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Six months therapy for abdominal tuberculosis (Protocol)

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TABLE OF CONTENTS

[Intervention Protocol]

Six months therapy for abdominal tuberculosis

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To compare the effects of six-month versus longer regimens for abdominal tuberculosis (TB), consisting of a two-month intensive phase with rifampicin, isoniazid, pyrazinamide, and ethambutol followed by a four-month or longer continuation phase including at least isoniazid and rifampicin.

BACKGROUND

Description of the condition

Tuberculosis (TB) is an infectious disease caused by infection with bacterial species of the *Mycobacterium tuberculosis* (*M. tuberculosis*) complex. The World Health Organization (WHO) has estimated that 9.6 million people developed the disease in 2014 (WHO 2015). Alongside human immunodeficiency virus (HIV), TB remains a leading cause of death worldwide and caused 1.5 million deaths in 2014, mostly in low- and middle-income countries (WHO 2015). There is also increasing incidence of TB in developed countries due to HIV co-infection, the increased use of immunosuppressive therapy, and migration from high TB burden countries (Debi 2014; Kim 2003).

TB affects mainly the lungs (pulmonary TB), but can spread to other organs (extrapulmonary TB, EPTB). The term abdominal TB refers to TB infection in any of the structures within the abdominal cavity, which includes the gastrointestinal tract, the peritoneum (the lining of the abdominal cavity), the lymph nodes within the abdomen, and any of the solid organs in the abdomen (liver, pancreas, spleen). Appendix 1 outlines the various forms of abdominal TB. Abdominal TB can present as isolated involvement of the gastrointestinal tract, the peritoneum, lymph nodes, or solid viscera, or as involvement of multiple sites (Debi 2014). The most common forms of abdominal TB affect the gastrointestinal tract with the ileocaecal area being the most common site involved, and the peritoneum (Bolukbas 2005). In children, adhesive peritonitis and lymphadenopathy are the commonest forms of abdominal TB (Tinsa 2010). Routine data collection by most national TB programmes worldwide does not currently report EPTB cases by organ system affected and estimates of prevalence vary considerably for abdominal TB, ranging from 3% to 17% of EPTB cases (Khan 2006; Sharma 2004; Sheer 2003). Some data reported abdominal TB as the sixth most frequent site of EPTB (Sheer 2003). Although abdominal TB can be detected in individuals of any

age, young adults between 25 and 45 years are most commonly affected (Lazarus 2007). Abdominal TB can result from swallowing infected sputum, ingestion of contaminated milk products or meat, haematogenous spread from tubercular focus in any other organ, spread via lymphatics from infected nodes, and contiguous spread from adjacent organs (Debi 2014; Lazarus 2007). The clinical presentation depends on the site infected. Abdominal pain, abdominal distension, diarrhoea, and constitutional symptoms of TB, such as weight loss and fever, are frequent manifestations of intestinal TB (Bolukbas 2005; Mamo 2013). The onset is insidious in most cases, but intestinal TB may present acutely with complications, such as intestinal obstruction and perforation. In addition to the common manifestations of abdominal TB, other symptoms may be present depending on the infected site. Colonic TB may present with chronic diarrhoea or recurrent partial intestinal obstruction and, uncommonly, with bleeding from the gastrointestinal tract, and rectal lesions such as anal fissures, fistulae, or perirectal abscesses (Golden 2005). Tuberculous peritonitis commonly presents with ascites (Debi 2014).

Microbiological diagnosis of abdominal TB by culture of the organism is difficult, and the diagnosis is usually based on histopathological and radiological findings (Debi 2014; Mamo 2013). Barium contrast and abdominal computerized tomography with enterography (CT-E) are helpful in establishing the diagnosis of gastrointestinal TB. Biopsy of the area affected in the gastrointestinal tract can be obtained by endoscopy or even laparotomy, in order to increase chances of definite diagnosis by identification of *M. tuberculosis*. Regarding TB peritonitis, examination of ascitic fluid usually shows characteristics of exudate, with high protein content, lymphocytic predominance, and high adenosine deaminase levels. Culture of peritoneal (ascitic) fluid has very low sensitivity for isolation of *M. tuberculosis*, although concentration methods such as centrifugation may improve the yield. Culture of peritoneal biopsy specimens has a higher sensitivity. Peritoneal specimens can be obtained with ultrasound guidance or via laparoscopy/laparotomy (Golden 2005).

Abdominal TB is considered a great mimicker of other diseases involving the abdomen. Regarding intestinal TB, the differential diagnosis includes Crohn's disease, cancers, and other infectious diseases such as amoebiasis, gastrointestinal histoplasmosis, and *Yersinia* enterocolitis (Bolukbas 2005). Therefore, a high index of suspicion is required to make a prompt diagnosis and to start antituberculous therapy, which is essential to limit complications and prevent death (Balasubramanian 1997; Lazarus 2007).

Description of the intervention

Standardized international recommendations for treating people with pulmonary TB consist of six-month antituberculous regimens, including isoniazid (H), rifampicin (R), and pyrazinamide (Z), usually with ethambutol (E) as a fourth drug during the first two months of treatment (intensive phase), followed by isoniazid and rifampicin for four additional months (continuation phase) (WHO 2010). In a person suffering from TB, *M. tuberculosis* is present in replicating and slow- or non-replicating states. Bacilli in slow- or non-replicating states are tolerant to some antituberculous drugs, and it is believed that these are responsible for the need for long antituberculous regimens with a combination of drugs (Raffetseder 2014; Zumla 2014). The discovery of new antituberculous drugs over the last decades, along with trials assessing different combinations and doses of antituberculous drugs, has allowed shortening of treatment duration for pulmonary TB to six months, also known as short-course antituberculous therapy (Menzies 2009; Zumla 2014). The basic principles of antituberculous treatment for pulmonary TB have been extrapolated to the extrapulmonary TB forms, with exceptions such as TB meningitis. Most current guidelines recommend the same six-month regimen for pulmonary TB for treating people with drug-sensitive abdominal TB (American Thoracic Society 2003; WHO 2010). However, these recommendations have not been supported by high quality evidence. EPTB cases were excluded from trials that evaluated the effectiveness of six-month antituberculous therapy, because of difficulties in establishing a microbiological diagnosis and the lack of clear and reliable parameters for assessing treatment outcome (Kim 2003). There is reluctance among physicians, especially in developing countries, to treat abdominal TB with six-month regimens. This is based on concerns that short-course antituberculous treatment may not be long enough to eliminate slow- or non-replicating bacilli in the infected site in order to prevent relapse of the disease, and because of the difficulties in assessing treatment response in abdominal TB (Park 2009). Thus, despite the current recommendations, many clinicians still treat patients with abdominal TB for more than six months (Debi 2014; Makharia 2015).

How the intervention might work

Some trials have reported that six-month antituberculous regimens are as effective as longer regimens in treatment of abdominal TB (Balasubramanian 1997; Makharia 2015). Long treatments are associated with poor adherence and loss of participants to follow-up, which leads to increased relapse rates and mortality. Poor patient compliance also facilitates the development of drug-resistant TB strains when programmatic conditions are not optimal (Zumla 2014). Finally, the other disadvantages of longer regimens are increased cost, and increased exposure to antituberculous drugs which may lead to increased drug toxicity (Park 2009).

On the other hand, relapse of the disease remains a concern when treating people with abdominal TB for six months. Short-course regimens may not be long enough to eliminate slow- or low-replicating mycobacteria in the infected sites, leading to higher relapse rates. Some manifestations of abdominal TB may affect absorption of the drugs, which could lead to specific concerns about whether the concentration of the drugs is sufficient at the site of infection in such patients.

According to the literature on pulmonary TB, most relapses occur within the first six to 12 months after completion of antituberculous treatment (American Thoracic Society 2003; Park 2009). By extrapolating basic principles of pulmonary TB treatment to EPTB treatment due to a lack of data for abdominal TB treatment, a minimum of six months follow-up after treatment completion is required to assess the relapse outcome. TB infection can relapse many years after initial treatment, so ideally long follow-up periods are required to assess relapse rates. However, most deaths associated with abdominal TB seem to occur within the first weeks after diagnosis (Mamo 2013). Deaths are reduced by prompt diagnosis and early initiation of antituberculous therapy (Debi 2014), and the role of duration of antituberculous therapy in reducing deaths is uncertain.

Why it is important to do this review

The key concern for acceptance of a six-month regimen for abdominal TB is whether six-month regimens achieve successful treatment rates that are as good as longer regimens without significantly increasing the number of relapses. Few trials have assessed the effectiveness of six-month regimens versus longer regimens for this form of TB (Makharia 2015; Park 2009; Tony 2008). As relapse is a relatively uncommon event, large numbers of participants are required to assess this outcome, and existing trials may be underpowered to detect a difference in relapse rates. Therefore, a meta-analysis may be helpful to estimate the effect of six-month antituberculous therapy on relapse rates in people with abdominal TB.

Two review authors (SJu and HR) conducted an evidence review to compare the effects of treatment with the six-month first-line regimen 2RHZE/4RH versus the nine-month regimen 2RHZE/7RH for abdominal TB for the Indian Extra-Pulmonary TB (INDEX-TB) guidelines, which forms the preliminary work for this Cochrane Review (INDEX-TB 2016).

OBJECTIVES

To compare the effects of six-month versus longer regimens for abdominal tuberculosis (TB), consisting of a two-month intensive phase with rifampicin, isoniazid, pyrazinamide, and ethambutol followed by a four-month or longer continuation phase including at least isoniazid and rifampicin.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) or quasi-RCTs.

Types of participants

Adults and children with a diagnosis of presumed drug-sensitive abdominal TB as defined by the trial authors, from all settings and countries.

Types of interventions

Short-course regimens

Six-month antituberculous regimens that contain a two-month intensive phase with rifampicin, isoniazid, pyrazinamide, and ethambutol, followed by a continuation phase of four months that includes at least isoniazid and rifampicin.

Prolonged-course regimens

Antituberculous regimens of more than six months that contain a two-month intensive phase with rifampicin, isoniazid, pyrazinamide, and ethambutol, followed by a continuation phase that includes at least isoniazid and rifampicin.

Types of outcome measures

Primary outcomes

- Relapse: participants who have new symptoms and signs of abdominal TB after resolution of disease and completion of antituberculous treatment.
- Clinical cure: participants who completed treatment according to the original treatment plan without evidence of treatment failure at the end of treatment (WHO 2013).[1]

[1]The WHO's definitions for TB outcomes are primarily based on the assessment of pulmonary TB patients, so sputum smear and culture status are important factors in defining outcomes. Generally, repeating biopsy of the infected tissue for histopathology and culture at the end of antituberculous therapy is not done routinely in patients with abdominal TB. Therefore, in practice, bacteriological status is not part of the definition of cure or successful treatment. We anticipate that trial authors may define cure and treatment failure in different ways, including symptomatic cure and resolution of lesions on radiological imaging or endoscopy. We will specify the definition of clinical cure used in each included trial and collect outcome data accordingly.

Secondary outcomes

- Death from any cause.
- Treatment failure: failure to improve with antituberculous treatment, or deterioration following initial improvement while on antituberculous treatment.

- Default: participants who discontinue antituberculous treatment before the end of treatment, or participants whose treatment is interrupted for eight weeks or more consecutively (WHO 2013).
- Poor adherence: lack of compliance with the treatment regimen, as reported by the trial authors, but does not meet the definition of 'default' outlined above.
- Complete healing of active lesions, documented by endoscopy or histopathology.

Adverse events

- Serious adverse events that are life-threatening or lead to hospitalization.
- Adverse events that lead to the discontinuation of antituberculous treatment.
- Other adverse events relating to antituberculous treatment.

Timing of outcome assessment

For RCTs that report on relapse, we will include those with a minimum of six months follow-up after antituberculous treatment completion.

Search methods for identification of studies

We will attempt to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and ongoing).

Electronic searches

We will search the following electronic databases, using the search terms and strategy described in Appendix 2: PubMed (including MEDLINE), EMBASE (accessed via OvidSP), the Cochrane Infectious Diseases Group (CIDG) Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL), LILACS, INDMED, and the South Asian Database of Controlled Clinical Trials. We will search ClinicalTrials.gov and the search portal of the WHO International Clinical Trials Registry Platform (www.who.int/trialsearch) to identify ongoing trials.

Searching other resources

We will check the reference lists of existing reviews and of all trials identified by the above methods that meet our eligibility criteria, for other potentially relevant trials.

Data collection and analysis

Selection of studies

Two review authors (SJu and SJa) will each independently screen the titles and abstracts of the studies identified by the literature search for studies that may meet eligibility criteria, and will remove duplicate reports. We will retrieve the full-text articles of potentially eligible studies. SJu and SJa will then independently assess the full-text studies for study eligibility using an eligibility form that is based on the predefined inclusion and exclusion criteria. We will resolve any disagreements by discussion, and will involve a third review author if necessary. Where eligibility is unclear we will attempt to contact the trial authors for clarification. We will list excluded studies together with the reasons for exclusion.

Data extraction and management

One review author (SJu) will pilot the data extraction form on two included trials. Based on the pilot results, we may modify the data extraction form and we will finalize it. Two review authors (SJu and SJa) will then independently extract data from the included trials according to the agreed data extraction tool. We will compare the data extracted by the two review authors to identify possible errors. We will resolve any discrepancies through discussion and by referring to the original articles. We will extract the following data.

- Country, setting, when the trial was conducted, study design, inclusion and exclusion criteria applied, number of participants recruited to each trial arm.
- Participant characteristics: age, gender, epidemiological data such as known contact with TB patient, duration of the disease at presentation, severity of disease at presentation (as reported by the trial authors), features of malabsorption, site of the disease, comorbidity (HIV, malnutrition, other immunosuppressive conditions, and other diseases), co-existing pulmonary TB or concurrent TB infection in any other organ, diagnostic methods and results (PPD skin test in mm, microscopy, culture, histology and cytology of ascitic fluid, lymph node aspirate or biopsy, other tissue biopsy, chest X-ray, abdominal X-ray, barium enema, CT of the abdomen, endoscopy, laparoscopy, surgery), number of bacteriologically confirmed and clinically diagnosed cases of abdominal TB, and history of previous antituberculous therapy received.
- Intervention data: antituberculous drugs, dose, route of administration in both the intensive and continuation phases, and duration of each phase. Administration of other drugs or therapeutic procedures. Administration of treatment under directly observed short-course therapy (DOTs) or unsupervised/home treatment.
- Outcome data: for relapse, we will extract data on relapse rate, clinical severity of relapse, method of diagnosis, and time

between end of treatment and relapse. For clinical cure, we will extract the exact definition used by the trial authors. For assessing defaulters and adherence, we will examine the methods for assuring adherence, including clinical history, direct observation, and tablet counting. We will extract data on the number of defaulters, and the number of participants with poor compliance, based on the definitions stated in the 'Secondary outcomes' section. For all the outcomes, we will extract, if available, data on site of disease and on HIV status.

- Follow-up: length of follow-up, the way participants were followed up, the number and characteristics of losses to follow-up.

For each established outcome, we will extract the number of participants randomized and the number of participants analysed in each treatment group. For dichotomous outcomes, we will extract the number of participants that experience the event. For count data outcomes, we will extract the number of events in the intervention and control group, the rate ratio, and the standard error.

Assessment of risk of bias in included studies

Two review authors (SJu and SJa) will independently assess the methodological quality of each included trial using the Cochrane 'Risk of bias' assessment tool, which addresses sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other biases (Higgins 2011). For each component, we will classify our judgments as either 'low', 'high', or 'unclear' risk of bias. We will resolve any discrepancies through discussion between the two review authors or we will contact a third review author if required. We will summarize the results of the assessment in 'Risk of bias' graphs and 'Risk of bias' tables, with supporting evidence from the trial reports.

Measures of treatment effect

We will calculate the risk ratio (RR) for dichotomous outcomes. We will use the rate ratio for count data outcomes. We will present the effect estimates with 95% confidence intervals (CIs). If the RR value is inappropriate to evaluate the effect estimate of uncommon events, we will use the risk difference.

Dealing with missing data

It is possible to impute data using best and worst-case scenario analyses (that is, the 'best-case' scenario is that all participants with missing outcomes in the experimental intervention group had good outcomes, and all those with missing outcomes in the control intervention group had poor outcomes; the 'worst-case' scenario is the converse). However this is an extreme adjustment, especially where outcomes are rare, as it would be very unlikely that all participants with missing data experienced an event for either treatment arm. Instead, we will perform imputations using the event rates observed in the available data. As an available case analysis implicitly assumes that the event rates observed also apply to the missing data, we will vary the observed event rates within reasonable limits, and apply these varied event rates to the missing data, so that the resulting sensitivity analyses represent plausible scenarios that may have occurred within the missing data. This will allow us to investigate how plausible missing data scenarios would impact the overall effect estimate.

Assessment of heterogeneity

We will assess clinical and methodological diversities by looking at the variability in participants, interventions, outcomes, study design, and risk of bias in the included trials. If possible, we will assess statistical heterogeneity by inspecting the forest plots for overlapping CIs, by applying the Chi^2 test with a P value of 0.10 used to indicate statistical significance, and by using the I^2 statistic with a value of 50% used to denote a moderate level of heterogeneity.

Assessment of reporting biases

If we include 10 or more trials, we will construct a funnel plot to assess publication bias.

Data synthesis

We will summarize all included trials in the 'Characteristics of included studies' tables. If data are available, we will group the included trials by site of disease: gastrointestinal tract, peritoneum, lymph nodes, and solid viscera. We will analyse the data with Review Manager (RevMan) (RevMan 2014). We will solicit guidance from a statistician of the Cochrane Infectious Diseases Group (CIDG) if required. To describe the effect of estimates, we will use RR and risk difference values when appropriate as a summary statistic for dichotomous data, with 95% CIs. We will conduct meta-analyses if appropriate, and will use a fixed-effect model in the first instance. If we detect moderate heterogeneity, we will use a random-effects model. If meta-analysis is inappropriate, we will present the data in text and tables using narrative summaries. We will assess the quality of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) principles (Guyatt 2011). We will construct 'Summary of findings' table(s) using the GRADEpro Guideline Development Tool (available from www.gradepro.org).

Subgroup analysis and investigation of heterogeneity

Death from abdominal TB can be related to mycobacterial burden and dissemination of infection, malabsorption, malnutrition, co-morbidities, and complications of the disease and treatment. Death in the first six months of treatment may not be related to

the total length of treatment, while death after six months of antituberculous therapy may be related to cessation of antituberculous treatment in participants treated for six months. Therefore we will explore heterogeneity by conducting subgroup analysis between death in the first six months and after six months of antituberculous treatment.

We anticipate that we will not obtain enough data to conduct further subgroup analyses. However, we may stratify results to describe differences between regimens that are longer than six months, participants who are HIV-positive or HIV-negative, and participants treated with intermittent and daily antituberculous treatment.

Sensitivity analysis

If there is a sufficient number of included trials, we will perform sensitivity analyses by limiting inclusion in the meta-analysis as follows, and we will compare the results to the primary meta-analysis.

- Trials at low risk of bias.
- Trials with little or no missing data.
- Any individual peculiarities we identify during the review process.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Forms of abdominal TB

Form	Anatomical site
Abdominal lymph node TB (abdominal TB lymphadenitis)	Lymph nodes (mesenteric, omental, at porta hepatis, at coeliac axis)
Peritoneal TB (TB peritonitis)	Peritoneum
Gastrointestinal TB	Ileocaecal area (ileocolonic TB) involving the ileum and caecum
	Jejunum
	Colon
	Oesophagus, stomach, duodenum
Visceral TB	Liver, spleen, pancreas

Appendix 2. Detailed search strategies

Search set	MEDLINE	EMBASE
1	tuberculosis [MeSH]	Tuberculosis [Emtree]
2	tuberculosis [ti, ab]	Tuberculosis [ti, ab]
3	1 or 2	1 or 2
4	Abdominal OR gastroenteric OR gastrointestinal OR intestinal OR enterocolitis OR peritonitis OR peritoneal OR hepatic OR liver OR splenic [ti, ab]	Abdominal OR gastroenteric OR gastrointestinal OR intestinal OR enterocolitis OR peritonitis OR peritoneal OR hepatic OR liver OR splenic [ti, ab]
5	3 and 4	3 and 4
6	"Peritonitis, tuberculous" [Mesh]	"Abdominal tuberculosis"[Emtree]
7	"Tuberculosis, Gastrointestinal"[Mesh]	5 or 6
8	"Tuberculosis, Hepatic"[Mesh]	5 or 7
9	"Tuberculosis, Splenic"[Mesh]	-
10	6 or 7 or 8 or 9	-
11	5 or 10	-

We will use these search terms in combination with the search strategy for retrieving trials developed by Cochrane (Lefebvre 2011). This is the preliminary search strategy for MEDLINE and EMBASE, which we will adapt for other electronic databases. We will report all search strategies in full in the final version of the review.

CONTRIBUTIONS OF AUTHORS

SJu and HR wrote the protocol, with input from VA and SJa.

DECLARATIONS OF INTEREST

SJu and HR are employed by the CIDG, which is funded by a grant from the Department for International Development (DFID), UK. SJa and VA have no known conflicts of interest.

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