

HATiP

HIV & AIDS Treatment in Practice

Issue 39 | 05 January 2005



In this issue:

HIV's impact on TB control: is it time to re-think TB control strategies?; *page 2*

- DOTS - Has it become outmoded?
- DOT during the continuation phase of treatment
- MSF's critique of DOTS
- Other approaches to support TB treatment adherence

HIV's impact on TB control: is it time to re-think TB control strategies?

DOTS - Has it become outmoded?

The impact the HIV pandemic would have upon TB control first began to be appreciated in the early 90's. TB transmission had become very rare in countries such as the US, but a growing number of documented de novo infections were occurring, often in clusters, among people exposed to AIDS patients with TB.

Then in 1991, there was a much-publicised outbreak of multi-drug resistant TB (MDR-TB) in New York and public health officials feared an epidemic of MDR-TB was possible.

Salvage therapy of MDR-TB is extremely challenging: drug sensitivity testing takes time, the duration of effective treatment is much longer, second line drugs tend to be less well tolerated and, in the early 90's, some of these medications were in very short supply. With limited options on the horizon (TB drug development having fizzled out decades earlier), a strategy was needed to avert a public health nightmare.

The strategy chosen was Directly Observed Treatment - Short course (DOTS) developed by the World Health Organization to improve adherence (and response) to TB treatment, and prevent the development of resistance. To ensure that every dose is taken correctly and at the right time, the treatment is 'directly observed' by treatment supporters (health workers, family members etc) assigned to monitor the patient.

Key principles for the success of DOTS programmes include:

- Government commitment to sustained anti-TB efforts (including education and training of prescribers and treatment supporters)
- Information systems for monitoring and reporting
- Adequate testing and facilities for case detection
- Regular and uninterrupted drug supplies, and, of course
- Observed treatment

Patients with active smear positive TB are directly treated a two-month induction course usually containing four anti-TB drugs (rifampicin (RF) and isoniazid (INH) and two other medications). The short course of induction therapy is followed by a less intense treatment continuation phase, usually with two drugs. Current WHO treatment guidelines for national TB programmes recommend using either a continuation phase of four months with the two most powerful TB drugs, RF/INH, or six months of INH and ethambutol (E).

If the key principles of DOTS are observed, WHO estimated that approximately 85% of TB patients could recover. At this cure rate, it was projected that the global burden of TB could be halved in ten years if at least 70% of active smear-positive cases, i.e. the most infectious patients, were detected and managed by DOTS.

The approach appeared to work well enough in low incidence settings like the States and Western Europe - probably helped along by the subsequent introduction of antiretroviral therapy for HIV.

However, DOTS based programmes are labour-intensive and effective implementation has proved a challenge in many resource-limited, high-prevalence areas where HIV still goes largely untreated. Twenty-three high-incidence countries account for

approximately 80% of all new cases. In many of these, TB incidence continues to rise.

A growing number of people working in HIV are now questioning whether DOTS is always the best approach to TB management.

"My concern about TB DOTS is that even in countries with fairly functional programs, such as Botswana, the TB numbers have continued to climb. Ditto in the mining industry in SA," said HATIP advisor, Dr. Francois Venter and clinical director of the Esselen Street Project in Hillbrow (Johannesburg). "At a national meeting, one of our most senior government figures, on seeing our TB numbers, said we 'should go back to the drawing board' as our programs were 'clearly not working'. If TB DOTS is as wonderful as WHO bravely proclaims, it's not showing. My sense is that DOTS would've worked pre-HIV, but in high prevalence countries, it's not enough."

In Chennai India, Dr Vijay Anthony Prabhu reports mixed results with DOTS. "We are experiencing serious problems with DOTS which from clinical experience seems to be inadequate. Problems of treatment failure, especially drug resistance or inadequate duration of continuation phase treatment are problems for ordinary people. What more when the patient is HIV positive."

DOT during the continuation phase of treatment

The debate on DOTS has been brought to the fore by the results of a large randomised study of TB treatment in resource-limited countries [recently published in The Lancet](#).

Briefly, one of the trial's major findings was that, after more than a year of follow-up, patients given four months of RF/INH continuation therapy had fewer poor outcomes than those given six months of E/INH.

If these study results were to impact WHO treatment guidelines, it could mean national TB control programmes (NTPs) would need to administer six months of directly observed therapy rather than two. This is because INH and RF are the two most potent drugs in the TB arsenal, and many TB experts think that continuation RF/INH needs to be directly observed lest non-adherent patients develop MDR-TB. A RF/INH resistant strain of TB would be virtually impossible to treat.

This gets to the root of one of the reasons why E/INH is a WHO recommended regimen in the first place - even though it was known to be less potent. Unlike rifampicin, ethambutol - which, it is important to point out, has no significant drug interactions with antiretroviral therapy - is not a cornerstone drug of TB care. Where long term directly observed therapy is not possible, E/INH is felt to be a less risky option that reserves the more crucial drug rifampicin for use in case a patient fails treatment. In its 2003 recommendations on TB treatment (Guidelines for National Programmes. WHO, 2003. p. 34), WHO noted that a six month continuation phase was "particularly appropriate for countries with limited public health care access and unable to organize a system of direct observation through health facilities, community health workers or volunteers."

The authors of the Lancet study were aware that their findings might provide evidence that could influence future treatment guidelines, but noted that their study could not take into account the potential effect of poor quality services on long-term outcomes. In other words, switching from E/INH continuation therapy to RF/INH may not have the desired positive outcomes if a national TB programme cannot provide adequate DOT or a suitable alternative to ensure adherence and prevent rifampicin resistance.

Nonetheless, in light of the study's findings, HIV/TB treatment advocates sent a letter urging WHO and the Stop TB Partnership, among other things, to issue new recommendations on TB treatment following the results of the trial:

"Switching continuation phase regimens from isoniazid/ethambutol to isoniazid/rifampicin should be a priority, especially in areas - such as the former Soviet states - with high rates of baseline resistance to INH - and in others with high rates of TB/HIV coinfection."

The advocates acknowledge that some NTPs "are resisting the change" partially because of "the reluctance to implement six months of directly-observed RF/INH therapy."

Switching to a regimen that requires direct observation for 6 months, rather than for 2 months, would, after all, effectively triple the direct observation workload for programmes that are already stretched thin.

But to ease the burden on NTPs, the treatment advocates suggest that: "alternatives to fully directly-observed therapy (DOT) need to be investigated and, where successful, expanded." They argue that ARV therapy has provided other models that seem highly effective at encouraging adherence, and that national programmes should step up community-based adherence support for TB treatment.

MSF's critique of DOTS

The advocate's letter echoes some of the opinions earlier voiced in a Medecins Sans Frontieres report that takes a critical look at DOTS (<http://www.accessmed-msf.org/prod/publications.asp?scntid=12520041420303&contenttype=PARA>).

The report notes that the DOTS strategy has demonstrated serious limitations - particularly in conflict areas and refugee camps, where there are migrants or nomadic people - and where public health systems are also struggling to manage the HIV/AIDS pandemic.

MSF points out that HIV disease also greatly increases the incidence of TB that is hard to diagnose (smear-negative and extrapulmonary disease) - which may represent up to 50% of TB cases where coinfection is common. Yet DOTS programmes sometimes leave these patients out in the cold - since control efforts are concerned primarily with treating the most infectious cases.

MSF's experience in places where coinfection is common and in resource challenged or turbulent settings has led them question to adequacy of DOTS both as a public health programme and as the best way to care for individuals living with TB.

Furthermore, MSF has treated over 10,000 patients with HIV demonstrating that HIV patients in resource-limited settings patients can be highly adherent to antiretroviral therapy - without resorting to direct observed therapy.

"MSF is fast recognising the paradox in the approaches to treating these two often coinciding diseases. In most MSF ARV programmes, people living with HIV/AIDS only come to the clinic once-a-month for follow up and to pick up their next monthly treatment dose. In standard TB programmes, patients are required to report to a health care worker several times a week, even every day. Yet both treatments require taking several drugs and doses a day, and interrupting either has equally life-threatening consequences."

Dr. Venter has observed the same "bizarre situation" in his clinic adding: "if we had to do DOTS for the ARV program, we may as well just pack up and go home, we don't have the resources."

As it is, national TB programmes in many high HIV-prevalence areas cannot even continue DOT at the recommended levels because of growing caseloads.

"The sheer numbers are going to work against the future of DOTS," says Chris Green, an HIV treatment advocate in Indonesia. "I heard in one setting that they treat around a thousand patients with TB. With these numbers, daily, or even three-times weekly observation is out of the question. If we are to scale up TB treatment in this country to achieve the WHO targets, it is difficult to imagine how this can be done with DOTS."

According to MSF, these programmes will either have to reduce observation (and risk rifampicin-resistance), exclude patients due to lack of resources for intensive DOT or develop alternative strategies to ensure and improve adherence. "WHO should lead the process of revising a global TB strategy that adequately addresses the HIV/AIDS pandemic and its consequences for TB care."

The MSF report suggests these changes:

- Ensuring access to treatment for smear-negative patients
- "Innovative means of improving treatment adherence must be found, including reduced need for direct observation."
- Resources to develop tools adapted to fight TB in resource-poor settings.

Other approaches to support TB treatment adherence

Dr. Venter agrees that a completely different strategy may be needed: "TB is on the increase, and needs a new approach, which probably needs to look at a different model of treatment, not just at new drugs or combinations. It will probably be different in different countries. Maybe in SA we could provide patients with an incentive to adhere to treatment. In my clinic, only 55% of patients complete their 6/12 course, despite very good nurses and friendly systems. Maybe a grant would help, paying people for each month they complete. People would probably come for diagnosis more quickly, and it may remove some obstacles (e.g., transport costs) for many patients."

Other ideas might be drawn from HIV adherence interventions.

Chris Green: "I agree with MSF that it makes no sense to treat TB patients for 6 months with DOTS, but treat people with HIV for life without a DOT approach. Though it must be accepted that there may be greater challenges with involving people for six months compared with those who must live with their condition for life. But some of the [adherence] approaches we have developed would still be applicable to people with TB. One approach must be to better integrate TB information into treatment literacy programmes."

People with TB are less likely to identify as a "community" than people living with HIV and thus cannot really be expected to take part as community caregivers/adherence supporters in the same way that people with HIV do for each other.

There are other dangers if "community" means people from the neighbourhood, village or tribe - or the community of people living with HIV. An obvious one is the danger of TB transmission to susceptible patients not presently on anti-TB treatment. Another is that patients may be subject to bias should their disease/s become known - and therefore avoid participation in programmes that might inadvertently reveal their condition to others in their community.

According to Dr. V.A. Prabhu: "The strategy of DOTS in coinfecting HIV/TB patients with involvement of community or community health care workers, with high levels of stigmatisation is difficult to implement."

While it is a good idea to try to apply some of the lessons learned from the management of patients with HIV, it is important to remember that patients who receive ART in the developing world are, in part, selected for their motivation and eagerness to be on treatment. This is not only inherently true but in many settings that are rolling out ART, patients are routinely pre-screening for their potential dedication and family/friend support (to help them be adherent) before even being considered for ART, which then, is not prescribed until patients are "trained," and deemed to really be ready to adhere to it.

This is simply not the case in patients with active TB who need to be treated regardless of how motivated or prepared they are - not just for their own health but to keep TB from spreading.

In the meantime, there may be other ways to improve and expand DOTS programmes to enable them to manage increasing case-burdens and provide better care for all people with TB. One approach might be to adapt directly observed therapy into directly

observed therapy and treatment training - put more effort during the first couple weeks of DOTS into training patients to be adherent on their own - and then, as with ART training, let them self-administer when they are adequately prepared and have an established and reliable support network.

Regardless, as the treatment advocates noted in their letter to WHO/STOP TB, any alternatives to DOTS derived from the HIV field would need to be evaluated clinically before completely over-hauling current TB control programmes.

Finally, as Chris Green points out "We tend to forget that the WHO's intent of DOTS is not just the observed treatment of patients. In fact this is only one of five elements of the strategy. The others (government commitment; case detection; information systems for monitoring and reporting; and regular supply of drugs) remain crucial, and indeed underpin ART programmes."

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