

Impact of tuberculosis preventive therapy on tuberculosis and mortality in HIV-infected children (Review)

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[Intervention Review]

Impact of tuberculosis preventive therapy on tuberculosis and mortality in HIV-infected children

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ABSTRACT

Background

Children with HIV are at an increased risk of acquiring TB. Tuberculosis is a common cause of acute and chronic respiratory disease and death in HIV-infected children living in areas of high TB prevalence. Even with treatment, HIV-infected children with TB have a worse outcome than HIV uninfected children. Hence preventing TB infection and disease in HIV-infected children is desirable and a potentially an important public health intervention. Isoniazid, an anti-tuberculosis medication, has been used to effectively prevent TB in HIV uninfected children. There are currently no guidelines on the use of TB preventive therapy in HIV-infected children.

Objectives

To determine the impact of TB preventive therapy on TB incidence and death in HIV-infected children

Search strategy

We searched the Cochrane Controlled Trials Register (CENTRAL/CCTR), Cochrane HIV/AIDS Group Specialized Register, MEDLINE/PubMed, EMBASE and AIDSearch. In addition we scanned reference lists, manually searched conference abstracts and contacted content experts.

Selection criteria

We included studies of HIV infected children randomised to receive TB preventive therapy or placebo, or alternative TB preventive regimen. Participants could be tuberculin skin test positive or negative.

Data collection and analysis

Two authors independently used the study selection criteria, assessed methodological quality and extracted data. Effects were assessed using hazard ratios.

Main results

One completed and two ongoing trials met the selection criteria for the review. The completed trial participants were HIV-infected children, most of whom were not on antiretroviral therapy. Subjects- were randomised to isoniazid and cotrimoxazole or placebo and cotrimoxazole, given daily or three times a week. The mean length of follow-up was 5.7 months. The trial showed a marked reduction in TB incidence and death in the isoniazid group. However there is as yet no long-term follow up data on the durability of the protective effect or possible long term adverse events. This trial was also unable to assess the impact of isoniazid prophylaxis on children receiving antiretroviral therapy.

Authors' conclusions

Isoniazid prophylaxis in HIV-infected children has the potential to play a major public health role by reducing TB incidence and death. However there is as yet not enough data to guide the duration of prophylaxis, given empirically, nor to support its use in children on HAART and in those living in low TB prevalence areas, other than in situations of known TB contact. Further studies are needed to assess whether TB preventive therapy is of benefit in all HIV-infected children irrespective of use of antiretroviral treatment, the optimal duration of preventive therapy or long term benefits and adverse events.

PLAIN LANGUAGE SUMMARY

The impact of tuberculosis preventive therapy on tuberculosis and death in HIV-infected children

Tuberculosis (TB) is a common cause of severe lung disease and death in children infected with HIV, particularly those living in areas of high tuberculosis prevalence. Hence preventing TB infection and disease in HIV-infected children is desirable and potentially an important major public health intervention. Isoniazid, a medication used in the treatment of TB, has been effectively used to prevent TB in HIV-uninfected children exposed to TB. However, it is unclear what impact TB preventive therapy such as isoniazid has on the rate of TB or death if given to HIV-infected children with and without exposure to TB. This review aimed to assess the impact of any TB preventive therapy on the rate of TB or death when given to HIV-infected children. We found only one published randomised controlled trial investigating TB preventive therapy in HIV-infected children. The trial showed a marked reduction in TB incidence and death in the group of children who received isoniazid as primary preventive therapy. Few adverse events occurred during the study and none were related to the isoniazid therapy. However there are currently no long-term follow up data on the durability of the protective effect or possible long term adverse events. This trial was also unable to assess the impact of isoniazid prophylaxis on children receiving antiretroviral therapy. Further studies are needed to assess whether TB preventive therapy is of benefit in all HIV-infected children irrespective of use of antiretroviral treatment; the optimal duration of preventive therapy or long term adverse effects.

BACKGROUND

Tuberculosis (TB) is an important cause of childhood morbidity and mortality (Kochi 1991; Donald 2002). Infection is caused by *Mycobacterium tuberculosis* and most commonly results in acute and chronic respiratory disease (Foster 2003). Dissemination to other organ such as bone or nervous system may also cause debilitating morbidity. The burden of childhood disease is not as well documented as that of adult disease, partly because of the difficulty of confirming the diagnosis. However, it has been estimated that in 2000 there were 884 019 TB cases in children (Corbett 2003) accounting for up to 11% of new cases of TB. The proportion is

higher in Africa where children have been estimated to account for 20-40% of the TB case load (van Rie 1999). Childhood infection represents transmission of TB within a community and hence is a reflection of disease control within that community (Marais 2005). Children infected with *Mycobacterium tuberculosis* have a high risk of progression to disease, the younger children being at the highest risk.

They may also be a source of mycobacterial transmission, although the likelihood of transmission is less than for older groups (Curtis 1999). Infected children represent a reservoir of future

adult disease. The incidence of childhood TB has increased in low to medium income countries (Nelson 2004). This resurgence is partly attributed to the coexisting burden of human immunodeficiency virus (HIV) disease (Barnes 1991; Corbett 2003), which is most pronounced in Sub-Saharan Africa. At the end of 2005 an estimated 38 million adults and 2.3 million children under 15 years were living with HIV, 25.8 million in the African subcontinent (UNAIDS/WHO 2005). In many HIV endemic areas there is a co-existing high TB prevalence.

Dual infection with TB has an important impact on HIV disease. TB accelerates the progression of HIV disease by increasing viral replication (Goletti 1996). It is a common cause of acute pneumonia in African HIV-infected children (Zar 2001; Jeena 2002) and frequently results in chronic lung disease including bronchiectasis (Jeena 1998). TB is a common cause of death in HIV-infected children (Chintu 2005). Antituberculosis drugs, such as rifampicin (RIF), have deleterious drug interactions with anti-retroviral therapy. Rifampicin, an inducer of cytochrome P450 CYP3A, decreases the concentration of both the protease inhibitors and non-nucleoside reverse transcriptase inhibitors, leading to sub-therapeutic levels, with an increased risk of inadequate viral suppression and drug resistance. The large pill burden of two multiple drug regimens increases the risk of adverse events such as liver toxicity and increases the likelihood of poorer adherence (Burman 2005).

Conversely, HIV infection impacts on TB disease. HIV infected children have a higher risk of developing primary TB as compared to seronegative children (Mukadi 1997). The clinical diagnosis of TB is more difficult in HIV-infected children as other opportunistic infections or HIV disease itself may mimic TB. Furthermore tuberculin skin testing is less sensitive due to immunosuppression and chest radiography less specific (Berggren Palme 2002; Chintu 2005). The outcome of HIV infected versus HIV uninfected children with TB co-infection is poorer, with mortality increased by six fold in HIV-infected children (Berggren Palme 2002; Hesselting 2005). The cure rate of TB in HIV infected children is significantly lower than that of HIV uninfected children (Mukadi 1997; Berggren Palme 2002) and there is a higher rate of recurrence (Schaaf 2005). HIV-infected children may therefore require a longer course of TB therapy (Perriens 1995, Schaaf 1998). HIV-infected children stable on HAART are less likely to develop TB and have a better outcome than those not on HAART. However, the initiation of highly active antiretroviral therapy (HAART) in the setting of TB co-infection can lead to a paradoxical worsening of TB as a consequence of the 'immune reconstitution syndrome' (Narita 1998; Puthanakit 2006). The immune reconstitution syndrome incorporates disease phenomena that are a consequence of the restoration of the immune response after initiation of antiretroviral therapy.

Hence, preventing TB infection and disease in HIV-infected children is potentially an important public health intervention. Isoniazid (INH) has been used successfully as preventive therapy in

HIV uninfected children at risk of TB disease (Smieja 1999). Preventive therapy has been reported to be effective for prevention of TB disease in HIV-infected adults with a positive tuberculin skin test (Woldehanna 2004), reducing the risk of disease by 36%. This benefit was found for all preventive drug regimens: INH alone, INH with RIF, RIF with pyrazinamide (PZA) and INH, RIF and PZA. No reduction in mortality was found. However, there is currently no information on the efficacy of TB preventive therapy in HIV-infected children. In contrast to adults, preventive therapy in children is aimed at preventing primary infection rather than reactivation disease. In settings of high TB prevalence the rate of re-infection of TB is high, with short course prophylaxis potentially being inadequate. Longer term prophylaxis or repeat courses may be necessary. Preventive therapy can lead to adverse events most notably liver toxicity, although this is uncommon and rarely requires cessation of anti-tuberculosis medication in children (Thompson 1982; Donald 2000).

In high TB prevalence areas TB preventive therapy may be effective in preventing infection and subsequent development of active disease in HIV infected children. The efficacy of preventive therapy may however be limited by adherence difficulties, adverse events and cost implications. Its efficacy needs to be clearly established and balanced against the occurrence of these events. Therefore a systemic review was undertaken to review the effectiveness and safety of TB preventive therapy for tuberculosis in paediatric HIV infected children.

OBJECTIVES

The primary objective of this review was to determine the effectiveness of TB preventive therapy in reducing TB disease in HIV-infected children. The secondary objectives were to investigate the impact of preventive therapy on mortality and on the incidence of drug resistant *Mycobacterium tuberculosis* infection and the incidence of adverse events.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) were included where participants had been randomly allocated to preventive therapy for TB and placebo or alternative TB preventive therapy regimens.

Types of participants

HIV-infected children, less than 13 years, who did not have TB currently were included. Children may have been tuberculin skin test (TST) positive or negative. Children on highly active antiretroviral therapy (HAART) were not excluded.

Types of interventions

Intervention group: any tuberculosis drug or drug combination
Comparison group: inactive placebo, alternative tuberculosis drug or drug combination or no preventive treatment

Types of outcome measures

The primary outcome measure was incidence of definite and probable TB. Definite TB was defined by a microbiological or histological identification of *Mycobacterium tuberculosis*. The diagnosis of probable TB was based on a combination of typical clinical symptoms and signs, tuberculin skin testing, chest radiography, a history of close TB contact and a documented response to anti-tuberculosis therapy.

The secondary outcome measures included

- Incidence of death

- Incidence of drug resistance in culture confirmed cases
- Incidence of adverse drug reactions leading to discontinuation of treatment

Search methods for identification of studies

See: HIV/AIDS Group comprehensive search strategy

Electronic searches

We carried out an exhaustive search of the following electronic databases on the 23 March 2007 and again on 28 February 2008: The Cochrane Controlled Trials Register (CENTRAL/CCTR), Cochrane HIV/AIDS Group Specialized Register, MEDLINE/PubMed, EMBASE and AIDSearch for randomised controlled trials of chemoprophylaxis in HIV-infected children. Highly sensitive standardised methodological filters were used to identify randomised controlled trials and HIV/AIDS as detailed in the Cochrane Reviewer's Handbook (Higgins 2006). In addition the following specific terms were used for the search strategy: (tuberculosis) AND (preventive therapy OR chemoprophylaxis OR prophylaxis). The search was limited to age <13 years where possible, starting from 1980 to date. There was no language restriction in our search. An identical search strategy was used for all electronic databases. See Table 1 for the full search strategy.

Table 1. Search Strategy MEDLINE

Search	Most recent queries
#6	Search #1 AND #2 AND #3 AND #4 Limits: Publication Date from 1980 to 2007
#5	Search #1 AND #2 AND #3 AND #4
#4	Search PREVENTIVE THERAPY OR CHEMOPROPHYLAXIS OR PROPHYLAXIS
#3	Search TUBERCULOSIS OR TB
#2	Search randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebo [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animals [mh] NOT human [mh])
#1	Search HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunodeficiency virus[tw] OR human immunodeficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunodeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "sexually transmitted diseases, viral"[MESH:NoExp]

Manual searches

The above search strategy was supplemented by hand searching reference lists of identified related articles and relevant review articles. In addition to the conference proceedings searched electronically through AIDSearch, a manual search was undertaken of abstracts or proceedings of the following conferences: The International Union Against Tuberculosis and Lung Disease World Congress (IUATLD), The American Thoracic Society International Congress (ATS) and The European Respiratory Society World Congress (ERS). Investigators of identified trials and other content experts were contacted to locate information on any further trials that may not have been included in the electronic databases or presented at conferences, whether these were completed, published or not or ongoing. The WHO search portal (www.who.int/trialsearch/) was accessed on 5 February 2008 to search for any relevant registered trials. Authors of ongoing studies were contact to find out about any relevant unpublished data. Relevant editorials, non-Cochrane reviews, expert opinions and letters to the editor were scrutinised for any additional relevant studies or unpublished data.

Data collection and analysis

Selection of studies

Studies identified by the search strategy were scrutinised independently for eligibility by two authors (DGRA and HZ64). Studies were included if they met the eligibility criteria stated earlier. Authors assessing study eligibility were not blinded to the names of the trial investigators, their institutions, journals of publication and results of study. Where a review author had authored an included study an independent party assisted in both the extraction of data and assessment of methodological quality of that study.

Data extraction and management

DGRA and TY extracted the data from the one study included in this review. As the other two authors were co-investigators of this study they were not involved in data extraction or assessment of methodological quality of this study to maintain independence of the review. Forms were designed for data extraction and for requests of additional information from study investigators. The following were noted on the data extraction form: the review title, study reference and publication status, date of extraction, and author's initials. Data was extracted under the following subheadings in the form: **methods** (method of generation of allocation sequence and concealment; blinding of those receiving care, providing care and assessing outcomes; losses to follow-up and how they were handled, ethical approval and consent); **participants** (inclusion and exclusion criteria, number of patients randomised, setting); **interventions** (allocated therapy and dosage regimen, length of treatment, degree of adherence to treatment); **outcomes** (TB disease, mortality, adverse events leading to cessation of treatment, drug resistant cultures); **study results** (number of participants with

the event and the total number in that study arm for dichotomous outcomes; mean and standard deviation and total number of participants for continuous outcomes), and other notes. Study investigators were contacted for clarification on methodology.

Assessment of methodological quality of included studies

The methodological quality of the included study was then assessed independently by DGRA and TY. The following was assessed:

- The adequacy of generation of allocation sequence and allocation concealment in preventing selection bias
- The presence or absence of blinding of the participant and provider to reduce performance bias.
- The method of outcome assessment: whether the same method of assessment was used in both groups and presence or absence of blinding of assessor in the prevention of detection bias
- Attrition bias by looking at the percentage of participants included in final analyses and the description of those not included. Whether or not an intention to treat analysis was performed was also assessed.

Disagreement amongst the two authors assessing the eligibility and quality of trials was resolved by discussion and obtaining further information from study statistician.

Data analysis

The effect of the intervention compared to control on the time to event (mortality and developing TB) was assessed with hazard ratios (95% confidence interval). The standard errors were inferred from the reported confidence intervals using the necessary log transformations.

Missing data from participant drop out was addressed by an intention-to-treat analysis. No meta-analysis was performed as there was only one study included in the review.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of ongoing studies](#).

Results of the search

MEDLINE/Pubmed yielded 2156 records, CENTRAL 45, EMBASE 109 and AIDSearch 226 in total. There was some overlap between the references retrieved in each database. One reference was eligible for inclusion in the review. Studies of TB preventive therapy in HIV-infected adults were checked for inclusion of people <13yrs. All the adult studies had clear criteria that excluded children <13yrs.

Included study

One trial was included (n=277) ([Zar 2007](#)). This was a prospective randomised placebo controlled trial conducted in two tertiary care

centres in Cape Town, South Africa. Participants are described in the table of included studies.

Children were randomised to receive prophylaxis with co-trimoxazole and INH/placebo either daily or three times a week on Monday, Wednesday and Friday. The dose of INH was 10mg/kg/day with a variability of 8-12 mg/kg depending on whether half or quarter tablets were required. Placebo tablets were identical in appearance to the INH tablets. The dose of cotrimoxazole was 5mg/kg/dose of the trimethoprim component. Cotrimoxazole was given until 12 months of age, whereafter it was continued in those children with CDC clinical category B or C disease, in those with severe immunosuppression (CD4 count < 15% of total lymphocyte count) and in those who had previous episode of *Pneumocystis jirovecii* pneumonia. Primary outcome was mortality and secondary outcome were the incidence of confirmed or probable TB and drug resistant TB. Children were classified as having confirmed TB if they were culture positive for *M. tuberculosis*. Probable pulmonary TB was diagnosed when chest radiography suggested TB (lymphadenopathy, miliary pattern, pleural effusion, bronchial compression, or parenchymal infiltrate) and the child had at least one of: a positive tuberculin skin test result, a history of a close contact with tuberculosis, loss of weight or failure to gain weight within the previous three months, or a positive smear result for acid fast bacilli. The diagnosis of probable TB was subject to independent review by a blinded investigator.

The study received ethical approval from the research and ethics committees of the University of Cape Town and Stellenbosch University, South Africa.

Ongoing studies

There are two ongoing studies registered with the World Health Organisation's International Clinical Trials Registry (Zar, Madhi). The intervention in both studies is isoniazid as compared with placebo. The Zar study is enrolling only children on HAART. The Madhi study includes children with perinatal exposure to HIV, both HIV-infected and HIV uninfected children. Most children will not yet be on HAART. The Zar study is still recruiting patients. The Madhi study has recently been discontinued. Data will be considered for inclusion in this review when available.

Risk of bias in included studies

Allocation sequence generation

Generation of allocation sequence was achieved by variable blocked randomisation lists prepared by the trial statistician and sent to each trial site pharmacist in a sealed opaque envelope.

Allocation concealment

The participants were allocated study numbers sequentially by the study nurse at enrolment. They were then sequentially allocated to treatment group by the pharmacist according to the prepared list.

Blinding

The participants, care givers, health care providers and outcome assessors were blinded to the randomisation. The independent reviewer of probable TB diagnoses was also blinded to randomisation arm.

Follow-up and exclusions

A total of 277 participants were randomised; 139 in the intervention group and 138 in the placebo group. Fourteen children were excluded from analysis, 7 in each group; 5 in each group because children were found to be HIV negative and 2 in each group were lost to follow-up before the first visit. Therefore 263 subjects were included in the analysis: 132 in the intervention arm and 131 in the placebo arm.

Children were followed up every 4 weeks for the first 6 months then every 6 weeks for next 6 months and then every two to three months thereafter. Follow-up was planned for 2 years however the placebo arm was ended early on the recommendation of the data safety monitoring board (DSMB) on the basis of interim analyses. The median length of follow-up was 5.7 months (IQR 2.0-9.7 months). The analysis is described as an intention to treat analysis. All patients were analysed in the group to which they were randomised. However 14 patients that were randomised were excluded. Ten children, 5 in each group, were excluded as they were found to be HIV negative. This is unlikely to introduce bias. Four children, 2 in each group, were excluded immediately post-randomisation as they did not receive any follow-up. This has the potential to introduce bias however the numbers are so small that this is extremely unlikely.

Effects of interventions

Incidence of Tuberculosis

The median age of participants was 24.7 months. Sixteen percent of children had had TB prior to enrolment on the study. Nine percent of children were TST positive. Overall 7% (18 in 263 children) had tuberculosis. The incidence was lower in the INH group than in the placebo group, 4% (5 of 132 children) vs. 10% (13 of 131 children). In this study preventive therapy reduced the chance of developing definite or probable TB by 72% (Hazard ratio 0.28, 95% CI 0.10 to 0.77), Figure 1. This effect was evident for both the dosing regimens of 10mg/kg isoniazid given either daily or three times a week.

We did not assess the influence of HAART on TB incidence as there were too few children on HAART at enrolment for a meaningful assessment (23 of 263 children).

Mortality

The overall mortality rate was 12% (32 deaths in 263 children). Mortality was lower in the INH group than in the placebo group, 8% (11 of 132 children) vs. 16% (21 of 131 children). Preventive therapy reduced mortality by 54% (Hazard ratio 0.46, 95% CI 0.22 to 0.94), Figure 2. This effect was evident for both the dosing regimens of 10mg/kg isoniazid given either daily or three times a week.

Drug resistant TB

Five cases of TB were confirmed on culture. All *M tuberculosis* isolates were sensitive to anti-tuberculosis drugs including isoniazid.

Adverse events

There were five (4%) events of grade 3 or 4 toxicity in the INH group and eight (6.1%) in the placebo group. Two events were increases in alanine transaminase blood levels, both in the placebo group, and 11 were haematological events including neutropenia, thrombocytopenia or anaemia.

DISCUSSION

In areas of high TB and HIV prevalence preventing TB infection and disease in HIV-infected children is an important public health intervention. This is particularly relevant in areas where HAART is not widely available. There has been only one published randomised control trial of TB preventive therapy in HIV-infected children to date (Zar 2007). The vast majority of participants in this trial were not receiving HAART, a reflection of poor access and unaffordability at that time. This trial showed a significant reduction in TB incidence and death in HIV-infected children taking isoniazid prophylaxis over a median period of 5.7 months (2.0 to 9.7 months interquartile range). The additional protective effect of concomitant cotrimoxazole prophylaxis is unlikely to have played a role in these results as all children were receiving prophylaxis irrespective of randomisation status.

The results of this study differed from the adult review in a number of areas. Firstly isoniazid had a greater protective effect on childhood TB, reducing the chance of developing probable or definite TB by 72%. This is greater than the 36% reduction in risk of active disease overall and 60% reduction in PPD positive adults, found in the adult review (Woldehanna 2004). The effect in children was the same irrespective of PPD status, probably reflecting the insensitivity of PPD testing in HIV-infected children or the efficacy of preventative therapy for primary TB disease. Secondly isoniazid had a significant impact on all-cause mortality, reducing the risk of death by 54% in contrast to the absence of effect on mortality in HIV-infected adults.

However there are a number of questions that require further study. The duration of the protective effect of INH is unclear as children from the study were followed-up for a median period of 5.7 months at the time of analysis. Information on long-term follow-up of HIV-infected children given TB preventive therapy is needed.

HAART itself is effective in reducing the risk of TB disease and death in HIV-infected children, but does reduce the risk to that in HIV uninfected children. This study was unable to assess the impact of INH prophylaxis in HIV-infected children receiving HAART. Whether HIV-infected children on HAART living in a

high TB prevalence area should receive TB preventive therapy can not be answered from currently available research.

There is no data on the efficacy of other preventive therapy regimens. The single study investigated isoniazid therapy used daily or three times a week. The effect was comparable between both dosing regimens. The adult studies also included multi-drug combination preventive therapy. However adverse events leading to discontinuation of treatment were more common in people using multi-drug therapy as opposed to isoniazid alone.

Although all cases of definite TB in the included study were sensitive to antituberculosis drugs including isoniazid, long-term data on the impact of prophylaxis on *M tuberculosis* sensitivity is needed.

The impact of TB preventive therapy in areas of low TB prevalence is not known and further studies are needed. It is possible that current recommendations as for HIV uninfected children, to use prophylaxis in response to known close contact with TB would be adequate.

The included study had a significant impact on mortality and TB incidence hence it is not likely that a similar study could ethically be carried out. However, this study was initiated before antiretroviral therapy was available in the country of origin. There are currently ongoing studies of TB preventive therapy in HIV-infected children on HAART. The results of these studies will be included in this review once available.

AUTHORS' CONCLUSIONS

Implications for practice

Isoniazid prophylaxis has a substantial protective effect on TB incidence and death in HIV infected children not on HAART. However there is no currently available research that assesses the impact of isoniazid prophylaxis in HIV-infected children on HAART. There is also no published information on the duration of protection, the long-term effects of prophylaxis and the impact of prophylaxis in areas of low TB prevalence. INH should be considered as a primary preventive strategy in HIV-infected children who are not taking HAART who live in a high TB prevalence area.

Implications for research

Trials assessing the impact of prophylaxis in HIV-infected children on HAART and those living in areas of low TB prevalence are needed. Trials to assess the long-term effects of tuberculosis prophylaxis are also needed to more adequately assess the length of benefit in different clinical settings.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Zar 2007

Methods	277 individuals randomised by variable blocked randomisation lists prepared by study statistician. Randomisation was stratified for site and previous cotrimoxazole usage. Blinding: study investigator, providers, participants.
Participants	HIV infected children attending two tertiary healthcare centres in Cape Town, South Africa. Inclusion criteria: Age > 8 weeks Weight > 2.5 kg Access to transport Informed written consent from parent or legal guardian Exclusion criteria: Chronic diarrhoea Current use of or need for INH prophylaxis Previous hypersensitivity to INH or sulphur containing drugs Haemoglobin < 70 g/l Neutrophil count < 400 cell/ul Platelet count < 50 000 x10 ⁹ /l Non reversible renal failure
Interventions	Intervention: Isoniazid (100mg tablets) Dose: 10mg/kg/dose with a variability of 8-12mg/kg depending on whether a quarter or half tablet were required Frequency: Randomised to daily or three days a week Monday, Wednesday and Friday Control: Placebo tablets identical in appearance to Isoniazid tablets Frequency: Randomised to daily or three days a week, Monday, Wednesday and Friday Cotrimoxazole (5mg/kg/dose of the trimethoprim component): Given to all children < 12 months and those older with clinical CDC category B or C disease, in those with severe immunological impairment (CD4 count of < 15% of total lymphocyte count), or in those with previous episode of <i>Pneumocystis jirovecii</i> pneumonia. Frequency: according to daily or three times a week as per randomisation Duration: Study was planned to run for 2 years however the placebo arm was terminated early on the recommendation of the data safety monitoring board (DSMB) on the basis of the results of interim analyses.
Outcomes	Primary outcome: Mortality Secondary outcomes: Incidence of confirmed or probable Tuberculosis
Notes	Adverse events were graded 1 to 4 according to the toxicity criteria of the National Institutes of Health's division of AIDS (DAIDS). Grade 3 and 4 events were reported.
<i>Risk of bias</i>	

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Characteristics of ongoing studies [ordered by study ID]

Madhi

Trial name or title	A Randomized, Double Blind, Placebo Controlled Trial to Determine the Efficacy of Isoniazid (INH) in Preventing Tuberculosis Disease and Latent Tuberculosis Infection Among Infants With Perinatal Exposure to HIV
Methods	
Participants	<p>Ages: 91 Days to 120 Days</p> <p>Inclusion Criteria:</p> <p>Mother is HIV infected. Hard copy documentation of the mother's HIV infection is unnecessary if a positive DNA PCR from her infant is available.</p> <p>Received Bacille Calmette-Guerin (BCG) vaccine up to and including the 30th day of life and at least 90 days prior to study entry</p> <p>Able to complete all study requirements</p> <p>Normal truncated Denver Developmental Test for peripheral neuropathy at study entry</p> <p>Normal deep tendon reflexes and muscle bulk, tone, and strength at study entry</p> <p>Plan to live in the study area for at least 4 years</p> <p>Exclusion Criteria:</p> <p>Previous diagnosis of TB infection</p> <p>Previous receipt of INH</p> <p>Contact with a known acid fast bacilli (AFB) sputum smear or culture-positive case of TB before study entry</p> <p>Current acute or recurrent (3 or more prior episodes) lower respiratory tract disease</p> <p>Chronic persistent diarrhea</p> <p>Significant drop in weight or failure to gain weight appropriately during a 2- to 3-month period</p> <p>Contraindications for use of INH or SMX/TMP</p> <p>Require certain medications</p> <p>Known or suspected immune system diseases other than HIV</p> <p>Current or previous diagnosis of or treatment for cancer</p> <p>Current immunosuppressive therapy greater than 1 mg/kg/day of prednisone or equivalent</p> <p>Anticipated long-term oral or intravenous corticosteroid therapy (greater than 3 weeks). Those receiving nonsteroidal anti-inflammatory agents and inhaled corticosteroids are not excluded.</p> <p>Grade 3 or greater AST/SGOT, ALT/SGPT, ANC, hemoglobin, platelet count, rash, neuropathy, or myopathy at screening</p> <p>Any Grade 4 clinical or laboratory toxicity within 14 days prior to study entry</p> <p>Other acute or chronic conditions that, in the opinion of the investigator, may interfere with the study</p>
Interventions	Isoniazid and cotrimoxazole versus placebo and cotrimoxazole

Madhi (Continued)

Outcomes	<p>Primary Outcome Measures:</p> <p>Time from randomization to development of tuberculosis (TB) disease or death among HIV infected children [Time Frame: At Week 96]</p> <p>Time from randomization to development of TB infection or death among perinatally exposed, HIV uninfected children [Time Frame: At Week 96]</p> <p>Secondary Outcome Measures:</p> <p>Time from randomization to development of TB infection, and time from randomization to development of TB disease among HIV infected and perinatally exposed, HIV uninfected children [Time Frame: At Week 96 and Week 192]</p> <p>Time from randomization to death among HIV infected and perinatally exposed, HIV uninfected children [Time Frame: At Week 96 and Week 192]</p> <p>Population pharmacokinetics (PK) model of isoniazid (INH) among HIV infected and perinatally exposed, HIV uninfected children at two dosing interval time points on two separate occasions (at Cape Town and Durban only) [Time Frame: Throughout study]</p> <p>Time from randomization to development of TB infection among HIV infected children [Time Frame: At Week 96]</p> <p>Time from randomization to AIDS-defining illness or death among HIV infected children [Time Frame: At Week 96 and Week 192]</p> <p>Time from randomization to development of TB disease among perinatally exposed, HIV uninfected children [Time Frame: At Week 96]</p> <p>Time from randomization to new first Grade 3 or higher sign or symptom [Time Frame: Throughout study]</p>
Starting date	March 2006
Contact information	<p>Shabir Madhi, MD University of the Witwatersrand</p> <p>George McSherry, MD UMD - New Jersey Medical School</p> <p>Charles D. Mitchell, MD University of Miami</p>
Notes	<p>Alternative ID: PACTG1041</p> <p>Currently recruiting</p> <p>Clinical trial registry ID: NCT00080119</p>

Zar

Trial name or title	Isoniazid prophylaxis with concomitant cotrimoxazole in HIV-infected children
Methods	
Participants	<p>Age: 8 weeks to 15 years</p> <p>Inclusion Criteria:</p> <p>HIV-infected children</p> <p>Resident in Cape Town</p> <p>Informed consent obtainable</p> <p>weight > 2.5kg</p>

Zar (Continued)

	Access to transport HAART use for not less than 2 months but not more than 12 months with no significant demonstrated toxicity and good adherence
Interventions	Isoniazid versus placebo Cotrimoxazole Both either three times a week or daily
Outcomes	Primary Outcome Measures: TB incidence mortality Secondary Outcome Measures: intercurrent infections adherence adverse events antimicrobial resistance
Starting date	Jan 2003
Contact information	Heather J Zar, MD PhD 27216585350 hzar@ich.uct.ac.za Contact: Mark Cotton, MD PhD 27219384219 mcot@sun.ac.za
Notes	Currently recruiting Clinical trial registry ID: NCT00330304

DATA AND ANALYSES

Comparison 1. Isoniazid versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Hazard ratio death	1		Hazard ratio (Random, 95% CI)	Totals not selected
5 Hazard ratio TB incidence	1		Hazard ratio (Random, 95% CI)	Totals not selected

Analysis 1.4. Comparison 1 Isoniazid versus placebo, Outcome 4 Hazard ratio death.

Review: Impact of tuberculosis preventive therapy on tuberculosis and mortality in HIV-infected children

Comparison: 1 Isoniazid versus placebo

Outcome: 4 Hazard ratio death

Study or subgroup	Isoniazid N	Placebo N	log [Hazard ratio] (SE)	Hazard ratio IV,Random,95% CI	Hazard ratio IV,Random,95% CI
Zar 2007	132	131	-0.7765 (0.3657)		0.46 [0.22, 0.94]

Analysis 1.5. Comparison 1 Isoniazid versus placebo, Outcome 5 Hazard ratio TB incidence.

Review: Impact of tuberculosis preventive therapy on tuberculosis and mortality in HIV-infected children

Comparison: 1 Isoniazid versus placebo

Outcome: 5 Hazard ratio TB incidence

Study or subgroup	Isoniazid N	Placebo N	log [Hazard ratio] (SE)	Hazard ratio IV,Random,95% CI	Hazard ratio IV,Random,95% CI
Zar 2007	132	131	-1.273 (0.5135)		0.28 [0.10, 0.77]

WHAT'S NEW

Last assessed as up-to-date: 20 March 2006.

24 June 2009	Amended	Added author whose name had inadvertently been omitted.
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HISTORY

Protocol first published: Issue 1, 2007

Review first published: Issue 1, 2009

21 March 2006	New citation required and conclusions have changed	Substantive amendment
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CONTRIBUTIONS OF AUTHORS

DG was the lead author. DG and HZ64 conducted the search and scrutinised identified studies for eligibility. DG and TY assessed the methodological quality of included studies. All authors critically reviewed the manuscript before submission.

DECLARATIONS OF INTEREST

Two of the review authors conducted a randomised control trial on the impact of Isoniazid prophylaxis in HIV-infected children. When this study was reviewed, the other two review authors completed data extraction and methodological quality assessment which avoided any potential bias.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- HIV/AIDS mentoring programme, South African Cochrane Centre, South Africa.
- Cochrane Child Health Field Bursary, Canada.

INDEX TERMS

Medical Subject Headings (MeSH)

AIDS-Related Opportunistic Infections [mortality; prevention & control]; Anti-HIV Agents [therapeutic use]; Antitubercular Agents [adverse effects; *therapeutic use]; HIV Infections [drug therapy; *mortality]; Incidence; Isoniazid [adverse effects; therapeutic use]; Randomized Controlled Trials as Topic; Trimethoprim-Sulfamethoxazole Combination [adverse effects; therapeutic use]; Tuberculosis, Multidrug-Resistant [epidemiology]; Tuberculosis, Pulmonary [drug therapy; *mortality; *prevention & control]

MeSH check words

Child; Humans