

Addressing TB drug resistance: What's in the new tools pipeline?

Currently used drug treatments for tuberculosis (TB) are at least 40 years old, and they are beginning to fail us. Drug resistant strains of *Mycobacterium tuberculosis* are increasing in prevalence, as is co-infection with HIV. Latest data indicates that one in ten new TB infections are resistant to at least one anti-TB drug; about 4% of all new and previously-treated cases of TB are resistant to the two most powerful 'first-line' anti-TB antibiotic drugs, isoniazid and rifampicin (multidrug-resistant or MDR TB).

"The present decade has seen a reawakening of TB drug research and development," open Ann Ginsberg and Melvin Spigelman in a recent commentary in *Nature Medicine*. But what is now needed to defeat TB drug resistance? How soon can any new drugs, diagnostics or vaccines be expected to make a difference?

Without new drugs it is unlikely that TB will be brought under control, either within the timeframe of the current global TB control targets or even thereafter. Unless any novel treatment is extremely potent, a single new drug is unlikely to be sufficient; to treat Extensively drug-resistant TB (XDR-TB) strains a whole new combination of drugs may be needed. Ideally, new drugs will have novel mechanisms of action against the TB bug, in order to avoid cross resistance in circulating strains.

Drugs that are capable of shortening treatment and effectively removing 'latent' TB infections are no less of a priority, especially if future development of drug resistance to prospective treatments is to be averted. Shorter treatment regimens reduce the complexity of treatment for patients and health care providers, and are far more likely to be adequately followed by both.

In addition, TB treatment can no longer be viewed as an isolated

challenge. It is vital that any new drugs are appropriate for use by people living with HIV (PLHIV) and have no adverse interactions with antiretroviral drugs (ARVs) used for treatment of HIV infection.

Limited progress can be made if the drugs are there but the patients are not. New treatments will be of limited use if case detection remains low. Diagnostic tests that can rapidly identify TB are essential for use in conjunction with new drugs. Simple tests for drug susceptibility are also urgently needed. New diagnostics need to be adapted for use in resource-poor settings, and must be effective in PLHIV and children. Currently, sputum microscopy, which gives no

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information on drug resistance, is the standard diagnostic technique in the field. Moving to routine culture-based methods is one of the next big steps that need to be taken in order to improve accuracy and diagnostic power.

An effective vaccine would accelerate the eradication of TB, drug resistant or not. The efficacy of the current BCG vaccine, (or Bacille Calmette-Guérin) is variable and its use has not stopped the recent surge in TB. A vaccine derived from TB itself, as opposed to the related bovine organism used to make BCG, could prove more effective. A safe, effective vaccine for TB that can be used in children and adults infected with HIV (BCG is not safe) is a lofty goal for research.

Drug resistant TB has been developing for the past 40 years. During that period, it was clear that increased investment in TB diagnostic, drug and vaccine development was required. How is it that these needs are only now being

addressed?

Given that 95% of the world's TB cases occur in developing countries, the simplistic answer is that market forces have failed to deliver. TB is not alone in being a neglected disease of the poor. To a degree, the problem was contributed to by medical apathy – TB was perceived, even in high-burden countries, as a curable disease under the control of the drug treatments available. Non-standardised prescribing of anti-TB drugs and very low rates of diagnosis, follow-up and patient engagement masked the scale of the problems until they grew too large to ignore.

The lack of a lucrative market for TB therapies remains a problem. Large global consortia with links to government, industry, academia, and donor organisations have the means to overcome some of these difficulties. Currently, only the Global Alliance for TB Drug Development (TB Alliance) works exclusively on TB.

The Foundation for Innovative New Diagnostics (FIND) and the Aeras Global TB Vaccine Foundation both have TB products in development. Last year, the Treatment Action Group (TAG) compiled an invaluable review of TB research and development funding, and a separate publication on TB drugs in development.

So what is in the pipeline? There are currently more potential TB drugs in development than at any stage during the past forty years. Seven compounds are in various stages of clinical development, and a further fifteen are looking promising in pre-clinical stages. Some of these candidates are based on older drugs, others have entirely new mechanisms of action.

Of the seven compounds in clinical development, moxifloxacin and gatifloxacin will be available the soonest. Moxifloxacin is under testing in two different regimens, replacing isoniazid or

ethambutol in first-line treatment. The results so far are promising: Replacing isoniazid, moxifloxacin produced comparable sputum culture conversion rates and was shown to be safe. A phase III trial planned for this year will attempt to demonstrate an effective, shorter treatment period. Moxifloxacin and gatifloxacin could be incorporated into TB control programmes by 2010.

TMC207, under development by Tibotec, is an entirely novel TB drug. It is potent against drug resistant TB, and is entering phase II trials in MDR-TB patients. However, TMC207 was shown to be more effective given to well-fed patients, and its activity is reduced by rifampicin, both potential drawbacks in front-line health care.

The TB Alliance and Otsuka Corporation are independently testing two other candidate drugs from the nitroimidazole family. The Alliance's PA-824 was shown to be safe and tolerable in phase I trials and is now in an extended trial of its early bactericidal activity in South Africa. If the compounds prove effective, they could be ready for use in 2012.

The remaining two candidates in clinical trials are LL-3858, a pyrrole developed by Lupin Limited, and Sequella Inc's SQ-109. These are in phase I and first-in-human trials, respectively. It is difficult to say with any clarity at this stage when they may be available. Other compounds in the pre-clinical stages may not make it past the initial trial, but of those that do, many years of further trials are needed before they potentially become available.

The drug development pipeline links basic scientific research with TB practice. Detailed TB research provides insights into the bacillus' metabolism, defensive mechanisms, and interaction with the human immune system. These clues are used to guide drug design that purposefully targets processes critical to the organism's survival.

However, there is a dearth of investment in translational research: turning laboratory findings into compound

development, screening and trials. This creates a bottleneck in the pipeline. The Alliance's ability to bridge this divide has been limited. New initiatives such as the Bill and Melinda Gates Foundation's TB drug development accelerator program look set to change this. Clinical trials are another major sticking point in the drug development process. The complex trials of new TB drugs in tandem with the old, with each other, and in HIV positive patients, can take months or years to set up, and further years to run.

Speaking at the TB Alliance Open Forum in London last year Dr Zhenkun Ma, Head of Research at the TB Alliance, emphasised the need to select optimal candidate compounds and regimens for trials.

However, trials for TB drugs need to show only non-inferiority to the standard regimen, not necessarily superiority – the standard regimen is so effective for non-resistant TB that this is impractical. But a systematized clinical trials infrastructure is lacking for TB, yet is sorely needed.

Drug resistant TB is not going to languish for five to ten years while drugs are developed. The world must act immediately to ensure the full implementation of all currently available TB control measures.

Preventing nosocomial transmission of drug resistant TB is particularly urgent, as evidenced by the Shanghai study and recent XDR-TB findings among South African PLHIVs. We must critically question practices that bring patients with different strains of TB into close contact, for any reason, including AIDS care services.

The most advanced drugs in the pipeline are not sufficiently novel to be effective against XDR-TB, although they will likely prove useful in treating MDR strains. Before then, strengthening TB infection control is an urgent priority, as outbreaks of XDR-TB are a continued threat, particularly in communities also heavily affected by HIV. Identifying and treating drug-susceptible TB effectively is key to the ultimate

prevention of MDR- and XDR-TB. "We must strengthen basic TB control, in order to prevent MDR-TB, and also HIV management," says Dr Paul Nunn of the World Health Organization's TB programme, continuing: "XDR-TB is a wake up call for both strengthening basic TB and HIV care, prevention and control, and scaling up the management of drug resistant TB. I think that success in this will also require us to put the concerns of individual patients right at the centre of TB control."



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>