The need for expanded access to experimental medicines for drug-resistant TB

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The risk of dying if you have multi-drug-resistant (MDR) or extensively drug-resistant (XDR) TB is very high. Data presented at last year's Conference on Retroviruses showed that 69% of patients died within one year of being of presenting with MDR TB in Tugela Ferry. For XDR TB it was even worse at 82%. Over time, deaths for patients with MDR TB declined from 87% to 45% but there was no significant decline in deaths for patients with XDR TB.1 At the same conference there was also data showing that of 72 patients treated for XDR TB in a Durban hospital, less than half were alive and in care at six months.2

Several new drugs are being developed for TB.3 The furthest along in the pipeline for the treatment of drug-resistant TB is Tibotec's TMC207. A small trial of 43 people showed quicker time to sputum-negative conversion with TMC207.4 Further data is expected to be presented at the World Lung Conference in Berlin later this year. A drug called OPC-67683, produced by a Japanese pharmaceutical company called Otsuka, is also in a phase II trial. No human trial data has yet been published fo r this drug, but it has been reported at a conference to have succeeded in a phase I safety, tolerability and pharmacokinetic testing as well as a 7-day early bactericidal study.5 Both are new classes of drug. TMC207 is a diarylquinoline and OPC-67683 is a nitroimidazole. They are both therefore expected to be active against current strains of drug-resistant TB.

There are compelling reasons to expand access to TMC207 and even OPC-67683 before they are approved by regulatory authorities:

? Patients with MDR-TB or XDR-TB might reasonably believe that the risk of not taking these drugs outweighs the risk of taking them, given the extremely high mortality and long treatment periods for these conditions. It is arguably unethical to deny patients access to these drugs when they are at high risk of death or need to get back to work or their life's activities.
? Health workers are at especially high risk of contracting MDR and XDR TB.6 People who risk contracting a fatal illness by doing their essential work should surely be entitled to extraordinary measures to save their lives if they become ill. Also, the health system is overstretched. Saving the lives of nurses with drug-resistant TB will help reduce the loss of skills as well as the loss of confidence of other health workers.
? There is a precedent for expanded access. In the late 1980s and throughout most of the 1990s, patients with HIV received expanded access to new antiretrovirals. Over 100,000 Americans benefited from expanded access programmes.7 More than 35,000 patients (about 22,000 in the US alone) received didanosine from 1989 to 1991 before it was registered. Patients with drug-resistant TB can therefore ask why the same cannot be done for their condition.

There are risks with expanded access:

? The new drugs might not work or their side-effects might be substantial. Several thousand people took an

experimental drug called adefovir as part of an expanded access programme in the 1990s, but it was never ultimately approved for HIV. With didanosine, there were fatal cases of pancreatitis. Nevertheless, given the high fatality rate with MDR and XDR TB a patient who chooses to take TMC207 is making a rational choice. We will know with greater confidence by the end of 2010 if the risks associated with TMC207 outweigh the benefits.
? The quick development of resistance for the same reasons that it developed with first-line drugs ?poor health systems unable to maintain consistent drug supplies and support patient adherence? is another legitimate concern. But adherence is as big an issue post-registration as it is pre-registration. Fear of resistance is not an excuse to not treat people; it is an excuse to improve health systems.
? Adding a single drug to failing regimens essentially puts some patients on monotherapy with the consequent high risk of treatment failure and resistance. But for patients in this situation monotherapy is better than nothing. Also the risk of monotherapy can be reduced in time once the pipeline becomes more robust and patients with XDR TB can be given multiple experimental drugs (eg both TMC207 and OPC-67683).
? There might be unknown interactions between the new drugs and other TB drugs or ARVs. Trials are underway for TMC207 in patients taking ARVs.
? People willing to take placebo are needed for clinical trials. But placebo patients can be recruited from the healthier end of the MDR TB spectrum and should expect to be placed on the intervention drug immediately after the placebo period if the drug performs well.

None of these risks outweighs the need for expanded access.

Expanded access programmes should also be used to collect additional safety and operational data on the new drugs. Only sites that can ensure a reliable drug supply, adequate resistance testing and high probability of patient adherence should be able to participate. Sites run by organisations like Medecins Sans and Partners in Health should qualify.

Drug trials are unfortunately not an adequate way to expand access, at least not in their current form. There are fewer than 900 places presently being recruited in trials for OPC-67683 and TMC207.8 But there were already nearly 30,000 notified cases of MDR-TB worldwide in 2007 and the number is expected to grow.9

Instead, either the drug companies responsible for the drugs or a respectable international NGO, such as TB Alliance, needs to administer expanded access. This will involve negotiating with regulatory authorities in multiple countries. These regulatory authorities also need to be flexible and co-operate with expanded access programmes. This mechanism should be set up by January 2011 ideally with published site and patient qualification criteria and a procedure for applying for the drugs.

Expanded access is necessary but not ideal. There would be fewer people needing expanded access if drugs moved through the pipeline quicker. The new TB drugs are taking extraordinarily long to reach the point where regulatory authorities can approve them. TMC207 was discovered in 2003. It is not expected to receive regulatory approval anywhere before 2012. Compare this with HIV drugs such as AZT. It's anti-AIDS effect was discovered in 1984 and it was registered three years later.10

Also compare current development times with the development times of the original TB drugs. The very first TB drug, streptomycin, moved from discovery in 1943 to successful completion of a controlled clinical trial in 1947.11 Many patients, including George Orwell, were using the drug by 1948.12 As the above death rates show, patients in the 1940s with TB were probably no worse off than current patients with drug-resistant TB.

While increasingly complex regulatory requirements are part of the problem, the main cause of the long time taken to bring new TB drugs to market is political will. Patients with MDR-TB today are for the most part poor and politically marginalised, much more so that TB patients of the late-1940s in Europe and people with HIV in the 1980s in the United States. Pharmaceutical companies, including Tibotec and Otsuka, public entities such as the National Institutes of Health and the governments of high drug-resistant TB burden countries like South Africa, China, India and Russia need to put up more research money for TB drugs and diagnostics. We cannot simply depend on the Gates Foundation, wh ich was by far the biggest contributor to the approximately $500m spent on TB research in 2008.13 Just as we have

a Global Fund to Fight AIDS, TB and Malaria, perhaps we need an international fund to drive TB drugs and diagnostics research.

1 Gandhi N et al. High Early Mortality among HIV-infected Patients with Extensively Drug-resistant or Multidrug-resistant TB in Rural South Africa. Poster abstract 784. http://www.retroconference.org/2009/Abstracts/36299.htm

2 O?Donnell M. et al. Improved Survival for Patients with Extensively Drug-resistant TB and HIV in South Africa. 16th CROI 2009. Poster abstract 785. http://www.retroconference.org/2009/Abstracts/34552.htm

3 TAG. TAG 2010 pipeline report. July 2010. http://www.treatmentactiongroup.org/uploadedFiles/About/Publications/TAG_Publications/2010/2010%20pipeline%20we

4 Diacon AH et al. The diarylquinoline TMC207 for multidrug-resistant Tuberculosis. N Engl J Med. 2009 June 4. 360, 2397-2405.http://content.nejm.org/cgi/content/abstract/360/23/2397

5 Ginsberg A and Spigelman M. Challenges in tuberculosis drug research and development. Nature Medicine 13 (3) March 2007. http://www.nature.com/nm/journal/v13/n3/full/nm0307-290.html

6 The O'Donnell study cited above shows that in the general Kwazulu-Natal population: the rate of MDR TB was 11/100,000. But in health workers it was 59 per 100,000 people (OR: 5.5; 95%CI; 4.7-6.5). For XDR TB the rate was 1/100,000 in the general population versus 4/100,000 in health workers (OR: 3.89 95%CI: 2.0-7.1).

7 Huff B. Uncertain future for early access. 2006. http://www.thebody.com/content/art13517.html

8 Including healthy subjects for phase I trials and placebo patients a search on clinicaltrials.gov in August 2010 reveals that there are just over 900 places presently being recruited for OPC-67683 and TMC207.

9 WHO. Global Tuberculosis control 2009.

10 Yarchoan M. 2006. The story of AZT: Partnership and conflict. http://www.scribd.com/doc/1049/The-History-of-AZT

11 Crofton J . The MRC randomized trial of streptomycin and its legacy: a view from the clinical front line. The James Lind Library. 2004. http://www.jameslindlibrary.org/trial_records/20th_Century/1940s/MRC_bmj/crofton.html

12 Bastian H. Down and almost out in Scotland: George Orwell, tuberculosis and getting streptomycin in 1948. The James Lind Library. 2004. http://www.jameslindlibrary.org/trial_records/20th_Century/1940s/MRC_bmj/bastian.html

13 TAG. 2009 Report on Tuberculosis Research Funding Trends, 2005-2008. http://www.treatmentactiongroup.org/uploadedFiles/About/Publications/TAG_Publications/2009/TAG_STBP%202009TB
