Treatment for tuberculosis due to sensitive strains: To shorten or not to shorten?

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The discovery of antibiotics is one of the greatest achievements of modern medicine and remarkably most bacterial infections can be cured with a few days of a single effective antibiotic. However, tuberculosis (TB) is an exception to this rule for two reasons[1]. First, a combination of drugs is necessary in order to kill all the different populations of *Mycobacterium tuberculosis* (MTB) which manage to survive in the different microenvironments present within the same host and also in order to avoid emergence of resistance. Second, a minimum of 6 months of treatment is necessary to reduce the percentage of relapses at acceptable levels[2].

The so-called 'short course' 6-month regimen used today is the result of a long line of trials starting after the Second World War. Streptomycin, the first anti-tuberculosis drug to be introduced (in 1946), was shown to lead to spectacular improvement in radiology and bacteriology[3]. Unfortunately, 5 years after treatment, mortality was similar between patients who had received treatment and those who had not, due to emergence of resistance. Para-aminosalicylic acid and the wonder-drug isoniazid (H) were the next steps in TB treatment and a combination of all the 3 known-at-the-time drugs was used to avoid resistance. The discovery of rifampicin (R) and pyrazinamide (Z) in the 1960s shortened treatment time from 18–24 months to 6–9 months rendering possible all oral regimens – also using ethambutol (E) – with limited side effects[3]. The social impact of this evolution was not negligible since the sanatoria were no longer needed and ambulatory treatment was possible[4]. The 6-month regimen used today – 2HRZE/4HR – was shown to be more effective than an 8-month combination with 6 months of EH in the continuation phase, in 2004[5].

Shortening the 'short course' regimen has been a major goal ever since. In 2009, Johnson et al.[6] investigated the possibility of shortening the standard TB treatment to 4 months in a subgroup of patients with non-cavitary tuberculosis. After 4 months of standard treatment, patients who were sputum culture negative at the 8th week were randomized to stop treatment at 4 months or continue for an additional 2 months, and were followed for 30 months after treatment initiation. Enrollment was discontinued at 394 patients when an increased risk was observed at the 4-month arm (7% vs 1.6% in the control 6-month arm)[6]. The same two points – cavitation at treatment initiation and sputum culture at 2 months of treatment – were used as risk factors in a retrospective study which showed that the combination of these two variables was associated with an increased risk of relapse after 6 months of treatment, with on OR of 15.56[7]. Although relapse was observed in 1.9% of the total of 317 patients in the 1st year after treatment, the rate increased to the unacceptable percentage of 18.2% when both risk factors were present[7]. This is the basis behind the ATS/CDC/IDSA recommendation of prolonging treatment to 9 months in cases of cavitary TB with a positive culture at 2 months[2]. The ATS/CDC/IDSA guidelines further advise to consider prolongation of treatment if one of these two factors is present or other indications of severe disease, such as HIV or diabetes, exist[2]. In this way the ATS/CDC/IDSA guidelines underline that the convenient one-size-fits-all approach may not be beneficial for all patients.

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The expectations of shortening TB treatment to 4 months were raised when the prominent bactericidal and sterilizing activity of fluoroquinolones against mycobacteria was discovered. In 2014 three randomized, double-blind, placebo-controlled, phase-3 trials were published, all in the New England Journal of Medicine[8-10]. In the studied regimens either H or E were replaced by a quinolone – moxifloxacin or gatifloxacin – and the standard 6-month regimen was used in the control arm. Unfortunately, non-inferiority of the 4-month regimen was not proven in any of the studies due to the remarkably higher recurrence rate in the experimental arms. The reason behind this observation is the difficulty to effectively address the subpopulation of mycobacteria which survive in hypoxic environments by switching to a state of low metabolism and are responsible for relapse[11]. Despite initial estimates that moxifloxacin and gatifloxacin could shorten TB regimens based on *in vitro* and animal studies, it was established that the inclusion of fluoroquinolones alone was not sufficient for TB regimen shortening, for a number of reasons such as the unsuitability of animal models and the fact that 800 mg of moxifloxacin instead of the standard 400 mg were needed for an effective kill of mycobacteria[11]. Most importantly, Prideaux et al.[12] showed that the penetration of moxifloxacin in the hypoxic pulmonary sites in TB patients is marginal compared to rifampicin. In other words, addition of moxifloxacin to the regimen is not enough to replace 2 months of rifampicin.

The patients included in the 4 randomized 4-month trials described above – three investigating quinolones[8-10] and one by Johnson[6] – were individually analyzed by Imperial et al.[13] in 2021 in order to identify patient characteristics that can safely predict the duration of TB treatment necessary for relapse-free cure[13]. The authors used 6 baseline parameters – HIV status, body mass index, acid-fast bacilli smear grade, gender, presence of cavitation at initiation, and culture status at month 2, in order to allocate patients into three risk groups. The lowest risk group, consisting of 23% of patients, showed excellent outcomes with 4 months of treatment. For the moderate risk group, consisting of 48% of patients, 6 months (but not 4 months) of treatment were sufficient. However, for the high-risk group, with the remaining 29% of patients, neither 4 nor 6 months of treatment appeared to be sufficient; possibly for these patients a longer duration was necessary[13]. There are two key messages from this study. First, it becomes quite clear that one size does not fit all in tuberculosis treatment and despite the fact that this is difficult to address in a low-income setting when cultures or stains may be unavailable, it cannot be overlooked in high income settings where nearly half of patients may receive regimens shorter or longer than standard. Second, instead of identifying patients who can safely receive shorter regimes, it is far more important to look for patients for whom the 6-month standard-of-care regimen is not enough[14]. Algorithms along with clinical experience are very useful in this direction, underlining the fact that guidelines can serve as advice or suggestions, but cannot entirely replace clinical judgment in the everyday medical practice.

Regarding children, a population with low bacterial load, Turkova et al.[15] showed that a 4-month regimen with rifampicin – 2RHZ(E)/2RH – is sufficient for children under 16 years old with sputum-negative TB that was non-severe, that is: a) pulmonary TB confined to one lobe with no cavitation or military pattern, no complex pleural effusion, no significant airway obstruction, no bilateral airway narrowing; or b) peripheral lymphnode TB. This trial led to new guidelines, by WHO[16], for the treatment of TB in children.

The next chapter in the history of TB treatment was written in 2021 when the study by Dorman et al.[17] was published. In this open-label, randomized, phase-3, controlled-trial two 4-month rifapentine (Rpt)-based regimens, one including moxifloxacin and one not, were compared to the standard 6-month regimen, for patients aged ≥12 years with pulmonary TB. The regimen consisting of Rpt (1200 mg), moxifloxacin 400 mg, H and Z for 8 weeks, followed by Rpt, moxifloxacin and H for another 9 weeks, was shown non-inferior to the standard regimen regarding the primary endpoint which was survival free of TB at 12 months from randomization. Rpt is a derivative of R, active against MTB. Its longer half-life increases the duration of exposure and maintains administration once daily. The absorption of Rpt increases with food[17]. Based on this study, WHO[18] and CDC[19] have issued new guidelines for TB treatment irrespective of disease severity. The impact of the two studies, described above, for children and adults is enormous since TB treatment becomes less cumbersome and possibly more cost-effective and the implications of this change can be significant, especially in high-incidence countries. The recommended and recently studied regimens are presented in Table 1.

On the other hand, Rpt is expensive and not available in Europe and intake with food may lead to adherence issues[1]. Furthermore, the inclusion of a widely administered drug such as moxifloxacin in the anti-TB regimen may pose several threats. First, resistance of MTB to moxifloxacin may exist due to its widespread use[1]. In order to overcome this obstacle, the CDC recommends that clinical consultation be obtained to determine if the regimen is an acceptable option for patients who had received more than 5 doses of any fluoroquinolone in the 30 days preceding treatment initiation and advises the performance of a baseline molecular drug sensitivity test to all 4 drugs of the regimen[19]. Second, in low-income, high-incidence countries where quinolones are not widely used, administration of this class of antibiotics for TB may promote resistance in other bacteria, therefore compromising their use in other infections[1].

Despite these pitfalls, it seems that the development of new shorter regimens is accelerated. The regimen with Rpt and moxifloxacin is the first to prove its effectiveness but many other options are being studied, such as R in high doses or drugs currently used for multi-drug resistant

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Table 1. Recommended and recently studied regimens for drug-sensitive tuberculosis (TB)

Regimen	Comment
2RHEZ/4-7RH	Recommended for pulmonary TB in countries where Rpt is not available, all ages[2,16] Recommended for extrapulmonary TB, all ages[2,16]
2RHEZ/2RH	Studied in adults who were sputum culture negative at 8 weeks, with no cavitation and failed[6]
2RHMZ/2RHM	Studied in adults with pulmonary TB and failed[8]
2RMEZ/2RM	Studied in adults with pulmonary TB and failed[8]
2RHGZ/2RHG	Studied in adults with pulmonary TB and failed[9]
2RMEZ/2Rpt*M (2 per week)	Studied in adults with pulmonary TB and failed[10]
2RMEZ/4RptM (1 per week)	Studied in adults with pulmonary TB and was shown non-inferior to 2RHEZ/4RH[10]
2RptHMZ/2RptMH	Recommended for pulmonary TB in patients aged ≥12 years[16,18,19]
2RH(E)Z/2RH	Recommended for children with pulmonary TB aged >3months and <16 years with non-severe pulmonary TB and peripheral node TB[16]

R: rifampicin. H: isoniazid. E: ethambutol. Z: pyrazinamide. M: moxifloxacin. G: gatifloxacin. Rpt: rifapentine at 1200 mg. Rpt*: rifapentine at 900 mg.

(MDR)-TB treatment[20]. In that sense, regimens for TB due to sensitive strains seem to follow the example of shorter regimens which have been recently introduced in the treatment of both latent[21] and MDR-TB[22]. Indeed, Rpt is currently used for the treatment of latent TB at a dose of 900 mg (instead of 1200 mg for active TB) along with H at 15 mg/kg once weekly for 12 doses[21].

TB is not a disease of the past and this is clearly shown by the fact that it is currently the second cause of death due to an infectious agent worldwide, the first being COVID-19. Moreover, TB treatment, 76 years after the introduction of the first anti-TB drug, continues to evolve. However, despite the remarkable changes in all fields of TB treatment (latent TB, TB due to sensitive strains, and MDR-TB), the main principles of treatment – combination of drugs for active disease and long duration – remain stable. Clinicians (and countries) need to keep up with these changes and assess the patients' response to treatment in order to make safe decisions regarding its duration.

CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none was reported.

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DATA AVAILABILITY

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DISCLAIMER

The views and opinions expressed in this article are those of the authors.

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