Long walk to treatment for XDR tuberculosis in South Africa

In 1988, while in prison, Nelson Mandela was diagnosed with tuberculosis after presenting with a pleural effusion and received treatment. In 2 years previously in 1986, South Africa had 269 cases of incident tuberculosis per 100 000 individuals. In 2012, the incidence was roughly 1000 cases per 100 000 individuals. The rise in incident cases has been largely attributable to HIV infection, but is also indicative of basic difficulties in tuberculosis control. Mandela was successfully treated with a short-course regimen, but now multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis require increasingly complex regimens. Although South Africa has about 18% of the global burden of laboratory-confirmed MDR tuberculosis and the highest number of confirmed XDR cases, drug-resistant tuberculosis has emerged as a threat worldwide (notably in the former Soviet Union, China, India, and Africa). The 2013 global tuberculosis report from WHO shows continuing progress in reduction of overall tuberculosis incidence worldwide. However, the decrease is slow: about 2% per year. Additionally, the report emphasises how little progress has been made in global control of MDR tuberculosis.

Elize Pietersen and colleagues’ study in The Lancet provides a stark reminder that drug-resistant tuberculosis threatens to reverse the modest but consistent gains in global control achieved in the past decade. Pietersen and colleagues followed up a cohort of 107 South African patients with XDR tuberculosis originally described in 2010. Despite lengthy treatment with a median of eight antimycobacterial drugs, treatment outcomes were dismal: after 24 months of follow-up, 49 patients (46%) had died and 25 (23%) had failed treatment; after 60 months, 78 (73%) had died and 11 (10%) had failed treatment. 5 years after treatment initiation, only 12 patients (11%) had favourable outcomes (ie, treatment cure or completion).

Of the 45 patients who were discharged from hospital into the community, 19 (42%) did not achieve sputum culture conversion. As a result—predictably—transmission of XDR strains in the community occurred, as established by molecular epidemiology techniques. Unsurprisingly, patients with HIV co-infection who were taking antiretroviral therapy had significantly lower mortality than did those who were not taking this therapy (24 [69%] of 35 died vs nine [100%] of nine). Later generation fluoroquinolones, which have been recommended for treatment of XDR tuberculosis and were associated with decreased mortality in the first follow-up report, were not associated with survival in Pietersen and colleagues’ study, although use of clofazamine was (hazard ratio 0·38, 95% CI 0·16–0·87).

Pietersen and colleagues’ study should serve as another urgent alarm for global tuberculosis control: MDR disease in all its forms is an out-of-control problem with potentially vast and devastating repercussions for global public health. Clearly, drug regimens that are more effective and better tolerated are needed to improve adherence, decrease mortality, and prevent the amplification of tuberculosis drug resistance on treatment. Although bedaquiline and delamanid—drugs representing two new classes—have been approved in Europe and the USA, they will have to be assessed in time-consuming and expensive clinical trials before they can be incorporated into combination regimens in the best and safest ways. Nevertheless, it will be many years before most patients with drug-resistant tuberculosis can be treated, irrespective of the drugs involved.

The need for timely and accurate diagnosis has been identified as the initial barrier to appropriate treatment for patients with MDR tuberculosis. Worldwide, only 84 000 (18·7%) of the 450 000 incident cases of MDR tuberculosis were diagnosed in 2012, and only 77 000 (17·1%) were started on second-line treatment.
introduction of new molecular diagnostics such as Xpert MTB-RIF could shorten time to diagnosis and increase the proportion of patients with MDR disease who are appropriately diagnosed (but not those with XDR disease because Xpert cannot detect second-line resistance to fluoroquinolones or second-line injectable agents). However, integration of this test into tuberculosis control programmes in resource-poor countries with dispersed populations will be an operational challenge. Additionally, early diagnosis is not enough. Beyond early diagnosis, an entire cascade of care needs to take place to ensure that patients with MDR tuberculosis have a high chance of a favourable outcome.

A cascade-of-care approach is used in HIV and other chronic health conditions to describe the complex and integrated steps needed to ensure quality care. In drug-resistant tuberculosis, a cascade-of-care approach should not only incorporate early diagnosis and drug-susceptibility testing, patient education and support, infection control, streamlined entry into treatment, access to second-line drugs, treatment of HIV coinfection, adherence support, and retention, but should also encompass the tragic fact that many patients will need palliative care.

In Pietersen and colleagues’ study, nearly half the patients who were discharged into the community had failed treatment. Of 17 individuals who had failed treatment for whom smear microscopy was requested, six (35%) were smear positive. Although patients who failed treatment had high mortality, they survived for a median of 19.84 months (IQR 4.16–26.04) when discharged into the community. Pietersen and colleagues show that these individuals were spreading drug-resistant tuberculosis. In South Africa and elsewhere, little advanced planning is done to ameliorate the situation of patients with drug-resistant tuberculosis who fail treatment, or to develop community infection-control plans to prevent transmission of resistant strains.

As Pietersen and colleagues and the WHO global report make clear, drug-resistant tuberculosis is an acute global health crisis. National control programmes must urgently develop strategies to use existing public health instruments for control of tuberculosis in all its forms. Major new investments in drug development, diagnostics, and operational research are needed. Unfortunately, as a report from Treatment Action Group indicates, global tuberculosis research budgets are shrinking, not growing. The situation regarding MDR and XDR tuberculosis is bleak.

*Max R O’Donnell, Neil W Schluger
Departments of Medicine and Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY 10461, USA (MRO’D); Centre for AIDS Programme of Research in South Africa, Durban, South Africa (MRO’D); College of Physicians and Surgeons and Mailman School of Public Health, Columbia University, New York, NY, USA (NWS); and World Lung Foundation, New York, NY, USA (NWS) max.odonnell@einstein.yu.edu

We declare that we have no conflicts of interest.