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Hot Topic

World Health Organization 2018 treatment guidelines for rifampicin-resistant tuberculosis: uncertainty, potential risks and the way forward

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ABSTRACT

The 2018 World Health Organization (WHO) treatment guidelines for multidrug-/rifampicin-resistant tuberculosis (MDR/RR-TB) give preference to all-oral long regimens lasting for 18–20 months. The guidelines strongly recommend combining bedaquiline, levofloxacin (or moxifloxacin) and linezolid, supplemented by cycloserine and/or clofazimine. The effectiveness of this combination in a long regimen has not been tested in any study to date, with corresponding uncertainty. The guidelines indicate that, ideally, all MDR-TB patients should have – as a minimum – the isolate tested for fluoroquinolones, bedaquiline and linezolid susceptibility before the start of treatment. Unfortunately, the capacity for drug susceptibility testing is insufficient in resource-limited settings. The risk of acquired bedaquiline resistance cannot be ignored, especially in patients with undetected resistance to fluoroquinolones. Both linezolid and cycloserine are known for their high frequency of serious adverse events. The combination of bedaquiline, moxifloxacin and clofazimine in the same regimen may excessively increase the QT interval. These expected adverse effects are difficult to monitor and manage in resource-limited settings, and may result in frequent modifications and a less effective regimen. The final STREAM results have confirmed the non-inferiority of the short regimen compared with the long regimen. Before evidence on the all-oral long and modified all-oral short treatment regimens is available, the WHO-recommended short MDR-TB regimens, with monitoring for ototoxicity, remain a better treatment option for the management of MDR/RR-TB patients who are eligible for short regimens in low- and middle-income countries. National tuberculosis programmes should also strengthen their capacity in the detection and management of fluoroquinolone-resistant MDR-TB following the WHO guidelines.

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The 2018 World Health Organization (WHO) treatment guidelines for multidrug-/rifampicin-resistant tuberculosis (MDR/RR-TB) give preference to all-oral long regimens lasting for 18–20 months. Injectable agents are no longer among the priority medicines. The guidelines recommend that long MDR-TB regimens should include at least four agents likely to be effective in the first 6 months, and three agents thereafter. The guidelines strongly recommend the use of bedaquiline, levofloxacin (or moxifloxacin) and linezolid, supplemented by cycloserine and/or clofazimine [1].

The recommendations on long MDR-TB regimens were informed by a meta-analysis using data from patients with pulmonary MDR-TB [2]. Individual drugs identified by the meta-analysis as most effective are recommended to constitute the

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backbone of the long regimens [1]. Taking patient history and drug susceptibility testing (DST) results into account, a regimen may be standardized or individualized. In addition to rapid molecular DST for rifampicin, isoniazid and fluoroquinolones, national programmes are recommended for countries with a high MDR/RR-TB burden to develop the capacity to conduct phenotypic DST for – at least – bedaquiline and linezolid. Patient-centred support for medication adherence and active drug safety monitoring and management are emphasized [3,4].

The WHO guidelines indicate that a regimen of 9–12 months may be used instead of a long regimen in MDR/RR-TB patients who have not been treated for more than 1 month with second-line medicines used in the short MDR-TB regimen, or in whom resistance to fluoroquinolones and second-line injectable agents has been excluded. The short regimen applied in stage I of the STREAM trial consisted of moxifloxacin, ethambutol, clofazimine and pyrazinamide throughout, supplemented by isoniazid, kanamycin and prothionamide in the intensive phase [5]. The WHO guidelines recommend amikacin instead of kanamycin, and warn that short regimens may be less effective than long regimens. Operational studies on modified short regimens with bedaquiline replacing the injectable are encouraged [1].

This paper reviews the evidence base for the new WHO guidelines and highlights important challenges in the use of long MDR-TB regimens [6]. It is proposed that short MDR-TB regimens, especially if gatifloxacin-based [7], are – unlike the proposed all-oral long regimens – evidence-based safe and effective options for the management of MDR/RR-TB in resource-limited settings.

1. Uncertain effectiveness of long regimens

This updated WHO recommendation [1] signifies a dramatic change from previous recommendations published in 2011 and 2016, which emphasized the use of injectable agents for 8 months [8,9]. The composition of the long regimen relies on the anticipated effectiveness of individual drugs under the assumption that the combined use of sufficiently effective medicines would maximize the likelihood of relapse-free cure. However, the effectiveness of the proposed combination of these individual drugs in a long regimen has not been tested in any study to date, and therefore remains hypothetical. Neither the specific bactericidal and sterilizing activity of drugs nor their toxicities seem to have been taken into account sufficiently to build an effective, safe and easy-to-use regimen [6]. Thus, implementation of the recommendation remains dependent on MDR-TB specialists.

While the efficacy of fluoroquinolones, bedaquiline and linezolid has been reported previously, it is difficult to conceive how cycloserine could emerge as a highly effective drug at the usual low dose. High activity was shown with high, probably too toxic, dosing alone [10], or as part of a regimen also including pyrazinamide and prothionamide [11]. Its DST has always failed to yield consistent interlaboratory results, a characteristic of any weak drug (e.g. ethambutol) [12]. Given their uncertain effectiveness, potential toxicity and long treatment duration, the newly recommended long regimen may not be able to considerably improve treatment outcomes of patients with MDR/RR-TB in resource-limited settings.

2. One or two core drugs

The new long WHO regimen uses two core drugs in a single regimen: a newer generation fluoroquinolone plus bedaquiline [1]. Besides rifampicin, these are likely to be the only two anti-TB drugs currently known to have both the necessary high bactericidal and sterilizing power to drive the effectiveness of a TB treatment regimen [6]. The use of two core drugs in one regimen may result in a considerable level of treatment success. However, like any treatment regimen, it cannot be successful in every patient. Acquired resistance to bedaquiline may develop, particularly in patients with undetected resistance to fluoroquinolones. The WHO guidelines indicate that, ideally, all MDR-TB patients should have – as a minimum – the isolate tested for fluoroquinolone susceptibility before the start of treatment, but they also acknowledge that capacity for DST may be lacking [1]. Given that DST capacity in resource-limited settings is insufficient and resistance to fluoroquinolones may not be detected, the risk of acquired bedaquiline resistance in fluoroquinolone-resistant pre-extensively-drug-resistant TB cannot be ignored. Indeed, high proportions of acquired bedaquiline and linezolid resistance were observed in patients treated with the combination (group A drugs plus cycloserine) that is now recommended [13].

3. Toxicity of the new long WHO regimen

The main role of the companion drugs is to protect the core drug from acquiring resistance and to help minimize the risk of relapse [14]. The choice of companion drugs must also take toxicity into account [6]. Both linezolid and cycloserine are known for their high frequency of serious adverse events: myelosuppression and neuropathy for linezolid; and psychiatric and other central nervous system adverse events for cycloserine, at times fatal [15–17]. Moreover, the combination of bedaquiline, moxifloxacin and clofazimine in one regimen may excessively increase the QT interval [18]. Therefore, implementation of active drug safety monitoring and management is crucial, which is not an easy task in low- and middle-income countries. These expected adverse effects will unavoidably lead to treatment interruptions – periods during which patients will essentially receive bedaquiline monotherapy, given its long half-life. This carries the risk of acquisition of bedaquiline resistance. Clinicians will have to individualize the regimen and replace the culprit by another 'likely active' drug. However, lessons from the past show that programmatic outcomes are poor when 'likely effective' drugs are 'lumped' together to constitute an individualized long MDR-TB treatment regimen [19]. Modified regimens may lack either bactericidal or sterilizing power, and allow the acquisition of resistance to the core drug used. Consequently, the anticipated effectiveness of the currently proposed new long WHO regimen may be considerably reduced.

4. The role of injectables

The complete retraction of injectables because of ototoxicity requires careful reconsideration. Normal hearing is critical to the quality of life, and any impairment undermines it considerably. Inherited mitochondrial DNA mutations may cause increased susceptibility to aminoglycoside-induced hearing loss. Although these mutations are rare [20,21], severe hearing impairment has been reported to occur among patients treated for MDR-TB with injectable drugs, especially among the elderly and patients infected with human immunodeficiency virus [22–24]. However, nowadays, the cumulative amount of injectables taken, which is strongly correlated with ototoxicity [25,26], is considerably reduced. Following the roll-out of Xpert MTB/RIF, resistance to rifampicin is rapidly identifiable [27], especially among patients who have been treated previously for TB who otherwise would have received a streptomycin-strengthened retreatment regimen [28]. The frequency of second-line-injectable-induced severe hearing impairment will be reduced further once that particular regimen has been phased out [28].

The risk of hearing impairment can be mitigated considerably by careful audiologic monitoring and adapted duration of injectable agents. Hearing impairment caused by injectable agents usually begins with hearing loss confined to the high frequencies due to hair cell damage in the lower basal turn of the cochlea [29].

Audiologic monitoring for ototoxicity may detect early changes in the hearing threshold, and therefore allow the injectable agents to be stopped before progression to damage in the lower frequencies of the human speech range. Patients with baseline hearing loss or who experience mild ototoxicity during treatment may be switched to modified short treatment regimens, replacing the injectable with new or repurposed drugs. Several types of screening audiometers that do not need a sound-proofed room are available [30]. Ototoxicity seems to be more manageable than bone marrow, neuro- and cardiotoxicity in patients treated with the new long WHO regimen in resource-limited settings.

The meta-analysis on which the 2011 WHO guidelines were based showed that outcomes improved with the use of injectables up to 8 months [19]. The 2018 meta-analysis assessed factors associated with treatment success and mortality, and reported that kanamycin and capreomycin were not associated with positive outcomes [2]. While injectables are unlikely to cure TB, their bactericidal activity against actively dividing bacilli makes them more effective than other mainly bacteriostatic companion drugs [31]: they allow eradication of mutants resistant to the core drug, and thus play an important role in assisting the prevention of failure due to acquired resistance. It is regrettable that the meta-analysis did not assess prevention of resistance acquisition to judge the activity and potential role of the injectables [2].

Amikacin might be more efficacious than other second-line injectables [32], but it is also known for its painful injections that may lead to refusal by the patient. Nearly all of the cohorts that used amikacin included in the meta-analysis were from affluent countries, where the drug is commonly given intravenously. The meta-analysis revealed that kanamycin was not associated with worse outcomes within low- or middle-income countries [2]. Furthermore, Cegielski *et al.*, assessing acquired resistance to fluoroquinolones during treatment of MDR-TB in nine countries, reported that resistance to kanamycin mattered. Acquired resistance to fluoroquinolones occurred in 37% of patients with baseline resistance to kanamycin, compared with 6% of patients without baseline resistance to kanamycin [33]. Kanamycin administered at an increased dose three times per week is likely to be equally effective but less toxic than the normal daily dose [34,35].

5. Short regimen is non-inferior under clinical trial conditions

The WHO guidelines make the short regimen optional (leaving the choice to the individual patient and physician), and questionably present it as a less effective treatment compared with the long regimen [2].

Although some definitions of unfavourable treatment outcomes may have favoured the long regimen [5], the final STREAM analysis has confirmed the non-inferiority of the short regimen compared with the long regimen [36], rendering the statement 'the short regimen is less effective than an individualized long regimen' unfounded. In the STREAM trial, the post-treatment follow-up period for patients treated with the short regimen was almost twice as long compared with that for the long regimen, and therefore provides a longer period during which relapse can be notified and absconding may occur. Furthermore, extension of treatment is an unfavourable outcome that is more likely to occur in patients on a short regimen than after an exhaustingly long regimen. A surprising finding of the STREAM trial was the excellent performance of the long regimen, contrary to the expectations of the investigators who had calculated the required sample size on the basis of globally reported average outcome proportions [5,19]. Nevertheless, the difference using a modified intention-to-treat efficacy endpoint was only 1% in favour of the long regimen (not statistically significant). Furthermore, in the per-protocol analysis, the difference was slightly in favour of the short regimen [36].

6. Clinical trial vs real life

The main reason for the better-than-expected performance of the long regimen in the STREAM trial probably lies in the experimentally controlled and thus artificial setting of a clinical trial providing tight control of follow-up and support above what will be available in a real-life programme setting, where many patients with gross irregularity would usually never return and could not be retrieved by staff. It has long been known that the power of a regimen that is not sufficiently sturdy may be lost during implementation. For instance, the old WHO standard 12-month isoniazid, thioacetazone and streptomycin regimen was shown to cure 92% of patients in a clinical trial [37], yet was associated with excessive loss-to-follow-up, failure, relapse and acquired resistance when implemented in programmes all over the world [14,38], very similar to what is reported for the long MDR regimen [39]. In contrast, the STREAM trial has confirmed the high success of the short regimen reported from the field, as shown by its results falling very close to the estimates used for the sample size calculation [5].

7. Limitations of the long–short comparative meta-analysis

Apart from data from the STREAM trial, the meta-analysis used to inform the new WHO guidelines was based on data from a large number of observational cohorts. Sophisticated statistical methods were applied to compare outcomes of short vs long regimens [1]. However, nearly all patients treated with the short regimen came from low- or middle-income settings, whereas most of those treated with the long regimen came from high–midle-income and high-income countries. Data from patients treated with a short regimen were retrieved from 15 countries, and represented the reality of most MDR-TB patients treated with the short regimen in a country or a region, whereas cohorts of patients treated with the long regimen were almost all from centres of excellence in 39 countries where access to laboratory tests, drug supply and supportive clinical care meet much higher standards than those in low-income settings [1]. In the face of these striking differences between the two study populations, it is difficult to assume that the calculated difference in the probability of treatment success between the two groups is generalizable to real-life MDR-TB programmes in high-burden settings.

Loss to follow-up from treatment was the only significantly different outcome in the meta-analysis, and was clearly lower for the short regimen [odds ratio (OR) 0.2, 95% confidence interval (CI) 0.2–0.3] [1]. For years, a relatively high proportion of patients lost to follow-up has been reported as one of the main challenges in the management of MDR/RR-TB [39]. Nevertheless, the long regimen was recommended because of a non-significant higher risk of failure/relapse with the short regimen (OR 2.0, 95% CI 0.96–4.00) [1]. In affluent countries, long regimens are invariably individualized and failure is not declared early at a pre-defined time, as for the short regimen. In some studies, failure may rarely be declared, as clinicians modify regimens until treatment outcome becomes cure, death or default. The risk of failure/relapse with the long regimen may therefore have been underestimated in the studies compared.

8. Challenges in resource-limited settings

In high-income settings, an individualized treatment regimen can be most effective because it can be applied under ideal conditions [40]. This will rarely be the case in low-income countries. The composition of the new long WHO regimen will need to fit many preconditions and will require adaption to frequent – and often serious – adverse events, so 'standardized regimen' may lose its

meaning. The recommended long regimen, with which not a single patient has been reported to have been treated to date, is likely to cause more serious adverse events than the one it is intended to replace. This may very well result in a lower-than-expected level of effectiveness. The conditions for its use are too complex to be met in low- and middle-income countries, where it may not be any better than the currently used long regimens with a reported success rate of 55% [39]. This would be disastrous because of the introduction of resistance to not one but two core drugs, leaving almost no further treatment options in resource-limited settings.

9. Short regimen for high-burden countries

The underlying thrust in the development of the short regimen was to provide countries with a high burden of RR-TB with a regimen that is effective for most patients, and easy to use despite limited resources [41]. This allows fast and complete coverage of the population and ensures long-term sustainability. Unfortunately, the current guidelines indicate that the short regimen should not be used if there is confirmed resistance or suspected ineffectiveness to any medicine used in the short MDR-TB regimen (apart from isoniazid), complicating its use considerably. This recommendation was not based on the evidence generated by the original studies [1,42]. Furthermore, the recommendation to switch from kanamycin to amikacin in the short regimen is based on a meta-analysis that only considered patients on the long regimen and only one aspect of activity of injectable agents. Combined with a powerful core drug (i.e. high-dose gatifloxacin), maximum protection against acquired resistance may have been achieved already by kanamycin, and cannot be improved upon by a switch to amikacin [14].

Although the moxifloxacin-based short regimen was non-inferior to the long regimen, a gatifloxacin-based short regimen would likely perform even better. The frequency of failure, relapse and acquired fluoroquinolone resistance of a moxifloxacin-based short regimen is higher than with a gatifloxacin-based regimen [22,43,44]. To improve the short regimen, it will be crucial to re-introduce high-dose gatifloxacin as the fluoroquinolone of choice for the suppression of often undetected heteroresistance [45] and low-level fluoroquinolone-resistant mutants [46]. Reserving bedaquiline as a replacement for gatifloxacin in the short regimen, based on rapid DST at the start of treatment, will assure successful outcomes for patients with fluoroquinolone-resistant TB and will support prolonged usability of both gatifloxacin and bedaquiline as core drugs.

In conclusion, a combination of efficacious drugs derived from an analysis of individual drugs instead of the combination of these drugs in a regimen may not necessarily result in high treatment success of an MDR-TB treatment regimen [14]. Studies to assess the effectiveness of the recommended long regimens in resource-limited settings are needed urgently. Given the inclusion of toxic companion drugs for a prolonged treatment period in combination with two core drugs, the performance of long MDR-TB regimens remains uncertain. Before evidence on the all-oral long and modified all-oral short treatment regimens is available, the WHO-recommended short MDR-TB regimens, with monitoring for ototoxicity and early switch to new or repurposed drugs, remain a better treatment option for the management of MDR/RR-TB patients who are eligible for short regimens in low- and middle-income countries. National tuberculosis programmes should also strengthen their capacity in the detection and management of fluoroquinolone-resistant MDR-TB following the WHO guidelines.

Declarations

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References

[1] World Health Organization. WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis. 2018 update. [Pre-final text] Geneva: WHO; 2018. WHO/CDS/TB/2018.15.
[2] Ahmad N, Ahuja SD, Akkerman OW, Alffenaar J-WC, Anderson LF, Baghaei P, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018;392:821–34.
[3] World Health Organization. Frequently asked questions on the WHO rapid communication: key changes to the treatment of multidrug- and rifampicin-resistant TB, Geneva: WHO; 2018. WHO/CDS/TB/2018.18.
[4] World Health Organization. Active tuberculosis drug-safety monitoring and management (aDSM). Framework for implementation. WHO/HTM/TB/2015.28. Geneva: WHO; 2015.
[5] Nunn AJ, Rusen ID, Van Deun A, Torrea G, Phillips PPJ, Chiang C-Y, et al. Evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (STREAM): study protocol for a randomized controlled trial. Trials 2014;15:353.
[6] 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.
[7] Chiang C-Y, Van Deun A, Rieder HL. Gatifloxacin for short, effective treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2016;20:1143–7.
[8] World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. 2011 update, Geneva: WHO; 2011. WHO/HTM/TB/2011.6.
[9] World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis. 2016 update, Geneva: WHO; 2016. WHO/HTM/TB/2016.04.
[10] Deshpande D, Alffenaar J-WC, Köser CU, Dheda K, Chapagain ML, Simbar N, et al. D-cycloserine pharmacokinetics/pharmacodynamics, susceptibility, and dosing implications in multidrug-resistant tuberculosis: a Faustian deal. Clin Infect Dis 2018;67(Suppl. 3):S308–16.
[11] Bignall JR, Lind A, Rist N. A comparison of regimens of ethionamide, pyrazinamide and cycloserine in re-treatment of patients with pulmonary tuberculosis. Bull Int Union Tuberc 1969;42:7–57.
[12] Hillemann D, Hoffner S, Cirillo D, Drobniewski F, Richter E, Rüsch-Gerdes S. First evaluation after implementation of a quality control system for the second line drug susceptibility testing of *Mycobacterium tuberculosis* joint efforts in low and high incidence countries. PLoS One 2013;8:e76765.
[13] Zimenkov DV, Nosova EY, Kulagina EV, Antonova OV, Arslanbaeva LR, Isakova AI, et al. Examination of bedaquiline- and linezolid-resistant *Mycobacterium tuberculosis* isolates from the Moscow region. J Antimicrob Chemother 2017;72:1901–6.
[14] Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council Tuberculosis Units, 1946–1986, with relevant subsequent publications. Int J Tuberc Lung Dis 1999;3(Suppl. 2):S231–79.
[15] Hwang TJ, Wares DF, Jafarov A, Jakubowiak W, Nunn P, Keshavjee S. Safety of cycloserine and terizidone for the treatment of drug-resistant tuberculosis: a meta-analysis. Int J Tuberc Lung Dis 2013;17:1257–66.
[16] Agyeman AA, Ofori-Asenso R. Efficacy and safety profile of linezolid in the treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis: a systematic review and meta-analysis. Ann Clin Microbiol Antimcrob 2016;15:41.
[17] Lee M, Lee J, Carroll MW, Choi H, Min S, Song T, et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. N Engl J Med 2012;367:1508–18.
[18] Harausz E, Cox H, Rich M, Mitnick CD, Zimetbaum P, Furin J. QTc prolongation and treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2015;19:385–91.
[19] Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med 2012;9:e1001300.
[20] Rahman S, Ecob R, Costello H, Sweeney MG, Duncan AJ, Pearce K, et al. Hearing in 44–45 year olds with m.1555A to G, a genetic mutation predisposing to aminoglycoside-induced deafness: a population based cohort study. BMJ Open 2012;2:e000411.
[21] Vivero RJ, Ouyang X, Yan D, Du L, Liu W, Angeli SI, et al. Mitochondrial DNA mutation screening in an ethnically diverse nonsyndromic deafness cohort. Genet Test Mol Bioma 2012;16:1146–8.

[22] Trébucq A, Schwoebel V, Kashongwe Z, Bakayoko A, Kuaban C, Noeske J, et al. Treatment outcome with a short MDR-TB regimen among patients with rifampicin-resistant TB in nine African countries. Int J Tuberc Lung Dis 2018;22:17–25.
[23] Harris T, Bardien S, Schaaf HS, Petersen L, de Jong G, Fagan JJ. Aminoglycoside-induced hearing loss in HIV-positive and HIV-negative multidrug-resistant tuberculosis patients. S Afr Med J 2012;102:363–6.
[24] Peloquin CA, Berning SE, Nitta AT, Simone PM, Goble M, Huitt GA, et al. Aminoglycoside toxicity: daily versus thrice-weekly dosing for treatment of mycobacterial diseases. Clin Infect Dis 2004;38:1538–44.
[25] Sturkenboom MGG, Simbar N, Akkerman OW, Ghimire S, Bolhuis MS, Alffenaar JWC. Amikacin dosing for MDR tuberculosis: a systematic review to establish or revise the current recommended dose for tuberculosis treatment. Clin Infect Dis 2018;67(Suppl. 3):S303–7.
[26] Modongo C, Pasipanodya JG, Zetola NM, Williams SM, Sirugo G, Gumbo T. Amikacin concentrations predictive of ototoxicity in multidrug-resistant tuberculosis patients. Antimicrob Agents Chemother 2015;59:6337–43.
[27] van Cutsem G, Isaakidis P, Farley J, Nardell E, Volchenkov G, Cox H. Infection control for drug-resistant tuberculosis: early diagnosis and treatment is key. Clin Infect Dis 2016;62(Suppl. 3):S238–43.
[28] World Health Organization. Guidelines for treatment of drug-susceptible tuberculosis and patient care, Geneva: WHO; 2017. 2017 update. WHO/HTM/TB/2017.05.
[29] Seddon JA, Godfrey-Faussett P, Jacobs K, Ebrahim A, Hesseling AC, Schaaf HS. Hearing loss in patients on treatment for drug-resistant tuberculosis. Eur Respir J 2012;40:1277–86.
[30] Quelapio MID, Idrissova M, Dravniece G, et al. Audiometry in the management of drug-resistant tuberculosis. KNCV Tuberculosis Foundation; 2017. Available at: https://www.challengetb.org/publications/tools/pmdt/Audiometry_in_the_Management_of_Drug_Resistant_TB.pdf (last accessed 28 February 2019).
[31] Jindani A, Aber VR, Edwards EA, Mitchison DA. The early bactericidal activity of drugs in patients with pulmonary tuberculosis. Am Rev Respir Dis 1980;121:939–49.
[32] Heifets L, Lindholm-Levy P. Comparison of bactericidal activities of streptomycin, amikacin, kanamycin, and capreomycin against *Mycobacterium avium* and *M. tuberculosis*. Antimicrob Agents Chemother 1989;33:1298–301.
[33] Cegielski JP, Dalton T, Yagui T, Wattanamornkiet W, Volchenkov GV, Via LE, et al. Extensive drug resistance acquired during treatment of multidrug-resistant tuberculosis. Clin Infect Dis 2014;59:1049–63.
[34] Srivastava S, Modongo C, Siyambalapitiyage Dona CW, Pasipanodya JG, Deshpande D, Gumbo T. Amikacin optimal exposure targets in the hollow-fiber system model of tuberculosis. Antimicrob Agents Chemother 2016;60:5922–7.
[35] World Health Organization. Technical report on the pharmacokinetics and pharmacodynamics (PK/PD) of medicines used in the treatment of drug-resistant tuberculosis, Geneva: WHO; 2018. WHO/CDS/TB/2018.6.
[36] Nunn AJ, Phillips PP, Meredith SK, Chiang C-Y, Conradie F, Dalai D, et al. A trial of a shorter regimen for rifampicin-resistant tuberculosis. N Engl J Med 2019;380:1201–13.
[37] East African Hospitals Clinics and Laboratories, East African/British Medical Research Council A pilot study of two regimens of intermittent thiacetazone plus isoniazid in the treatment of pulmonary tuberculosis in East Africa. Tubercle 1974;55:211–21.
[38] Toman K. Tuberculosis case-finding and chemotherapy. Questions and answers. Geneva: World Health Organization; 1979.
[39] World Health Organization. Global tuberculosis report 2018. WHO/CDS/TB/2018.20. Geneva: WHO; 2018.
[40] Yu M-C, Chiang C-Y, Lee J-J, Chien S-T, Lin C-J, Lee S-W, et al. Treatment outcomes of multidrug-resistant tuberculosis in Taiwan: tackling loss to follow-up. Clin Infect Dis 2018;67:202–10.
[41] Van Deun A, Aung KJM, Halim MA, Kumar Das P, Ranjan Sarker M, Daru P, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J Respir Crit Care Med 2010;182:684–92.
[42] Van Deun A, Chiang C-Y. Shortened multidrug-resistant tuberculosis regimens overcome low-level fluoroquinolone resistance. Eur Respir J 2017;49:1700223.
[43] Piubello A, Hassane Harouna S, Souleymane MB, Boukary I, Morou S, Daouda M, et al. High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. Int J Tuberc Lung Dis 2014;18:1188–94.
[44] Aung KJM, Van Deun A, Declercq E, Sarker MR, Das PK, Hossain MA, et al. Successful "9-month Bangladesh regimen" for multidrug-resistant tuberculosis among over 500 consecutive patients. Int J Tuberc Lung Dis 2014;18:1180–7.
[45] Operario DJ, Koeppel AF, Turner SD, Bao Y, Pholwat S, Banu S, et al. Prevalence and extent of heteroresistance by next generation sequencing of multidrug-resistant tuberculosis. PLoS One 2017;12:e0176522.
[46] Deshpande D, Pasipanodya JG, Bendet P, Srivastava S, Koeuth T, Gumbo T, et al. Gatifloxacin pharmacokinetics/pharmacodynamics-based optimal dosing for pulmonary and meningeal multidrug-resistant tuberculosis. Clin Infect Dis 2018;67(Suppl. 3):S274–83.