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Main article: Isoniazid preventive therapy

"From an individual point of view, I have no doubts about isoniazid preventative therapy (IPT)... If you can do IPT in Muhimbili Medical Centre and in Cape Town, why not? But from the perspective of most national TB programmes, it is almost insurmountable. Going for HIV-infected patients with preventive therapy is extremely complicated, you have to exclude active disease," said Dr Hans Rieder, a TB expert and consultant to the International Union against TB and Lung Disease, in a very critical appraisal of treatment for latent TB in people with HIV.

Dr Rieder was one of a number of speakers at the 36th Union World Conference on Lung Health a month ago in Paris to address the controversial issue of whether isoniazid should be more widely used to prevent active tuberculosis in patients with HIV in resource-constrained settings.

The question gets very different answers depending upon who is being asked, the local prevalence of TB and HIV coinfection, and whether they come from the HIV community or the TB world. But with the release at the World Conference of the final results from an important study of IPT in children with HIV, and presentations on a number of programmes that have begun to offer IPT to adults with HIV, there is increasing pressure to use IPT more widely – even though the logistics may render the efficacy questionable.

IPT background

Isoniazid treatment has been used to prevent active TB for over thirty years, particularly in the US and other industrialized nations. Several placebo-controlled trials in people with latent TB infection have shown that giving isoniazid daily for 6-12 months substantially reduces the subsequent risk of developing active TB (Smieja).

However, other countries, including the UK, have been more wary of using IPT in members of the general population exposed to TB for a number of reasons. First, in countries with a low TB burden, the rate of TB activation in a person without HIV is very low (perhaps one out of one thousand persons exposed to TB) – so a large number of patients would be exposed to treatment needlessly. Also, it is difficult for healthy people to adhere to a six to twelve month course of daily treatment – and if TB infection actually becomes active in someone who is taking the treatment erratically, they are at risk of developing drug resistance. Furthermore, enthusiasm for casually dispensing isoniazid to anyone who was possibly exposed to TB was dampened by reports in the 1970's of fatal liver damage in some patients. Even though these adverse events can be kept to a minimum by monitoring for elevated liver enzymes, the potential for harm exists and probably outweighs the benefit that the drug offers people not at high risk of active TB.

HIV's effect on the risk-benefit equation

However, HIV may change the balance of risk to benefit because the virus dramatically increases the likelihood of progression to active TB in co-infected patients. In addition, many patients with HIV develop TB that is particularly hard to diagnose and manage.

In his presentation, Dr Reider referenced a study on mycobacteria tuberculosis (MTB) septicaemia among febrile patients at Muhimbili Medical Centre, Dar es Salaam, Tanzania. In the study, only three cases of MTB septicaemia were observed

among 235 HIV-negative patients, but of 282 subjects with HIV, 57 had MTB septicaemia. 23 of these had no respiratory symptoms. About half of the patients with HIV and MTB septicaemia died from the illness (Archibald). "From this point of view, it is highly desirable that we intervene before such undiagnosable conditions occur," said Dr Reider.

And yet, there is no guarantee that IPT will work as well in people with HIV. A number of factors could adversely affect the efficacy of IPT in people with HIV such as impaired drug absorption, the aggravation of side effects from antiretroviral therapy and other drugs used to manage AIDS-related conditions, which could in turn increase adherence problems.

In general, treatment of latent TB is associated with a lower incidence of active TB in people with HIV compared with placebo, according to a recent Cochrane Review analysis of eleven placebo-controlled studies with 8130 HIV-positive participants, (RR, 0.64; 95% CI, 0.51-0.81). The impact is particularly pronounced among those with a positive tuberculin skin test (RR 0.38, 95% CI 0.25 to 0.57) (Woldehanna and Volmink).

However, there was only a trend towards reduced mortality; and the review leaves a lot of practical questions unanswered, such as whether the treatment works as well in people across the spectrum of CD4 cell counts, in patients on antiretroviral therapy or in settings with varying degrees. Despite noting the Cochrane Review findings, in November's Bulletin of the World Health Organization, Onyebujoh et al. write "assumptions about the effective protective potential associated with preventive therapy in those infected with HIV remain to be adequately quantified, especially within programme settings."

IPT through National TB Programmes (NTPs)

Dr Reider's talk addressed the practicalities of providing IPT to HIV-positive patients through NTPs.

Dr Reider focused on four key determinants for the effectiveness of preventative therapy in a public health setting:

- The probability of infection with MTB.
- The risk of active tuberculosis given infection.
- The efficacy of the regimen.
- Adherence to treatment.

As already noted, the risk of developing active TB is high among HIV coinfecting patients. But it is not so easy to tell whether a person has been exposed to TB.

Problems with the tuberculin skin test

"Still mostly in the world, we have this old technique, we inject something in the skin and we look at the red bump," said Dr Reider. "But like any other test, the tuberculin skin test (TST) has characteristics (such as sensitivity, specificity) that will determine how good [it is at predicting] whether MTB infection is actually there."

He cited a survey of 60,000 Tanzanian school children with a TB prevalence of around 13%. Using a cut-off of 5 mm (for the size of the induration or bump), the TST only had a two-thirds positive predictive value (Styblo). If a positive TST result were to be used as the sole basis for giving IPT, "we would be giving a hepatotoxic drug to people with no risk of TB – so this is an ethical dilemma." Noting the experience with rifampicin and pyrazinamide in the US, which caused a number of deaths when used to prevent TB. "You can't afford to kill people who maybe didn't need the drug in the first place."

The TST also has limited negative predictive value in patients with advanced HIV who may be anergic and fail to generate a reaction despite TB exposure. This has led some to call for using a lower cut off point (5mm instead of 10mm) for a positive TST result in adults with HIV. This view “has its roots in the United States,” said Dr Reider, “but it has no scientific basis whatsoever.” In fact, a large study from Tanzania presented at last year’s World Conference found: “...In HIV infection, most loss of TST sensitivity is due to anergy. Reducing the cut-off from 10 to 5 mm in this population provides limited gain in sensitivity whereas it is likely to result in considerable loss of specificity...” (Egwaga).

While recent studies suggest that newer TB tests, such as the enzyme-linked immunospot assay (ELISPOT) assay (T-SPOT TB) or other gamma-interferon assays may be better suited than the TST at diagnosing latent tuberculosis in people with HIV-associated immunosuppression, these tests are simply beyond the reach of NTPs in resource constrained settings (Dhedda). “Most African countries cannot even afford to have TSTs in the periphery,” said Dr Reider.

Duration of treatment

According to Dr Reider, the duration of IPT that is used most commonly, six months, is too short and suboptimal. He blames the US Centers for Disease Control, which in the late 80’s looked at an intent-to-treat analysis in a study comparing the benefits of IPT after six and twelve months. Because of poor adherence after six months, there did not seem to be much difference between the two arms, and the CDC concluded that six months would be more cost-effective – and the rest of the world followed its recommendation.

“However, we are not allowed to do that!” said Dr Reider. “We recommend efficacy, and in terms of efficacy, we look at completers/compliers [patients who completed their prescribed regimen]. And here it is obvious, 12 months is *much* superior to six. So we have to recommend 12 months” (see Table 1).

He noted however, that the CDC has revised their recommendation due to a retrospective analysis by George Comstock of some early studies that found that the benefit of IPT appears to level off around 9 months. “But it will probably take the rest of the world another five years until they copy the CDC again, which by that time, may have another recommendation.”

Six months of IPT was generally used in the trials in people with HIV in Africa. Showing long term follow-up from one of these studies, Dr Reider said, “six months is useless. Now is it useless because it was six months, and that’s not enough? Or was it compounded by the fact that these patients had HIV? Most likely, HIV-infected patients need at least the same length of therapy as uninfected patients if not more.”

He added that shorter and more potent rifampicin-containing combination regimens cannot be used in African countries that can’t afford enough rifampicin to treat active TB. “It’s out of the question. We have to stick with isoniazid.”

Table 1: Protection Against Tuberculosis Among Persons with Fibrotic Lesions, by Length of Isoniazid Preventive Therapy

http://www.aidsmap.com/images/mail/hatip/051202_table1.gif

Operational research and adherence issues

Dr Reider then cited three studies showing that early attempts at delivering IPT to people with HIV in the field have proved disappointing. In each study, of patients tested for HIV, only a portion return for their results, and at each stage of the process, the number of participants gets smaller. Few people make it through the referral process for TB testing and get those results – and some of these have symptoms of active TB. So only a small fraction of the original pool of people with HIV actually received IPT in these studies, and fewer than half of those (at best) were adherent and completed their regimen, which, at six months duration, is of dubious efficacy (Bakari, Aisu). The results seen in a recent South African study was better but also limited (Grant) (see <http://www.aidsmap.com/en/news/A82A1807-EF2A-4188-A2F2-FE67524FDF.asp>).

Dr Reider then presented a table showing using different values for his four key determinants for effectiveness (see Table 2). “Even with everything optimised, we still have to treat five patients to prevent one case.”

“Now what you choose to do here is simply a question of the resources you have. But most of these countries in Africa don’t even have drugs to treat active TB. I have several programme managers from countries in Africa who tell me, it simply cannot be. Highly desirable but the constraints are insurmountable. Finally, despite its theoretical advantages, preventive therapy has been inefficient in many HIV-affected populations.”

Table 2: Effectiveness of Preventive Chemotherapy

Probability of infection	Risk of active TB	Efficacy of regimen	Adherence to treatment	Overall effectiveness	Number to treat to prevent 1 case
0.80	0.05	0.60	0.30	0.007	139
0.80	0.10	0.60	0.30	0.014	69
0.80	0.30	0.60	0.30	0.043	23
0.80	0.30	0.90	0.30	0.065	15
0.80	0.30	0.90	0.50	0.108	9
0.90	0.30	0.90	0.80	0.194	5

IPT in Botswana

Ironically, immediately after Dr Reider’s presentation, a nurse from an African NTP reported that a developing country *can* implement a large scale IPT programme for people with HIV. Granted, that country was Botswana, one of the wealthiest nations on the continent, with a government that is committed to fighting AIDS.

However, it has no choice. The country has one of the highest rates of coinfection in the world. According to the nurse, Ms Oaitse Motsamai, Director of the Botswana ITP Programme, TB was almost under control in the country until the HIV epidemic struck in the 1990s and the TB case rate shot up by 162%. Currently, the HIV prevalence is 37.4% (ANC data) and the estimated rate of HIV co-infection is 60-80% in TB patients.

In 1998, autopsy reports showed that approximately 40% of AIDS deaths were due to TB. In a study the following year, surveyed Botswana said that they would be more likely to seek out voluntary counselling and HIV testing if they received some benefit such as IPT. So a working group was formed and a pilot study was conducted in three health districts in 2000-2001.

The pilot study was to determine whether a national ITP programme was feasible, and also to develop an optimal screening algorithm to exclude people with active TB.

Entry to the pilot was through VCT and MTCT sites. The pilot included a total of 935 participants, 71% of these were women (from the MTCT sites) who received daily isoniazid and vitamin B6 for six months. Participants were mainly asymptomatic on assessment. Chest x-rays were part of the algorithm to screen out active TB (and were normal in 96%), but were later deemed to an obstacle for asymptomatic clients, and had a low yield for active TB anyway. Given the high prevalence of TB in the population, the programme doesn't bother to perform TSTs.

Patient acceptance of IPT and the programme was high, and an external review recommended the programme to be expanded nationally.

The current programme was rolled out to the whole country by June 2004. It is the collaboration between the Ministry of Health, and the US Centers for Disease Control (which pays the staff salaries and has allocated over \$600,000 to the programme). So far, the IPT programme had enrolled over 30,000 clients. The programme has trained practitioners and counsellors (including community-based counsellors who are supposed to follow-up patients who default on treatment).

The programme has not been without its share of problems. Centrally administered, the programme essentially shut down when it had to move offices – and found that the new offices weren't ready. Ms Motsamai also said that the programme is inadequately staffed at the national level, there is poor record keeping and follow-up of clients at some sites, very mobile clients make follow-up difficult, some practitioners are not participating in the programme, and there is a high turnover of staff at local clinics, since "as you know, most of our health care workers in Africa are constantly going to greener pastures in Western countries," Ms Motsamai said.

As yet, there is little information about how much of an effect the programme is having on the incidence of active TB. That impact may be limited because, at present, the programme is offering only six months of isoniazid. To give Botswana some credit, however, they are concurrently conducting a randomised study comparing six months to continuous IPT in patients with HIV. The study plans to enrol 1800 patients to be followed for two to three years and could provide the definitive answer on the appropriate duration of IPT in adults with HIV.

IPT in children

But Botswana is often the exception to the African rule. Nevertheless, some developing countries have more resources than others, and in the question and answer session after his talk, Dr Reider was pressed about whether he thought better resourced NTPs should attempt IPT.

He responded, "I tell the national programme, implement first where it is simple, and if that works we go to the next [stage]... For example, we recommend preventive therapy for children under the age of five who live in the same household as a newly diagnosed smear-positive case. That is the easiest group to do. Everybody agrees, it's simple, you give it to the patient, who gives it to the kid.

Toxicity is minimal, they are under five, even if you miss a lymphadenopathy, no problem, the American Academy of Pediatrics has found this for years. It's safe. It's in every manual of the national TB programmes in Africa – I've seen it – but I have not seen a single country where they have systematically implemented it."

"What I am hearing is, 'I cannot do the simple things, please let me do the complicated things.' And as long as I see that they don't give their under fives who are exposed to smear-positive cases preventive therapy – where we don't even need the tuberculin skin test just to decide are you healthy or are you sick. If this simple thing is not done, why should we try to complicate it?"

IPT is indeed standard of care for children living in same household as a smear-positive TB case because of the high risk of transmission. And yet in countries with a high burden of TB, children may be exposed to infection from other sources as well. In a session on contact tracing in children, Professor Nulda Beyers said that many children are actually infected outside of the home. According to a study using DNA fingerprinting, only 30% of children had the same strain as their parent, while 57% got the infection from someone else in the community, and in 13% the strain was unique and found in no one else in the community.

Children with HIV are at greatly increased risk of contracting TB and of developing severe forms of the disease so they would seem to be natural candidates for IPT treatment. However, many paediatricians and public health experts worry that it may be too difficult to exclude a diagnosis of active TB in children with HIV to recommend that IPT be more widely used in this population. The fear seems to be that there is too great a risk of missing subclinical disease and under treating more serious forms of TB that may develop in children with HIV.

But so far the clinical data look promising. At the World AIDS Conference in Bangkok last year, preliminary results a placebo-controlled South African study found that IPT halved risk of death for children with HIV

(see

<http://www.aidsmap.com/en/news/4346AD91-01A8-4760-AA4C-9D9B6C3BAC21.asp>). Shortly afterwards, in an issue of HATIP, our advisory panel discussed the study (see

<http://www.aidsmap.com/cms1001025.asp>). The majority wanted to withhold judgment on the study's public health consequences until final results were available.

The complete results were presented during a plenary at this year's World Conference, and generally the results are consistent with what was reported in Bangkok, with the primary exception being that, in addition to the reduced mortality the treatment has now also been shown to reduce the incidence of culture-confirmed and probable TB.

In the initial results, the survival benefit was observed in an analysis of 148 subjects. At that point, the trial's Data Safety and Monitoring Board recommended stopping the placebo arm and offering IPT to all participants. However, between the December 2003 analysis and the DSMB decision on May 17th 2004, 115 additional subjects had enrolled.

Final Results (intent-to-treat analysis)

INH	Placebo	HR
11/132 (8.3%)	21 /131 (16%)	0.46 [95%CI:0.22 to 0.95], p=0.0308

The children's age or CDC classification had no influence on the difference between arms.

Overall, 32 children died: there were five confirmed cases of bacterial sepsis on placebo versus 6 (50%) on INH, pneumonia or diarrhoea or sepsis occurred in 4 (33%) on INH and 10 (50%) on placebo. No deaths were suspected to be due to having TB. The effect on survival was independent of previous TB but could be affected by current TB treatment.

Eighteen out of 263 patients developed tuberculosis or probable tuberculosis. There were no culture confirmed and five probable cases on IPT compared to five culture confirmed and eight probable cases on placebo.

Dr Cotton cited a number of potential concerns regarding more widespread use of INH prophylaxis in children with HIV, including the need to exclude active TB, what sort of infrastructure, resources would be needed to deliver it, and to encourage consistent adherence, and the potential for the development of resistance.

He's also like to study the long-term effect of INH in these children. Unfortunately, the study's sponsorship from the Rockefeller Foundation is finished, and Dr Cotton and colleague, Dr Heather Zar are looking for a new funder simply to help them conduct follow-up on the study participants.

But this will not be the last study to evaluate this IPT in children with HIV. Another, larger study (target enrolment 1300) has recently begun in infants born to HIV-infected mothers in South Africa.

However, many of the TB experts already seem ready to adopt IPT for children with HIV in areas with a high burden of coinfection. According to a presentation by Dr Robert Gie, of the University of Stellenbosch, and member of the Child TB subgroup of the DOTS Expansion Working Group, active TB "can be successfully screened by using symptoms." According to one proposed treatment algorithm the subgroup is working on, children with HIV and without symptoms of active TB should be given nine months of IPT — at least until a better short course comes along.

IPT as part of the basic package of care

Many people attending Dr Reider's presentation seemed frustrated with him for playing the cynic about NTP programmes distributing IPT to people with HIV. And yet, he was simply saying that NTPs are under-resourced to do it, and there are significant logistical hurdles for NTPs in trying to provide IPT and assure adherence to it in otherwise healthy HIV-positive individuals. Which begs the question, are NTPs really the best way expand to IPT treatment?

According to Dr Phalkun Chheng, the answer is simple. "Just add it to the basic package of care where people with HIV are already receiving care," he said. Dr Chheng of the Gorgas TB initiative and his colleague Dr Chawalit Natpratan of Family Health International both gave presentations on a novel TB/HIV programme in Battambang, Northwest Cambodia.

In his presentation Dr Chheng described how the pilot project developed a system for TB/HIV cross-referral in an area with a high incidence of coinfection. The objectives of the programme are to initiate active TB case finding and treatment access for HIV positive clients in a systematic way, to enable access to VCT services for TB patients, to assess the feasibility of adding IPT as a part of the comprehensive continuum of care package for HIV-positive clients and to establish an infrastructure for operational research.

Patients who test positive at VCT clinics are referred to TB screening (which is aggressive, with CXR, smear microscopy and culture on 3 sputum samples per patient), and from TB screening to either TB treatment or IPT. IPT is given via home-based care for nine

months, with follow-up every six months for two years. In the meantime, TB patients are referred for HIV testing and care. (See results on Table 3 and graph below.)

Adherence in the patients who qualify for IPT is over 80% — the direct result of a strong People Living with AIDS support group. Dr Natpratan explained that the group Mondul Mith Chouy Mith, or Friends Helping Friends, is an essential component within the continuum of care framework. With support from NGOs working on home-based care, a positive people network and support group has been established that reaches into villages directly. These home-based teams play an important role to provide care, follow-up people who miss appointments, and education and information for families and communities on HIV/AIDS.

Such community-based approaches will likely represent the optimal way to deliver IPT — and be certain that patients actually take it. Furthermore, side effects or breakthrough cases of TB are more likely to be picked up by care-givers and other community members.

Table Results of TB/IPT Screening (Sep 03 Aug 05)

Indicators	BTB-RH	MRS-RH	Total
HIV testing	8,289	1,853	10,142
HIV positive	1,845 (22.3)	473 (25.5)	2,318 (22.9)
HIV positive referred for TB/IPT screening	1,560	521	2,081
HIV positive screened for TB/IPT	1,832	559	2,391
Active TB cases	266 (14.5)	160 (28.6)	426 (17.8)
- Smear positive	94 (35.3)	35 (21.9)	129 (30.3)
- Smear negative	108 (40.6)	33 (20.6)	141 (33.1)
- EPTB	64 (24.1)	82 (51.3)	146 (34.3)
IPT enrolled	73 (4.7)	37 (9.3)	110 (5.6)

Outcomes of IPT (N=55) in Battambang (BTB) and Moug Russey (MRS) Referral Hospitals (RH) (Sep 03-Aug 05)

http://www.aidsmap.com/images/mail/hatip/051202_table3.gif

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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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