

# HATiP

HIV & AIDS Treatment in Practice

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## Update: Cotrimoxazole Prophylaxis

From HATIP #1 - [click here](#) to read original article.

### EXPANDING THE EVIDENCE BASE FOR CO-TRIMOXAZOLE USE

The 2 May issue of the journal *AIDS* reports a study from Malawi (Zachariah et al) which adds to the evidence that co-trimoxazole can reduce mortality among people with HIV diagnosed with TB. This evidence is discussed by Dr Peter Godfrey-Faussett of the London School of Hygiene and Tropical Medicine in a related editorial.

Godfrey-Faussett's editorial sets out the challenge very starkly. In Malawi, which closely follows WHO's DOTS strategy and has done so for many years, "one in every three patients who starts anti-tuberculous chemotherapy is dead before the end of the course". Given that three quarters are HIV positive, the main reason is likely to be AIDS-related. In 1999 two randomised controlled trials in Cote d'Ivoire found survival benefits from offering co-trimoxazole prophylaxis to people with HIV whose CD4 counts were below 500, or who had symptomatic HIV disease. This led to the early cessation of other randomised controlled trials of co-trimoxazole prophylaxis. This has left the evidence base weak and open to argument (as expressed in the differences of view among our Advisory Panel).

Reviewing the study (described below) Godfrey-Faussett argues that while it adds to the evidence, it is still insufficient as a basis for national policy. He proposes that Malawi and similar countries should respond by rolling out a programme, district by district, and include an element of randomisation when deciding which districts should start each year. In this way, the evidence base could be strengthened further and serious outstanding questions, such as the impact on community prevalence of drug-resistant bacterial infections and malaria, might be answered. The study by Zachariah and others an international collaboration between local healthcare staff, the Malawi National Tuberculosis Control Programme, the NGO *Medecins sans Frontieres* and researchers in Luxembourg and Liverpool, compares the experience of patients treated for TB before the introduction of HIV counselling, testing, and cotrimoxazole prophylaxis, with the experience in the same district once these services had been provided. Thyolo district, Malawi, has "one government hospital, a mission hospital, and 18 health centres which are involved in TB control activities".

National guidelines for TB treatment were unchanged during the study, although it is impossible to be certain that the standard of care did not change in some way. Several additional staff were employed to provide HIV VCT in this population and additional training for all staff was provided, for example, on how to recognise and manage cotrimoxazole rashes. However, an important feature of this study was that the extra input was kept to a minimum, which means that the intervention should be relatively simple to implement on a wider scale.

In the year from 1 July 1999, all 1061 TB patients in the district were enrolled in the study and offered pre-test counselling and HIV testing the "intervention group". 90 per cent accepted HIV testing and 964 were tested, of whom 740 (77%) were found to be HIV positive. Six died before they were even able to receive the results. Those who tested positive were offered cotrimoxazole - 400mg sulphamethoxazole + 80mg trimethoprim, twice daily - in addition to standard TB treatment. Exceptions were made for those with known allergies to sulpha-containing drugs, pregnant women, women

breastfeeding babies under the age of 2 months, and babies of unknown HIV status. 13 who declined to be told their HIV test results agreed to take cotrimoxazole nonetheless; a delicate compromise which may say a lot about the commitment of the clinical staff to their patients. Cotrimoxazole treatment was provided to a total of 693 patients throughout TB treatment and indefinitely afterwards. Adherence to the treatment seems to have been excellent (evidence for this included positive urine tests for trimethoprim). 14 patients (2%) had a dermatological reaction (a skin rash), all within the first two months of treatment, all of which reversed when treatment was stopped.

The control group, registered in the previous year, consisted of 925 patients. HIV prevalence in the control group was not measured, but in the context of a still-rising HIV epidemic in Malawi would most likely have been lower than in the intervention group.

Record-keeping and follow-up were of consistently high quality, which is a credit to all of the staff concerned and to the National Tuberculosis Control Programme. Death rates in the first month of TB treatment were similarly high in both groups, but by four months there was a clear advantage in favour of the intervention group as a whole. The benefit of cotrimoxazole was however limited in this study to those patients with smear-negative or extra-pulmonary TB, who were probably the most immunosuppressed. (Also, only 60% of HIV positive patients with smear-positive pulmonary TB took cotrimoxazole.) The researchers calculate that to save one life during the eight months of TB treatment, it would be necessary to treat 12.5 people with cotrimoxazole.

### REFERENCES

Godfrey-Faussett P. *District-randomized phased implementation: strengthening the evidence base for cotrimoxazole for HIV-positive tuberculosis patients*. *AIDS* 17:1079-1081, 2003.

Zachariah R et al. *Voluntary counselling, HIV testing and adjunctive cotrimoxazole reduces mortality in tuberculosis patients in Thyolo, Malawi*. *AIDS* 17:1053-1061, 2003.

## Update: Combining ARVs with treatment for tuberculosis

From HATIP #3 - [click here](#) to read original article

### MANAGING IMMUNE RECONSTITUTION DISEASE

In comments that arrived after the last issue was sent out, Dr Desmond Martin writes, from South Africa:

"Immune reconstitution disease (IRD, also known as Immune reconstitution inflammatory syndrome, IRIS) is a topic of its own. We are seeing more and more of this syndrome in our patients. In brief: "If one is able to delay ARV treatment this will lead to a reduction in the incidence of IRD. If however one is forced to commence ARV treatment early in the course of the TB treatment one must have a heightened awareness of the possibility of IRD and almost expect it to happen. It seems to be a lot more common in our setting compared to areas where TB is not endemic."

The key things to watch out for are fever, pulmonary infiltrates, abdominal pain, enlarging glands (both hilar or abdominal or elsewhere).

The typical scenario is a patient who commences ARVs in the face of significant immunosuppression (CD4+ < 50). It can occur in patients who were previously non-reactive on a Mantoux test.

Remember in our setting the majority of the population are likely to be positive to a Mantoux at some stage of their lives and non-reactivity implies immunosuppression [rather than not having been exposed to TB].

"Steroids are often used as an adjunct to therapy; I however am ambivalent as to their use. One just has to sit tight on the situation and see it through. I have used steroids in certain circumstances (e.g. enlarging hilar node obstructing bronchus). When used the dose of cortisone would be something like 40-60 mg daily, typically for four to six weeks."

#### WHEN DOES A NEGATIVE TB SKIN TEST MEAN "NOT EXPOSED"?

A research letter published in the most recent issue of AIDS reports a US study which assessed the ability of 110 HIV positive patients to respond to several antigens, including PPD (TB proteins), in relation to their CD4 counts. When the CD4 count was below 50, as many as one third were anergic. When it rose between 50 and 100, the majority of those who had previously been anergic became reactive, and when it rose above 100, almost all were reactive. In this population, only 13 had been exposed to TB, but these included two individuals who had tested negative when their CD4 counts had

been lower, before starting on ARV treatment. The implication is likely to be, that negative skin test results for TB can only be taken as truly negative when the CD4 count is above 100.

#### REFERENCE

Fisk TL et al. *Detection of latent tuberculosis among HIV-infected patients after initiation of highly active antiretroviral therapy*. AIDS 17:1102-1104, 2003.

## Update: Nevirapine-based fixed-dose combination ARVs

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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).

For further information please visit the HATIP section of [aidsmap.com](http://aidsmap.com)