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Cardiac safety of extensively drug-resistant tuberculosis regimens including bedaquiline, delamanid and clofazimine

To the Editor:

I read with interest the recent article by TADOLINI et al. [1] describing QT (ECG Q-T wave interval) prolongation in a patient with extensively drug-resistant tuberculosis (XDR-TB) being treated with both bedaquiline and delamanid. QT prolongation is a recognised safety concern for both these drugs. In a placebo-controlled trial of delamanid in multidrug resistant-TB, QTcF intervals (using the correction for heart rate of FRIDERICIA [2]) increased 12.1 ms more from baseline in delamanid recipients over 6–10 weeks [3]. An increase of similar magnitude was observed in an open-label 24-week trial of bedaquiline, with most of the effect becoming apparent within the first 1–2 weeks [4]. The authors are correct that there is currently no clinical information regarding QT prolongation when these two drugs are co-administered.

However, readers may be less aware of QT prolongation due to clofazimine, which this patient also received as part of XDR-TB treatment. Clofazimine is a potent inhibitor of hERG potassium channel signalling, with essentially complete inhibition occurring *in vitro* at sub-therapeutic concentrations [4, 5]. hERG mutations can result in QT prolongation and potentially fatal arrhythmias, including ventricular tachycardia and torsade de pointe [6, 7]. *In vitro* measurement of hERG signalling effects is an important preclinical drug development tool to identify potential arrhythmia-inducing compounds [8], although recent studies indicate the modulating effects of other channels [9]. Testing for hERG signalling effects was not available at the time clofazimine was developed, some 50 years ago.

Two studies and one case report have confirmed the QT prolonging effects of clofazimine. In one study, 105 patients with newly diagnosed drug-sensitive TB were treated for 2 weeks with one of seven drugs or regimens (n=15 per arm), of which four included clofazimine 100 mg daily [10]. By day 14, QT intervals in patients receiving clofazimine alone increased from baseline by a mean of 17 ms. Patients receiving regimens containing both clofazimine and bedaquiline had increases of 20–21 ms. Patients receiving neither drug had no change in QT (−3 to 2 ms). Given the unusual pharmacokinetics of clofazimine, it is unlikely that this short treatment interval (14 days) was sufficient to reach steady state effects.

In a second study, 233 patients with drug-resistant TB were treated for 24 weeks with bedaquiline in an open label, single arm trial, in combination with an individualised background regimen [4]. 10 patients not receiving clofazimine at the time of enrolment were started on bedaquiline plus a background regimen including clofazimine. By week 24, their mean±SE QTcF interval had increased 41.5±8.4 ms from baseline. In contrast, in patients whose background regimen did not include clofazimine, the QTcF interval increased by only 12.9±4.1 ms (p=0.009).

Finally, one case report describes ventricular tachycardia and torsade de pointe occurring in a 66 year-old man who had been treated for recurrent erythema nodosum leprosum with 300 mg of clofazimine per day for 11 months [11].

These findings indicate that clofazimine may indeed have been an important contributor to the QT prolongation in the patient reported by TADOLINI et al. [1]. Studies are needed to determine if clofazimine potentiates the combined QT prolonging effects of bedaquiline plus delamanid as it does with bedaquiline

alone. The safety of regimens containing bedaquiline plus delamanid may be substantially improved if clofazimine can be omitted.

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Clofazimine prolongs the QT interval and can potentiate the QT effects of other MDR-TB drugs
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Robert S. Wallis
Aurum Institute, Johannesburg, South Africa.

Correspondence: Robert S. Wallis, Aurum Institute, 29 Queens Rd, Parktown 2193, Johannesburg, South Africa.
E-mail: rwallis@auruminstitute.org

Conflict of interest: None declared.

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From the authors:

We read with great interest the comments by R.S. Wallis on our article describing the first case of extensively drug-resistant tuberculosis (XDR-TB) treated with both delamanid and bedaquiline [1], as recommended by the European Respiratory Society hosted TB Consilium experts [2, 3].

The patient developed QTc (corrected QT or the measure of time between the start of Q wave and the end of T wave in the heart's electrical cycle (ECG)) prolongation a few days after beginning treatment, that included not only the two new anti-TB drugs but also clofazimine (which, according to Wallis, may have played a role in QTc prolongation). Clofazimine-related cardiotoxicity has been described in a single case-report on an Indian male with leprosy with electrolyte abnormalities treated with clofazimine for 11 months [4]. We agree that there are ongoing safety concerns about QTc prolongation when clofazimine is combined with bedaquiline; safety data remains sparse, although serious life-threatening arrhythmias resulting from this combination have not been described yet.

Our patient had XDR-TB with a single certified active drug, clofazimine, which was the rationale for its inclusion in the salvage regimen. Given the fairly sudden rise in QTc within a week of starting the combination, the TB Consilium experts considered bedaquiline as the culprit for the adverse event. Clofazimine, in fact, requires several weeks to reach the steady state due to its peculiar pharmacokinetics, while bedaquiline at that time was being loaded and, considering its long half-life, the experts recommended to stop it. The patient presented with hypokalaemia during that period, which may have