Emergence of bedaquiline resistance in a high tuberculosis burden country

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Bedaquiline resistance emerged in >15% of *Mycobacterium tuberculosis* complex strains obtained from follow-up isolates of MDR-TB patients. Insufficient backbone regimens and cavitary disease were associated with treatment failure and death. https://bit.ly/2UHoVyG

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Abstract

Rationale Bedaquiline has been classified as a group A drug for the treatment of multidrug-resistant tuberculosis (MDR-TB) by the World Health Organization; however, globally emerging resistance threatens the effectivity of novel MDR-TB treatment regimens.

Objectives We analysed pre-existing and emerging bedaquiline resistance in bedaquiline-based MDR-TB therapies, and risk factors associated with treatment failure and death.

Methods In a cross-sectional cohort study, we employed patient data, whole-genome sequencing (WGS) and phenotyping of *Mycobacterium tuberculosis* complex (MTBC) isolates. We could retrieve baseline isolates from 30.5% (62 out of 203) of all MDR-TB patients who received bedaquiline between 2016 and 2018 in the Republic of Moldova. This includes 26 patients for whom we could also retrieve a follow-up isolate.

Measurements and main results At baseline, all MTBC isolates were susceptible to bedaquiline. Among 26 patients with available baseline and follow-up isolates, four (15.3%) patients harboured strains which acquired bedaquiline resistance under therapy, while one (3.8%) patient was re-infected with a second bedaquiline-resistant strain. Treatment failure and death were associated with cavitary disease (p=0.011), and any additional drug prescribed in the bedaquiline-containing regimen with WGS-predicted resistance at baseline (OR 1.92 per unit increase, 95% CI 1.15–3.21; p=0.012).

Conclusions MDR-TB treatments based on bedaquiline require a functional background regimen to achieve high cure rates and to prevent the evolution of bedaquiline resistance. Novel MDR-TB therapies with bedaquiline require timely and comprehensive drug resistance monitoring.