Rational use of moxifloxacin for tuberculosis treatment

Despite intensified efforts in recent years, tuberculosis is uncontrolled in many regions.[1] Although drug-susceptible tuberculosis is a treatable disease, the 6 month duration of therapy, often administered under daily direct observation, can result in poor outcomes because of the demands that this regimen places on patients and health systems. Therapy for multidrug-resistant (MDR) tuberculosis is even more demanding: it lasts 2 years and is associated with distressing and often severe side-effects.[2] Unsurprisingly, treatment outcomes for MDR tuberculosis are considerably poorer than for drug-susceptible tuberculosis, even in optimum conditions.[3]

After decades of neglect, efforts to develop new drugs against tuberculosis have revived. Thanks to the Global Alliance for TB Drug Development (TB Alliance) and a few pharmaceutical companies, at least seven new chemical entities are in clinical development. In view of the urgent need for new drugs to treat drug-susceptible and drug-resistant tuberculosis, a pressing question for researchers, policy makers, and clinicians is, should new tuberculosis drugs be prioritised for the treatment of drug-susceptible or drug-resistant tuberculosis? The importance of this question is emphasised by the case of moxifloxacin, a newer generation fluoroquinolone. This drug is being trialled in a first-line regimen that aims to shorten the treatment of drug-susceptible tuberculosis,[4] and is increasingly used in the treatment of MDR and extensively drug resistant (XDR) tuberculosis.

Moxifloxacin is widely available in developed countries and commonly used for upper respiratory tract infections. On the basis of its efficacy against *Mycobacterium tuberculosis*,[5] a phase 3 trial to assess the efficacy of a 4-month first-line regimen incorporating moxifloxacin is underway. However, even if successful, a 4-month regimen is not expected to improve cure rates, reduce mortality, or reduce community transmission.

There is also evidence to support the use of moxifloxacin for treatment of drug-resistant tuberculosis. At present therapeutic options are scarce and outcomes are particularly poor in the presence of resistance to the most commonly used fluoroquinolone, ofloxacin.[3,6] Moxifloxacin has enhanced antituberculosis activity compared with ofloxacin, might be effective against isolates phenotypically resistant to ofloxacin or ciprofloxacin,[7,8] and has less potential to promote fluoroquinolone resistance.[9–11] It has also improved outcomes for patients with XDR tuberculosis.[6]

Although there are many reasons to incorporate moxifloxacin into a first-line regimen, there is also a risk. If moxifloxacin is incorporated into the existing first-line regimen, the efficacy of all fluoroquinolones in drug-resistant tuberculosis treatment could be severely compromised. Without widespread drug-susceptibility testing, patients infected with tuberculosis strains with pre-existing first-line resistance would be treated with inadequate first-line regimens, leading to resistance amplification.[12]

In view of the epidemiological reality, we recommend reserving moxifloxacin as a second-line drug for the treatment of drug-resistant tuberculosis. This approach will improve the treatment of a substantial and growing proportion of the global drug-resistant tuberculosis caseload (including patients with XDR tuberculosis), without preventing its use as a first-line drug once potent partner drugs have been developed. This opportunity would be lost if moxifloxacin were to become available for widespread use in first-line regimens in the short term.

Furthermore, accessibility and affordability of moxifloxacin is poorest where it is needed most. In South Africa, where an estimated 14 000 incident cases of MDR tuberculosis arise every year,[1] the price of moxifloxacin (€2·83 per 400 mg tablet) is almost 30 times more expensive than ofloxacin (€0·10 per 400 mg tablet). Despite widespread use in high-resource settings, the manufacturer (Bayer) has thus far been unwilling to supply moxifloxacin to routine tuberculosis programmes other than in trial settings, on the grounds that no regulatory indication for this disease has yet been filed. Bayer's patent on the basic molecule expired in 2009, but the company has been granted patents on adjusted forms of the molecule in many countries and has also filed patent applications in countries with generic manufacturing potential, including India. Removal of patent barriers and greater generic competition are needed to substantially reduce cost and improve accessibility.

We believe that the research priorities and drug development strategies of the TB Alliance and industry need to be coordinated, and should reflect both short-term and long-term goals for new tuberculosis drugs.

Although there are encouraging changes, such as fast-track regulatory procedures,[13,14] the urgent need for MDR tuberculosis treatment demands a shift in focus. The view that drug-resistant tuberculosis is a theoretical, rare event that can be averted by improving treatment of drug-susceptible tuberculosis, needs to change towards its recognition as an extant, major epidemic that, without prevention and appropriate treatment, could become the prevailing form of tuberculosis in many settings.

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1 WHO. Global tuberculosis control 2009: epidemiology, strategy, financing. 2009. http://www.who.int/tb/publications/global_report/2009/pdf/full_report.pdf (accessed March 26, 2009).

2 Nathanson E, Gupta R, Huamani P, et al. Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. *Int J Tuberc Lung Dis* 2004; **8:** 1382–84.

3 Orenstein EW, Basu S, Shah NS, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. *Lancet Infect Dis* 2009; **9:** 153–61.

4 Clinicaltrials.gov. Controlled comparison of two moxifloxacin containing treatment shortening regimens in pulmonary tuberculosis (REMoxTB). March, 2009. http://clinicaltrials.gov/ct2/show/NCT00864383?term=moxifloxacin&rank=1 (accessed Feb 28, 2010).

5 Rustomjee R, Lienhardt C, Kanyok T, et al. A phase II study of the sterilising activities of ofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2008; **12:** 128–38.

6 Jacobson KR, Tierney DB, Jeon CY, Mitnick CD, Murray MB. Treatment outcomes among patients with extensively drug-resistant tuberculosis: systematic review and meta-analysis. *Clin Infect Dis* 2010; **51:** 6–14.

7 Kam KM, Yip CW, Cheung TL, Tang HS, Leung OC, Chan MY. Stepwise decrease in moxifloxacin susceptibility amongst clinical isolates of multidrug-resistant *Mycobacterium tuberculosis*: correlation with ofloxacin susceptibility. *Microb Drug Resist* 2006; **12:** 7–11.

8 Von Groll A, Martin A, Jureen P, et al. Fluoroquinolone resistance in Mycobacterium tuberculosis and mutations in gyrA and gyrB. *Antimicrob Agents Chemother* 2009; **53:** 4498–500.

9 Dong Y, Xu C, Zhao X, Domagala J, Drlica K. Fluoroquinolone action against mycobacteria: effects of C-8 substituents on growth, survival, and resistance. *Antimicrob Agents Chemother* 1998; **42:** 2978–84.

10 Hooper DC. Minimizing potential resistance: the molecular view—a comment on Courvalin and Trieu-Cuot. *Clin Infect Dis* 2001; **33** (suppl 3)**:** 157–60.

11 Rodriguez JC, Cebrian L, Lopez M, Ruiz M, Jimenez I, Royo G. Mutant prevention concentration: comparison of fluoroquinolones and linezolid with *Mycobacterium tuberculosis*. *J Antimicrob Chemother* 2004; **53:** 441–44.

12 Cox HS, Niemann S, Ismailov G, et al. Risk of acquired drug resistance during short-course directly observed treatment of tuberculosis in an area with high levels of drug resistance. *Clin Infect Dis* 2007; **44:** 1421–27.

13 Global Alliance for TB Drug Development. Global partners join forces to speed development of new TB drug combinations. March 18, 2010. http://www.tballiance.org/newscenter/view-brief.php?id=904 (accessed April 5, 2010).

14 US Food and Drug Administration. Development of drugs to treat multi-drug resistant tuberculosis (MDR-TB). June 3, 2009. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM161859.pdf (accessed April 25, 2010).

HIV-2 down, HIV-1 to go? Understanding the possibilities of treatment as prevention

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As emphasised by the 18th International AIDS Conference in Vienna, and recent publications,[1,2] an effective, evidence-based, combination strategy approach is urgently needed to fight the HIV/AIDS epidemic. One important, although debated question, is whether treatment as prevention should form a central part of such an approach—ie, reducing incidence rates by lowering community viral loads with high-coverage antiretroviral treatment (ART). If yes, the subsequent question is how best to integrate this strategy with the other elements in the fight against HIV/AIDS.

Three routes predominate attempts to validate the conceptual aspect of treatment as prevention: mathematical modelling; direct comparison of HIV incidence rates between settings with high versus low ART coverage, separated either temporally or geographically; and study of infection rates in serodiscordant couples for whom the infected partner might, or might not, be undergoing ART.[3-7] Sufficient challenges have been made against each approach to lead critics to argue that further supporting research is needed before implementation of the method can be considered both reasonable and feasible.[2,8] Thus, additional validation and evaluation methods are needed. We suggest that the HIV-2 epidemic represents an overlooked, yet unique opportunity for estimation of central aspects of the efficacy and necessities of treatment as prevention in connection with HIV-1.

First, the aim of HIV prevention programmes is to decrease the incidence rate, and ultimately, prevalence of