

HATiP

HIV & AIDS Treatment in Practice

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Treating latent TB

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Summary

Globally, tuberculosis (TB) is the single most important disease associated with HIV and AIDS.

It is obviously desirable to prevent active TB among people with HIV and one strategy for this is to treat people who have been exposed to the tubercle bacilli (*Mycobacterium tuberculosis* or MTb) before it makes them ill.

Treating latent TB is a proven strategy for preventing active TB but diagnostic methods and available treatments are far from ideal, which is why the subject remains controversial.

In practice, daily 300mg isoniazid (INH) treatment for six months is the main option available now to achieve this - known as "Isoniazid Preventive Therapy" or IPT. Alternatives - rifampicin plus pyrazinamide or rifampicin only - have been proposed and tested in clinical trials and adopted e.g. in the USA, but require closer monitoring.

Whether treatment for latent TB is safe and appropriate depends on the quality of the services provided to treat TB, the level of TB risk, and the resources available to HIV treatment services in a particular community. It may therefore not currently be appropriate in some settings. Nonetheless, given the scale of the public health need and the relatively low cost, it must be seriously considered.

The twin epidemics

The effect of HIV epidemics on tuberculosis, outlined in HATIP #3 (and see news, [here](#)), has led many experts to conclude that in addition to pursuing the WHO DOTS strategy there is a need to offer treatment for latent TB to turn around this major public health problem.

Co-trimoxazole prophylaxis, as discussed in HATIP #1 and HATIP #4, should be used to prevent further life-threatening infections in people made highly vulnerable by HIV and TB, but does not in itself treat TB.

ARV treatment also reduces the risk of TB in people with HIV, but people with HIV are at increased risk of TB long before their CD4 count reaches the level at which they become eligible for ARV treatment under present guidelines.

Treatment for latent TB with isoniazid (isoniazid preventive therapy) has successfully been used for many years to control outbreaks of TB in relatively low-incidence and high-resource settings. From 1998, it has been recommended by WHO and UNAIDS for people diagnosed with HIV who have positive skin tests for TB and do not have active TB, as part of a wider package of treatment and care. However, this recommendation has not been adopted universally.

Treatment usually means a 6 or 9 month course of isoniazid (INH) as a single agent although an alternative 2 or 3 month dual regime of rifampicin and pyrazinamide has also been tested in clinical trials.

If treatments for latent TB were highly effective, fast-acting, free of side effects and did not carry risks of spreading resistance to treatments required for active disease, there is no doubt they would

be adopted everywhere with great enthusiasm, and especially for HIV positive populations.

Unfortunately, existing treatments have limitations which have made this approach controversial and led to different approaches being taken in different settings. This article aims to clarify the issues and provide a framework for practitioners treating people with HIV to think about how best to identify, advise and support patients who might benefit.

Identifying latent TB

Routine use of skin tests for TB in people with HIV will identify many who do have latent TB although, as noted in HATIP #4, it will miss cases among people who are most immunosuppressed. Current skin tests are not wholly specific for *Mycobacterium tuberculosis* (MTb), the bacteria which cause TB, but can also indicate past exposure to BCG vaccine or environmental mycobacteria. Typically, a Mantoux reaction of more than 4mm would indicate a positive tuberculin skin test in an HIV positive adult.

The need for a second clinic visit to evaluate the test limits its usefulness in some settings. In South Africa some clinicians therefore work on the basis that all people with HIV have been exposed to TB, without using the tests at all. This might be reasonable in some populations, but it does go beyond current guidelines. The evidence on which those guidelines are based refers only to populations who have tested positive.

New and more specific tests are being developed in a WHO-supported programme, including one that is based on ELISPOT techniques that look for cellular immune responses to MTb specific proteins. These are being investigated in HIV positive populations and are showing promise. However, they are still experimental and are some years away from availability for routine use.

Screening for active TB, including extrapulmonary TB, is vital before prescribing treatment for latent TB to limit the risk of under-treatment and spreading drug resistance. The most cost-effective form of screening remains to be established. It may be sufficient to carry out a careful clinical examination and history taking to exclude coughing, recent significant weight loss, fever and night sweats.

Strengths and limitations of isoniazid

Randomised controlled trials have shown that isoniazid (INH) is effective in reducing the risk of active TB by at least 40% among people with HIV who test positive for TB on skin tests.

The treatment is simple - one 300mg tablet a day - and inexpensive since it is widely available from competing manufacturers. In southern Africa, the standard course of treatment for HIV positive people who test positive for TB lasts 6 months; in the USA, the standard recommended course lasts 9 months. It is possible that future treatment regimens will be based on less frequent dosing, although whether this is easier to keep to may be questioned.

It is generally very well tolerated and the side effects are well known - including peripheral neuropathy, rash and (rarely) hepatotoxicity. The risk of peripheral neuropathy can be reduced by supplementing with vitamin B6 (pyridoxine, 25-50mg daily). A risk of stomach upsets can be minimised by taking it with food. These side effect risks are lower, when the drug is given to people who are relatively healthy rather than people with advanced disease.

INH is compatible with most ARVs although the overlap in side effects - especially peripheral neuropathy from d4T (stavudine), ddI (didanosine) and other nucleoside analogues - discourages some

practitioners from prescribing it. INH should not be combined with the (now rarely used) ddC (zalcitabine) - both on account of the neuropathy risk and a direct interaction. There is an argument that if ARVs are provided, then INH preventive treatment should not be a priority.

Monthly clinic visits to monitor for side effects and for the development of active TB are provided for people on INH in the pilot programmes established in Southern Africa, and this is likely to be the best model for wider service provision. These clinic visits are also an opportunity to encourage people to continue to take their treatment - important, since adherence to treatment can be a problem (though occasional missed doses are not as risky as for ARVs) - and to ensure that any other medical problems are picked up early.

In low-prevalence and low-exposure settings, among people who are HIV negative, isoniazid has long lasting effects. However, in high prevalence settings among people with HIV, there is some uncertainty about how long the benefit lasts. At best, it could be two years after the course of treatment ends and at worst the benefit may end as soon as the treatment does. If the main risk of active disease comes from primary exposure to TB in the community, then there may be a case to extend INH treatment for as long as an increased risk of TB exists, i.e. for as long as there is immunodeficiency and for as long as there are no significant side effects.

INH is an important treatment drug, to which circulating TB strains are increasingly showing some level of resistance. There are theoretical concerns that this tendency may be increased if INH is taken inconsistently and on a large scale by people with HIV, some of whom may have undiagnosed active TB disease. However, there is no evidence that this has yet happened anywhere that INH preventive therapy has been introduced. If the screening for active disease works, then the only people who get treated with INH would be those who either have no bacilli at all, or only very low numbers. In these circumstances, drug resistance is unlikely to develop.

The bottom line is that the public health value of INH prophylaxis will depend on the quality of TB diagnosis and treatment in the community. If the latter is poor, then INH prophylaxis is and will remain problematic. Once it is good, then the issue of protecting the most vulnerable population at risk of developing active TB comes to the fore.

Rifampicin and Pyrazinamide

As an alternative to INH for the treatment for latent TB, US guidelines have recommended a two month course of twice-weekly rifampicin and pyrazinamide. Clinical trials on this combination have been carried out among HIV positive people in Zambia and Haiti as well as in the USA.

However, after a number of reports of deaths from liver damage in community treatment (which didn't happen in the carefully monitored clinical trials), it is stressed that this should be approached very cautiously when there is a history of liver damage or alcoholism. This regimen requires close monitoring for safety: US CDC guidelines recommend bilirubin blood tests at baseline, 2, 4 and 6 weeks, and a further clinic visit at 8 weeks to check on completion of the course of treatment.

A course of four months of daily rifampicin is another alternative option.

In contrast to INH, these drugs are best taken on an empty stomach. Rifampicin, as discussed in HATIP #3, is a powerful inducer of liver enzymes that affect the body's handling of many other drugs, including protease inhibitors and non-nucleoside reverse transcriptase inhibitors among ARVs. It also interacts with alcohol which causes problems for some patients.

Despite these problems, there is clinical trial evidence that a two- or three-month course of combined treatment can bring about a

longer lasting reduction in the risk of active TB than a 6- or 9-month course of INH.

A wide range of publications on treatment for HIV. For details contact:

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While further research may be justified, the main reason this option is not currently preferred in most countries is the cost of the drugs and monitoring, which is higher than for more extended INH treatment. In countries with DOTS programmes on the WHO model, it may also be restricted for the time being by (well-founded, evidence-based) national rules on who is allowed to prescribe rifampicin and pyrazinamide.

Who could benefit most?

People with HIV who test positive on tuberculin skin tests and have CD4 counts that are too high to commence on ARVs may be the population that stands to benefit most from INH preventive therapy. This is one of the very few proven useful interventions that can be offered to people in this category.

One reason why INH treatment has not been pursued, for example, in Senegal, is that HIV treatment services there are heavily oriented towards people with HIV in more advanced stages of HIV disease whose risks of side effects from INH and whose chances of having undiagnosed TB would be higher than in relatively asymptomatic populations.

Some health services offer INH preventive treatment to HIV positive contacts of people diagnosed with active pulmonary TB, including healthcare workers and work contacts as well as household contacts.

For people with HIV and CD4 counts below 200, while co-trimoxazole and ARVs should be the priority, INH could help avoid the problems with ARV therapy that would come about if full-scale four-drug TB treatment had to be provided (as described in HATIP #3).

Although the evidence is still not conclusive, many clinicians are convinced that an episode of TB is one of the worst things that can happen to people with HIV, accelerating the course of their disease. On this basis, any HIV positive patient in a high TB prevalence setting who is a regular attender at clinics and therefore clearly able and willing to be monitored closely could be offered a six-month course of INH treatment.

How to provide support

Community education, consistent message giving by all healthcare staff as to the value of treatment when prescribed, and inclusion of household members and/or other treatment supporters in explanations of how and why the drug(s) need to be taken.

Further information on aidsmap

Tuberculosis references were given at the end of the feature in HATIP #3, which is available on aidsmap.com [here](#).

aidsmap

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