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Hope rises out of despair: bedaquiline and linezolid for the treatment of drug-resistant TB

IN 2006, THE DEADLY OUTBREAK of a highly resistant strain of TB in Tugela Ferry in the heart of KwaZulu Natal, South Africa, brought the global TB care community to its knees.¹ With a mortality rate approaching 90%—and with most deaths occurring within 15 days of diagnosis—the disease which later became known as ‘extensively drug-resistant TB’ (XDR-TB; defined as strains of *Mycobacterium tuberculosis* resistant to isoniazid and rifampicin, a fluoroquinolone, and at least one of the injectable second-line drugs) challenged many of the assumptions regarding TB at the time: that the disease takes months to years to kill, that drug-resistant TB (DR-TB) would go away on its own, and that there was no need to perform drug susceptibility testing (especially against second-line medications).¹ It also showed how DR-TB could devastate people living with HIV and the front-line providers caring for them, highlighting the powerlessness of the health care system in addressing this airborne infectious disease.

KwaZulu-Natal became the epicenter for XDR-TB and HIV in South Africa. Throughout the province, there was a sense of despair.¹ But something else was blossoming in the verdant rolling hills of the province—determination. Building on the rich network that had been successful in tackling the HIV crisis, South Africa launched a concerted effort to tackle this deadly form of TB. It was a daunting task—diagnosis was difficult, treatment was worse than the disease, and death was more common than cure.² But with the newer tools that the National TB Programme of South Africa put great effort into rolling out (including the Xpert® MTB/RIF test [Cepheid, Sunnyvale, CA, USA], line-probe assays for second-line drugs, and new/repurposed medications, including bedaquiline [BDQ] and linezolid [LZD]), the country began to transform into a model for managing DR-TB in a setting of rapid access to innovation.³

This is why the paper by Padayatchi et al. reported in this issue of the *Journal* is so important.⁴ The study describes the treatment outcomes of 151 individuals who received BDQ and LZD for the treatment of DR-TB between January 2014 and November 2015 (known as the ‘BLIX cohort’) compared with historical controls (August 2009 to July 2011) from the same hospital who did not receive these medications. Among the patients who received BDQ- and

LZD-based regimens, 83% had culture conversion and 63% were cured of their disease. No one could imagine achieving such numbers—especially since the historical control group had a cure rate of only 25.7%. However, in addition to the relatively high rates of treatment success, patients receiving BDQ and LZD also experienced high rates of adverse events. Most of these (24.1%) were related to the drug LZD, which has been associated with significant levels of bone marrow toxicity, peripheral neuropathy, and optic neuritis in cohorts of people living with DR-TB who have received the medication.⁵ A large global study on adverse events in the treatment of multidrug-resistant TB showed almost 13% adverse events in the overall cohort of patients receiving LZD.⁶ A recent report showed no severe adverse events in a selected population on a lower dose of LZD (<300 mg daily).⁷ Clearly, additional work is needed to optimize the dose of LZD so that its efficacy can be preserved while its tolerability and safety are improved. There are several ongoing or planned trials that aim to assess this. While there was an increase in QTc prolongation—a known adverse event seen with BDQ, clofazimine, and moxifloxacin—there were no clinically significant cardiac events in the study. Furthermore, these rates of adverse events are lower than those reported in many cohorts of individuals receiving injectable-based therapy, where as many as 61% of people developed permanent hearing loss.⁸

Another concern is that rates of loss to follow-up between the BLIX cohort and the historical controls were similar and unacceptably high (14.6% in the BLIX cohort and 16.2% in the historical controls). It is clear that we need to improve the system within which DR-TB care is delivered, regardless of which medication is used. Patient-centered care that addresses the psychosocial and socioeconomic needs of individuals are badly needed and cannot be overlooked in the setting of therapeutic innovation.⁹ New options for monitoring treatment adherence such as video-observed therapy can be successful,¹⁰ but a human rights-based approach is needed to develop a true partnership between people living with DR-TB and those providing care so that optimal outcomes can be achieved.¹¹ It is also important to note that although the rates of cure in the BLIX cohort are high relative to those from historical controls, they are

nowhere near the rates set out in the WHO's End TB Strategy, or what people suffering from DR-TB deserve.

There are important lessons to be learned from the BLIX cohort. First, these findings confirm those of other studies showing that BDQ and LZD are powerful tools in the treatment of DR-TB.¹² The WHO now recommends these medications as standard for all people living with the disease as part of all-oral regimens, some of which can be administered for a period of 9–12 months.¹³ Unfortunately, most countries do not offer such treatment to people living with DR-TB, and it is estimated that fewer than 15% of people in need of BDQ receive it.¹⁴ Many countries (and the groups that advise them) still insist on injectable-based regimens, although these medications have been shown to be ineffective in treating DR-TB and cause significant harm to patients.¹⁵ South Africa is a role model in offering all-oral, BDQ and LZD-based regimens to all people living with DR-TB,¹⁶ offering hope where once there was only despair.

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