT.</td>
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<td>1 (760) [33]</td>
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<td>2 (856) [33]</td>
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<td>Mycobacterium vaccae immunotherapy v placebo</td>
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<td>21 studies [34]</td>
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<td>Shorter (3 months or less) compared with longer courses (5 months or more) of rifampicin</td>
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</table>

What are the effects of second-line treatments for tuberculosis in HIV-positive people?

<table>
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<th>Number of studies (participants)</th>
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<th>Type of evidence</th>
<th>Quality</th>
<th>Consistency</th>
<th>Directness</th>
<th>Effect size</th>
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<tbody>
<tr>
<td>2 (375) [17] [35]</td>
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<td>Antituberculosis drugs v placebo/no treatment (after successful completion of conventional antituberculosis treatment)</td>
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<td>−1</td>
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<td>2 (375) [17] [36]</td>
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<td>Antituberculosis drugs v placebo/no treatment (after successful completion of conventional antituberculosis treatment)</td>
<td>4</td>
<td>−3</td>
<td>0</td>
<td>−1</td>
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<td>Very low</td>
<td>Quality points deducted for no blinding in 1 RCT, subgroup analysis, and for uncertainty about diagnosis of tuberculosis. Directness point deducted for uncertainty about generalisability to people with non-symptomatic HIV. Effect-size point added for RR &lt;0.5.</td>
</tr>
</tbody>
</table>

Type of evidence: 4 = RCT; 2 = Observational
Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio