Treatment of active tuberculosis in HIV-coinfected patients: a systematic review and meta-analysis

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CRD summary
This review evaluated whether treatment duration and schedule affected the effectiveness of rifamycin and antiretroviral therapy in treating active tuberculosis in human immunodeficiency virus-positive patients. It concluded that at least eight months duration of rifamycin therapy, initial daily dosing and concurrent antiretroviral therapy might be associated with better outcomes. Various uncertainties made the reliability of the conclusion unclear.

Authors' objectives
To evaluate the impact of duration and dosing schedule of rifamycin and use of antiretroviral therapy in the treatment of active tuberculosis (TB) in HIV-positive (human immunodeficiency virus-positive) patients.

Searching
The authors searched MEDLINE (from 1950), EMBASE (1988) and Cochrane Central Register of Controlled Trials (CENTRAL) for relevant studies published in English, French or Spanish until April 2008. Search terms were reported in an online appendix.

Study selection
Eligible studies were either cohort studies, randomised controlled trials (RCTs) or (if cases represented a consecutive cohort) case-control studies of patients with serologically confirmed HIV infection who were treated with standardised regimens that contained rifampin or rifabutin. Eligible studies stratified treatment outcomes by regimen. Studies were eligible within the primary analysis if all patients had microbiologically confirmed active TB and reported microbiologically confirmed failure or relapse. Studies were eligible for secondary analysis if some patients received a clinical diagnosis. Studies were excluded if patients had multidrug-resistant TB infection or were given twice-weekly therapy during the initial intensive phase.

Most of the included studies were performed in South America or southern Africa. Publication year ranged from 1991 to 2006. In most studies, the TB site was pulmonary only and patients had not been treated for TB previously. Further details were provided in the review.

Two reviewers performed the study selection. Disagreements were resolved by consensus or arbitration with a third reviewer.

Assessment of study quality
It appeared that the review assessed study quality in terms of loss to follow-up, missing outcome data and method of randomisation (for randomised controlled trials).

The number of reviewers who performed the quality assessment was not reported.

Data extraction
Data required to calculate pooled failure rates, risk ratios (RRs) and adjusted risk ratios (aRRs), all with 95% confidence intervals (CIs), were extracted using a standardised form for a range of outcomes by one reviewer; one third of the articles were independently extracted by a second reviewer to assess accuracy of the extraction process.

Failure was defined as a positive smear or sputum culture after at least five months of treatment; relapse was defined as occurrence of a positive smear or culture after apparently successful completion of treatment.
Methods of synthesis
Overall pooled rates with 95% CIs were calculated using a random-effects model using the exact binomial likelihood method for the outcomes cumulative failure, relapse and death after treatment. Different study arms were treated as independent cohorts. Heterogeneity was assessed using the $I^2$ statistic.

Subgroup analyses were used to assess the influence of clinical heterogeneity (such as duration of treatment and dosing schedule in the intensive treatment phase) on outcome. Meta-regression was used to further explore sources of heterogeneity.

Results of the review
Twenty-seven studies (n=3,543, range eight to 553) were included in the review: six randomised controlled trials and 21 cohort studies. Loss to follow-up during treatment ranged from 0% to 32.8%; loss to follow-up after treatment, where reported, ranged from 0% to 39.7%. Where reported, follow-up duration ranged from zero to 24 months. Two of the three trials with head-to-head comparisons had adequate randomisation, one had adequate allocation concealment and all three had significant loss to follow-up after treatment (at least 10%).

Pooled failure rates for all studies was estimated to be 0.03 (95% CI 0.02 to 0.04, $I^2=53.0$%). Pooled relapse rates was 0.12 (95% CI 0.05 to 0.19, $I^2=91.8$%). Pooled death rates was 0.05 (95% CI 0.12 to 0.17, $I^2=76.7$%). The denominators in these pooled rates were not reported.

Meta-regression analysis: Adjusting for a number of variables (it was unclear which variables), the reviewers indicated that risk of relapse was higher if rifampin therapy was of two-months rather than eight-months duration (this difference was not statistically significant) and if the initial phase of intermittent therapy was administered three times a week instead of daily. Compared with daily initial phase intermittent therapy, three times a week initial phase therapy was associated with a higher risk of treatment failure. Compared with treatment duration of more than eight months, rifampin therapy was associated with a higher risk of death.

Authors' conclusions
The review raised serious concerns about recommendations for treatment of HIV-tuberculosis co-infection. At least eight months duration of rifamycin therapy, initial daily dosing and concurrent antiretroviral therapy might be associated with better outcomes; adequately powered randomised trials were needed urgently to confirm this.

CRD commentary
The review question was somewhat unclear, but supported by clearly stated study selection criteria. More than one database was searched in more than one language. No measures were reported to identify unpublished studies, which raised the risk of publication bias. Sufficient primary study details were reported. Study quality assessment and data extraction both appeared adequate. It was unclear how many reviewers performed the validity assessment. More than one reviewer performed study selection and data extraction, which reduced risks of reviewer error and bias. Most of the included studies were cohort studies (which had substantially higher risk of bias than RCTs). The methods of synthesis generally appeared appropriate, although different arms of RCTs were treated as different cohorts, which lost the value of randomisation. The results were not clearly reported, as the denominator for the pooled failure rates (such as events per week, month or year) was not made clear and the variables controlled for within the multivariate regressions was not clear. These uncertainties made the reliability of the conclusion unclear.

Implications of the review for practice and research
Research: The authors stated that randomised trials were needed urgently to assess the questions about treatment of active TB in HIV co-infected patients raised by the review.

Practice: The authors did not state any implications for practice.

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