

Bedaquiline plus delamanid for XDR tuberculosis

We read with interest the correspondence by Caitlin Reed and colleagues, reporting a patient with a severe case of extensively drug-resistant (XDR) tuberculosis who was treated with bedaquiline and subsequently denied delamanid because of concerns over additive cardiac toxic effects.¹ Here we report the case of a man with XDR tuberculosis who was treated with a regimen containing bedaquiline and delamanid in combination.

A 20-year-old man from Democratic Republic of the Congo was diagnosed with pulmonary tuberculosis in October, 2014. Sputum smears were positive. Cultures confirmed an XDR *Mycobacterium tuberculosis* strain. On the basis of genotypic and phenotypic drug susceptibility testing, an individualised combination of ethambutol, para-aminosalicylic acid, linezolid, cycloserine, ethionamide, and bedaquiline was initiated with directly observed treatment. After some initial improvement, the patient showed clinical and radiological worsening. In March, 2015, after the consilium organised by the French National Reference Center for Mycobacteria, a pulmonary lobectomy was done and the patient was initiated on a new tuberculosis treatment regimen under close medical supervision: ethambutol, para-aminosalicylic acid, linezolid, and bedaquiline to which delamanid, imipenem, and amoxicillin plus clavulanic acid were added. Serum potassium, calcium, magnesium, and albumin were measured before treatment initiation. An electrocardiography was done before treatment, and repeated twice a week during the first month, once a week for 2 months, and twice a month thereafter. After 6 months of treatment the patient had favourable clinical, microbiological, and

radiological responses. No QT interval prolongation was observed. No other known adverse events were reported except nausea.

This is, to our knowledge, the first patient with XDR tuberculosis in whom a bedaquiline–delamanid combination has been initiated. The combination was initiated in a patient in whom an effective treatment cannot be designed, in the consideration that its potential life-saving benefits outweigh its unknown adverse event risks; in a department in which more than 100 tuberculosis cases a year are admitted to hospital, of which 14 cases are multidrug-resistant or XDR disease; after a multidisciplinary consultation at the national level; and after patient's informed consent. Conditions for this combination use described by Alberto Matteelli and colleagues² were therefore fulfilled. Moreover, this combination was initiated under close cardiac monitoring and was well tolerated over a 6 month period. These data need to be confirmed in a larger number of patients and ideally in clinical trials. In the meantime, from an individual and societal perspective, compassionate use of these combinations should not be denied to specific patients if conditions such as those enumerated by Matteelli and colleagues² are respected.

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- 1 Reed C, Mason L, Cox H, Seaworth B, Lessem E, Furin J. Compassionate and optimum use of new tuberculosis drugs. *Lancet Infect Dis* 2015; **15**: 1131.
- 2 Matteelli A, D'Ambrosio L, Centis R, Tadolini M, Migliori GB. Compassionate and optimum use of new tuberculosis drugs. *Lancet Infect Dis* 2015; **15**: 1131–32.

Diagnostic strategies for Ebola virus detection

Mobile laboratories for highly dangerous pathogens were deployed in west Africa during the 2014–16 outbreak of Ebola virus disease. These laboratories have substantially reduced the burden on medical professionals by providing on-site diagnostics.¹ One study estimated that if 60% of patients with Ebola virus disease are diagnosed within 1 day of symptom onset, instead of the current average of 5 days, the virus attack rate drops from 80% to nearly 0%.² This finding emphasises the substantial effect of a rapid, accurate, clinical diagnosis of Ebola virus disease supported by laboratory tests. Several diagnostic assays were authorised by the US Food and Drug Administration (FDA) for emergency use during the outbreak (appendix). Here, we analyse the use of the three kits that were also approved by WHO (table): RealStar Filovirus Screen RT-PCR Kit 1.0 (Altona Diagnostics GmbH, Hamburg, Germany),³ ReEBOV Antigen Rapid Test Kit (Corgenix, Broomfield, CO, USA),⁴ and Xpert Ebola Assay (Cepheid AB, Sunnyvale, CA, USA).⁵

The RealStar device is a real-time quantitative PCR (RT-qPCR) test for detecting the L gene. The device takes 4–6 h to provide a negative result, roughly 2 h for a positive result, and



See Online for appendix

	Manufacturer	Detection technique	Viruses detected	Target viral gene	Time to results	Limit of detection	Patient specimen needed
RealStar Filovirus Screen RT-PCR Kit 1.0 (Nov 2014) ³	Altona Diagnostics GmbH	RT-qPCR	Ebola virus, Sudan virus, Reston virus, Tai Forest virus, Bundibugyo virus, Marburg virus	L	4–6 h (negative), less for a positive	1 plaque-forming unit (about 3400 copies) of Ebola virus or Sudan virus per mL plasma	Plasma collected in EDTA, cell-free bodily fluids, swab washes
ReEBOV Antigen Rapid Test (Feb 2015) ⁴	Corgenix	Rapid chromatographic immunoassay	Ebola virus	VP40	15–25 min	2·11 × 10 ⁸ RNA copies per mL (extrapolated) or 1 × 10 ⁸ plaque-forming units per mL (FDA calculated)	Finger-prick (capillary) whole blood, venous whole blood, or plasma collected in EDTA
Xpert Ebola Assay (May 2015) ⁵	Cepheid AB	RT-qPCR	Ebola virus	Nucleoprotein and glycoprotein	90 min	82·0 RNA copies per reaction (95% CI 39·7–3193·6)	Venous whole blood collected in EDTA

FDA=Food and Drug Administration.

Table: Assays for detecting filovirus infections approved for emergency use by the US FDA and WHO

has a limit of detection of 1 plaque-forming unit per mL, or about 3400 copies per mL. ReEBOV is a rapid chromatographic immunoassay against VP40; it takes 15–25 min to produce a final result and has a limit of detection of 2·11 × 10⁸ copies per mL (by extrapolation), or 1 × 10⁶ plaque-forming units per mL (FDA calculated⁶).

The Xpert Ebola Assay is an RT-qPCR test for detecting viral nucleoprotein and glycoprotein. The assay takes 90 min to produce results and has a limit of detection of 82·0 RNA copies per reaction. The ReEBOV test was used in two clinics in Sierra Leone during the Ebola outbreak and was found to be 100% specific for Ebola.⁷ Cycle threshold values of the tested patients ranged from 15·9 to 26·3 (mean 22·6).⁷ However, at these values, most patients will be showing clinical signs of moderate to severe Ebola virus disease, and values less than 20 are associated with terminal disease.

Rapid diagnostic tests are also important for detecting and confirming infected patients who have not yet progressed to advanced disease (cycle threshold >30), at a time when they are less infectious to others, and with a greater chance of survival with clinical intervention. The high limit of detection suggests that the ReEBOV test is currently not sufficiently sensitive to optimally inform and manage suspect cases or outbreaks. Rather, in view of the

quick turnaround time, the test is more applicable for rapid screening of patients with advanced disease, in whom a positive result would raise the alarm and push for confirmation by RT-qPCR and next-generation sequencing. RT-qPCR-based assays have a lower limit of detection; however, the longer turnaround time plus the time needed for viral RNA extraction suggests that the RealStar test and the Xpert Ebola Assay are better suited to confirmation or diagnosis of suspected cases early after onset of Ebola virus disease. Future research efforts should prioritise lowering the limit of detection of assays based on RT-qPCR to improve diagnostics for Ebola and detect and manage potential outbreaks at the earliest opportunity.

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