## Tuberculosis treatment: one-shot approach or cascade of regimens?

Both later generation fluoroquinolones and bedaquiline are known as the cornerstone agents (ie, core drugs) of second-line treatment regimens for patients with rifampicin-resistant tuberculosis because of their high bactericidal and sterilising effect.[1] Without effective core drugs and an adequate background regimen, treatment success is as low as 56%.[2]

Tweed and colleagues[3] showed that bedaquiline, pretomanid, and pyrazinamide, complemented by moxifloxacin, for rifampicin-resistant tuberculosis, resulted in a 2 month liquid culture conversion of 96% for pyrazinamide-susceptible tuberculosis, and 80% for pyrazinamide-resistant tuberculosis. However, reasons for the ultimate sterilising effect of the regimen and its permissiveness to treatment failure and acquired resistance remain unknown. Nevertheless, Tweed and colleagues speculate that this regimen could replace the current second-line, as well as first-line, regimens if phase 3 studies show superior outcomes and shortened treatment durations.[3]

With mass application, a degree of treatment failure and relapse, with acquired resistance to core drugs, has always been inevitable, particularly if resistance to companion drugs is widespread. About half of rifampicin-resistant tuberculosis isolates worldwide are pyrazinamide resistant, with resistance to fluoroquinolone also increasing.[2] Pyrazinamide is essential in combinations with bedaquiline and pretomanid, which explains the conversion difference related to pyrazinamide.[3] The encouraging 2 month results for pyrazinamide-susceptible tuberculosis do not exclude a considerable risk of amplified resistance to bedaquiline.

Rather than using a one-shot approach, with two second-line, core drugs in one rifampicin-resistant tuberculosis regimen, we prefer a cascade (figure). This cascade only requires rifampicin susceptibility testing, followed by fluoroquinolone susceptibility testing if resistance to rifampicin is detected. Provided that resistance to rifampicin is correctly excluded, first-line regimens that use rifampicin throughout the treatment course are very effective,[1] and acquired rifampicin resistance is rare. This type of first-line regimen also works well in isoniazid-resistant tuberculosis. For fluoroquinolone-susceptible, rifampicin-resistant tuberculosis, the second-line, 9 month regimen of gatifloxacin (in Bangladesh) resulted in 954 (98%) of 978 patients who were relapse free and had virtually no acquired resistance to its core drug.[4] For fluoroquinolone-resistant, rifampicin-resistant tuberculosis, long and individualised regimens of bedaquiline are recommended because evidence on short standard regimens is insufficient for this indication. In such an individualised, third-line regimen, bedaquiline acts as a core drug.[1] However, if bedaquiline has already been used in a regimen that did not successfully treat this tuberculosis type, the drug might no longer work.

When drug-safety monitoring identifies severe or potentially debilitating adverse events, the agent should be replaced with a drug that has similar bacteriological activity.[1] For instance, when abnormalities are detected during systematic audiometry,

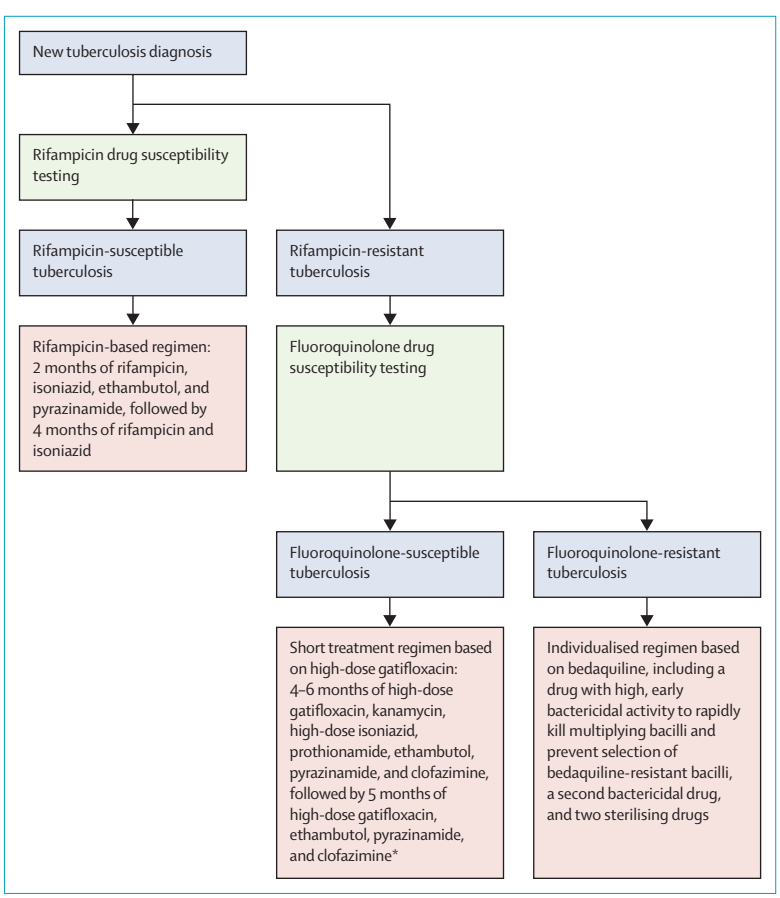


***Figure:*** **Cascade approach to tuberculosis treatment**
Blue indicates tuberculosis diagnosis. Green indicates drug susceptibility testing. Red indicates recommended treatment regimen. *Kanamcyin (or another second-line injectable) can be replaced with linezolid in case of audiometry abnormalities, or another drug with high early bactericidal activity for children, pregnant woman, and patients with diabetes.

replacing the second-line injectable with oral linezolid can prevent serious hearing loss.[5]

By relying on standard regimens with time-proven efficacy for the first two steps, the cascade of regimens' approach is widely applicable and safeguards our second-line core drugs for highly effective management of drug resistant-tuberculosis in the long term.

We declare no competing interests.

*Tom Decroo, Bouke C de Jong, Alberto Piubello, Lutgarde Lynen, Armand Van Deun*
**tdecroo@itg.be**

Unit of HIV and Coinfections, Department of Clinical Sciences (TD, LL) and Unit of Mycobacteriology, Department of Biomedical Sciences (BCdJ), Institute of Tropical Medicine, 2000 Antwerp, Belgium (TD); Research Foundation Flanders, Brussels, Belgium (TD); Damien Foundation, Niamey, Niger (AP); International Union Against Tuberculosis and Lung Disease, Paris, France (AP); and Independent Consultant, Leuven, Belgium (AVD)

1 Van Deun A, Decroo T, Piubello A, de Jong BC, Lynen L, Rieder HL. Principles for constructing a tuberculosis treatment regimen: the role and definition of core and companion drugs. *Int J Tuberc Lung Dis* 2018; **22:** 239–45.
2 WHO. Global tuberculosis report. 2018. https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf?ua=1 (accessed Nov 26, 2019).
3 Tweed CD, Dawson R, Burger DA, et al. Bedaquiline, moxifloxacin, pretomanid, and pyrazinamide during the first 8 weeks of treatment of patients with drug-susceptible or drug-resistant pulmonary tuberculosis: a multicentre, open-label, partially randomised, phase 2b trial. *Lancet Respir Med* 2019; **7:** 1048–58.
4 Van Deun A, Decroo T, Kuaban C, et al. Gatifloxacin is superior to levofloxacin and moxifloxacin in shorter treatment regimens for multidrug-resistant TB. *Int J Tuberc Lung Dis* 2019; **23:** 965–71.
5 Piubello A, Souleymane MB, Harouna SH, et al. Management of multidrug-resistant tuberculosis with shorter treatment regimen in Niger: nationwide programmatic achievements. *Respir Med* 2019; **161:** 105844.