# Intermittent regimens for tuberculosis treatment: Back to the Future?

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**Once weekly bedaquiline, rifapentine and pyrazinamide has sterilising activity and is ready for further exploration in a clinical trial, including appropriate safety and pharmacokinetic assessment** https://bit.ly/3ivrY4m

**Cite this article as:** Alffenaar J-WC, Tiberi S, Cirillo DM, *et al*. Intermittent regimens for tuberculosis treatment: Back to the Future? *Eur Respir J* 2020; 56: 2002510 [https://doi.org/10.1183/13993003.02510-2020].

Despite all efforts to accelerate the response against tuberculosis (TB), many countries are struggling to achieve the milestones of the End TB strategy [1]. The investment required in a strong healthcare system to combat TB is significant. Lack of a short and highly active sterilising TB treatment regimen is the main reason for treatment failure and emergence of drug resistance [2]. With increasing drug resistance, the treatment becomes longer and more difficult to manage due to use of more toxic and less active drugs. Although treatment management is focused on prevention of adverse drug reactions, most patients will experience drug toxicity during treatment [3] which can result in nonadherence.

Optimisation of TB treatment is key to reducing the global burden of TB. Attempts have been made to shorten the current treatment for drug susceptible TB, consisting of isoniazid, rifampicin, pyrazinamide and ethambutol, by adjusting the first line regimen. Replacing ethambutol with moxifloxacin did not result in the foreseen shortening of treatment from 6 months to 4 months [4]; explanations may be low moxifloxacin drug exposure due to rifampicin drug–drug interaction [5] or lack of penetration in caseous lesions [6]. It is expected that shortening of TB treatment is possible in well-defined patients (without cavities and of female gender). Using a combination of moxifloxacin and rifapentine in a 4-month regimen was not non-inferior to the standard first line regimen either [7]. Optimisation of the dosing of the first line drugs has shown favourable results for rifampicin [8], but final results of phase III studies are still pending.

Besides dose optimisation and attempts to replace less-active drugs in regimen with those that are more active, other approaches have been trialled to optimise treatment. Simple regimens requiring less frequent dosing to increase adherence and make direct observation of treatment easier have been studied for the first line regimen. It was shown that thrice-weekly intermittent dosing schedules were associated with increased risk of acquired drug resistance [9], which made the World Health Organization (WHO) decide

Received: 26 June 2020 | Accepted: 26 June 2020

to not recommend these regimens. The acquired resistance could be explained by the fact that suppression of resistance was associated with the rifampicin free peak concentration-to-minimal inhibitory concentration (MIC) ratio exceeding 175 [10]. This can only be achieved at a much higher dosage than traditionally used in first line treatment. The use of a second agent to protect rifampicin is therefore of critical importance. Isoniazid has fulfilled this role as part of the continuation phase of treatment but, despite the combination of rifampicin and isoniazid, acquired resistance still occurs [11]. The complex isoniazid concentration dependent prevention of acquired resistance is partly the underlying problem [12]. As both rifampicin and isoniazid show a considerable variability in drug exposure, personalised dosing could be a solution to overcome the problems experienced with intermittent treatment. However, this would be highly unpractical as tools are not readily available [13, 14].

With the recent introduction of new anti-TB drugs like bedaquiline [15], delamanid [16] and pretomanid [17], new highly active drugs have become available to treat TB [18]. Although the new drugs are currently registered for drug-resistant TB, the drugs are trialled for shortening treatment for drug-susceptible TB as well (see trial registered at clinicaltrials.gov as NCT03338621). This would make the step towards the design of a pan-TB treatment regimen easier [19]. Since pharmacokinetics and pharmacodynamics have played a more prominent role in TB drug development, the selection of the combination of drugs and their corresponding dosages is more scientifically based than in the past [20]. This will hopefully prevent the introduction of suboptimal dosages of anti-TB drugs in future regimens. Kort *et al.* [21] present the findings of their study in which they tested their hypothesis that a once weekly regimen containing bedaquiline, rifapentine and pyrazinamide (figure 1), with or without moxifloxacin or moxifloxacin and clofazimine, has a sterilising activity. The core bactericidal drugs of the regimen, bedaquiline and rifapentine, have both a long half-life and their efficacy is driven by area under the concentration time curve (AUC) to MIC ratio [22, 23]. The most important finding from their study was that the relapse rate of the experimental once-weekly regimen was significantly lower assessed at 3 months after completion of a 4- or 6-month treatment regimen compared to standard first line treatment [21].

How to translate the results from this preclinical study to clinical practice is an important question. First, as the efficacy of bedaquiline and rifapentine was related to AUC/MIC, the drug exposure in the animal model mimicking the human exposure of the drug needs to be confirmed. In this study the drug–drug interaction between rifapentine and bedaquiline present in humans was mimicked by dose reduction of

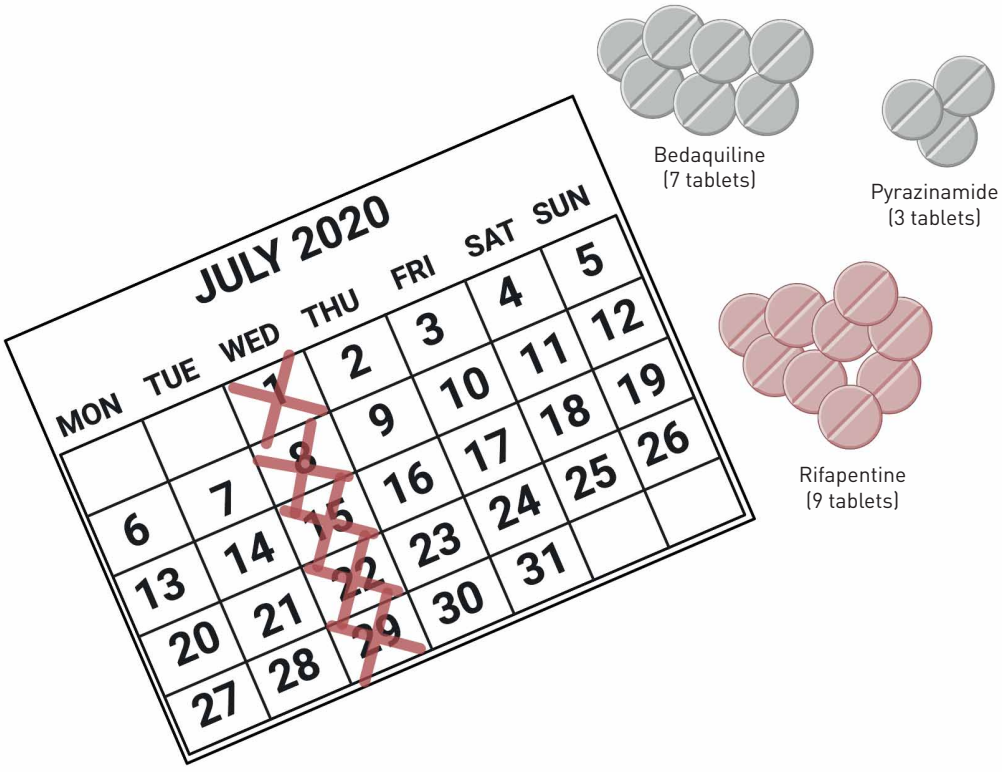


FIGURE 1 Once weekly bedaquiline, rifapentine and pyrazinamide regimen. Artwork by Anne-Grete Märtson.

bedaquiline. Rifapentine is considered a strong inductor of CYP3A4 [24], while bedaquiline is a substrate [25] resulting in a considerable reduction of AUC of approximately 75%. Although adjusting bedaquiline dose may be considered appropriate, the actual assessment of drug exposure would have been preferred [26]. Second, the preclinical model should resemble the mode of TB disease and relapse rate as seen in humans to be informative for future trial design for the experimental regimen in humans. Use of the appropriate *Mycobacterium tuberculosis* strain, inoculum and route of infection are equally important to produce relevant results. Use of a control group receiving the standard treatment regimen including isoniazid, rifampicin and pyrazinamide is important for the validity of the results with respect to translation to humans. Third, drug safety will be different in humans than in animals due to underlying clinical condition and co-morbidities and co-administered drugs. When drugs are evaluated in clinical trials, safety of participants is assured by scheduled assessments of critical parameters, as well as a system for reporting of adverse events. In real-life, drug safety assurance is a considerable issue, as resources for assessment are less compared to clinical trials. The introduction of active drug safety monitoring in daily practice has been successfully implemented to evaluate the frequency and severity of adverse events of new drugs like bedaquiline [27]. As Kort *et al.* [21] rightfully mention, the tested regimen including bedaquiline, clofazimine and moxifloxacin may not be a treatment regimen that fits all patients due to the increased risk of QT prolongation [28]. As more data is collected on both individual drugs and on their combinations, a patient-centred approach will likely be a solution [29, 30].

Kort *et al.* [21] have shown that once weekly bedaquiline, rifapentine and pyrazinamide has sterilising activity and is ready for further exploration in a clinical trial including appropriate safety and pharmacokinetic assessment.

Acknowledgements: The project is part of the activities of the Global Tuberculosis Network (GTN) and of the WHO Collaborating Centre for Tuberculosis and Lung Diseases, Tradate, ITA-80, 2017-2020- GBM/RC/LDA. The authors wish to thank Anne-Grete Märtson for her editorial assistance and for preparing the artwork for figure 1.

Conflict of interest: None declared.

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