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Effect of preventive treatment for tuberculosis in adults infected with HIV: systematic review of randomised placebo controlled trials

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Abstract

Objective: To determine whether preventive treatment for tuberculosis in adults infected with HIV reduces the frequency of tuberculosis and overall mortality.

Design: Systematic review and data synthesis of randomised placebo controlled trials.

Main outcome measures: Active tuberculosis, mortality, and adverse drug reaction requiring cessation of the study regimen. Outcomes stratified by status of purified protein derivative skin test.

Results: Four trials comprising 4055 adults from Haiti, Kenya, the United States, and Uganda were included. All compared isoniazid (6-12 months) with placebo, and one trial also compared multidrug treatment for 3 months with placebo. Mean follow up was 15-33 months. Overall, frequency of tuberculosis (relative risk 0.57, 95% confidence interval 0.41 to 0.79) was reduced in those receiving preventive treatment compared with placebo: mortality was not significantly reduced (0.93, 0.83 to 1.05). In subjects positive for purified protein derivative receiving preventive treatment, the risk of tuberculosis was reduced substantially (0.32, 0.19 to 0.51) and the risk of death was reduced moderately (0.73, 0.57 to 0.95) compared with those taking placebo. In adults negative for purified protein derivative receiving preventive treatment, the risk of tuberculosis (0.82, 0.50 to 1.36) and the risk of death (1.02, 0.89 to 1.17) were not reduced significantly. Adverse drug reactions were more frequent, but not significantly so, in patients receiving drug compared with placebo (1.45, 0.98 to 2.14).

Conclusions: Preventive treatment given for 3-12 months protects against tuberculosis in adults infected with HIV, at least in the short to medium term. Protection is greatest in subjects positive for purified protein derivative, in whom death is also less frequent. Long term benefits remain to be shown.

Introduction

Strategies to control tuberculosis comprise case treatment, preventive treatment, and vaccination with BCG, with the expectation that improved socioeconomic conditions will lead to a decline in disease incidence.^{1,2} Preventive treatment aims to eradicate latent infection with *Mycobacterium tuberculosis* before active disease develops. Latent infection is shown by a positive reaction to intradermal injection with purified protein derivative (tuberculin skin test). Trials in people with tuberculosis infection but not infected with HIV have shown that isoniazid given for 6-12 months substantially reduces the incidence of active tuberculosis.³

Infection with HIV has changed the natural history of infection with *M tuberculosis*.⁴ People who are infected with HIV and who have a positive tuberculin skin test have a 30% or more lifetime risk of developing active tuberculosis,⁵ and tuberculosis is the most common HIV related disease in developing countries.^{1,4} Thus, preventive treatment may be an important intervention to reduce the burden of tuberculosis in people infected with HIV, and their contacts, but its efficacy cannot simply be extrapolated from studies in people not infected with HIV.

As several fairly small trials have been done, we conducted this systematic review to summarise the evidence available to date as to whether preventive treatment for tuberculosis is effective in reducing the incidence of active tuberculosis and of death.

Subjects and methods

Criteria for selecting studies for review

We included only randomised controlled trials that compared drug regimens aimed at preventing tuberculosis with placebo. Trials were considered irrespective of setting or target group, and we included all different drug regimens tested. Preventive treatment was defined as tuberculosis chemotherapy given to people who have

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Table 1 Characteristics of randomised placebo controlled trials of preventive treatment for tuberculosis in adults infected with HIV included in review

Study (country)	Method	Participants	Interventions	Outcomes
Pape et al ⁹ (Haiti)	Randomised by computer Allocation not described Double blind*	Symptom free, newly diagnosed (n=118) No active tuberculosis (91/118 (77%) were women) Positive or negative for tuberculin†	Isoniazid 300 mg daily for 12 months	Subjects assessed every 3 months Mean follow up 33 months No loss to follow up
Hawken et al ¹⁰ (Kenya)	Block randomised by computer Allocation concealed Double blind‡	Mostly symptom free (n=684) No active tuberculosis Positive or negative for tuberculin	Isoniazid 300 mg daily for 6 months	356/509 (70%) of expected subjects seen at the end of the trial Median follow up 20 months
Gordin et al ¹¹ (USA; 74% New York)	Randomisation not described Allocation concealment not described No data on number of eligible patients not enrolled	HIV infected (119/517 (23%) had AIDS) Negative for tuberculin Anergic At high risk of tuberculosis	Isoniazid 300 mg daily for 6 months	326 (63%) patients completed treatment 6% and 7% of treatment and placebo groups were lost respectively Mean follow up 33 months
Whalen et al ¹² (Uganda)	Block randomised by computer Allocation concealed§ Double blind	Mild HIV disease (n=2736) Positive for tuberculin Anergic	Isoniazid 300 mg daily for 6 months then isoniazid plus rifampicin 600 mg daily for 3 months then isoniazid plus rifampicin plus pyrazinamide 2 g for 3 months Anergic: isoniazid 300 mg daily for 6 months	80-89% of the different groups completed the trials No data on follow up procedures Mean follow up 15 months

*Tuberculin as purified protein derivative.

†21 of 60 patients in placebo arm accepted offer of isoniazid at time of interim analysis, but all were analysed in placebo arm.

‡12 of 696 enrolled patients were excluded and 14 of 684 failed to return after recruitment.

§9095 people were screened; 4306 (47%) did not complete baseline investigations and 2053 (23%) were ineligible.

a particular risk of developing tuberculosis. Particular risk refers to people who are infected with HIV and either infected with *M tuberculosis* (positive for purified protein derivative), or who are negative for purified protein derivative but live in a community where tuberculosis is endemic, or have a high risk of infection.⁶ Our definition of negative for purified protein derivative allowed inclusion of anergic patients (defined as a skin test reaction of <5 mm to 5 tuberculin units, and <2 mm reaction to mumps, tetanus toxoid, and candida antigen). In some instances we were unable to stratify outcomes by anergy in subjects negative for purified protein derivative as not all trials tested for it.

Search strategy

We searched Medline using the search terms HIV, tuberculosis, preventive therapy, and chemoprophylaxis. We also searched the Cochrane Controlled Trials Register, the most comprehensive source of controlled trials (disk issue 1, 1998).⁷ In addition, we searched references of all retrieved articles and contacted relevant researchers to ensure that all completed trials had been identified.

Review procedure

Trials considered for inclusion were examined to determine completeness of reporting. One of us (DW) collated data on study methods, participants, interventions, and outcomes for each study, and another (PG) checked the collated data. Authors of incomplete or abstracted trials were contacted for further details. The quality of each trial was graded using predefined criteria, assessing method of allocation sequence generation, allocation concealment, inclusion of all randomised participants, follow up of subjects, and analysis by intention to treat.

Outcome measures

The outcome measures were (a) frequency of active tuberculosis, defined microbiologically (preferably by culture) or histologically, or as a clinical syndrome consisting of typical symptoms, independently assessed chest x ray, and a documented response to treatment,⁸ (b) frequency of mortality, and (c) occurrence of adverse

drug reaction (defined as a reaction resulting in cessation of the study drugs). Where possible, outcome measures were stratified by purified protein derivative status (positive, negative, and unknown). Owing to the small number of subjects with unknown purified protein derivative status no stratum specific analysis of this group is reported.

Statistical analysis

We used the Mantel-Haenszel method to calculate summary statistics (relative risk and 95% confidence interval). A fixed effects model was used, and results were little different when using a random effects model. All analyses were done with Revman 3.0.1. (Update Software, Oxford).

Results

Included trials

Of seven identified trials, four were eligible for inclusion in this review.⁹⁻¹² Of the remaining three, one was reported to be incomplete after contacting the investigators,¹³ one compared two different drug regimens,¹⁴ and a third had not yet been published—the authors declined inclusion of their data in our review.

Exclusion criteria were similar in all trials and included past history of tuberculosis, current tuberculosis, pregnancy, abnormal liver enzymes, and serious intercurrent illness. All treatment was self administered and adherence was monitored variously through self reporting, attendance at scheduled clinic appointments, and urine testing (both routine and unscheduled). No data on adherence were reported by Pape et al⁹; Hawken et al reported that 31% of subjects missed at least 5 weeks' preventive treatment, and 70% had at least 50% positive urine tests¹⁰; Gordin et al reported that only 63% of patients completed preventive treatment within 6 months¹¹; and Whalen et al reported that 75% of scheduled and 80% of unscheduled urine tests were positive.¹² Follow up was generally short, ranging from an average of 15 to 33 months (table). All trials were analysed by intention to treat.

The figure summarises the outcomes of the four trials. Overall, the frequency of tuberculosis was reduced in subjects who received preventive treatment compared with those who received placebo (relative risk 0.57, 95% confidence interval 0.41 to 0.79). Risk of death (0.93, 0.83 to 1.05) was not significantly different in the two groups.

In two trials, when comparing subjects positive for purified protein derivative who received preventive treatment with those who received placebo, the 95% confidence interval for the relative risk of both tuberculosis and mortality included one (fig), indicating non-significant results. The pooled risk of tuberculosis in those receiving preventive treatment compared with placebo was 0.32 (0.19 to 0.51), indicating substantial protection against active disease. The pooled relative risk of mortality was 0.73 (0.57 to 0.95), indicating a moderate reduction in the risk of death in those receiving preventive treatment. Hawken et al did not define adverse drug reaction by purified protein derivative status and thus no stratified analysis of this outcome measure is reported here.¹⁰

In adults with a negative tuberculin skin test the estimates of effect in all trials included one, indicating non-significant results (fig). The pooled risk of tuberculosis in subjects with a negative tuberculin skin test who received preventive treatment was 0.82 (0.50 to 1.36) compared with placebo, confirming that no substantial protection was conferred by the intervention. Similarly, the pooled relative risk for mortality was 1.02 (0.89 to 1.17) confirming that no substantial protection was conferred by the intervention.

Overall, adverse drug reactions were more common, but not significantly so (1.45, 0.98 to 2.14), in patients receiving active drug (86/2551; 3.4%) compared with those receiving placebo (43/1386; 3.1%).

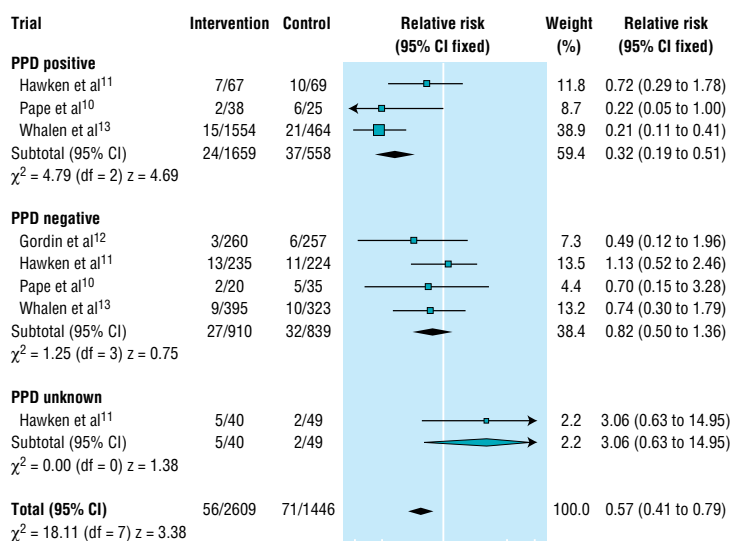
Discussion

Available evidence to date indicates that preventive treatment reduces the frequency of active tuberculosis in adults infected with HIV by approximately half. Protection against tuberculosis is greatest in adults infected with HIV who have a positive tuberculin skin test (approximately 70% reduction), and reduced incidence of mortality is also observed in this group (approximately 25%). Average follow up in these trials was 15 to 33 months, and it is not possible to conclude that benefit persists beyond this time. A small and non-significant reduction in tuberculosis incidence was observed in adults with a negative tuberculin skin test, and no effect on mortality was observed in this group.

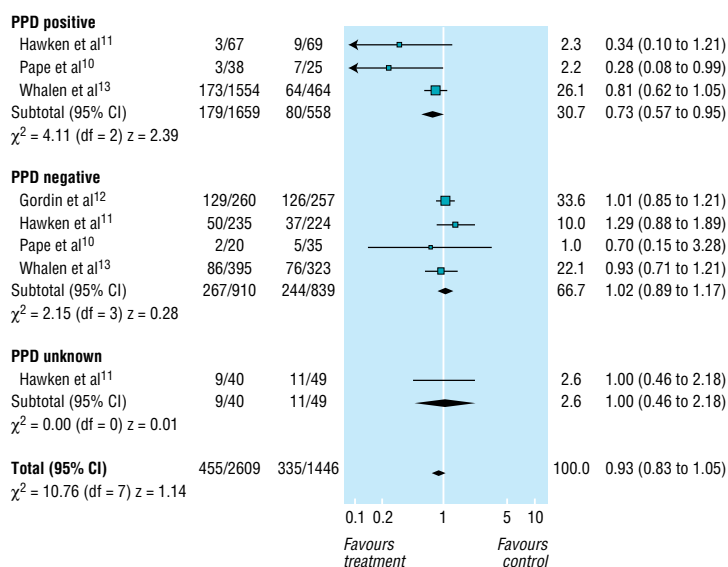
Thus, in settings where testing for purified protein derivative is possible, preventive treatment might best only be offered to adults infected with HIV with a positive tuberculin skin test. In settings where testing for purified protein derivative is not possible, if preventive treatment is given to all adults infected with HIV, it is likely that the frequency of tuberculosis will still be reduced, but to a smaller extent.

Our review shows the value of systematic review and meta-analysis. Most of the trials studied were underpowered and reported results of borderline significance. By combining data we are able to provide more precise estimates of effect for the main outcome measures. The direction of effect of the intervention in

No with active tuberculosis



No of deaths



Effect of preventive treatment for tuberculosis in adults infected with HIV on active tuberculosis and mortality, stratified by purified protein derivative status

the different settings was the same (fig), supporting the validity of combining data. A meta-analysis of individual patient data would be required to provide summary estimates of measures such as time to disease and death, and efforts to gather data to conduct such an analysis are under way.

Possible biases

A systematic review may be biased if trials reporting negative findings are not published. The trial reported to be incomplete¹³ published positive findings in abstract form, and the trial in preparation has also reported positive results. We found no statistical evidence of heterogeneity in this meta-analysis, but the power to detect heterogeneity was limited by the small number of trials. While there seems to be some clinical heterogeneity (fig) this tends to be limited to one trial

in each subgroup, and varying levels of adherence in the different trials might explain this, at least in part.

It may be difficult to generalise our findings to all populations, as the baseline risk of tuberculosis varied substantially by setting. Gordin et al observed a very much lower incidence of tuberculosis than expected.¹¹ Preventive treatment works mainly by preventing reactivation of latent infection. Recent infection may account for 30-40% of the burden of tuberculosis in both developed¹⁵ and developing countries.¹⁶ The relative importance of these two mechanisms may vary by setting and is likely to influence effectiveness of preventive treatment. When given for only a few months, there is little opportunity for preventive treatment to protect against exposure to infection with *M tuberculosis* in adults negative for purified protein derivative. Adults positive for purified protein derivative are at risk of new infection after preventive treatment has been stopped.

Choice of drug regimen

Which drug regimen should be recommended? This review did not set out to answer this question. However, in the trial which tested three different regimens against placebo, isoniazid had the greatest effect,¹² although isoniazid and rifampicin combined and isoniazid, rifampicin, and pyrazinamide combined also reduced the incidence of tuberculosis. Halsey et al compared two regimens and reported similar protection conferred by twice weekly isoniazid given for 6 months and combined rifampicin and pyrazinamide given for 2 months.¹⁴ Trials using combination treatment report higher rates of adverse drug reaction than do those using isoniazid alone. Adherence to preventive treatment was generally poor in these trials. Choice of regimen to implement in practice is likely to depend on anticipated adherence, cost, availability of drugs, concern over adverse drug reactions, and prevalence of drug resistance in the population. The strongest available evidence is for the use of isoniazid.

Although not reported as a problem in subjects who developed tuberculosis in these trials, widespread and unsupervised use of tuberculosis drugs is of concern, and monitoring for the development of drug resistance should take place. Adverse drug reactions were reported infrequently in these trials and although reassuring, monitoring of large numbers of subjects will be required to determine the incidence of infrequent but life threatening events such as hepatitis in association with isoniazid.

Preventive treatment and tuberculosis control

Although reduction in individual risk of tuberculosis is substantial, unless a large proportion of the affected population receives preventive treatment it seems unlikely that this intervention will substantially reduce disease transmission in countries with a high tuberculosis prevalence. The priority for tuberculosis control remains the early detection and treatment of active cases. Preventive treatment may be a useful intervention for individuals and for targeted groups such as factory workers, hospital staff, police, and the armed forces¹⁷ who may have access to HIV testing, counselling, and ongoing care. These conclusions are in accord with current recommendations from the World Health Organisation and the International

Key messages

- One third of the world's population is infected with *Mycobacterium tuberculosis*
- People infected with HIV are at much increased risk of developing active tuberculosis
- Short term preventive drug treatment given to people infected with HIV reduces the occurrence of active tuberculosis
- The benefit is greatest in people with latent infection, as shown by a positive skin test for tuberculosis, and this group also exhibits a survival benefit

Union Against Tuberculosis and Lung Disease.¹⁸ This policy, and future refinements to it, can now be based on a body of systematically reviewed data from relevant trials that provides accurate estimates of effect, and that is constantly updated.¹⁹

There remains a need to determine the long term impact of preventive treatment on tuberculosis and death, and the results of trials testing the efficacy of life long preventive treatment in adults infected with HIV are awaited. It will also be important to study the logistical barriers to implementing preventive treatment in different settings.²⁰

This review is concurrently available on the infectious diseases module of the Cochrane Database of Systematic Reviews and will be updated as new data become available. We thank Dr Mark Hawken, who made original trial data available rapidly and courteously.

Contributors: DW generated the idea for this review, developed the protocol, conducted the review, and wrote the paper; he will act as guarantor for the paper. SBS provided input on the protocol development and interpretation of the review and commented on the manuscript. PG was coordinating editor for the review and oversaw its quality throughout, provided methodological support, and commented on the manuscript.

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Conflict of interest: None.

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Antibiotic resistance among enterococci causing endocarditis in the UK: analysis of isolates referred to a reference laboratory

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Enterococci account for 5-15% of cases of bacterial endocarditis.¹ They are the most resistant bacteria commonly encountered in this type of infection, which is still associated with a mortality of 20-30%.² The treatment regimen for enterococcal endocarditis recommended by the British Society for Antimicrobial Chemotherapy and the American Heart Association is a synergistic bactericidal combination of a penicillin or glycopeptide with an aminoglycoside, usually gentamicin or streptomycin.^{3,4} However, enterococci can acquire high level resistance to aminoglycosides, which abolishes this synergy.¹ Enterococci can also exhibit high level resistance to penicillin or to glycopeptides.¹ Our laboratory undertakes testing of bacteria from cases of endocarditis as a routine service; we analysed resistance among isolates from 120 cases of enterococcal endocarditis, received over 27 months.

Methods and results

Results of tests for antibiotic susceptibility were analysed for enterococci referred from patients with a clinical diagnosis of endocarditis between January 1995 and March 1998. Isolates exhibiting high level resistance to gentamicin or streptomycin were defined as those where the concentration of antibiotic required to inhibit growth on laboratory media (minimum inhibitory concentration) exceeded 2000 mg/l.¹ Resistance to other antibiotics was defined according to criteria specified by the British Society for Antimicrobial Chemotherapy.⁵

The isolates, which were from 60 UK hospitals, comprised 106 *Enterococcus faecalis*, 13 *E faecium*, and one *E avium*. The table shows the major resistance characteristics of these isolates. Overall, 26% of isolates had high level resistance to both gentamicin and streptomycin (22% of *E faecalis* isolates; 62% of *E faecium* isolates). A further 28 *E faecalis* isolates showed high

level resistance to either gentamicin (7 isolates) or streptomycin (21 isolates); four *E faecium* isolates and the sole *E avium* isolate showed high level resistance to streptomycin but not to gentamicin.

All the *E faecalis* isolates remained susceptible to ampicillin (minimum inhibitory concentration 0.5-4 mg/l for 105 isolates and 8 mg/l for 1 isolate), but 6 were resistant to vancomycin, with 2 exhibiting cross resistance to teicoplanin. One isolate resistant to glycopeptides also had high level resistance to both gentamicin and streptomycin. The 13 *E faecium* isolates were all resistant to ampicillin (>8 mg/l), with 3 also resistant to vancomycin but not teicoplanin. Two of these vancomycin resistant isolates showed high level resistance to gentamicin and streptomycin.

Comment

Treatment for enterococcal endocarditis comprises a bactericidal synergistic combination of a penicillin (usually ampicillin or benzylpenicillin) or glycopeptide with an aminoglycoside, usually gentamicin or streptomycin for at least 4 weeks.^{2,3} It is therefore disturbing

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Resistance of enterococci from 120 cases of endocarditis to aminoglycosides and to cell wall active antibiotics

Antibiotic	No (%) of isolates showing resistance			
	All species (n=120)	<i>E faecalis</i> (n=106)	<i>E faecium</i> (n=13)	<i>E avium</i> (n=1)
Aminoglycosides:				
Gentamicin and streptomycin	31 (26)	23 (22)	8 (62)	0
Gentamicin only	7 (6)	7 (7)	0	0
Streptomycin only	26 (22)	21 (20)	4 (31)	1
Neither aminoglycoside	56 (47)	55 (52)	1 (8)	0
Cell wall active agents:				
Ampicillin	13 (11)	0	13 (100)	0
Vancomycin and teicoplanin	2 (2)	2 (2)	0	0
Vancomycin, but not teicoplanin	8 (7)	4 (4)	3 (23)	1