# RR-TB treatments, testing bedaquiline and injectable kanamycin

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## Here, Professor Andre Nunn from Medical Research Council Clinical Trials Unit at UCL, explores tuberculosis with a focus on RR-TB treatments (rifampicin-resistant) and their drug combinations

Tuberculosis (TB) is one of the oldest diseases known to man and its management remains a challenge to public health worldwide. According to the most recent World Health Organisation (WHO) report over 10 million persons fell ill with tuberculosis in 2021. It occurs within all the countries of the world but is most prevalent in low and middle-income countries. A total of 1.6 million people died from TB worldwide in 2021 making it the 13th leading cause of death and the second leading infectious disease killer after COVID-19.

### Ongoing studies and persistent research for RR-TB treatments

As reported in a previous Open Access Government article, February 2022, treatment for drug-sensitive disease was dramatically shortened from 18 months to 6 months in the 1970s following the discovery of the antibiotic rifampicin. Approximately half a million patients, however, have rifampicin-resistant (RR-TB), which has proved to be much more difficult to treat effectively than the drug-sensitive disease. RR-TB can occur through inadequate treatment, poor adherence to treatment or exposure to patients already infected with resistant disease. Little progress was made until a series of cohort studies suggested that a nine-month regimen, which included a higher than usual dose of the fluoroquinolone moxifloxacin, could be as effective as the considerably longer regimen recommended by WHO. This was confirmed in Stage 1 of the STREAM trial, published in 2019.[1]

In an article published in September 2022 of Open Access Government the results of two more phase III trials in RR-TB, ZeNix and TB-PRACTECAL, were discussed; they represented a major step forward in treatment. This has led to an update in WHO consolidated guidelines.[2] In particular it is now recommended that the 6-month BPaLM regimen, comprising bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin, may be used programmatically in place of 9-month or longer (>18 months) regimens, in patients aged ≥15 years with RR-TB who have not had previous exposure to bedaquiline, pretomanid and linezolid. The regimen could be used without moxifloxacin (BPaL) in the case of documented resistance to fluoroquinolones. Bedaquiline and pretomanid are both new anti-tuberculosis drugs and linezolid is a repurposed antibiotic which has been found to be effective in treating TB.

In November 2022 Stage 2 of the STREAM trial was published.[3] Patients were allocated to one of four regimens, the long regimen or nine-month regimen studied in Stage 1 or two experimental regimens both containing bedaquiline.

## Testing the injectable kanamycin replacement, bedaquiline

The primary objective was to evaluate whether the nine-month regimen would be equally effective if the injectable kanamycin was replaced by bedaquiline. A limitation of the injectable is the inconvenience of administration both for the health providers and the patients and the problems of toxicity, particularly ototoxicity encountered by some patients. This can result in irreversible deafness in a small number of patients if not picked up early. The trial was conducted in seven countries in Africa, Asia and Eastern Europe. The results were encouraging; 162 (83%) of 196 patients receiving the fully oral regimen had a successful outcome compared to 133 (71%) of 187 on the injectable containing control regimen. The primary outcome was a composite measure involving not only TB-related events but also changes and modifications of treatment due to adverse side-effects, loss to follow-up and death from any cause. Outcomes based on bacteriological findings were in the minority. The proportion of patients for who there was definite or probable evidence of failure or recurrence as assessed by an independent clinician, blinded to treatment allocation, was 0.11 for the control regimen and only 0.02 for the oral regimen. Evidence of severe sensorial hearing loss was reduced from 9% on the control regimen to 2% on the oral regimen.

## Testing bedaquiline and with injectable kanamycin together

The second experimental regimen was of six months' duration and included a shorter duration of the kanamycin injectable in addition to bedaquiline; 122 (91%) of 134 participants on the 6-month regimen had a favourable outcome compared with 87 (69%) of 127 on the control. The proportion of patients for who there was definite or probable evidence of failure or recurrence was 0.13 for the control regimen and only 0.02 for the six-month regimen. Severe sensorial hearing loss occurred in 4% of patients on the six-month regimen, half that on the control regimen but more than on the fully oral regimen.

These results indicate that both of the bedaquiline-containing regimens are not only non-inferior but significantly superior to a nine-month injectable- containing regimen. A reduction in levels of ototoxicity reported corresponded to the reduction or elimination of the injectable in the regimen. The new regimens offer promising alternative RR-TB treatment options.

An important observation from both the STREAM and PRACTECAL trials is that the majority of unfavourable outcomes were not because of poor TB outcomes but due to drug toxicity.

## Continuing research to improve RR-TB treatments

There is no doubt that RR-TB treatments are in a much better place than it was five years ago. However, more research is needed to confirm findings from the recently published trials in special populations such as children and adolescents and patients with extra-pulmonary disease. It is also important to obtain programmatic data to document efficacy and safety of the new regimens in a variety of settings world-wide. It will be essential to be alert to the risks of the development of drug resistance to bedaquiline and pretomanid which could so easily occur with uncontrolled use. Fluoroquinolone resistance is already a substantial problem in some parts of the world.

## References


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3. Goodall RL, Meredith SK, Nunn A J, et al. Evaluation of two short standardised regimens for the treatment of rifampicin-resistant tuberculosis (STREAM stage 2): an open-label, multicentre, randomised, non-inferiority trial. The Lancet. 2022;400(10366):1858-1868.


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