

# HATiP

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# Isoniazid prophylaxis treatment for children with HIV: is it ready for implementation?

## Introduction

The care and management of children with HIV in resource-limited settings has long been a neglected issue. Perhaps because of the small size of the paediatric HIV market in Europe and North America, the pharmaceutical industry has been slow to develop antiretroviral formulations or dosages that can be given to small children - and when they have, these are rarely priced for use in the developing world. In most cases, pharmacists and clinicians in resource limited settings are forced to crush up adult tablets, and then guess the appropriate portion to give a child based upon his or her size and/or weight.

Diagnosis of HIV in infants is also a challenge since antibody testing is unreliable in children below 18 months. The alternative PCR test is too expensive for routine diagnostic use in many countries and difficult to use outside of well-equipped laboratories. [The problems that make effective clinical management of children with HIV issues difficult are addressed in an article on [www.aidmap.com](http://www.aidmap.com) "Treatment for children must become global priority, urges MSF."]

Given the hurdles in providing care to children with HIV, it is perhaps not surprising that clinical research in children with HIV also lags behind that in adults. Similarly, both the management (and study) of childhood tuberculosis is notoriously challenging - and even more so in children with HIV (see below).

So when a clinical trial comes along that shows clear, though preliminary, benefits in children with HIV, the practical implications of that research merit discussion particularly when that research concerns tuberculosis in children with HIV.

One such study was recently presented as a late-breaker at the Fifteenth International AIDS Conference in Bangkok. The study, conducted in the Western Cape province of South Africa, demonstrated a clear survival benefit when HIV-positive infants and small children were treated with isoniazid (given as prophylaxis to prevent tuberculosis). Before describing the study, a short discussion of tuberculosis in children with HIV is perhaps warranted.

## TB in children

Childhood tuberculosis differs somewhat from the illness in adults in a number of ways, particularly when the child is co-infected with HIV. For instance, the disease may be transmitted congenitally - and co-infected mothers are more likely to pass the infection on to their children who then may develop active disease while neonates. The disease can strike much more quickly: most cases occur within one year of infection - and the cases with the most serious complications (such as meningeal TB and other forms of extrapulmonary TB) have the shortest incubation periods. TB can also infect unusual sites such as the middle ear. Chronic fever is commonly associated with TB in children with HIV.

Definitive diagnosis can be both difficult and time consuming.

1) Finding a source case (the adult from whom the infection was acquired) is very important for diagnosis but not always possible

2) Chest x-rays are of little use due to the similar presentation of other lung conditions in children with HIV (such as lymphocytic interstitial pneumonitis, or LIP)

3) A negative tuberculin skin test (TST) does not exclude TB in up to half the cases

4) AFB smears have a low yield (5-10%) in children and AFB cannot distinguish *M.tuberculosis* from non-tuberculous mycobacteria

5) Culturing, the gold standard for diagnosis, can take up to eight weeks

6) Physical signs of tuberculosis such as enlarged lymph nodes are common in children with HIV

7) Others symptoms may also mimic other conditions in children with HIV

Not surprisingly, both under and over diagnosis of TB in children occur commonly.

By the time a constellation of symptoms and other findings indicate a diagnosis of TB, the disease has usually become severe and very difficult to treat.

Not that a response to therapy is all that easy to assess in children with tuberculosis either. Even when treatment is effective, chest x-rays often show little improvement in children. After 6 months of treatment, about 60% of children will still have an abnormal chest x-ray; and it could take more than two years for the chest x-ray to become normal.

This then forces clinicians and/or investigators to use other clinical markers to monitor response, such as improved growth. Likewise, failure and/or relapse can be difficult to measure. Chest x-rays are again not helpful; microbiology (culture) can only be used to confirm relapse in severe cases. In fact, there is no standardized definition of treatment failure - other than apparent severe clinical deterioration and death. All of these factors make it particularly difficult to detect when the child has drug resistant tuberculosis.

Given the difficulties in diagnosis and treatment, one would think that there would be a greater emphasis on prevention. But according to Dr. Haruna Jabril, a paediatrician working in Gaborone, Botswana: "The fear has always been that making the diagnosis of TB in children is so difficult and, as exclusion of TB disease is a prerequisite to isoniazid prophylaxis, the risk of giving monotherapy to the children that harbour the disease may be real."

All of which makes the South African study's findings quite provocative and potentially important in areas with a high incidence of TB. Such is the case in the Western Cape, where the study was performed. The South African Province has one of the highest incidences of TB in the world - and children there have a 4.1% annualised risk of developing TB.

## The South African prophylaxis study

The investigators, including Professor Heather Zar and Dr. Mark Cotton, conducted a prospective placebo controlled trial involving children recruited from two treatment centres (Stellenbosch University and the University of Cape Town). The aim of the study was to see if isoniazid prophylaxis reduced mortality in HIV infected children. A secondary aim of the study was to establish the impact of isoniazid prophylaxis on the incidence of tuberculosis.

The study recruited HIV-positive children between 8 weeks and 12 years of age. The study also compared daily versus 3 times weekly trimethoprim-sulfamethoxazole (co-trimoxazole) which is given to all asymptomatic infants below 12 months and all

symptomatic children over 12 months. The median age of children enrolled to the study was 23.5 months.

All the children in the study were randomized to receive co-trimoxazole (TMP-SMX) prophylaxis (which is protective against PCP and certain other infections to which individuals with immune suppression are vulnerable). Co-trimoxazole was given either daily or three times a week. The children in each co-trimoxazole group were then randomised to receive either isoniazid prophylaxis or a placebo to be taken at the same dosing frequency as TMP-SMX.

Isoniazid (INH) was dosed at 10mg/kg. The study used 100 mg isoniazid scored tablets dosed at 10mg/kg in whole or half tablets. Quarter tablets were used where the infant's weight lay between 2.5 and 3.5kg (one quarter) or 6.5 and 8.5 kg (three quarters). The medication was planned to be administered for 2 years with interim re-evaluations for toxicity and efficacy.

Enrolment started in January 2003 with the aim of recruiting 425 patients but only 278 were enrolled when the placebo arm of the study was discontinued after the Data Safety Monitoring Board reviewed the findings in May 2004.

By this point there had been a total of 32 deaths: 20 in the placebo group and 12 in the INH group, a statistically significant difference ( $p=0.026$ ). Isoniazid treatment was associated with a 53% reduction in mortality.

Isoniazid prophylaxis also helped to prevent cases of tuberculosis. Of the 14 incident cases of tuberculosis that occurred during the study period: nine were in the placebo group and five in the isoniazid group. This difference tended towards but did not, however, reach statistical significance using a 2-tail test;  $p = 0.077$ .

Analysis of the causes of death is still underway, however, according to Professor Zar many were due to bacterial sepsis in both arms.

HATIP notes that it is possible that the survival benefit conferred by isoniazid treatment may not be entirely explained by the drug's anti-tuberculosis effect. It is possible that some of the benefit could be due to increased protection offered by isoniazid against other infections to which children with HIV are susceptible, much like co-trimoxazole's effect on organisms other than just PCP.

A number of laboratory studies have demonstrated that once isoniazid is "activated" inside the body, it acts as an inhibitor of an enzyme necessary for fatty acid synthesis in a variety of bacteria and parasites. There may even be a synergistic effect when it is combined with co-trimoxazole. For instance, one company has conducted studies of a co-formulation of cotrimoxazole/isoniazid against malaria.

Dr. Cotton said "we do not know yet whether there was a decrease in other infections." However, Professor Zar is sceptical of any alternative explanation for isoniazid's activity aside from its antimycobacterial effect.

The survival benefit appeared early during prophylactic treatment with isoniazid (within 50 days), and was apparent in all CDC categories of HIV disease severity and at both treatment centres.

Dr Cotton says he cannot explain why isoniazid appeared to have such a rapidly protective effect. "We were surprised by our findings but the role of TB may be under appreciated even in an area of high prevalence. Some of the early effects of TB infection may precede clinical disease."

Young age was an independent risk factor for death. The risk of death was nine times higher in children below the age of eight months when compared to children of 21 months age and over but there was no interaction between age and isoniazid treatment.

The reported survival benefit had decreased somewhat from what was reported the abstract (see abstract below).

In a subsequent interview with HATIP, Dr Cotton explained "The initial survival analysis was based on 146 subjects with follow-up beyond 1 month and 21 deaths by end of December 2003. At placebo closure, an additional 11 deaths had occurred and were re-analysed, the follow-up data for all subjects was not included as our complete data set (278 subjects) had not been entered on the database."

When asked whether there was a difference between isoniazid regimens employed, Dr. Cotton replied that preliminary analysis favours 3x weekly.

As noted, there were breakthrough cases of tuberculosis on INH. One major concern in any TB patient on prophylaxis or treatment has always been poor adherence and resulting drug resistance. The investigators are still awaiting completion of the study for final analysis of the adherence cohort.

But drug resistance can be extremely difficult to detect in children - in many situations the source case (the adult with tuberculosis to whom the child was exposed) may have had drug resistant tuberculosis. There is also a danger of increased resistance due to possible over (or under)-treatment with INH. Dr. Cotton agreed that is indeed a major concern.

## Implications

These data are preliminary and restricted to two sites. The investigators certainly are not trying to suggest that guidelines be adapted. Yet HATIP has recognised a tendency in HIV/AIDS medicine to change clinical practice on the basis of a ten-minute conference presentations of incomplete trial data. At the same time, it can be problematic to run more placebo-controlled studies when a survival benefit has been demonstrated. We are aware that some clinicians plan to implement isoniazid prophylaxis on the basis of the evidence presented. It's a catch 22 situation.

The study investigators themselves urge caution:

Professor Heather Zar commented: "I think one needs to be quite careful... really one should wait for publication of the study before reporting this as potentially very important with widespread public health implications."

Dr. Cotton believes that the final findings eventually could warrant that "INH prophylaxis could be considered for HIV-infected children in regions of high prevalence" However: "What is most important is to stress that the findings are still preliminary and await analysis of our full data set."

HATIP then asked a cross-section of experts and care providers for children with HIV in resource limited settings the following questions:

1) Should clinical guidelines be adjusted so that children with HIV are offered INH or should more placebo-controlled studies be conducted in other settings?"

2) Should ALL children with HIV now be offered isoniazid prophylaxis or should it only be given to those in areas with a high incidence of TB?"

3) Is this preliminary analysis enough to make you consider changing how you treat children in your practice, or will you wait for a) publication of the final analysis of the complete data set or b) other confirmatory trials in your setting, or c) until formal WHO or national guidelines are changed?"

Almost all the responses we received agreed on the need for caution and further analysis of the complete data set (and possibly further study) before even considering changing clinical practice.

Says Dr. Haruna Jabril: "The result of the impact of INH prophylaxis on the mortality as reported is quite impressive but my

feeling is that we need to complete the data analysis and take it up from there.

"I think that it is time to have another look at the question of INH prophylaxis in children. It may just be that we are denying children with HIV/AIDS something that will make a difference to their survival or even an improvement in their quality of life."

"If we improve our yield of AFB positivity in a given setting enough to develop an acceptable degree of confidence in its sensitivity, we should be able to use it to rule out TB disease with some degree of confidence. We are looking at gastric washings (in combination with other diagnostic parameters) now in children in an attempt to do this. Perhaps we will be able to develop that confidence in diagnosing TB disease."

"Most importantly however we need to replicate it elsewhere. Perhaps a multicentre collaborative study may be the way to go. We will be quite happy to participate."

Dr. Siobhan Crowley of WHO commented: "I think this work could be of relevance to practitioners in resource constrained settings where there is a large burden of TB, but we need further data and analysis and other studies to determine at this stage whether to change international guidelines."

Also we need to look at the impact of greater access to ARVs and improved diagnostic capability for HIV infection in infants and children as in many countries practitioners are unable to diagnose infections prior to 15-18 months, except in those who are very unwell or have an AIDS defining diagnosis, and it may well be that in these children INH is necessary and beneficial but in those who are symptomatic it is not as protective, and that in infants on ARVs the need for INH is outweighed by its interference with ART."

"We need to look more closely at this data set first and see if this gives us enough data to at least then introduce in areas where TB prevalence is the same or higher, then need some studies in TB less burden settings, but agree we need to try to avoid placebo controls otherwise we may be withholding survival benefit."

Others were concerned that the strategy might be harmful to children.

Dr Françoise Railhet, Manager of the LLL France Medical Associate Program said: "TB is more and more resistant. It seems to me that a "prophylactic" treatment is not a very good idea : this sort of treatment increases resistance. And isoniazid has iatrogenic effects (beginning with hepatic toxicity)."

Others questioned the high death rate, particularly those who work on breastfeeding issues in children. Jackie Nutt, a colleague of Dr. Railhet, works with women trying to achieve exclusive breastfeeding in South Africa:

"I am intrigued to see that there is no mention of adjusting for feeding method of infants in the report of the study. Perhaps in a setting with a lot more support for breastfeeding than the Western Cape, the death rates might have been different, or of different causes [since] bacterial sepsis is something that breastfeeding protects against. I would assume that these children were not breastfed [or] some of the children might have been orphans already, or perhaps the mothers were already too ill to breastfeed."

"I am also interested in the balance between drug benefits and the counter-productive effects they have on an infant's immature gut (e.g. gut irritation by co-trimoxazole). How well is isoniazid tolerated - any information? How sure are the researchers that some of the adverse effects were not due to drug side effects?"

She thinks the placebo arm may have been dropped prematurely:

"In HIV treatment we have to weigh up the pros and cons of every intervention. It appears that dropping the placebo arms from recent

MTCT trials of AZT vs NVP might have been premature. It seems that many researchers focus entirely on transmission rates and not on eventual health outcomes."

"The apparent synergistic effects of isoniazid outside the context of TB is thought provoking - another reason why I think it would be important to continue with a placebo arm in a non-TB area."

"Where TB is a non-issue, will survival be improved by adding a drug (which has serious side effects) "just in case"? And even in the Western Cape, what will we see a few months hence - perhaps children "saved" from TB, yet with non-functioning livers? Or greater resistance? The placebo needs to be there for the next trial, I firmly believe."

## Conclusion

We are excited about the reduction in mortality that this strategy might offer, but because of the difficulties and dangers involved in the management of tuberculosis in children with HIV, it seems necessary to exercise caution before altering clinical practice. Additional studies are almost certainly needed in regions where healthcare practices are different from the Western Cape - which is much less-resource restricted than the rest of Africa and the developing world.

Furthermore, the strictest protocols should be in place to be certain that children offered isoniazid prophylaxis do not already have active tuberculosis, and that parents or caretakers 1) understand how to consistently administer the correct dose of the medication (including when to increase the dose as the child grows), and 2) when to return to the clinic because of early signs of toxicity and/or illness.

Finally, the study underscores the need for improved diagnosis of both HIV and tuberculosis in children since the greatest benefits of this strategy are to a population that is difficult to identify for healthcare workers in most resource-limited settings. Finding "asymptomatic" HIV+ infants below the age of one year requires PCR testing to detect HIV RNA, which despite price reductions is still far beyond the reach of most developing nations to use routinely for screening in asymptomatic infants. And the day when a first-tier healthcare worker will have a simple and affordable method to reliably and consistently detect latent or early active tuberculosis infection in all children with HIV seems even further off.

## Reference

Zar H et al. Early and unexpected benefit of isoniazid in reducing mortality in HIV-infected children in an area of high tuberculosis prevalence. Fifteenth International AIDS Conference, Bangkok, late breaker abstract LbOrB12, 2004.

## Abstract

XV International AIDS Conference Abstract number: LbOrB12

Early and unexpected benefit of isoniazid in reducing mortality in HIV-infected children in an area of high tuberculosis prevalence

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Background:

Both tuberculosis and Pneumocystis pneumonia are major opportunistic infections in HIV-infected African children. The effect of INH prophylaxis on mortality and TB incidence in HIV infected children has not been studied.

Aims:

To investigate the effect of long term INH prophylaxis on mortality in HIV-infected children from a high TB prevalence area. Secondary outcomes included investigation of the incidence of TB.

**Methods:**

A two-centre prospective double blind placebo controlled trial in Cape Town, South Africa, comparing isoniazid (INH) versus placebo given with trimethoprim-sulphamethoxazole (TMP-SMX) either daily or three times weekly in HIV-infected children aged 8 weeks or older. INH was given according to the frequency of the TMP-SMX schedule.

**Results:**

Enrolment began in January 2003. Interim analysis performed in December, 2003 found 21 deaths in 148 (14.1%) subjects who had 1 month or more of follow-up. The mortality rate amongst those on placebo [16 of 21 (76.2%)] was significantly higher than those on

INH by "intent to treat" ( $p = 0.004$ ) and "time on treatment" analysis using person-time exposure ( $p = 0.0005$ ). The survival benefit appeared within 50 days, occurred in all CDC categories of clinical disease severity and in both study centres. Of 14 cases of tuberculosis, 9 were in the placebo and 5 in the INH group (intent to treat analysis:  $p = 0.077$ ; log-rank).

**Conclusion:**

INH prophylaxis has an early and significant survival benefit and reduces TB incidence in HIV-infected children. Based on these results and the recommendation of the data safety monitoring board, the placebo arm of the study has been discontinued.

## about HATiP

A regular electronic newsletter for health care workers and community-based organisations on HIV treatment in resource-limited settings.

The newsletter is edited by Theo Smart (Cape Town) and Keith Alcorn, NAM's Senior Editor (London).

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