Bedaquiline and clofazimine: successes and challenges

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Bedaquiline, a novel therapeutic drug, and clofazimine, a re-purposed drug, are front-line therapies recommended by WHO to treat rifampicin-resistant or multidrug-resistant tuberculosis. Both drugs have been in use in South Africa at least 10 years: bedaquiline since 2007 and clofazimine since 2010. The use of bedaquiline in programmatic settings in South Africa has reduced the risk of all-cause mortality threefold (hazard ratio 0·35, 95% CI 0·28–0·46)[1] and achieved treatment success in at least 70% of patients.[2] The inclusion of clofazimine in combination therapy has reduced treatment duration from 18–24 months to 9–12 months. South Africa has adopted both drugs extensively in the modified short and long regimens for rifampicin-resistant or multidrug-resistant tuberculosis. According to the electronic drug-resistant tuberculosis register, as of June 1, 2020, 29 193 individuals in South Africa have received bedaquiline, and 30 599 have received clofazimine. Emerging resistance and cross-resistance have been reported.[3,4]

In *The Lancet Microbe*, Camus Nimmo and colleagues[5] used whole-genome sequencing of 676 *Mycobacterium tuberculosis* isolates from 391 patients with drug-resistant tuberculosis in KwaZulu-Natal, South Africa, to identify variants associated with resistance to bedaquiline and clofazimine.[5] Their study provides additional evidence of emerging resistance to these drugs. Among the cohorts analysed, 16 (4%) of 391 patients had genotypic resistance; of those who had a resistance pattern defined, 11 (79%) of 14 had pre-extensively drug-resistant or extensively drug-resistant tuberculosis and harboured unique *Rv0678* mutations. Interestingly, identical *Rv0678* mutations were only observed among patients who developed resistance during treatment, emerging between 2 and 20 months after exposure. Selection of these mutations could reflect adaptive responses requiring further investigation, although the authors noted that primary nosocomial transmission is the most likely reason.

Measuring resistance to bedaquiline and clofazimine is a challenge. Two multi-country quality studies showed poorer reproducibility[6] and false resistance[7] for the agar method used by Nimmo and colleagues (ie, the 1% proportion method on Middlebrook 7H11 agar)[5] Furthermore, clinical trial data did not show a substantial difference in culture conversion at 24 weeks between high and low minimum inhibitory concentrations (MICs) using this method.[8] Determination of genetic resistance is also problematic as not all mutations in the *Rv0678* gene confer large increases in MIC, with some mutations having the opposite effect.[9] Population-level analysis of these data is useful, although for individual patient management the evidence base for specific mutations, levels of resistance, and final treatment outcomes is sparse and requires further research.

The number of patients with rifampicin-resistant or multidrug-resistant tuberculosis in sub-Saharan Africa was estimated to be 77 000 in 2018 while only 19 730 were reported to have started treatment, and of these patients 9558 (48%) were treated in South Africa. The bold decision in South Africa to use these new and repurposed drugs in shortened treatment regimens was based on operational research data and the ethical need for effective, patient-friendly, injection-free regimens. The introduction of bedaquiline was accompanied by a national surveillance programme to monitor the emergence of drug resistance. Data generated led to the criteria for resistance adopted by WHO in 2018.[4] Additionally, two crucial changes in South African policy occurred in 2018: the modified short regimen was strengthened with linezolid, and a standardised laboratory testing protocol to detect resistance to bedaquiline, clofazimine, and linezolid was introduced. These interventions overlap in time with the study by Nimmo and colleagues,[5] pre-emptively addressing the concerns raised. The approach applied by South Africa should be used as an example for other countries when adopting these new regimens at scale. A rapid assay that can screen for resistance to either bedaquiline or clofazimine at treatment initiation is still urgently needed.

Of interest is the phylogenetic analysis by Nimmo and colleagues[5]—which included the genome sequences from their study, publicly available sequences from previously published studies in southern Africa, and sequences indexed in the National Center for Biotechnology Information Sequencing Read Archive originating from samples collected in southern African countries—showing emergence of *Rv0678* mutations preceding the introduction of bedaquiline, which was also reported in a previous study.[10] The current study highlights the propensity of these mutations to occur

For **WHO guidelines on treatments for rifampicin-resistant or MDR tuberculosis** see https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/

For the **estimated number of patients with rifampicin-resistant or multidrug-resistant tuberculosis** see https://www.who.int/tb/publications/en/

For the **electronic drug-resistant tuberculosis register** see https://edrweb.net/

For the **South African guidance on the use of bedaquiline and clofazimine** see http://www.tbonline.info/media/uploads/documents/dr_tb_clinical_guidelines_for_rsa_september_2018.pdf

For the **South African national surveillance programme** see https://www.nicd.ac.za/assets/files/Introduction%20of%20new%20drugs%20and%20drug%20regimens%20for%20the%20management%20of%20drug%20resistant%20TB%20in%20SA%20-%202015.pdf

For **WHO's criteria for drug resistance** see http://www.who.int/tb/publications/2018/WHO_technical_report_concentrations_TB_drug_susceptibility/en/

For the **drug resistance testing protocol** see https://www.nicd.ac.za/wp-content/uploads/2020/05/Memo_Standardisation-of-phenotypic-pDST-for-TB_2-August-2018.pdf

in specific strain lineages, and the need for further investigation into the nature of these occurrences. Are these sporadic mutations unrelated to selection pressure and well established among mycobacteria? Alternatively, selection pressure could be due to the azole group of antifungal agents, which would have different implications for control, especially in sub-Saharan Africa, where they are commonly used.

The excellent successes achieved with bedaquiline and clofazimine require scale-up if the poor global outcomes for rifampicin-resistant or multidrug-resistant tuberculosis are to be addressed. However, upscaling the use of these drugs comes at the cost of resistance emergence, which needs to be mitigated. Early detection of resistance is essential, requiring development of new rapid technologies combined with strengthening of laboratory capacity to support the introduction of new regimens. Additionally, effective combination therapies and adherence to these regimens are crucial factors in curbing emergence of resistance. Unfortunately, the pipeline for new drug classes for tuberculosis is running at a trickle when compared with HIV, and if not addressed urgently, we will find ourselves in a pre-antibiotic era, which we cannot afford as we set our sights on ending tuberculosis by 2035.

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