

# EVIDENCE-BASED HEALTH CARE

## TREATMENT OF LATENT TUBERCULOSIS INFECTION IN HIV-INFECTED PERSONS

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### Background

Only 5-10% of HIV-negative people infected with *Mycobacterium tuberculosis* ever go on to develop active tuberculosis (TB).<sup>1</sup> In the remainder the infection remains latent. HIV-infected people are at higher risk of progression, with a lifetime risk of approximately 30%, or 5-8% annually.<sup>2</sup>

Antituberculous treatment of latent TB (i.e. those with evidence of infection such as a reactive skin test but no active disease) reduces later active TB in people who are HIV negative.<sup>3</sup> This does not necessarily mean that the same benefits will occur in HIV-infected people. The immune response is different, absorption of drugs may be reduced in HIV infection, drug interactions with antiretroviral therapy may occur and poor adherence (due to illness or the adverse effects of many drugs) may play a part.

### So what is the question?

To get the right answer one first needs the right question. One question might be: 'In people with latent TB infection, what is the effect of antituberculous drugs on progression to active TB?'

### The type of evidence to look for, and where to look for it

Treatments are best assessed by randomised controlled trials.\* If more than one trial has been performed, the best evidence, if available, will usually come from a systematic review\* of valid randomised controlled trials. The Cochrane Library is an electronic collection of over 2000 high-quality systematic reviews, and is a good first port of call when looking for evidence on interventions. In South Africa the Cochrane Library is accessible (after registering) free of charge at <http://www.sahealthinfo.org/evidence/databases.htm>.

### Aims

This feature on evidence-based healthcare aims to present useful practice-related information on topics relevant to readers of *Current Allergy & Clinical Immunology*. The treatment of each topic is not comprehensive. The main aim is to illustrate selected aspects of the process of i) getting the evidence straight and ii) applying valid evidence to practice. The box entitled 'Some terms explained' enlarges on the technical terms mentioned in the text and marked with an asterisk(\*).

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### What was found

A Cochrane systematic review does exist.<sup>4</sup> It includes all randomised controlled trials in adults, some on anti-retroviral therapy, and was last updated in November 2003. (One advantage of Cochrane systematic reviews is that they are regularly updated. A new electronic version of the Library is published every 3 months, and individual reviews are updated regularly.)

### What the review authors did

The review authors tried to identify all existing trials by searching a wide range of databases (not just PubMed), scanned reference lists of articles and contacted authors and other researchers in the field. To be as accurate as possible two authors decided which studies should be included, assessed study quality and extracted data from the articles independently – and then checked themselves against each other. The outcomes and the analyses performed were pre-specified, to avoid a 'fishing expedition' for chance findings.

### Results

The review identified 11 trials involving 8 130 participants. The main findings, comparing any anti-tuberculous drug or combination of drugs with placebo were:

Outcome	Subgroup risk	Relative interval	95% confidence
Development of active TB	All	0.64	0.51-0.81
	Skin test pos	0.38	0.25-0.57
	Skin test neg	0.83	0.58-1.18
Death	All	0.95	0.85-1.06
	Skin test pos	0.80	0.63-1.02

### Other findings

- No detectable difference in effectiveness between different drug regimens
- Multi-drug regimens were stopped more often because of adverse drug reactions
- Insufficient evidence to assess long-term benefit (beneficial effect still present after 2.5 years of follow up, but the size of the effect was diminishing)
- Insufficient evidence on whether effects were different with differing degrees of severity of immunocompromise.

### Some comments

From this review, the 'best guess' (point estimate) is that antituberculous treatment reduces the risk of active TB in people with a reactive tuberculin skin test to 38% of the risk without treatment (i.e. relative risk\* 0.38). The 95% confidence interval\* (0.25-0.57) suggests that the 'true' value lies between 25 and 57%.

However, just because the treatment is effective does not necessarily mean that it must be used. Some people will get TB despite treatment while most will not get active TB at all, even without treatment. In other

words, several people need to be treated for one to benefit. The 'cost' of preventing one case would thus include the adverse effects of treating the people who do not benefit. If the benefit of preventing one case outweighs this cost (and if the resources would not have been better used doing something else), then treatment is worthwhile. Using the average risk of TB in the HIV-infected people with a reactive skin test in these trials, the number needed to treat (NNT)\* to prevent one case of active TB in the first two years is around 20. The judgement as to whether this is worthwhile will depend on local circumstances

These trials were performed in adults, so the findings do not necessarily apply to children.

As with most topics, this review offers some answers, and more questions. There is insufficient evidence on the duration of the effect of anti-TB treatment and on the effects in people with different levels of immunosuppression.

### \*Some terms explained

**Confidence interval.** Although not strictly correct, for practical purposes a 95% confidence interval indicates the range within which the true size of the effect is likely to fall. In the review featured here, the point estimate ('best guess') of the relative risk (RR) for active TB in HIV-infected people with a positive skin test is 0.38. The 95% confidence interval indicates that the true size of the effect (which is never exactly known) has a 95% chance of falling between 0.25 and 0.57. Note here that the 'worst case' is a relative risk of 0.57, which is beneficial. On the other hand, the relative risk for death of 0.80 suggests benefit, but the 95% confidence interval of 0.63 to 1.02 indicates a meaningful degree of uncertainty i.e. the true effect could be anything from meaningfully beneficial (RR 0.63) to marginally harmful (RR 1.02). This lack of evidence of a reduction in mortality (i.e. we can't be sure either way) is different from evidence that it does not in fact reduce mortality.

**Meta-analysis.** This is a statistical technique that summarises the results of several studies in a single estimate, in which more weight is given to results of studies with more events. The effect is similar to – but definitely not the same as – pooling several smaller studies to produce one larger trial. The terminology on different sides of the Atlantic confuses the picture. In North America, a systematic review (and not just the statistical technique used in the review) may be called a 'meta-analysis'. On our side of the Atlantic a meta-analysis refers only to the statistical technique. Although a systematic review need not necessarily include a meta-analysis, a meta-analysis should only be done in the context of a systematic review. Otherwise, 'garbage in, garbage out'.

**Number needed to treat (NNT)** is the number of people who need to be treated over a specific period of time to prevent one bad outcome. For instance, in this review the NNT using anti-tuberculous treatment to prevent active TB for 2 years

## REFERENCES

1. Enarson DA, Rouillon A. The epidemiological basis of tuberculosis control. In: Davis PDO, ed. *Clinical Tuberculosis*. 1st ed. London: Chapman & Hall, 1994: 19-32.
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3. Smieja MJ, Marchetti CA, Cook DJ, Smail FM. Isoniazid for preventing tuberculosis in non-HIV infected persons (Cochrane Review). In: *The Cochrane Library*, Issue 3. Chichester, UK: John Wiley & Sons, 2004.
4. Woldehanna S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons (Cochrane Review). In: *The Cochrane Library*, Issue 3. Chichester, UK: John Wiley & Sons, 2004.

in HIV-infected people with a reactive skin test was approximately 20. The NNT depends not only on how effective the treatment is, but also on how common the outcome is. If the untreated risk of TB in these trials had been half of what it was, the NNT would have doubled.

**Relative risk (risk ratio)** is the ratio of the risk of an outcome in the treated group to the risk in the control group. A relative risk of 1 means that the risk of the outcome is the same in both groups, i.e. the treatment has no effect. A relative risk below 1 means that the intervention reduces the risk of the outcome. Above 1 means increased risk. A relative risk below 1 for a bad outcome is thus a good thing, but for a good outcome (e.g. recovery) it means the treatment did harm (by reducing the 'risk' of recovery).

**Randomised controlled trial.** In a controlled trial patients are actively allocated to either receive treatment or be in a control group. The control group allows comparison of the treatment with the outcome without treatment. However the two groups need to be as similar as possible *before* the trial starts, so that any differences at the end can be attributed to the treatment. *Randomly* allocating participants to treatment or control is the best way we know of ensuring that the groups are comparable.

**Systematic review.** This is a literature review conducted itself like a research study, in order to minimise the many unintended (and sometimes subtle) biases that can creep into traditional literature reviews. It uses specified systematic methods to identify, appraise and summarise studies aimed at answering a defined question. A Cochrane review is a systematic review performed under the auspices of an international collaboration called the Cochrane Collaboration. There are however many systematic reviews performed outside of the Cochrane Collaboration.