

# HIV challenging accepted truths about TB control and drug resistance

*What we now know about the extent of drug resistant TB, and its potential for concentration among populations and communities heavily affected by HIV, brings into question accepted truths about how TB drug resistance occurs and spreads. If doubts are confirmed, and drug resistance turns out to be mostly the result of poor infection control and not Mendelian evolution (as previously thought), the implications for current TB programmes will be profound.*

Last year, the humanitarian organisation Médecins Sans Frontières (MSF) raised the alarm, claiming: "The current situation in relation to the emergence of XDR-TB clearly demonstrates the need for a re-evaluation of our approach to treating TB overall."

At the time, the New York Times laid responsibility for drug resistant TB at the door of international donors, saying that "stinginess created the problem", and "generosity is needed to take it away."

Is the emergence of TB drug resistance a consequence of poor scientific thinking, inadequate resources, or both?

An estimated one-third of the world's population has 'latent', or inactive TB infection. That is, the bacterium that causes TB is detectable in the bodies of about 2 billion people, but does not cause any symptoms of TB.

Active TB causes the clinical symptoms recognised as TB disease. Active TB results from either 'activation' of latent TB infection or from

rapidly progressing disease following recent infection with *Mycobacterium tuberculosis*.

One of the factors known to significantly increase TB activation is co-infection with HIV, which is thought to increase the lifetime risk of active TB up to 50-fold. Other factors thought to be associated with TB activation are concomitant conditions, including other lung conditions, nutritional and other general health indicators.

Predictably, TB activation tends to predominate in countries that have achieved good control of TB transmi-

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ssion, but most TB disease in endemic countries is thought to be due to recently transmitted infection.

Active TB is infectious and can be easily spread from one person to another. The indicator used to predict the infectiousness of a given patient is the presence of TB bacteria in their sputum (also known as a positive 'smear' test).

Most active TB is also treatable. The vast majority of active TB cases that occur each year are naturally sensitive to the antibiotic drugs used to treat the disease.

These simple facts form the cornerstones of the global TB control policies recommended by the World Health Organization (WHO). The thinking goes that because most TB is caused by recently transmitted infection, anti-TB

strategies should first reduce the number of smear positive TB cases, through prompt diagnosis and effective treatment of symptomatic patients with infectious disease. This forms the basis of the DOTS strategy (directly-observed treatment short-course), for example.

The accepted truth about development of drug resistance in *M. tuberculosis* is that it is mostly 'acquired' as a result of incomplete or inadequate treatment (e.g., poor patient drug adherence, the use of too few drugs, drugs for too short a time, or use of poor quality drugs). This leads to the natural selection of resistant sub-strains in individual patients. Without a complete course of antibiotic treatment, they stand a

greater chance of TB recurring in a drug resistant form.

'Primary' drug resistance – or becoming newly infected/re-infected with a drug resistant strain of TB – is viewed as an important, but less significant factor.

A recently published study in Shanghai, China, which used genetic fingerprinting to track a set of individual drug resistant TB cases over several years, brings that assumption into doubt. Researchers found that most drug resistance was not caused by poor treatment regimes, but by patients being re-infected with a different, drug-resistant strain of TB.

These observations were independent of HIV status. In countries with the highest rates of HIV, the TB context is quite distinct. Up to three-quarters of TB cases are thought to be HIV-associated.

In Africa, TB is often the first manifestation of HIV infection and is the leading cause of death among people with HIV. Incredibly, death rates among African people with HIV-associated TB are similar to that among those with TB before any form of effective anti-TB treatment was available.

Immune suppression leaves people living with HIV (PLHIV) particularly vulnerable to activation of latent TB, to acquisition of new TB infections, and to primary disease following infection with TB. Not surprisingly, these same factors also place PLHIV at high susceptibility when exposed to drug resistant TB strains.

Even the potential benefit of antiretroviral (ARV) treatment is in doubt, because many PLHIV with TB seek medical help before ARVs are prescribed, or go undiagnosed.

The pressing question is whether the public health basis for anti-TB strategies takes sufficient account of TB drug resistance, sub-clinical disease and, in particular, the impact of HIV. Has DOTS failed to contain TB transmission in areas where HIV epidemics drive the spread of TB? Local studies in South Africa provide some initial clues.

In the district of Kwa-Zulu Natal Province where high rates of XDR-TB have been documented, a government-sponsored TB treatment programme using the DOTS strategy has been in place in the district for nearly 15 years. According to DNA fingerprinting, and WHO conclusions, transmission of XDR-TB strains is probably occurring in these communities. Contact tracing has also revealed that the main points of contact among patients were specific clinics, indicating transmission of TB inside health centres.

It is also surprising that relatively high levels of

resistance to second-line anti-TB drugs (SLDs) should be seen in settings where the use of those drugs is not yet widespread. This suggests that inadequate treatment is not sufficient to explain the extent of drug resistant TB in specific South African communities. This is evidence that transmission of resistant TB strains is common among exquisitely vulnerable HIV-positive individuals.

In many African settings the potential for nosocomial transmission of TB is high. Even low cost strategies to reduce transmission of TB in health care facilities are rarely implemented. Improvements in infection control are crucial to break the cycle of transmission of drug resistant TB.

High TB rates and limited resources mean that many TB programmes focus on case detection and treatment using solely the DOTS strategy. But HIV is clearly challenging DOTS as the sole TB control strategy for Africa, for example. In areas of high HIV prevalence DOTS is an essential but insufficient minimum.

Fixing the weak links in TB services should be the urgent implementation priority in southern Africa. This must include:

- Improving TB laboratory services
- Conducting representative drug resistance surveillance
- Managing individual MDR-TB and XDR-TB cases
- Improving infection control measures
- Supporting SLD procurement and management

TB is an aggressive, HIV-associated opportunistic infection that arises at higher median CD4 counts than do most other AIDS-defining disorders. The transmission and treatment of MDR-TB and

XDR-TB must be urgently addressed if survival of people with HIV is to be improved.

More willingness to look beyond current TB control strategies will help accelerate the essential re-examination of how TB drug resistance occurs, spreads and takes advantage of HIV-associated vulnerability.



### On-line campaign on drug resistant TB

Drug-resistant TB poses a grave global public health threat, especially in populations with high rates of HIV, and requires an immediate and urgent global response.

In the 50 days leading up to World TB Day (Saturday 24th March, 2007), Health and Development Networks and the AIDSCareWatch Campaign are focusing on drug resistant TB.

The campaign aims to increase awareness, bring front-line perspectives to current MDR- and XDR-TB discussions, and advocate for TB patients to receive the best possible care.

If you are already a member of the **Stop-TB eForum**, do nothing. To join, go to the campaign website.

For a campaign update or further information, or to give your suggestions how the Campaign can be improved, please get in touch with us.

**10% of new TB infections are resistant to at least one anti-TB drug**

<http://www.healthdev.org/stop-tb>