Should we worry about bedaquiline exposure in the treatment of multidrug-resistant and extensively drug-resistant tuberculosis?

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Factors known to have an impact on bedaquiline exposure are present in patients with M/XDR-TB. As we have seen with fluoroquinolones the impact of variable drug exposure needs to be studied to understand the impact on treatment outcome. http://bit.ly/2JMlJJF


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To the Editor:

Recently, the World Health Organization (WHO) released the updated guideline on the treatment for multi-drug resistant tuberculosis (MDR-TB) treatment regimens based on new experimental and observational evidence [1]. In this new guidance the most important drugs are the late-generation fluoroquinolones (i.e. levofloxacin and moxifloxacin), linezolid and bedaquiline. Despite the new guidance, MDR- and extensively drug resistant (XDR) TB treatment is challenging due to the risk of drug-related adverse events (AE) and drug–drug interactions (DDI). Precision medicine-based approach to minimise the risk of resistance emergence and amplification and to provide patients with the highest standard of care has been recommended [2]. Variable exposure to second-line anti-TB drugs, which has been proved in several studies, can cause either adverse events or lack of response because of too high or low concentrations, respectively. Therapeutic drug monitoring (TDM) has, therefore, been recommended to provide information on the individual drug concentration [2, 3]. In the past decade, TDM has been frequently prescribed in well-resourced settings with promising results; on this basis, the American Thoracic Society TB guidelines have endorsed TDM in specific situations [4, 5]. The strongest evidence on
TDM in the management of M/XDR-TB is related to fluoroquinolones and linezolid [6, 7]. *In vitro* studies showed a clear relationship between drug exposure, susceptibility of *Mycobacterium tuberculosis*, and reduction in bacterial load, and cure. Observational research proved that slow therapeutic response and acquired drug resistance are likely associated with poor drug exposure. In the recently updated WHO guideline on MDR-TB treatment, TDM has been recommended for fluoroquinolones, linezolid and aminoglycosides, especially when “the dose is at the upper and lower ends of the range to minimise the adverse therapeutic consequences of over- and under-exposure” [1]. Unfortunately, randomised controlled studies on TDM have not been planned until now.