

# Managing tuberculosis in people with HIV

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## Executive summary/Key messages

Tuberculosis is one of the most frequent causes of death in people infected with HIV in resource poor countries. Each year about 741,000 cases of active tuberculosis occur in people who are HIV positive, resulting in 248,000 deaths.

## Preventing tuberculosis in people with HIV

In people who are HIV and tuberculin skin test positive, antituberculosis prophylaxis drugs reduced the frequency of tuberculosis over 1–3 years but did not reduce mortality. The benefit of prophylaxis may diminish with time after treatment is stopped.

In people who are HIV positive but tuberculin skin test negative, antituberculosis prophylaxis drugs had no effect on the frequency of tuberculosis or death from any cause.

Isoniazid monotherapy for 6–12 months and combination treatment (isoniazid plus rifampicin, rifampicin plus pyrazinamide, or isoniazid plus rifampicin plus pyrazinamide) for 2–3 months were equally effective. However, adverse effects leading to treatment discontinuation were more common with combination treatment than with isoniazid monotherapy.

## Treating tuberculosis in people with HIV

There is consensus that conventional antituberculosis treatment (2 months of rifampicin, isoniazid, and pyrazinamide [plus ethambutol in areas where drug resistant tuberculosis is likely] followed by 4–7 months of rifampicin and isoniazid) is effective for the treatment of tuberculosis in people with HIV.

We found insufficient evidence about the effects of conventional antituberculosis treatment compared with regimens containing rifabutin or quinolones. Thiacetazone (a quinolone) is associated with a greater number of adverse effects, including fatal mucocutaneous reactions among HIV positive children.

Adding *Mycobacterium vaccae* immunisation to antituberculosis treatment achieved no additional benefits in survival or negative sputum *Mycobacterium tuberculosis* culture rates.

Observational cohort studies suggest that directly observed therapy, short course (DOT) produces low treatment failure rates.

Further research is needed regarding:

- optimum duration of treatment
- the effects of adding early initiation of highly active antiretroviral treatment to conventional antituberculosis treatment
- different regimens of antituberculosis treatment after failure of first line treatment for tuberculosis in people with HIV.

## Introduction

Worldwide, HIV infection kills more people than any other infectious disease.[1] Infection with *Mycobacterium tuberculosis* is among the most important HIV related opportunistic infections, particularly in resource poor countries. 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

Tuberculosis most commonly affects the lungs, but it can also affect many other organs such as lymph nodes, kidneys, liver, gastrointestinal tract, and the central nervous system. In Africa and South America, 40–80% of HIV positive people presenting with tuberculosis have pulmonary disease.[2] 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 topic deals with the prevention and treatment of active tuberculosis (pulmonary and extrapulmonary) in people with HIV.

## Scope of the problem

About one third of the world's population has latent *M. tuberculosis* infection.[3] Each year about 741,000 cases of active tuberculosis occur in people who are HIV positive, resulting in 248,000 deaths.[1] HIV infection has been a major factor in the increase in the number of cases of tuberculosis occurring worldwide. [4] [33] Most people infected with HIV live in subSaharan Africa. In several countries of this region, over 40% of people who develop tuberculosis are infected with HIV.[4][5][6][7] Tuberculosis is the most frequent cause of death in people infected with HIV in Zaire.[8] The situation is probably similar in many other subSaharan African and other resource poor countries.

Risk factors for tuberculosis include social factors such as poverty, overcrowding, and homelessness and medical factors such as steroid treatment. In people co-infected with HIV and *M. tuberculosis*, in the USA, the annual risk of developing active tuberculosis is about 5–10%, [9][10][11] more than 10 times greater than for people infected with *M. tuberculosis* who do not have HIV. The annual risk of tuberculosis in coinfecting patients may be higher in resource poor countries than in established market economies because of additional risk factors such as poor nutrition and poverty. Without preventive treatment around 30% of HIV-positive people with latent tuberculosis will develop active tuberculosis.[9] Preventive therapy aims to reduce this risk.

Without treatment, active tuberculosis would most likely 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 pre-highly active antiretroviral treatment era, in the USA, the median survival of HIV infected people treated for tuberculosis was 16 months. [12] However, only 13/99 (13%) of the deaths were attributed to tuberculosis. The other common causes of death were *Pneumocystis* pneumonia (24%), bacterial pneumonia (14%), wasting syndrome (9%), and Kaposi's sarcoma (9%).[12] In Malawi, 47% of HIV positive people with tuberculosis died during 32 months of follow up. [34] The commonest causes of death among people with HIV in subSaharan Africa are wasting syndrome, chronic diarrhoea, cryptococcal meningitis and chest infection. [35] The differences in cause of death between subSaharan Africa and the USA, may be due to the availability of diagnostic tests as much as due to genuine differences in the underlying causes.

Recurrence of tuberculosis after completion of treatment is more common among people with HIV than among HIV uninfected people. 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.[13] In a study 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 to 0.4 per 100 person years of follow up in HIV negative people.[36] These figures are higher than the 5.4% recurrence rate reported among HIV positive people who completed tuberculosis treatment in New York.[11]

## Key questions relevant to resource poor settings

The key questions selected were based on previous *Clinical Evidence* reviews of interventions to prevent and treat tuberculosis in people with HIV:

- What are the effects of prophylaxis against tuberculosis in people infected with HIV?
- As there is consensus that conventional antituberculosis treatment is effective, questions about initial treatment of tuberculosis focussed on:
  - Antimycobacterial treatment combinations containing rifabutin, thiacetazone, or quinolones (compared with conventional treatment)
  - Short versus longer courses of treatment
  - Adjuvant immunotherapy using *Mycobacterium vaccae* combined with conventional treatment (compared with conventional treatment alone)
  - Early initiation of highly active antiretroviral therapy (compared with delayed initiation of highly active antiretroviral treatment)
  - Directly observed versus unsupervised therapy
  - Anti-mycobacterial treatment combinations for second line treatment in people for whom first line treatment has failed (comparison between treatment regimens)

The outcomes of interest for prophylaxis against tuberculosis were mortality, development of tuberculosis (defined clinically or microbiologically), and adverse effects of treatment.

The outcomes of interest for treatment of tuberculosis were mortality, the presence of *M. tuberculosis* in sputum during treatment or at the end of treatment (culture or smear test), recurrence of tuberculosis, and adverse effects of treatment.

## Methods

For prevention of tuberculosis, the search was undertaken in December 2004. For treatment of tuberculosis, the search was undertaken in July 2005. The following sources were searched for systematic reviews, randomized controlled trials and cohort studies: Medline, Embase, Cochrane Database of Systematic Reviews, CENTRAL, Database of Reviews of Effects, HTA Database, Trip Database, AIDsearch, African Journals Online, African Index Medicus, Global Index Medicus, LILACS, Index Medicus for South East Asia Region. Abstracts of the studies retrieved were assessed independently by two information specialists using pre-determined criteria to identify relevant studies, and then sent to the author for further assessment of the full articles.

The author 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. Placebo controlled trials have been performed on prophylaxis against tuberculosis. We considered smaller RCTs and systematic reviews of non-controlled studies if large RCTs were not available. They included studies from resource poor countries and from established market economies. Our review discusses the situations where data is only available for studies from established market economies and the limitations this creates for applicability to resource poor countries.

Some of the studies of the treatment of tuberculosis in people with HIV were difficult to interpret because many participants 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 infected people only. Where studies included both people without HIV infection and people with HIV infection, results for people with HIV infection are presented if subgroup analysis was pre-specified. Studies performing post-hoc subgroup analysis 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. The majority of studies described in this review are on pulmonary tuberculosis. This was not a deliberate intention of the search and is largely a consequence of pulmonary tuberculosis being more easily and reliably diagnosed than extrapulmonary tuberculosis. However the results may not be directly applicable to extrapulmonary tuberculosis, particularly for central nervous system disease.

Two months of rifampicin, isoniazid, and pyrazinamide (plus ethambutol in areas where drug resistant tuberculosis is likely) followed by between 4 and 7 months of rifampicin and isoniazid is generally regarded as the conventional treatment for tuberculosis. Most studies of treatment of tuberculosis used this regimen as their comparator.

# What are the effects of prophylaxis against tuberculosis in people infected with HIV?

## Antituberculosis prophylaxis versus placebo

One systematic review found that in people who are both HIV and tuberculin skin test positive, antituberculosis prophylaxis drugs reduced the frequency of tuberculosis compared with placebo over 1–3 years. However it found no significant difference between treatments in the risk of death from any cause. The review found no significant difference between antituberculosis prophylaxis drugs and placebo in the frequency of tuberculosis, or death from any cause in people who were HIV positive but tuberculin skin test negative. One RCT found that the benefit of prophylaxis diminished with time after treatment was stopped.

## Benefits of antituberculosis prophylaxis versus placebo:

We found one systematic review (search date 2002, 7 RCTs, 5664 HIV positive adults from Haiti, Kenya, Spain, Uganda, USA, and Zambia).[28] The RCTs identified by the review compared isoniazid (6–12 months) or combination treatment (rifampicin plus pyrazinamide, isoniazid plus rifampicin, or isoniazid plus rifampicin plus pyrazinamide, for 2–3 months) versus placebo. Mean follow up varied from 1 to 3 years. The main outcomes, stratified by tuberculin skin test positivity, were tuberculosis (either microbiological or clinical) and death (from any cause). In one of the RCTs included in the review,[28] many people taking placebo were offered isoniazid after randomisation.[29]

### Mortality:

The review found no significant difference between prophylaxis and placebo in the risk of death from any cause in tuberculin skin test positive adults (4 RCTs, 2378 people; 195/1760 [11.0%] with treatment v 84/618 [13.6%] with placebo; RR 0.80, 95% CI 0.63 to 1.02). The review found no significant difference among tuberculin skin test negative adults between antituberculosis prophylaxis and placebo in the risk of death (from any cause; 373/1629 [23%] with treatment v 298/1193 [25%] with placebo; RR 1.02, 95% CI 0.89 to 1.15). [28]

### Development of tuberculosis:

The review found that antituberculosis prophylaxis significantly reduced the incidence of active tuberculosis in tuberculin skin test positive adults compared with placebo (4 RCTs, 2378 people; incidence of active tuberculosis: 39/1760 [2.2%] with treatment v 46/618 [7.4%] with placebo; RR 0.38, 95% CI 0.25 to 0.57).[28] The review found no significant difference among tuberculin skin test negative adults between antituberculosis prophylaxis and placebo in the risk of tuberculosis (7 RCTs, 2822 people: 66/1629 [4.1%] with treatment v 54/1193 [4.5%] with placebo; RR 0.83, 95% CI 0.58 to 1.18) Two RCTs included in the systematic review reported the results of long term follow up of antituberculosis prophylaxis on the risk of tuberculosis infection.[29] [30] The first RCT, compared isoniazid or rifampicin plus pyrazinamide versus placebo after a mean of 3 years' follow up (see comment below).[29] Intention to treat analysis found that overall, isoniazid or rifampicin plus pyrazinamide significantly reduced the overall risk of tuberculosis at 2.5 years compared with placebo (1053 Zambian adults; 161 tuberculin skin test positive, 517 negative, the rest unknown; cumulative RR of tuberculosis: 0.55, 95% CI 0.32 to 0.93), although the benefit

diminished over this time.[28] The second RCT compared four treatments, isoniazid, isoniazid plus rifampicin, isoniazid plus rifampicin plus pyrazinamide, and placebo.[30] It found no significant difference between isoniazid (given for 6 months) and placebo in the risk of active tuberculosis in tuberculin positive people at 3 years (2736 Ugandan adults, 2018 tuberculin skin test positive and 718 negative; RR 0.67, 95% CI 0.42 to 1.07). It also found that isoniazid plus rifampicin (for 3 months), or isoniazid plus rifampicin plus pyrazinamide (for 3 months) significantly reduced the risk of active tuberculosis infection in tuberculin positive people compared with placebo at 3 years (isoniazid plus rifampicin versus placebo adjusted RR 0.49, 95% CI 0.29 to 0.82; isoniazid plus rifampicin plus pyrazinamide versus placebo adjusted RR 0.41, 95% CI 0.22 to 0.76). It found no significant difference between isoniazid (given for 6 months) and placebo in people with a negative tuberculin skin test at 1 or 2 years' follow up (at 1 year: RR 0.74, 95% CI 0.30 to 1.79; at 2 years: adjusted RR 0.61, 95% CI 0.32 to 1.16).[30]

### **Harms of antituberculosis prophylaxis versus placebo:**

The systematic review found that antituberculosis prophylaxis significantly increased the risk of adverse events resulting in discontinuation of treatment compared with placebo (7 RCTs; 5427 people; 137/3554 [3.9%] with antituberculosis prophylaxis v 33/1873 [1.8%] with placebo: RR 2.49, 95% CI 1.64 to 3.77).[28]

### **Comment:**

Without prophylaxis, people who are HIV and tuberculin skin test positive have a 30% or more lifetime risk of developing tuberculosis compared with a 10% lifetime risk in people who are HIV positive but tuberculin skin test negative.[9]

#### **Prophylaxis versus placebo**

##### **Recommendation 1:**

In HIV positive people with positive tuberculin skin tests, clinicians should routinely administer antituberculosis prophylaxis.

##### **Recommendation 2:**

In HIV positive people with negative tuberculin skin tests, clinicians should not routinely administer antituberculosis prophylaxis.

**GRADE:** (strong recommendation, high quality evidence)

### **Isoniazid prophylaxis for 6–12 months (compared with combination treatment for 2–3 months)**

One systematic review found no significant difference in the risk of tuberculosis or death (any cause) between isoniazid monotherapy for 6–12 months and combination treatment (isoniazid plus rifampicin, rifampicin plus pyrazinamide, or isoniazid plus rifampicin plus pyrazinamide) for 2–3 months. The review found that adverse effects leading to treatment discontinuation were more common with combination treatment than with isoniazid monotherapy.

## **Benefits of isoniazid prophylaxis for 6–12 months (v combination treatment for 2–3 months):**

We found one systematic review comparing isoniazid monotherapy for 6–12 months and combination treatment (isoniazid plus rifampicin, rifampicin plus pyrazinamide, or isoniazid plus rifampicin plus pyrazinamide) for 2–3 months (search date 2002).[28]

### **Mortality:**

The review found no significant difference in the risk of death (any cause) between isoniazid monotherapy and combination treatment (4 RCTs, 1385 people; 71/683 [10.39%] with isoniazid v 67/702 [9.54%] with isoniazid plus rifampicin; RR 1.09, 95% CI 0.80 to 1.50; 6 RCTs, 3137 people; 299/1597 [18.72%] with isoniazid v 283/1540 [18.37%] with rifampicin plus pyrazinamide; RR 1.03, 95% CI 0.89 to 1.19; 1 RCT, 998 people; 58/536 [10.82%] with isoniazid v 58/462 [12.55%] isoniazid plus rifampicin plus pyrazinamide; RR 0.86, 95% CI 0.61 to 1.21).[28]

### **Development of tuberculosis:**

The review found no significant difference in the risk of active tuberculosis (3 RCTs, 1390 people; 14/683 [2.05%] with isoniazid v 14/707 [1.98%] with isoniazid plus rifampicin; RR 1.05, 95% CI 0.51 to 2.17; 6 RCTs, 3196 people; 73/1597 [4.57%] with isoniazid v 73/1599 [4.56%] with rifampicin plus pyrazinamide: RR 1.00, 95% CI 0.73 to 1.38; 1 RCT, 998 people; 7/536 [1.31%] with isoniazid v 10/462 [2.16%] isoniazid plus rifampicin plus pyrazinamide; RR 0.60, 95% CI 0.23 to 1.57).[28] The systematic review did not find significant heterogeneity in outcomes in people whose tuberculin skin test result at baseline was positive, negative, or unknown.[28]

## **Harms of isoniazid prophylaxis for 6–12 months (v combination treatment for 2–3 months):**

The systematic review found that combination treatment (for 2–3 months) increased the risk of treatment discontinuation owing to adverse effects compared with isoniazid monotherapy for 6–12 months (3 RCTs, 1390 people; 24/683 [3.51%] with isoniazid v 33/707 [4.66%] with isoniazid plus rifampicin; RR 0.75, 95% CI 0.46 to 1.24; 4 RCTs, 3196 people; 66/1597 [4.13%] with isoniazid v 102/1599 [6.38%] with rifampicin plus pyrazinamide; RR 0.64, 95% CI 0.48 to 0.86; 1 RCT, 998 people; 3/536 [0.56%] with isoniazid v 26/462 [5.62%] with isoniazid plus rifampicin plus pyrazinamide; RR 0.10, 95% CI 0.03 to 0.33).[28]

### **Comment:**

There is concern about emergence of rifampicin resistance if this drug is used in antituberculosis prophylaxis, although we found no reports of this. There is a theoretical risk that widespread, unsupervised use of isoniazid alone could promote resistance to this drug. A systematic review was unable to establish whether this has occurred.[32]

### **Isoniazid monotherapy prophylaxis**

#### **Recommendation 3:**

In HIV positive people with positive tuberculin skin tests, clinicians may prefer prophylaxis with isoniazid monotherapy to combination therapy as there is no proven benefit with shorter course combination treatment over longer course monotherapy and some evidence of increased discontinuation due to adverse effects.

**GRADE:** (weak recommendation, high quality evidence)

## **What are the effects of first line treatments for tuberculosis in people infected with HIV?**

### **Antimycobacterial treatment combinations**

#### **Benefits of conventional antituberculosis treatment:**

There is consensus that conventional antituberculosis treatment (2 months of rifampicin, isoniazid, and pyrazinamide [plus ethambutol in areas where drug resistant tuberculosis is likely] followed by 4–7 months of rifampicin and isoniazid; see glossary term) is effective for the treatment of tuberculosis in people with HIV.

#### **Mortality:**

We found insufficient evidence about the effects of conventional antituberculosis treatment compared with regimens containing rifabutin or quinolones. One RCT found no significant difference in survival between conventional antituberculosis treatment and a thiacetazone containing regimen.[17] For details of the RCTs comparing conventional antituberculosis treatment with treatments containing rifabutin, quinolones or thiacetazone, see the relevant sections below.

#### **Smear conversion after 2 months of therapy:**

We found insufficient evidence about the effects of conventional antituberculosis treatment compared with regimens containing rifabutin or quinolones. One RCT provided limited evidence that conventional antituberculosis treatment increased the proportion of people with negative sputum culture after 2 months of treatment compared with a thiacetazone containing regimen.[17]

#### **Harms of conventional antituberculosis treatment:**

Hardly any of the published RCTs report on the frequency of adverse effects of conventional antituberculosis 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 infected and 26 HIV negative adults with culture confirmed pulmonary tuberculosis in Uganda) found that adverse effects occurred in over one third of HIV infected participants (98/265 [37.0%]) who received conventional antituberculosis treatment (including ethambutol).[14] The most common adverse effects were arthralgia (59/265 [22.3%]), peripheral neuropathy (18/265 [6.8%]), skin rash (7/265 [2.6%]), hepatitis (2/265 [0.8%]), and gastrointestinal intolerance (2/265 [0.8%]).[14] Adverse effects requiring termination of treatment were rare (2/265 [0.8%]).[14] However the frequency of serious adverse effects varies widely between study cohorts. One RCT conducted in the USA found that 17.2% of participants receiving conventional antituberculosis treatment experienced an adverse effect which was potentially life threatening or

which required termination of treatment.[15] This RCT may have employed a lower threshold for termination of treatment compared with the Ugandan study.[14] One RCT found fewer adverse effects with conventional antituberculosis treatment than with a thiacetazone containing regimen.[17]

## **Antituberculosis treatment containing rifabutin (compared with conventional treatment)**

One small RCT provided insufficient evidence about the effects of a rifabutin containing regimen compared with conventional antituberculosis treatment as the first line treatment for tuberculosis in people infected with HIV.

### **Benefits of antituberculosis treatment containing rifabutin versus conventional antituberculosis treatment:**

We found one RCT (50 HIV positive adults in Uganda, with sputum smear positive pulmonary tuberculosis; 1 person in the rifabutin group was excluded from analysis because of *Mycobacterium fortuitum* infection).[16] It compared rifabutin (150 mg/day for people < 50 kg and 300 mg/day for people ≥ 50 kg) plus the conventional daily doses of isoniazid for 6 months plus ethambutol and pyrazinamide for the first 2 months versus a 6 month course of conventional antituberculosis treatment including rifampicin for the initial 2 months.

#### **Mortality:**

Mortality was higher in people receiving rifabutin compared with conventional treatment (AR 4/24 [16.7%] with rifabutin containing regimen v 2/25 [8.0%] with conventional treatment). However, the RCT did not assess the significance of the difference between groups.

#### **Smear conversion after 2 months of therapy:**

It found that the rifabutin containing regimen increased the proportion of people with negative sputum culture for *Mycobacterium tuberculosis* at 2 months compared with conventional treatment (AR for negative sputum culture at 2 months: 18/24 [75.0%] with rifabutin containing regimen v 11/25 [44.0%] with conventional treatment).

#### **Smear conversion at end of therapy:**

The difference between groups had decreased by the end of treatment (AR for negative sputum culture at end of treatment: 22/24 [91.7%] with rifabutin containing regimen v 22/25 [88.0%] 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  $P < 0.05$ ).

#### **Recurrence of tuberculosis:**

This outcome was not assessed.

## **Harms of antituberculosis treatment containing rifabutin versus conventional antituberculosis treatment:**

The RCT found no significant difference in reported adverse effects between people treated with the rifabutin containing regimen and conventional antituberculosis treatment (no further data reported). Reported adverse events in both treatment groups included arthralgia (AR for mild arthralgia 31%, moderate 22%, severe 4.4%), myalgia, nausea, vomiting, gastrointestinal discomfort, and loss of appetite (no further data reported).[16] 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 reported). [16]

### **Rifabutin treatment**

#### **Recommendation 4:**

There is consensus that conventional antituberculosis treatment using rifampicin is effective as first line therapy. If rifampicin use needs to be avoided, in HIV positive people with active tuberculosis, clinicians might use rifabutin as part of antituberculosis treatment as first line therapy.

**GRADE:** (weak recommendation, moderate quality evidence)

## **Antituberculosis treatment containing thiacetazone (compared with conventional treatment)**

One RCT provided limited evidence that a thiacetazone containing regimen decreased the proportion of people with negative sputum culture at 2 months compared with conventional antituberculosis treatment (i.e. the thiacetazone containing regimen was associated with a higher rate of treatment failure). It found no significant difference in survival between treatments. However the thiacetazone containing regimen was associated with a greater number of adverse effects, mostly skin rash. One observational study reported a high rate of fatal mucocutaneous reactions among HIV positive children receiving thiacetazone containing regimens. Many countries no longer use thiacetazone because of the high frequency of adverse events associated with this drug.

## **Benefits of antituberculosis treatment containing thiacetazone versus conventional antituberculosis treatment:**

We found one RCT (191 HIV positive adults in Uganda with smear positive pulmonary tuberculosis) which compared a 12 month course of thiacetazone (150 mg daily) plus isoniazid (300 mg daily) plus streptomycin (0.75 g/day for people weighing < 50 kg or 1 g/day for people  $\geq$  50 kg for the first 2 months) with a 9 month course of conventional antituberculosis treatment (not including ethambutol).[17]

## **Mortality:**

The RCT found no significant difference in survival between groups at 1 year (AR: 65% with thiacetazone containing regimen v 72% with conventional treatment; log rank  $P > 0.2$ ).

## **Smear conversion after 2 months of therapy:**

At 2 months, significantly fewer people had negative sputum culture for *Mycobacterium tuberculosis* with the thiacetazone containing regimen compared with conventional treatment (21/57 [36.8%] with thiacetazone 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.

## **Smear conversion at end of therapy:**

This outcome was not assessed.

## **Recurrence of tuberculosis:**

This outcome was not assessed.

## **Harms of antituberculosis treatment containing thiacetazone versus conventional antituberculosis treatment:**

The RCT found significantly more adverse effects with the thiacetazone containing regimen compared with conventional treatment (12 events [18.2 per 100 person years of observation] with thiacetazone containing regimen v 1 event [1.6 per 100 person years of observation] with conventional treatment; RR 11.7, 95% CI 1.52 to 90.0).[17] The most common adverse effect was skin rash, which was also significantly more common with the thiacetazone containing regimen compared with conventional treatment (10 events [15.2 per 100 person years of observation] with thiacetazone containing regimen v 1 event [1.6 per 100 person years of observation] with conventional treatment; RR 9.7, 95% CI 1.24 to 75.8).[17] Skin rash has been reported as a common problem among HIV positive people receiving thiacetazone. In a retrospective survey, 24/79 [30.4%] Zambian HIV positive adults who were treated with a thiacetazone containing antituberculosis regimen were found to have developed a skin rash which required a change of treatment.[18] A cohort study of Zambian children aged 1 month to 15 years also reported a high rate of adverse effects among HIV positive children treated with thiacetazone (19/88 [21.6%]).[19] Twelve children (13.6%) developed a severe mucocutaneous reaction (Stevens-Johnson syndrome) and 11 (12.5%) of these children died.[19]

### **Thiacetazone treatment**

#### **Recommendation 5:**

In HIV positive people with active tuberculosis, clinicians should not administer thiacetazone as part of antituberculosis treatment as first line therapy.

**GRADE:** (strong recommendation, moderate quality evidence)

## **Antituberculosis treatment containing quinolones (compared with conventional antituberculosis treatment)**

One RCT and one post hoc analysis of people with HIV within another RCT provided insufficient evidence about the effects of a quinolone (levofloxacin) containing regimen compared with conventional antituberculosis treatment.

### **Benefits of antituberculosis treatment containing quinolones versus conventional antituberculosis treatment:**

We found one RCT.[15] People included in the RCT came from areas where at least 10% of people had isoniazid resistant *M. tuberculosis*. [15] All people included 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. The exclusion of a large proportion of people from analysis post-randomisation may have resulted in the groups not being balanced for confounding factors; therefore the results of this RCT should be interpreted with caution.

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 antituberculosis 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 antituberculosis treatment alone (see comment below).[15] The conventional antituberculosis treatment regimen in this study used daily dosing for 2 weeks, followed by a 6 week course of three times weekly rifampicin 600 mg, isoniazid 900 mg (if  $\geq 50$  kg) or 600 mg (if  $< 50$  kg), pyrazinamide 2.5 g (if  $\geq 50$  kg) or 2.0 g ( $< 50$  kg) and 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 antituberculosis treatment).

We also 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).[20] 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 antituberculosis treatment (rifampicin 600 mg/day and isoniazid 300 mg/day, plus pyrazinamide 25 mg/kg/day during the initial 4 months, and ethambutol 15 mg/kg/day during the initial 2 months).

### **Mortality:**

The RCT found no significant difference between treatments in mortality during the initial 8 weeks of treatment (1/53 [1.9%] with levofloxacin containing regimen v 3/48 [6.2%] with conventional treatment; P reported as not significant).

### **Smear conversion after 2 months of therapy:**

The RCT found no significant difference between treatments in the proportion of participants with cultures negative for *Mycobacterium tuberculosis* after 8 weeks of treatment (46/48 [95.8%] with levofloxacin containing regimen v 36/37 [97.3%] with conventional treatment; P = 1.00).[15]

### **Smear conversion at end of therapy:**

This outcome was not assessed in the RCT.[15]

The post hoc analysis 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).

### **Recurrence of tuberculosis:**

This outcome was not assessed by the RCT because the study was in two phases and in the second phase the effects of treatment duration on recurrence of tuberculosis were studied (see short versus longer courses of treatment).[15]

The post hoc analysis found no significant difference between treatments in recurrence of tuberculosis during the first 6 months after completion of treatment (AR: 3/25 [12.0%] with ciprofloxacin containing regimen v 0/30 [0%] with conventional treatment; P = 0.09).[20]

### **Harms of antituberculosis treatment containing quinolones versus conventional antituberculosis 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 antituberculosis treatment (AR: 15/87 [17.2%] with levofloxacin containing regimen v 15/87 [17.2%] with conventional treatment; P = 1.00).[15]

#### **Quinolones treatment**

##### **Recommendation 6:**

In HIV positive people with active tuberculosis, we make no recommendation on the use of quinolones as part of antituberculosis treatment as first line therapy.

**GRADE:** (no recommendation, low quality evidence)

## **Short versus longer courses of treatment of rifampicin containing regimens**

RCTs provided insufficient evidence about the effects of regimens longer than 6 months compared to conventional short course (6 months) antituberculosis treatment. One systematic review of observational evidence found that antituberculosis regimens including rifampicin for at least 5 months reduced recurrence of tuberculosis compared with regimens containing rifampicin for 3 months or shorter.

### **Benefits of longer courses of antituberculosis treatment versus conventional short course treatment:**

We found two RCTs [15] [21] one systematic review of prospective cohort studies.[22]

The first RCT enrolled 335 HIV positive people in Zaire with smear positive pulmonary tuberculosis, all of whom received 6 months of conventional antituberculosis treatment (including ethambutol).[21]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 if weight  $\geq$  50 kg or 450 mg for people  $<$  50 kg] plus isoniazid [15 mg/kg]) or placebo. In the first RCT, as people who remained culture or smear positive after 6 months of treatment were excluded from randomisation, the results of this study may not be generalisable to all HIV positive people commencing antituberculosis treatment.[21]

The second RCT included 101 HIV positive people aged over 13 years from the USA with culture positive pulmonary tuberculosis who had completed 2 months of treatment with either conventional treatment (including ethambutol) alone or conventional treatment plus levofloxacin (see benefits of antituberculosis treatment containing quinolones).[15] 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 if weight  $\geq$  50 kg or 600 mg if weight  $<$  50 kg).

The systematic review of prospective cohort studies (search date 2002, 47 studies, 21 studies including people with HIV) assessed rifampicin based treatment regimens for tuberculosis.[22] Studies were included which compared treatment regimens which differed by constituent drugs as well as by treatment duration.

### **Mortality:**

The first RCT found no significant difference between treatments in survival at 12 months after randomisation (102/121 [84.3%] with 12 months' treatment  $\nu$  100/119 [84.0%] with 6 months' treatment;  $P = 0.95$ ).[21] The second RCT found no significant difference between treatments in mortality during a minimum of 2 years of follow up (26/50 [52.0%; 27.1 per 100 person years] with 9 months' treatment  $\nu$  21/51 [41.2%; 21.1 per 100 person years] with 6 months' treatment; RR 1.3, CI not reported;  $P = 0.38$ ).[15]

### **Smear conversion after 2 months of therapy:**

This outcome was not assessed.

### **Smear conversion at end of therapy:**

This outcome was not assessed.

### **Recurrence of tuberculosis:**

The first RCT found that 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 v 9% with 6 months' treatment;  $P < 0.01$ ).[21] The second 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 per 100 person years] with 9 months' treatment v 2/51 [3.9%; 2.1 events per 100 person years] with 6 months' treatment; P reported as not significant).[15]

The systematic review of cohort studies concluded that, in people with HIV, there is a significantly higher rate of tuberculosis recurrence with regimens containing 2–3 months of rifampicin than with regimens containing 5–6 months of rifampicin or 7 months or over (2–3 months v 5–6 months: RR 3.2, 95% CI 1.6 to 4.7; 2–3 months v  $\geq 7$  months: RR 4.6, 95% CI 1.7 to 7.4).[22] Overall (i.e. in both HIV infected and non-infected people), there was no significant difference in tuberculosis recurrence between regimens containing 5–6 months of rifampicin and regimens of 7 months or longer ( $P = 0.17$ ).[22] However these studies are largely on pulmonary tuberculosis and are not directly applicable to central nervous system disease, where 12 months therapy is generally recommended.

### **Harms of longer courses of antituberculosis treatment versus conventional short course treatment:**

The first RCT did not report the frequency of adverse effects by treatment group.[21] Overall, common adverse effects of treatment were arthralgia (78% of people), paraesthesia (21% of people), and skin rash (11% of people).[21] The second RCT found no significant difference in the rate of serious adverse effects between 9 months' and 6 months' treatment (8/50 [16.0%] with 9 months' treatment v 4/51 [7.8%] with 6 months' treatment;  $P = 0.23$ ).[15] Most of the adverse effects in this study were reportedly hepatic toxicities (no further data not reported).[15]

### **Comment:**

#### **Antituberculosis treatment containing $\geq 5$ months of rifampicin versus rifampicin for 3 months or shorter:**

#### **Short versus long treatment**

##### **Recommendation 7:**

In HIV positive people with active tuberculosis, clinicians should administer conventional antituberculosis treatment as first line therapy incorporating rifampicin for at least 5 months.

**GRADE:** (strong recommendation, very low quality evidence)

##### **Recommendation 8:**

In HIV positive people with active tuberculosis, we make no recommendation on the use of conventional antituberculosis treatment as first line therapy for longer than 6 months.

## **Adjuvant immunotherapy using *Mycobacterium vaccae* combined with conventional treatment (compared with conventional treatment alone)**

RCTs found that antituberculosis treatment plus *Mycobacterium vaccae* immunisation achieved no additional benefits in survival or negative sputum *Mycobacterium tuberculosis* culture rates compared with antituberculosis treatment plus placebo immunisation.

### **Benefits of adjuvant immunotherapy using *Mycobacterium vaccae* combined with conventional treatment versus conventional treatment alone:**

We found two RCTs.[23] [24] The first RCT randomised 374 South African adults with smear positive pulmonary tuberculosis, 119 of whom were HIV positive.[23] Participants in both arms received 6 months of conventional antituberculosis treatment (including ethambutol). The HIV positive treatment groups in this RCT may not have been balanced for potentially confounding factors because of the small number of participants with HIV and the fact that randomisation was not stratified by HIV status.[23] Therefore the results of this RCT should be interpreted with caution. The RCT compared *Mycobacterium vaccae* immunisation versus placebo immunisation on day 8 of conventional treatment.[23] The second RCT randomised 1229 adults from Zambia and Malawi, 760 of whom were HIV positive.[24] In Zambia, participants in both arms received 8 months of isoniazid and ethambutol, plus rifampicin and pyrazinamide during the first 2 months. In Malawi, participants in both treatment arms received 2 months of streptomycin, isoniazid, rifampicin, and pyrazinamide followed by a further 6 months of isoniazid and ethambutol. This RCT compared *M. vaccae* immunisation during the first 2 weeks of treatment with placebo immunisation.

#### **Mortality:**

In the second RCT, 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 [29.1%] with *M. vaccae* immunotherapy v 107/386 [27.7%] with placebo; HR 1.03, 95% CI 0.79 to 1.35; P = 0.8).[24]

#### **Smear conversion after 2 months of therapy:**

In the first RCT, pre-specified subgroup analysis in HIV positive participants found no significant difference between treatments in the proportion of people with negative *Mycobacterium tuberculosis* sputum culture at 2 months (43/60 [71.7%] with *M. vaccae* immunotherapy v 49/58 [84.0%] with placebo; P = 0.15).[23]

#### **Smear conversion at end of therapy:**

In the first RCT, pre-specified subgroup analysis in HIV positive participants found no significant difference between treatments in the proportion of people with negative *Mycobacterium tuberculosis* sputum culture at 6 months (46/48 [95.8%] with *M. vaccae* immunotherapy v 48/48 [100.0%] with placebo; P = 0.48).[23] The second RCT found no significant difference between

treatments in the proportion of people with negative *M. tuberculosis* sputum culture at 12 months (187/374 [50.0%] with *M. vaccae* immunotherapy v 201/386 [52.1%] with placebo; P reported as not significant).[24]

### **Recurrence of tuberculosis:**

This outcome was not assessed.

### **Harms of adjuvant immunotherapy using *Mycobacterium vaccae* combined with conventional treatment versus conventional treatment alone:**

The first RCT did not report adverse effects for HIV positive people separately.[23] Overall, erythema, vesiculation, and ulceration at the injection site occurred more frequently with *M. vaccae* immunisation than with placebo (erythema: 98.4% with *M. vaccae* immunotherapy v 9.2% with placebo; vesiculation: 50.3% with *M. vaccae* immunotherapy v 1.1% with placebo; ulceration: 22.2% with *M. vaccae* immunotherapy v 1.1% with placebo; significance not reported). However, the frequency of serious adverse events was similar between groups (37/189 [19.6%] with *M. vaccae* immunotherapy v 34/185 [18.4%] with placebo; significance not reported).[23] In the second RCT, the only reported adverse effects of *M. vaccae* immunisation 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.[24]

### **Comment:**

Adjuvant immunotherapy with *M. vaccae* aims to stimulate the host immune system to produce a more effective response against *M. tuberculosis*.

#### ***Mycobacterium vaccae* treatment**

##### **Recommendation 9:**

In HIV positive people with active tuberculosis, clinicians should not administer *Mycobacterium vaccae* as part of antituberculosis treatment as first line therapy.

**GRADE:** (strong recommendation, high quality evidence)

### **Early initiation of highly active antiretroviral treatment (HAART) compared with delayed initiation of highly active antiretroviral treatment**

We found no RCTs comparing antituberculosis treatment plus adjuvant highly active antiretroviral treatment versus conventional antituberculosis treatment with delayed initiation of highly active antiretroviral treatment.

## **Comment:**

The use of HAART in patients 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 antituberculosis regimens including rifampicin and HAART drugs. 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 HIV and tuberculosis drugs. It has therefore been recommended that HAART should be delayed for 4-8 weeks after starting antituberculosis treatment.[27] However recommendations regarding the timing of commencement of antituberculosis drugs and HAART are largely based on expert opinion and observational studies rather than on the results of RCTs.

### **Highly active antiretroviral therapy (HAART)**

#### **Recommendation 10:**

In HIV positive people with active tuberculosis, we make no recommendation on the timing of the introduction of highly active antiretroviral therapy with conventional antituberculosis treatment as first line therapy.

**GRADE:** (no recommendation, very low quality evidence)

## **Directly observed therapy, short course (compared with unsupervised treatment)**

We found no RCTs comparing directly observed therapy, short course (DOT) versus unsupervised treatment for tuberculosis in people with HIV. Cohort studies suggest that DOT produces low treatment failure rates.

## **Benefits of directly observed therapy, short course (compared with unsupervised treatment):**

We found one review of cohort studies of DOT (Medline search limited to 1990–2000; 34 eligible studies including 78 253 analysable people).[25] Although the review did not focus specifically on HIV infected people, the review's authors stated that it was limited to the era in which HIV became highly prevalent and they claimed that a high proportion of the participants would have been HIV infected.

We also found one subsequent non-randomised study from Zambia, which compared a cohort receiving daily supervision of antituberculosis treatment (DOT) with a control population receiving 8 months of unsupervised antituberculosis treatment (168 people with smear positive pulmonary tuberculosis).[26] All participants received 8 months of isoniazid and ethambutol plus rifampicin and pyrazinamide during the first 2 months. It was estimated that 70–80% of the people with tuberculosis in these areas were likely to be HIV infected.[27]

### **Mortality:**

The nonrandomised study from Zambia found no significant difference between groups in mortality at the end of treatment (16/72 [22.2%] with DOT v 18/96 [18.8%] with unsupervised treatment; P reported as not significant).[26]

### **Smear conversion after 2 months of therapy:**

The nonrandomised study from Zambia found that similar proportions of participants in both groups had negative sputum smear for acid fast bacilli 2 months after starting treatment (54/72 [75.0%] with DOT v 64/96 [66.7%] with unsupervised treatment; significance not reported). [26]

### **Smear conversion at the end of therapy:**

The review found that the mean treatment failure rates were 2.4% ( $\pm$  standard deviation 2.2%) in 21 analysable *Mycobacterium tuberculosis* culture based studies and 2.5% ( $\pm$  standard deviation 1.7%) in nine analysable acid fast bacilli smear based studies.[25] If people who did not adhere to treatment or were lost to follow up were counted as treatment failures (conservative intention to treat analysis), mean treatment failure rates increased 11.1% ( $\pm$  standard deviation 6.7%) in 20 culture based studies and 10.0% ( $\pm$  standard deviation 7.5%) in nine smear based studies. The nonrandomised study from Zambia found that significantly more participants receiving DOT had a negative sputum smear at the end of treatment (39/72 [54.2%] with DOT v 20/96 [20.8%] with unsupervised treatment;  $P < 0.001$ ).[26]

### **Recurrence rates:**

The review found that the mean tuberculosis recurrence rates were 3.6% ( $\pm$  standard deviation 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. [25]

### **Harms of directly observed therapy, short course (compared with unsupervised treatment):**

The systematic review and subsequent non randomised study gave no information on adverse effects, which could be attributed to the use of DOT compared with unsupervised treatment. [25] [26]

#### **Directly observed therapy**

##### **Recommendation 11:**

In HIV positive people with active tuberculosis, clinicians should administer conventional antituberculosis treatment using a DOT approach, as directly observed therapy is strongly recommended by WHO on the basis of evidence from successful tuberculosis programmes.

**GRADE:** (strong recommendation, very low quality evidence)

## **What are the effects of second line treatments for tuberculosis in people infected with HIV?**

### **Antimycobacterial treatment combinations (comparison between different antituberculosis regimens)**

We found no RCTs comparing different regimens of antituberculosis treatment after failure of first line treatment for tuberculosis in people with HIV.

#### **Second line treatment**

##### **Recommendation 12:**

In HIV positive people with active tuberculosis, we can make no recommendation on which drugs should be incorporated into antituberculosis treatment after failure of first line therapy due to lack of evidence.

**GRADE:** (no recommendation, very low quality evidence)

## Appendix 1: Summary of recommendations based on GRADE profiles

### Recommendation 1: **Prophylaxis versus placebo**

In HIV positive people with positive tuberculin skin tests, clinicians should routinely administer antituberculosis prophylaxis. (strong recommendation, high quality evidence)

### Recommendation 2: **Prophylaxis versus placebo**

In HIV positive people with negative tuberculin skin tests, clinicians should not routinely administer antituberculosis prophylaxis. (strong recommendation, high quality evidence)

### Recommendation 3: **Isoniazid monotherapy prophylaxis**

In HIV positive people with positive tuberculin skin tests, clinicians might prefer prophylaxis with isoniazid monotherapy to combination therapy. (weak recommendation, high quality evidence)

### Recommendation 4: **Rifabutin treatment**

There is consensus that conventional antituberculosis treatment using rifampicin is effective as first line therapy. If rifampicin use needs to be avoided, in HIV positive people with active tuberculosis, clinicians might use rifabutin as part of antituberculosis treatment as first line therapy. (weak recommendation, moderate quality evidence)

### Recommendation 5: **Thiacetazone treatment**

In HIV positive people with active tuberculosis, clinicians should not administer thiacetazone as part of antituberculosis treatment as first line therapy. (strong recommendation, moderate quality evidence)

### Recommendation 6: **Quinolones treatment**

In HIV positive people with active tuberculosis, we make no recommendation on the use of quinolones as part of antituberculosis treatment as first line therapy. (no recommendation, low quality evidence)

### Recommendation 7: **Short versus long treatment**

In HIV positive people with active tuberculosis, clinicians should administer conventional antituberculosis treatment as first line therapy incorporating rifampicin for at least 5 months. (strong recommendation, very low quality evidence)

### Recommendation 8: **Short versus long treatment**

In HIV positive people with active tuberculosis, we make no recommendation on the use of conventional antituberculosis treatment as first line therapy for longer than 6 months. (no recommendation, low quality evidence)

### Recommendation 9: **Mycobacterium vaccae treatment**

In HIV positive people with active tuberculosis, clinicians should not administer *Mycobacterium vaccae* as part of antituberculosis treatment as first line therapy. (strong recommendation, high quality evidence)

### Recommendation 10: **Highly active antiretroviral therapy (HAART)**

In HIV positive people with active tuberculosis, we make no recommendation on the timing of the introduction of highly active antiretroviral therapy with conventional antituberculosis treatment as first line therapy. (no recommendation, very low quality evidence)

Recommendation 11: **DOT**

In HIV positive people with active tuberculosis, clinicians should administer conventional antituberculosis treatment using a DOT approach. (strong recommendation, very low quality evidence)

Recommendation 12: **Second line treatment**

In HIV positive people with active tuberculosis, we make no recommendation on which drugs should be incorporated into antituberculosis treatment after failure of first line therapy. (no recommendation, very low quality evidence)

## Appendix 2: Explanation of the GRADE statements for the quality of evidence and strength of recommendations

The evidence was assessed according to the methodology describe by the GRADE working group. Briefly, in this system evidence is classified as “high”, “moderate”, “low”, or “very low” based on methodological characteristics of the available evidence for a specific health care problem. The definition of each is listed below.

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

Recommendations are classified as “strong” or “weak” recommendations, as delineated in the GRADE methodology. “Strong” recommendations can be interpreted as:

- Most individuals should receive the intervention
- Most well informed individuals would want the recommended course of action and only a small proportion would not
- Could unequivocally be used for policy making

“Weak” recommendations can be interpreted as:

- The majority of well informed individuals would want the suggested course of action, but an appreciable proportion would not
- Widely varying values and preferences
- Policy making will require extensive debates and involvement of many stakeholders

## Appendix 3: GRADE evidence profiles for recommendations 1-13

### GRADE Evidence Profile – Recommendations 1 and 2

**Author(s):** R Bellamy

**Date:** 14.06.06

**Question:** Is anti-tuberculosis prophylaxis effective at preventing tuberculosis compared to placebo?

**Patient or population:** HIV-positive patients

**Settings:** Haiti, Kenya, Spain, Uganda, USA, Zambia

**Systematic review:** Woldehanna et al, 2002 [28]

Quality assessment						Summary of findings			
						No of patients		Effect	
No of studies	Design	Limitations	Consistency	Directness	Other considerations	Prophylaxis	Placebo	Relative risk (95% CI)	
<b>Mortality</b>									
4 <sup>1</sup>	RCT	No serious limitations	No significant inconsistency	Directly applicable	None	195/1760 [11%] <sup>2</sup>	84/618 [13.5%] <sup>2</sup>	0.80 (0.63 – 1.02)	⊕⊕⊕⊕ High
<b>Development of tuberculosis</b>									
4 <sup>1</sup>	RCT	No serious limitations	No significant inconsistency	Directly applicable	None	39/1760 [2%] <sup>3</sup>	46/618 [7%] <sup>3</sup>	0.38 (0.25 – 0.57)	⊕⊕⊕⊕ High
<b>Adverse effects</b>									
7 <sup>1</sup>	RCT	No serious limitations	No significant inconsistency	Directly applicable	None	137/3554 [4%] <sup>4</sup>	33/1873 [2%] <sup>4</sup>	2.49 (1.64 – 3.77)	⊕⊕⊕⊕ High

#### Footnotes:

<sup>1</sup>The studies included in the systematic review compared either isoniazid monotherapy or combination treatment (rifampicin plus pyrazinamide, isoniazid plus rifampicin, or isoniazid plus rifampicin plus pyrazinamide) against placebo. Follow-up was 1 to 3 years.

<sup>2</sup> This result is for tuberculin skin test positive patients. There was no significant difference in all-cause mortality among tuberculin skin test negative patients between those receiving treatment and those receiving placebo (373/1629 with treatment v 298/1193 with placebo)

<sup>3</sup>This result is for tuberculin skin test positive patients. There was no significant difference in risk of developing tuberculosis among tuberculin skin test negative patients between those receiving treatment and those receiving placebo (66/1629 with treatment v 54/1193 with placebo)

<sup>4</sup>Combined results for tuberculin skin test positive and skin test negative patients

### GRADE Evidence Profile – Recommendation 3

**Author(s):** R Bellamy

**Date:** 14.06.06

**Question:** Is combination therapy with rifampicin plus isoniazid for 2-3 months more effective than isoniazid monotherapy for 6-12 months at preventing tuberculosis in people with HIV?

**Patient or population:** HIV-positive patients

**Settings:** Spain, Uganda

**Systematic review:** Woldehanna and Volmink, 2002 [28]

Quality assessment						Summary of findings			
No of studies	Design	Limitations	Consistency	Directness	Other considerations	No of patients		Effect	Quality Importance
						Isoniazid	Rifampicin plus isoniazid	Relative risk (95% CI)	
<b>Mortality</b>									
4 <sup>1</sup>	RCT	No serious limitations	No significant inconsistency	Directly applicable	None	71/683 [10.4%]	67/702 [9.5%]	1.09 (0.80 – 1.50)	⊕⊕⊕⊕ High
<b>Development of tuberculosis</b>									
3 <sup>1</sup>	RCT	No serious limitations	No significant inconsistency	Directly applicable	None	14/683 [2%]	14/707 [2%]	1.05 (0.51 – 2.17)	⊕⊕⊕⊕ High
<b>Adverse effects requiring discontinuation of treatment</b>									
3 <sup>1</sup>	RCT	No serious limitations	No significant inconsistency	Directly applicable	None	24/683 [4%]	33/707 [5%]	0.75 (0.46 – 1.24)	⊕⊕⊕⊕ High

**Footnotes:**

<sup>1</sup>The studies included in the systematic review compared isoniazid monotherapy with combination treatment (rifampicin plus isoniazid)

**GRADE Evidence Profile – Recommendations 3**

**Author(s):** R Bellamy

**Date:** 14.06.06

**Question:** Is combination therapy with rifampicin plus pyrazinamide for 2-3 months more effective than isoniazid monotherapy for 6-12 months at preventing tuberculosis in people with HIV?

**Patient or population:** HIV-positive patients

**Settings:** Brazil, Haiti, Mexico, Spain, USA

**Systematic review:** Woldehanna and Volmink, 2002 [28]

Quality assessment						Summary of findings			
No of studies	Design	Limitations	Consistency	Directness	Other considerations	No of patients		Effect	Quality Importance
						Isoniazid	Rifampicin plus pyrazinamide	Relative risk (95% CI)	
<b>Mortality</b>									
6 <sup>1</sup>	RCT	No serious limitations	No significant inconsistency	Directly applicable	None	299/1597 [19%]	283/1540 [18%]	1.03 (0.89 – 1.19)	⊕⊕⊕⊕ High
<b>Development of tuberculosis</b>									
6 <sup>1</sup>	RCT	No serious limitations	No significant inconsistency	Directly applicable	None	73/1597 [5%]	73/1599 [5%]	1.00 (0.73 – 1.38)	⊕⊕⊕⊕ High
<b>Adverse effects requiring discontinuation of treatment</b>									
4 <sup>1</sup>	RCT	No serious limitations	No significant inconsistency	Directly applicable	None	66/1597 [4%]	102/1599 [6%]	0.64 (0.48 – 0.86)	⊕⊕⊕⊕ High

**Footnotes:**

<sup>1</sup>The studies included in the systematic review compared isoniazid monotherapy with combination treatment (rifampicin plus pyrazinamide)

**GRADE Evidence Profile –Recommendation 3**

**Author(s):** R Bellamy

**Date:** 14.06.06

**Question:** Is combination therapy with rifampicin plus pyrazinamide plus isoniazid for 2-3 months more effective than isoniazid monotherapy for 12 months at preventing tuberculosis in people with HIV?

**Patient or population:** HIV-positive patients

**Settings:** Uganda

**Systematic review:** Woldehanna and Volmink, 2002 [28]

Quality assessment						Summary of findings			
No of studies	Design	Limitations	Consistency	Directness	Other considerations	No of patients		Effect	Quality Importance
						Isoniazid	Rifampicin plus pyrazinamide plus isoniazid	Relative (95% CI)	
<b>Mortality</b>									
1 <sup>1</sup>	RCT	No serious limitations	Only one study	Directly applicable	None	58/536 [11%]	58/462 [12.5%]	0.86 (0.61 – 1.21)	⊕⊕⊕⊕ High
<b>Development of tuberculosis</b>									
1 <sup>1</sup>	RCT	No serious limitations	Only one study	Directly applicable	Sparse or imprecise data <sup>2</sup> (-1)	7/536 [1%]	10/462 [2%]	0.60 (0.23 – 1.57)	⊕⊕⊕○ Moderate
<b>Adverse effects requiring discontinuation of treatment</b>									
1 <sup>1</sup>	RCT	No serious limitations	Only one study	Directly applicable	None	5/536 [1%]	26/462 [6%]	0.10 (0.03 – 0.33)	⊕⊕⊕⊕ High

**Footnotes:**

<sup>1</sup>The study included in the systematic review compared isoniazid monotherapy with combination treatment (rifampicin plus pyrazinamide plus isoniazid)

<sup>2</sup> Sparse or imprecise data, only one trial

**GRADE Evidence Profile – Recommendation 4**

**Author(s):** R Bellamy

**Date:** 04.06.06

**Question:** Anti-tuberculous treatment containing rifabutin (compared with conventional treatment)

**Patient or population:** HIV-positive patients with active tuberculosis

**Settings:** Uganda

**RCT(s):** Schwander et al, 1995 [16]

Quality assessment						Summary of findings			
No of	Design	Limitations	Consistency	Directness	Other	No of patients		Effect	Quality Importance
						Rifabutin	Conventional	Relative	

studies					considerations	arm	therapy	(95% CI)	
<b>Mortality</b>									
1	RCT	No serious limitations	Only one trial	Directly applicable	Sparse or imprecise data <sup>1</sup> (-1)	4/24 [17%]	2/25 [8%]	ns	⊕⊕⊕○ Moderate
<b>Smear conversion at 2 months</b>									
1	RCT	No serious limitations	Only one trial	Directly applicable	Sparse or imprecise data <sup>1</sup> (-1)	18/24 [75%]	11/25 [44%]	1.70 (1.03-2.81)	⊕⊕⊕○ Moderate
<b>Smear conversion after end of treatment</b>									
1	RCT	No serious limitations	Only one trial	Directly applicable	Sparse or imprecise data <sup>1</sup> (-1)	22/24 [92%]	22/25 [88%]	1.04 (0.86-1.26)	⊕⊕⊕○ Moderate
<b>Recurrence of tuberculosis</b>									
0									○○○○ Not assessed
<b>Adverse effects</b>									
1	RCT	No serious limitations	Only one trial	Directly applicable	Sparse or imprecise data <sup>1</sup> (-1)			No difference reported	⊕⊕⊕○ Moderate

**Footnotes:**

<sup>1</sup>Sparse or imprecise data, only one trial

**GRADE Evidence Profile – Recommendation 5**

**Author(s):** R Bellamy

**Date:** 04.06.06

**Question:** Anti-tuberculous treatment containing thiacetazone

**Patient or population:** HIV-positive patients with active tuberculosis

**Settings:** Uganda; Zambia

**RCT(s) and cohort studies:** Okwera et al, 1994 [17]; Kelly et al, 1994 [18]; Chintu et al, 1993 [19]

Quality assessment						Summary of findings			
No of studies	Design	Limitations	Consistency	Directness	Other considerations	No of patients		Effect	Quality Importance
						Thiacetazone arm	Conventional therapy	Relative (95% CI)	
<b>Mortality</b>									
1	RCT	No serious limitations	Only one trial	Directly applicable	Sparse or imprecise data (-1) <sup>1</sup>	35%	28%	1.01 (0.65-1.57)	⊕⊕⊕○ Moderate
<b>Smear conversion at 2 months</b>									
1	RCT	Some limitations <sup>2</sup> (-1)	Only one trial	Directly applicable	Sparse or imprecise data (-1) <sup>1</sup>	21/57 [37%]	55/74 [74%]	0.50 (0.34-0.71)	⊕⊕○○ Low
<b>Smear conversion after end of treatment</b>									
0									○○○○ Not assessed

Recurrence of tuberculosis										
0										○○○○ Not assessed
Adverse effects										
3	RCT and cohort	Some limitations <sup>3</sup> (-1)	No significant inconsistency	Directly applicable	None	12/57 [21%] <sup>4</sup>	1/74 [2%] <sup>4</sup>	11.7 (1.52-90.0)		⊕⊕⊕○ Moderate

**Footnotes:**

<sup>1</sup>Sparse or imprecise data, only one trial

<sup>2</sup>Intention to treat analysis was not performed, therefore 60 subjects who had died or were lost to follow up were not included.

<sup>3</sup>One study was an RCT which had no serious limitations for reporting adverse effects. Two studies were cohort studies without comparator arms.

<sup>4</sup>Data shown refers to the randomised controlled trial. The cohort studies reported adverse effects in 24/79 and 19/88 patients treated with a thiacetazone-containing regimen.

**GRADE Evidence Profile – Recommendation 6**

**Author(s):** R Bellamy

**Date:** 04.06.06

**Question:** Anti-tuberculous treatment containing quinolones (compared with conventional anti-tuberculous treatment)

**Patient or population:** HIV-positive patients with active tuberculosis

**Settings:** Hawaii and New York, USA; Tanzania

**RCT(s):** El Sadr et al, 1998 [15] ; Kennedy et al, 1996 [20]

Quality assessment						Summary of findings			
						No of patients		Effect	Quality Importance
No of studies	Design	Limitations	Consistency	Directness	Other considerations	Quinolone arm	Conventional therapy	Relative (95% CI)	
Mortality									
1	RCT	Some limitations <sup>1</sup> (-1)	Only one trial	Directly applicable	Sparse or imprecise data <sup>2</sup> (-1)	1/53 [2%]	3/48 [6%]	ns	⊕⊕○○ Low
Smear conversion at 2 months									
1	RCT	Some limitations <sup>1</sup> (-1)	Only one trial	Directly applicable	None	46/48 [96%]	36/37 [97%]	0.98 (0.91-1.07)	⊕⊕⊕○ Moderate
Smear conversion after end of treatment									
0 <sup>3</sup>									○○○○ Not assessed
Recurrence of tuberculosis									
1 <sup>3,4</sup>	RCT	Serious limitations <sup>5</sup> (-2)	Only one trial	Directly applicable	Sparse or imprecise data <sup>6</sup> (-1)	3/25 [12%]	1/30 [3%]	. <sup>7</sup>	⊕○○○ Very low
Adverse effects									

1	RCT	Some limitations <sup>1</sup> (-1)	Only one trial	Directly applicable	Sparse or imprecise data <sup>2</sup> (-1)	15/87 [17%]	15/87 [17%]	ns	⊕⊕○○ Low
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**Footnotes:**

<sup>1</sup>Open label study

<sup>2</sup> Sparse or imprecise data, only one trial

<sup>3</sup>The El Sadr study was also used to compare longer versus shorter courses of therapy. Therefore data on smear conversion at end of treatment and on recurrence risk is not possible to interpret for the treatment regimen

<sup>4</sup>The data shown is for the study by Kennedy et al.

<sup>5</sup>This study performed post-hoc sub-group analyses on people with HIV and was open label and has therefore been scored as having serious design limitations

<sup>6</sup>Sparse or imprecise data, only one trial

<sup>7</sup>Not calculable as 0 events with rifampicin, isoniazid, ethambutol, pyrazinamide

**GRADE Evidence Profile - Recommendations 7 and 8**

**Author(s):** R Bellamy

**Date:** 04.06.06

**Question:** Short versus longer courses of treatment

**Patient or population:** HIV-positive patients with active tuberculosis

**Settings:** Zaire; Hawaii and New York, USA; many countries for the 21 studies in the systematic review

**RCT(s) and other studies:** Perriens et al, 1995 [21]; El Sadr et al, 1998 [15]; Korenromp et al, 2003 [22]

Quality assessment						Summary of findings			
No of studies	Design	Limitations	Consistency	Directness	Other considerations	No of patients		Effect	Quality Importance
						Longer course	Short course	Relative (95% CI)	
<b>Mortality</b>									
2	RCT	Some limitations <sup>1</sup> (-1)	No significant inconsistency	Directly applicable	Sparse or imprecise data (-1) <sup>2</sup>	43/171 [25%]	49/170 [29%]	ns	⊕⊕○○ Low
<b>Smear conversion at 2 months</b>									
0									○○○○ Not assessed
<b>Smear conversion after end of treatment</b>									
0									○○○○ Not assessed
<b>Recurrence of tuberculosis</b>									
3	2 RCTs and 1 systematic review of cohort studies	Some limitations <sup>1</sup> (-1)	No significant inconsistency	Directly applicable	Sparse or imprecise data (-1) <sup>2</sup>	1.9% and 1/50 <sup>3</sup>	6% and 2/51 <sup>3</sup>	ns	⊕⊕○○ Low

Adverse effects									
1	RCT	Some limitations <sup>1</sup> (-1)	Only one trial	Directly applicable	Sparse or imprecise data (-1) <sup>2</sup>	8/50 [16%]	4/51 [8%]	ns	⊕⊕○○ Low

**Footnotes:**

<sup>1</sup>One RCT was an open label study. The other RCT randomised patients after completion of 6 months treatment (therefore the results may not be generalisable). The systematic review of cohort studies compared treatment regimens from different studies and the patient groups were not directly comparable.

<sup>2</sup> Sparse or imprecise data.

<sup>3</sup>The data shown is for the RCTs. The systematic review of cohort studies found that patients who received a regimen containing 2-3 months of rifampicin had 3.2 times the risk of tuberculosis relapse compared to those who received 5-6 months.

**GRADE Evidence Profile – Recommendation 9**

**Author(s):** R Bellamy

**Date:** 04.06.06

**Question:** Adjuvant immunotherapy using *Mycobacterium vaccae* combined with conventional treatment (compared to conventional treatment alone)

**Patient or population:** HIV-positive patients with active tuberculosis

**Settings:** South Africa; Zambia and Malawi

**RCT(s):** Durban immunotherapy trial group, 1999 [23] ; Mwinga et al, 2002 [24]

Quality assessment						Summary of findings			
No of studies	Design	Limitations	Consistency	Directness	Other considerations	No of patients		Effect	Quality Importance
						<i>M vaccae</i> arm	Conventional therapy	Relative (95% CI)	
<b>Mortality</b>									
1	RCT	No serious limitations	Only one study	Directly applicable	None	109/374	107/386	ns	⊕⊕⊕⊕ High
<b>Smear conversion at 2 months</b>									
1	RCT	No serious limitations	Only one study	Directly applicable	Sparse or imprecise data <sup>1</sup>	43/60 [72%]	49/58 [84%]	0.71 (0.50 – 1.02)	⊕⊕⊕○ Moderate
<b>Smear conversion after end of treatment</b>									
2	RCT	No serious limitations	No significant inconsistency	Directly applicable	None	233/422 [55%]	249/434 [57%]	ns	⊕⊕⊕⊕ High
<b>Recurrence of tuberculosis</b>									
0									○○○○ Not assessed
<b>Adverse effects</b>									
2	RCT	No serious limitations	No significant inconsistency	Directly applicable	None	39/563 [7%]	35/571 [6%]	ns	⊕⊕⊕⊕ High

<sup>1</sup>Sparse or imprecise data, only one trial

**GRADE Evidence Profile – Recommendation 10**

**Author(s):** R Bellamy

**Date:** 04.06.06

**Question:** Adjuvant highly active antiretroviral treatment (compared with delayed initiation of highly active antiretroviral treatment)

**Patient or population:** HIV-positive patients with active tuberculosis

**Settings:** None

**RCT(s):** None

Quality assessment						Summary of findings			
						No of patients		Effect	Quality Importance
No of studies	Design	Limitations	Consistency	Directness	Other considerations	HAART	Delayed initiation Of HAART	Relative (95% CI)	
<b>Mortality</b>									
0									○○○○○ Not assessed
<b>Smear conversion at 2 months</b>									
0									○○○○○ Not assessed
<b>Smear conversion after end of treatment</b>									
0									○○○○○ Not assessed
<b>Recurrence of tuberculosis</b>									
0									○○○○○ Not assessed
<b>Adverse effects</b>									
									○○○○○ Not assessed

**Footnotes:**

No cohorts or RCTs were found.

**GRADE Evidence Profile – Recommendation 11**

**Author(s):** R Bellamy

**Date:** 04.06.06

**Question:** Directly observed therapy, short course (compared with unsupervised treatment)

**Patient or population:** HIV-positive patients with active tuberculosis

**Settings:** Zambia; many countries in the 34 studies included in the systematic review

**Studies:** Hill et al, 2002, [25] ; Miti et al, 2003 [26]

Quality assessment						Summary of findings		
						No of patients		Effect
No of	Design	Limitations	Consistency	Directness	Other	DOT	Unsupervised	Relative

studies					considerations		therapy	(95% CI)	
<b>Mortality</b>									
1	Cohort	Serious limitations <sup>1</sup> (-2)	Only one study	Directly applicable	Sparse or imprecise data <sup>2</sup> (-1)	16/72 [22%]	18/96 [19%]	ns	⊕○○○ Very low
<b>Smear conversion at 2 months</b>									
1	Cohort	Serious limitations <sup>1</sup> (-2)	Only one study	Directly applicable	Sparse or imprecise data <sup>2</sup> (-1)	54/72 [75%]	64/96 [67%]	ns	⊕○○○ Very low
<b>Smear conversion after end of treatment</b>									
2	Systematic review of cohort studies and one cohort	Serious limitations <sup>3</sup> (-2)	Some inconsistency between studies <sup>4</sup> (-1)	Directly applicable	None	39/72 [54%] <sup>5</sup>	20/96 [21%]	-	⊕○○○ Very low
<b>Recurrence of tuberculosis</b>									
1	Systematic review of cohort studies	Serious limitations <sup>3</sup> (-2)	Some inconsistency between studies <sup>6</sup> (-1)	Directly applicable	None	3.6% <sup>7</sup>			⊕○○○ Very low
<b>Adverse effects</b>									
0									○○○○ Not assessed

**Footnotes:**

<sup>1</sup>The cohort design means that the groups may not have been comparable in this study by Miti et al. Information on HIV status was not available for patients, although it was estimated that 70-80% would be HIV positive

<sup>2</sup>Sparse or imprecise data, only one trial

<sup>3</sup>In the systematic review, no comparator arm was available for patients who had not received DOT, therefore the data is difficult to interpret. Data on HIV status generally not available. The cohort design means that the groups may not have been comparable in the study by Miti et al. Information on HIV status was not available for patients, although it was estimated that 70-80% would be HIV positive

<sup>4</sup>In the systematic review the standard deviation between studies for the treatment failure rate was 2.2%

<sup>5</sup>The figures shown are for the cohort study by Miti et al. In the systematic review of cohort studies the treatment failure rate among patients receiving DOT was 2.4% in studies based on culture

<sup>6</sup>In this systematic review the standard deviation between studies for recurrence of tuberculosis was 2.4%

<sup>7</sup>This figure is for studies based on culture

**GRADE Evidence Profile – Recommendation 12**

**Author(s):** R Bellamy

**Date:** 04.06.06

**Question:** What are the effects of second line treatments for tuberculosis in people infected with HIV?

**Patient or population:** HIV-positive patients with active tuberculosis

**Settings:** None

**RCT(s):** None

**Summary of findings**

						No of patients		Effect	Quality Importance
No of studies	Design	Limitations	Consistency	Directness	Other considerations	Treatment 1	Treatment 2	Relative (95% CI)	
<b>Mortality</b>									
0									○○○○○ Not assessed
<b>Smear conversion at 2 months</b>									
0									○○○○○ Not assessed
<b>Smear conversion after end of treatment</b>									
0									○○○○○ Not assessed
<b>Recurrence of tuberculosis</b>									
0									○○○○○ Not assessed
<b>Adverse effects</b>									
0									○○○○○ Not assessed

Footnotes:

## Appendix 4: Trials summary

**Table 1: Randomised controlled trials of tuberculosis treatment in people with HIV**

Ref	Participants randomised	Treatments compared	Numbers analysed in each arm	Smear conversion at 2 months RR* (95% CI)	Smear conversion after completion of treatment RR* (95% CI)	Recurrence RR* (95% CI)
<b>Treatment containing rifabutin versus conventional treatment</b>						
[16]	50 HIV positive people with smear positive pulmonary tuberculosis, 49 of whom were eligible for analysis.	Rifabutin, isoniazid, ethambutol, pyrazinamide v rifampicin, isoniazid, ethambutol, pyrazinamide	24 v 25	1.70 (1.03 to 2.81)	1.04 (0.86 to 1.26)	
<b>Treatment containing thiacetazone versus conventional treatment</b>						
[17]	191 HIV positive people with smear positive pulmonary tuberculosis. Only 131 people had sputum examined at 2 months	Streptomycin, thiacetazone and isoniazid v rifampicin, isoniazid, pyrazinamide	57 v 74	0.50 (0.34 to 0.71)		
<b>Treatment containing quinolones versus conventional treatment</b>						
[15]	174 HIV positive people with suspected pulmonary tuberculosis, of whom 135 had a culture confirmed diagnosis. Only 85 people had sputum examined at 12 months.	Rifampicin, isoniazid, ethambutol, pyrazinamide, levofloxacin v rifampicin, isoniazid, ethambutol, pyrazinamide	48 v 37	0.98 (0.91 to 1.07)		
[20]	58 HIV positive people with smear positive pulmonary tuberculosis. Only the 55 people who successfully completed treatment were evaluated further	Rifampicin, isoniazid, ciprofloxacin v rifampicin, isoniazid, ethambutol, pyrazinamide	25 v 30			Not calculable as 0 events with rifampicin, isoniazid, ethambutol, pyrazinamide
<b>Short versus longer courses of treatment</b>						
[21]	335 HIV positive people with smear positive pulmonary tuberculosis. Only the 240 people who successfully completed treatment were evaluated further	12 months' treatment v 6 months' treatment	121 v 119			0.11 (0.01 to 0.85)
[15]	101 HIV positive people with smear positive pulmonary tuberculosis who completed the first two months of tuberculosis treatment	12 months' treatment v 6 months' treatment	50 v 51			0.51 (0.05 to 5.45)

Adjuvant immunotherapy using <i>Mycobacterium vaccae</i> versus conventional treatment						
[23]	119 HIV positive people with smear positive pulmonary tuberculosis. 118 people had sputum evaluations at 2–3 months and 96 had sputum evaluations at the end of treatment	<i>M. vaccae</i> immunisation v placebo	60 v 58 then 48 v 48	0.85 (0.70 to 1.03)	0.96 (0.90 to 1.02)	
[24]	760 HIV positive people with smear positive pulmonary tuberculosis	<i>M. vaccae</i> immunisation v placebo	374 v 386		0.96 (0.84 to 1.10)	

\*RR refers to the first treatment in comparison with the second. For further details on the design, patient eligibility criteria, dose, and duration of the treatments administered, the length of follow up and the definition of smear conversion and/or recurrence used in each study please see the main text. Several studies included people who were not infected by HIV. For these studies the number of participants randomised refers only to those people who were infected with HIV. Numbers analysed are fewer than those enrolled for some studies because the study authors did not perform an intention to treat analysis.

## Appendix 5: Glossary

**Conventional treatment** For the purposes of this review conventional treatment is defined as: two months of rifampicin, isoniazid, and pyrazinamide (plus ethambutol in areas where drug resistant tuberculosis is likely) followed by 4–7 months of rifampicin and isoniazid. The conventional daily doses recommended by WHO are: rifampicin 600 mg daily (for people weighing  $\geq 50$  kg) or 450 mg daily ( $< 50$  kg); isoniazid 300 mg daily; ethambutol 15 mg/kg daily; and pyrazinamide 2000 mg daily ( $\geq 50$  kg) or 1500 mg daily ( $< 50$  kg).[31] 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.

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

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

**Smear test** Direct Ziehl-Nielsen staining of sputum or other specimen to detect acid fast bacilli. 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 of being smear negative than HIV negative people, owing to the fact that a lower mycobacterial load is required to produce an active (i.e. symptomatic) infection.[2]

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