# The role of moxifloxacin in tuberculosis therapy

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ABSTRACT    Tuberculosis (TB) remains a global threat with more than 9 million new infections. Treatment remains difficult and there has been no change in the duration of the standard regimen since the early 1980s. Moreover, many patients are unable to tolerate this treatment and discontinue therapy, increasing the risk of resistance. There is a growing tide of multidrug resistance and few effective antibiotics to tackle the problem. Since the turn of the millennium there has been a surge in interest in developing new therapies for TB and a number of new drugs have been developed. In this review the repurposing of moxifloxacin, an 8-methoxy-fluoroquinolone, for TB treatment is discussed. The evidence that underpins the development of this agent is reviewed. The results of the recently completed phase III trials are summarised and the reasons for the unexpected outcome are explored. Finally, the design of new trials that incorporate moxifloxacin, and that address both susceptible disease and multidrug resistance, is described.

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## Introduction

It is universally acknowledged by those treating patients with tuberculosis (TB) that the current recommended regimen requires improvement. Treatment takes too long, many patients are unable to tolerate the combination, and there is a growing threat from multidrug-resistant (MDR)- and extremely drug-resistant (XDR)-TB [1]. All of the current components of the standard anti-TB regimen were discovered between 1946 and 1967, yet it was not until the early 1980s following a series of clinical trials in the UK and USA that the current 6-month regimen was settled [2].

Since the turn of the millennium there has been increasing interest in addressing the challenges of anti-TB treatment and research has focussed around repurposing existing antibiotics as well as the development of novel compounds with effective activity against TB [3, 4]. Two new compounds have been approved for the treatment of multidrug resistance, bedaquiline [3, 5] and delamanid [6]. Another new agent, pretomanid, is now in phase III clinical trial (see later) [7] and several other novel agents are in early-phase development [8]. The important approach to TB drug development that can yield results rapidly is to repurpose drugs that also have activity against TB. Moxifloxacin is an example of this process and will be the focus of this review, which is timely as the results of three phase III clinical trials utilising a fluoroquinolone as a key component in the treatment of susceptible infection have been reported recently [9–11] and novel moxifloxacin regimens for the treatment of MDR disease are in progress [12]. Moxifloxacin also has an important role in the management of patients who are unable to tolerate a

standard regimen or have multidrug resistance. This review summarises the literature describing the use of moxifloxacin, including the results of recent phase III clinical trials, and outlines its role in the management of hepatoxicity and in the treatment of MDR-TB.

## Repurposing moxifloxacin

Moxifloxacin is an 8-methoxy-fluoroquinolone that has proved an important fluoroquinolone for the treatment of a wide range of infections, including community-acquired pneumonia, and has a good safety record [13].

### Pharmacokinetics

The pharmacokinetics of this compound make it especially suitable to be an anti-TB agent. After oral dosing it achieves a peak serum concentration of >4 mg·L$^{-1}$ [14, 15]. The mean maximum concentration of drug in serum and the area under the concentration–time curve from 0 to 24 h (AUC$_{0–24 h}$) have been reported as 3.4 mg·L$^{-1}$ and 30.2 mg·h·L$^{-1}$, respectively, with higher values at day 10. Peak concentrations are achieved rapidly, with all patients achieving this within 2 h [16]. The mean elimination half-life is reported as ~12 h [17, 18]. Mean epithelial lining fluid (ELF), alveolar macrophage and bronchial mucosa concentrations at 2.2, 12 and 24 h were: 2.2 h: 20.7 mg·L$^{-1}$, 56.7 mg·L$^{-1}$ and 5.4 mg·kg$^{-1}$; 12 h: 5.9 mg·L$^{-1}$, 54.1 mg·L$^{-1}$ and 2.0 mg·kg$^{-1}$; and 24 h: 3.6 mg·L$^{-1}$, 35.9 mg·L$^{-1}$ and 1.1 mg·kg$^{-1}$, respectively [19]. Moreover, it achieves good concentrations inside macrophages [15]. The achievable concentrations in serum, ELF and macrophages must be compared with a minimum inhibitory concentration (MIC) of <0.125 mg·L$^{-1}$ for susceptible strains [20, 21] and the most active of the currently available fluoroquinolones [20, 22, 23]. A retrospective pharmacokinetic analysis showed an AUC$_{0–24 h}$/MIC ratio <100 in eight out of 16 patients with variation in protein binding affecting the unbound AUC$_{0–24 h}$ considerably. Taken together, these pharmacokinetic parameters suggest that moxifloxacin is ideal for daily dosing. It should be noted that co-administration of moxifloxacin and rifampicin reduced the plasma concentrations of moxifloxacin [24], and this must be considered in TB regimens that contain rifampicin.

An advantage of repurposing an existing antibiotic is that there is extensive safety data to support the proposed dosing from the regulatory package in its previous indications with data to support long-term use being obtained through early-phase clinical studies. Some authors have used an *in vitro* pharmacodynamic model to calculate that a dose of 800 mg·day$^{-1}$ could result in higher bactericidal activity and an improved outcome [25]. Although superficially it might be attractive to consider using a higher dose to improve bactericidal activity, in order to implement it in a novel treatment regimen it would be necessary to complete a new safety package before such a regimen could be recommended [26].

## Early-phase development
### Mouse studies

Similarly, early mouse studies confirmed that moxifloxacin was bactericidal *in vivo* [22, 27]. More importantly, combination studies showed that substitution of isoniazid by moxifloxacin resulted in a reduction in the time to culture conversion [28] and that regimens of shorter duration could result in a stable cure [29].

## Early-phase clinical studies of moxifloxacin

Moxifloxacin moved into clinical development for use in TB through early-phase clinical trials where the drug was given as monotherapy for a short period and confirmed that the drug was highly bactericidal, which, although less active than isoniazid, was very potent [30, 31]. Combined with isoniazid there was no increase in bactericidal activity [32]. Comparative early bactericidal studies demonstrated clearly that moxifloxacin and high-dose levofloxacin had a similar early bactericidal activity, a little higher than for gatifloxacin [33].

Thus, having demonstrated that moxifloxacin may be of benefit as an anti-TB agent it was necessary to address a common question in TB drug development for this indication: all TB therapy is with multidrug regimens, so how is a new drug to be incorporated into a novel and improved therapy? Adding the novel agent to an existing regimen or substituting it for one of the current components could achieve an improvement in bactericidal activity. One approach was to substitute moxifloxacin for ethambutol during the first 8 weeks as was done in three phase IIb studies. There was some variation in the methodologies and end-points used, but patients were followed weekly and sputum cultured for the presence of *Mycobacterium tuberculosis*. The end-point was the proportion of patients culture-negative after 8 weeks of therapy. In a multisite study in North America and Africa, moxifloxacin substitution for ethambutol resulted in a greater chance of being culture-negative at many of the early time points, but not at 8 weeks, the trial's primary end-point [34]. Another study of similar design performed in Brazil found that subjects on the moxifloxacin substitution arm had an increased chance of being culture-negative throughout and at

week 8 [35]. A further study compared regimens where moxifloxacin, gatifloxacin or ofloxacin was substituted for ethambutol with a standard HRZE (isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E)) control regimen. Additional information was obtained using a modelling approach. Nonlinear mixed-effects modelling showed that the moxifloxacin substitution arm appeared to provide better bactericidal activity during the early phase of a biexponential decline in sputum bacterial viability. There was a significant increase in the rate of bacillary elimination during the late phase of the 8 weeks of treatment for both gatifloxacin and moxifloxacin. For ofloxacin, there was no such difference from the control regimen. These findings were supported by estimates of time to culture conversion, using Cox regression analysis, but there were no significant differences in the proportion of patients culture-negative by arm at 8 weeks [36].

The alternative to an ethambutol substitution is to switch moxifloxacin for isoniazid, and this was tested in a phase IIb study performed in Europe, North America and sub-Saharan Africa. The moxifloxacin substitution arm had a small but nonsignificant increase in the proportion of patients culture-negative at 8 weeks [37]. Taken together, these data suggested that either an ethambutol or an isoniazid substitution might result in shortening the duration of TB treatment from 6 to 4 months.

## Phase III studies of fluoroquinolone-containing regimens for treatment shortening in susceptible TB

The last leap to a shorter regimen occurred in the 1980s when the role of redosed pyrazinamide was discovered in a series of trials that allowed a reduction from 9 to 6 months [38, 39]. In 2014, three trials were reported that relate to treatment shortening based on the substitution of a fluoroquinolone [9–11].

### REMoxTB

REMoxTB was conceived with a number of objectives over and above the trial of two fluoroquinolone substitution regimens that might be capable of reducing treatment time from 6 to 4 months. It used a standardised, regulatory methodology to establish this capability of registering one of the experimental arms [9]. It was a randomised placebo-controlled trial that compared two experimental regimens that substituted moxifloxacin for either isoniazid or ethambutol in the first 4 months, as described in figure 1. Patients were monitored intensively, with sputum sampled weekly in the first 2 months, then two samples monthly until the end of 6 months, after which sampling was each 3 months. *M. tuberculosis* was cultured by both the Lowenstein–Jensen (solid) medium and the Mycobacteria Growth Indicator Tube (MGIT) methods. This approach was adopted to ensure that the results were "backwards compatible" with the series of trials conducted by the UK Medical Research Council and US Public Health Service, and also "forwards compatible" with future trials that are likely only to use the automated growth system [2, 40]. Given the high cure rate of the standard regimen it was necessary to use a noninferiority design as described previously [41]. As the trial used three of the components of the standard regimen and there were two comparators (isoniazid and ethambutol substitution), the margin of noninferiority was set at 6% with a 97.5% confidence interval. This meant that to be able to conclude the experimental regimens were "noninferior" the upper bound of the 97.5% confidence interval had to be <6% lower than the control arm.

1931 patients from nine countries were randomised to the control or either of the experimental regimens, *i.e.* isoniazid substitution or ethambutol substitution. 555, 568 and 551 patients, respectively, were included in the modified intention-to-treat (MITT) analysis, and 510, 514 and 524 patients, respectively, were included in the per protocol analysis. Both the isoniazid-containing and ethambutol-containing regimens converted to culture negativity sooner than the control arm: the hazard ratios for time to culture negativity in both solid and liquid media ranged from 1.17 to 1.25 (95% CI >1.0). These data confirmed the results from phase IIb studies that predicted the substitution of moxifloxacin for either ethambutol or isoniazid could be more bactericidal [35, 36]. In contrast, the time to an unfavourable outcome (including patients who failed therapy or relapsed, or died from any cause during the treatment period or from TB during the follow-up phase) was shorter in the isoniazid group than in the control group (hazard ratio 1.87, 97.5% CI 1.07–2.67) and was further reduced in the ethambutol group (hazard ratio 2.56, 97.5% CI 1.51–3.60).

In the per protocol analysis, which was the primary end-point, a favourable outcome was reported in fewer patients in the isoniazid group (the ethambutol substitution) (85%) and the ethambutol group (the isoniazid substitution) (80%) than in the control group (92%), for a difference favouring the control group of 6.1 percentage points (97.5% CI 1.7–10.5) *versus* the isoniazid group and 11.4 percentage points (97.5% CI 6.7–16.1) *versus* the ethambutol group. Results were consistent in the MITT analysis and all sensitivity analyses. Importantly, there was no variation from site to site and between the continents, giving a high degree of confidence in the results. Thus, we were unable to recommend either of the experimental arms for treatment of uncomplicated susceptible infection.
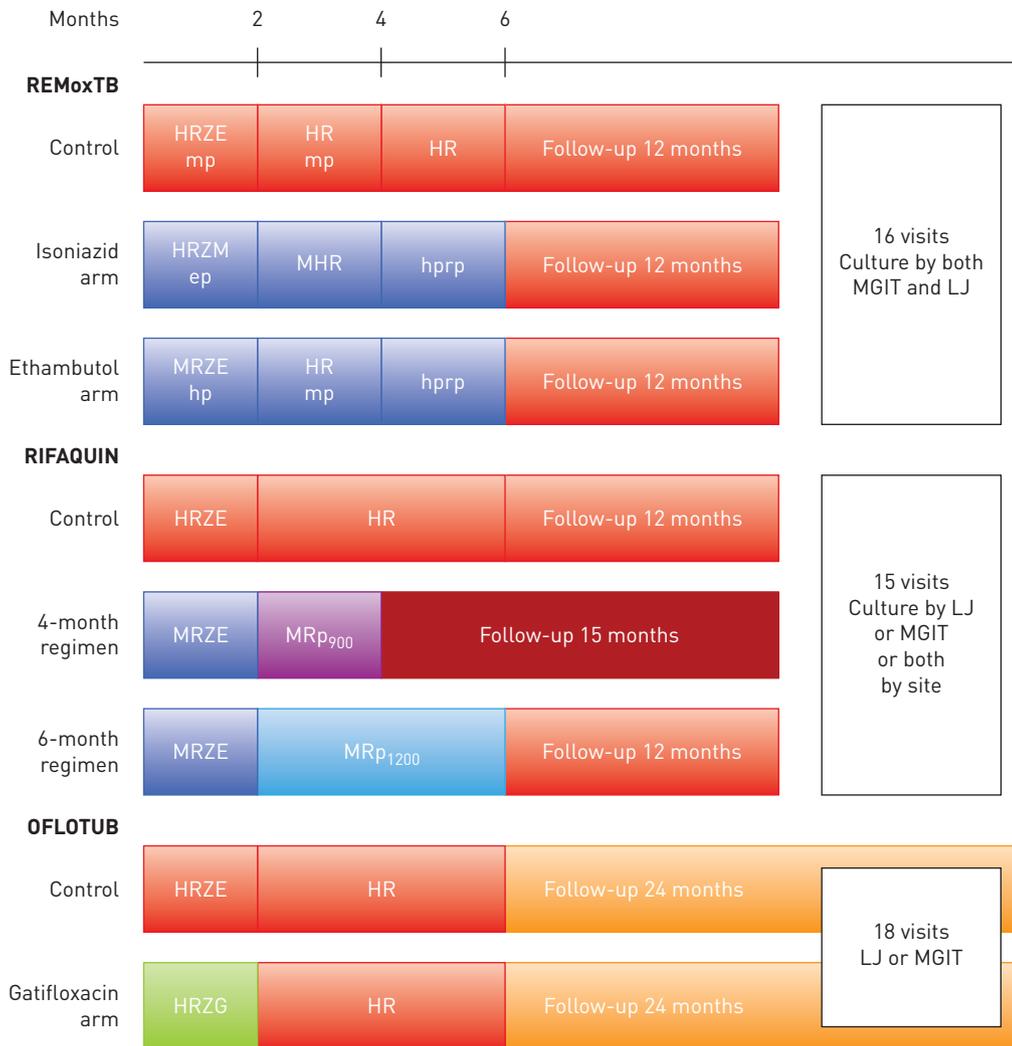
FIGURE 1 Description of the design of three recent phase III clinical trials incorporating fluoroquinolone antibiotics in treatment-shortening regimens for pulmonary tuberculosis: REMoxTB [9], RIFAQUIN [10] and OFLOTUB [11]. Note that moxifloxacin/rifapentine 900 mg was administered twice weekly and moxifloxacin/rifapentine 1200 mg was administered weekly. H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol; M: moxifloxacin; Rp: rifapentine (with a subscript defining dose); G: gatifloxacin; ep, mp, rp and hp: placebos for ethambutol, moxifloxacin, rifampicin and isoniazid, respectively; LJ: Lowenstein–Jensen; MGIT: Mycobacteria Growth Indicator Tube.

### RIFAQUIN

RIFAQUIN, as with REMoxTB, was a trial with a noninferiority design that investigated a regimen substituting moxifloxacin for isoniazid in the intensive phase, and compared both a 4- and a 6-month experimental regimen against a standard HRZE regimen [10]. In the consolidation phase, however, the rifamycin component of the regimen was changed from daily rifampicin to rifapentine 900 mg twice weekly and moxifloxacin was given twice weekly for 2 months. A second experimental arm also trialled an isoniazid substitution in the intensive phase, but varied the consolidation phase to once-weekly moxifloxacin and rifapentine 1200 mg to complete 6 months of therapy. The end-point was unfavourable outcome as defined as bacteriological failure or relapse; laboratories used either MGIT or LJ medium to culture *M. tuberculosis*, and one site used both methods. The noninferiority margin was 6%, but the confidence was wider at 90% compared with 97.5% in REMoxTB. 827 patients from southern Africa were randomised, of whom 28% were co-infected with HIV. The late exclusion rate varied between 8 and 13%, leaving 188, 193 and 212 patients in each arm for the MITT analysis, and 163, 165 and 188 patients in the per protocol analysis. Of the 219 patients assessed at 2 months who received isoniazid for the first 2 months, 187 (85.3%) had a negative culture as compared with 394 (90.4%) out of 436 patients who received moxifloxacin for the first 2 months (p=0.06).

In the per protocol analysis, the unfavourable rate was 4.9% in the control group, 3.2% in the 6-month group (90% CI −6.1–2.4) and 18.2% (90% CI 8.1–19.1) in the 4-month group. This means that the

6-month regimen proved noninferior, but noninferiority could not be declared for the 4-month isoniazid substitution regimen.

### OFLOTUB

The OFLOTUB study was similar in design to the ethambutol substitution arm in REMoxTB, but it compared a standard HRZE regimen with one where ethambutol was substituted with gatifloxacin (400 mg·day$^{-1}$) rather than moxifloxacin in the intensive phase. Although this trial used a different fluoroquinolone, which has been shown to be a little less active in phase IIB studies and to have a risk of dysglycasaemia, the additional data may be useful [33, 36, 42, 43]. Of 5845 subjects screened, 1836 patients in five sub-Saharan countries were randomised: 917 and 919 to the control and experiment arm, respectively. The end-point (treatment failure, recurrence or death, or study dropout during treatment) was measured 24 months after the end of treatment as defined by culture on LJ medium. A noninferiority design was adopted with a 6% margin, adjusted for country [11].

The outcome was similar in both the experiment and control arm at 2 months and at the end of treatment. The difference in the risk of an unfavourable outcome, however, was 3.5 percentage points in the MITT analysis (95% upper bound 7.7). In the per protocol analysis the difference was 5.5 percentage points with 95% upper bound at 9.4. The unfavourable rate in the control was high at 17.2%. There was also significant heterogeneity in the outcome between sites with differences in the rate of an unfavourable outcome ranging from −5.4 percentage points in Guinea to 12.3 percentage points in Senegal (p=0.02 for interaction), and in baseline cavitary status (p=0.04 for interaction) and body mass index (p=0.10 for interaction). The control HRZE regimen was associated with a higher dropout rate during treatment as compared with the gatifloxacin-containing regimen (5.0% *versus* 2.7%) and more treatment failures (2.4% *versus* 1.7%). Despite, this patients on the control arm had fewer recurrences (7.1% *versus* 14.6%).

## Safety of moxifloxacin-containing regimens

Standard TB therapy is recognised to cause significant toxicity with many patients unable to complete the recommended regimen because of adverse events. Raised liver enzymes that may lead to hepatic encephalopathy occur at a rate of ∼8% [44, 45] and are a common challenge in clinical practice. Hepatoxicity is associated with increased patient morbidity, interruption of TB treatment and worse patient outcomes [46, 47]. Previously reported rates of hepatotoxicity for the HRZE regimen vary widely from 5% to 40% [44, 48]. Predisposing factors include age and alcohol, and co-infection with HIV is associated with an increase in some reports. Moxifloxacin is often used in "liver-sparing" regimens [44]. This approach is supported by the absence of additional toxicity from the addition of a fluoroquinolone that has been demonstrated in observational studies [49] and the good safety profile demonstrated in a range of early-phase clinical studies [30, 35, 37, 50].

In the REMoxTB study there was no significant difference in the incidence of grade 3 or 4 adverse events, with events reported in 127 (19%) patients in the isoniazid group, 111 (17%) patients in the ethambutol group and 123 (19%) patients in the control group, and there was a small nonsignificant reduction in incidence of hepatotoxicity for both of the experimental moxifloxacin-containing arms [9]. Similarly, the experimental regimens in RIFAQUIN and OFLOTUB proved to have similar rates of adverse events [10, 11]. Taken together, the results from early-phase clinical studies, phase III studies and meta-analysis of clinical studies in wider infection practice suggest a low risk of hepatoxicity [51]. In a prospective study of the management of drug-induced liver injury in TB, Ho *et al.* [49] compared three liver-sparing regimens in 134 patients who received a liver-sparing regimen that included either ethambutol, levofloxacin or moxifloxacin with or without streptomycin. There was no difference in the time to liver enzyme normalization. Thus, we have a consistent message that moxifloxacin is safe for the treatment of TB. Importantly, it could be used as a highly bactericidal component of a liver-sparing regimen.

## Observations on the outcome of phase III treatment-shortening trials

Despite three different phase III trials, none has been able to declare noninferiority in comparison with a standard regimen of HRZE despite the promising *in vitro*, mouse and early-phase clinical trials [29, 30, 35]. This is disappointing and context is provided by a comparison with earlier trials in table 1. *Post hoc* reports have suggested that the outcome could have been predicted by a different mouse model: a chronic TB low-dose inhalation infection in BALB/c mice and in C3HeB/FeJ mice, which unlike other strains develop caseous lung lesions and may better resemble human TB [52]. A statistical explanation is that the best of the phase IIb studies reported a hazard ratio for the time to culture conversion for the moxifloxacin-containing regimen, as compared with the standard regimen, of 1.73 (95% CI 1.15–2.60), suggesting a shorter duration regimen might be possible [36]. This study had relatively low power with only 50 patients per arm. REMoxTB was able to evaluate more than 600 subjects in each group, giving a more precise estimate of the hazard ratio at 1.25 (95% CI 1.10–1.40). This result was consonant with the

TABLE 1 Summary of 4-month treatment trials in pulmonary tuberculosis, indicating their design, unfavourable rate and follow-up

| Study [ref.] | Experimental regimen duration | Regimens | Patients on experimental arms n | Relapse or unfavourable rate % | Follow-up |
|---|---|---|---|---|---|
| **Second French study [79]** | 18 weeks | 2SHRZ/HRZ | 180[#] | 3 | 24 months |
| MEHROTRA *et al.* [80] | 19 weeks | 3SHRZ/RH | | 0 | 12 months |
| | | 3SHRZ/SHZ | | 0 | |
| | | 3SHRZEmide | | 5 | |
| **East African/British Medical Research Council [81]** | 19 weeks | 2SHRZ/2HRZ | 104 | 16 | 24 months |
| | | 2SHRZ/2RH | 104 | 11 | |
| | | 2SHRZ/2HZ | 98 | 32 | |
| | | 2SHRZ/2H | 105 | 30 | |
| | | 2HRZ/2H | 100 | 40 | |
| **Singapore/British Medical Research Council [82]** | 4 months | 2SHRZ/HRZ | 80 | 11 | >24 months |
| | | 2SHRZ/HR | 81 | 6 | |
| **REMoxTB [9]** | 17 weeks | 2MHRZ/2MHR | 655 | 15 | 12 months |
| | | 2EMRZ/2MR | 636 | 20 | |
| **RIFAQUIN [10]** | 4 months | 2MHRZ/2MRp (twice weekly) | 275 | 18.2 | 12–18 months |
| **OFLOTUB [11]** | 4 months | 2HRZG/2HR | 694 | 21 | 24 months |

S: streptomycin; H: isoniazid; R: rifampicin; Z: pyrazinamide; Emide: ethionamide; M: moxifloxacin; E: ethambutol; Rp: rifapentine; G: gatifloxacin [#]: 204 patients in the trial and data analysed from 180.

previously reported estimate, but with a much more modest estimate of the bactericidal effect for which the confidence intervals are narrower. If this smaller effect size had been know it might not have suggested progression to a phase III trial.

Alternatively, it is likely that the organisms that we have been cultivating in the laboratory may not fully represent the bacteria in patients. There are several clinical reports that our current methodologies miss hidden populations, either growing only on liquid media or requiring resuscitation-promoting factors to grow [53, 54]. These can often be characterised by the presence of lipid bodies within the bacteria [55]. The importance of lipid-positive bacteria has been emphasised by a recently published *in vitro* study demonstrating that lipid-body-positive cells can be found in all mycobacterial cultures tested and when purified lipid-rich cells are tested they are phenotypically resistant to antibiotics irrespective of whether they are derived from "old" or "young" cultures, indicating that the presence of a lipid body is associated with phenotypic antibiotic resistance [56]. Lipid-body-positive cells are known to be more resistant to drugs and the concentration of drug required to clear all bacteria (the minimum bactericidal concentration) increases significantly [56]. In sequential sputum samples obtained from patients on HRZE between day 21 and 28 the change in the odds ratio of an unfavourable outcome for each percentage point rise in percentage lipid-body-positive and the acid fast bacilli count was 1.21 (95% CI 0.97–1.50; p=0.088). Thus, it appears that patients with a greater percentage of lipid-body-positive mycobacterial cells detected in their sputum smear at later time points are more likely to have an unfavourable outcome [57]. Could this be due to phenotypic resistance to the components of anti-TB therapy [56]? This might suggest that we need a different approach to treatment shortening.

There may also be pharmacokinetic reasons that help to explain the disappointing outcome from treatment-shortening phase III trials. The crucial role of pyrazinamide in treatment shortening has been known for some time [58]. Mouse studies investigating potential treatment-shortening combinations found that the inclusion of pyrazinamide in the optimal combinations could result in even shorter treatment [59]. PRIDEAUX *et al.* [60] used matrix-assisted laser desorption/ionization mass spectrometry imaging to show that rifampicin and pyrazinamide penetrate to the site of TB infection in lung, and there is evidence that rifampicin may accumulate in the caseum. Moxifloxacin, in contrast, was shown not to diffuse well into the caseum and this may explain the unexpectedly poor outcome due to relapses [9].

Taken together, these data illustrate the difficulties of moving from phase IIb to phase III based on studies that recruit only a relatively small number of patients, which inevitably means that any estimate of drug effect has wide confidence intervals. Also, as we learn more about the pathology of TB and understand the importance of mycobacterial dormancy, we may need to use drugs targeted against these dormant states. Such a compound has been developed to address the dormancy that was achieved through the anaerobic WAYNE and HAYES [61] model: pretomanid (see later) [62].

### Moxifloxacin in the management of MDR-TB

Fluoroquinolones are considered critical components of MDR-TB regimens as they have been shown to be associated with better outcomes [63, 64]. World Health Organization (WHO) treatment guidelines draw attention to the higher bactericidal activity of the later-generation fluoroquinolones such as levofloxacin, moxifloxacin and gatifloxacin over ofloxacin and ciprofloxacin [65].

Effective treatment for MDR-TB depends on constructing a regimen consisting of several agents to which the infecting organism is susceptible and that are bactericidal. This aim is hampered by the paucity of agents that are both highly bactericidal and nontoxic [46]. The latter is especially important in the context of the long duration of MDR treatment of up to 24 months where toxicity can limit the number of patients able to complete the treatment. Importantly, the lower bactericidal activity and higher toxicity of many second-line agents such as linezolid [66], prothionamide and cycloserine mean that treatment response can be slow. This also explains the need for long treatment durations. Toxicity or treatment fatigue can cause patients to discontinue part of the treatment regimen and this may lead to an increased risk for further resistance emergence. Suboptimal treatment can increase the rate at which resistance emerges leading to MDR-TB [67, 68] with the risk that patients enter a vicious cycle of failing regimens and increasing resistance leading ultimately to complete resistance [69]. Much of this problem is exacerbated by the absence of effective drug susceptibility testing in many high-burden countries, which means that administering a regimen uncontrolled by susceptibility testing runs the risk of further resistance amplification with decreasing options for treatment [70].

### New regimens and trials

In developing new regimens for the MDR indication, a number of principles have been enunciated: they should contain at least one new drug class, be broadly applicable for the MDR/XDR indication and should have three to five drugs from different classes. The direction of travel is towards an all-oral regimen, with low toxicity, simple dosage schedule and limited interaction with antiretrovirals [71].

#### The STREAM trial

There has been considerable interest in addressing the increasing problem of MDR-TB and regimens much shorter than the 18–24 months usually prescribed have been reported [72]. A regimen of 9 months of treatment with gatifloxacin, clofazimine, ethambutol and pyrazinamide throughout the treatment period supplemented by prothionamide, kanamycin and high-dose isoniazid during an intensive phase of a minimum of 4 months has been trialled in an adaptive design study, which produced a relapse-free cure rate of 87.9% [73]. The improved outcome associated with this regimen may be due to the added activity of gatifloxacin compared with ofloxacin often used in the setting of MDR-TB. The inclusion of clofazimine, which has been shown in a systematic review of 12 studies comprising 3489 patients to be effective, could be considered as an additional therapeutic option in the treatment of DR-TB, although it was noted that the optimal dose was yet to be determined [74].

The International Union Against Tuberculosis and Lung Diseases, in collaboration with the British Medical Research Council, has developed the STREAM trial, which will assess whether the 9-month study regimen is noninferior to the comparator WHO-approved MDR-TB regimen. It will also assess the comparative safety of the regimen.

The study opened for recruitment in 2012 in South Africa, Ethiopia and Vietnam, and patients will be randomised to receive either the WHO-approved MDR regimen or a regimen of ethambutol (E), pyrazinamide (Z), moxifloxacin (M) and clofazimine (C) throughout, supplemented by kanamycin (K), prothionamide (P) and isoniazid (H) in the first 4 months (4KCMEHZP/5MEZC). In this instance the dose of moxifloxacin was adjusted by weight up to 800 mg daily for subjects >50 kg, although it was recognised that this might result in a higher rate of adverse events [12]. To obviate this problem, all patients will have a 12-lead ECG and if the QTc is >500 ms they are not eligible for the study. The trial recruited its final patient in March 2015 but, since the end-point will be defined at 27 months post-randomisation, the final outcome is still some way off.

#### The STAND trial

The bactericidal activity and good safety profile demonstrated in the REMoxTB trial have underpinned a further development of a treatment-shortening regimen. Moxifloxacin is a key component of the experimental arms of a trial that is intended both to shorten treatment from 6 to 4 months for patients with susceptible disease and to provide an all-oral 6-month treatment for patients with MDR-TB. This provides a significant advantage over the standard-of-care MDR-TB regimen that includes an injectable antibiotic for at least 3 months. Along with moxifloxacin and pyrazinamide, a new agent will be deployed: pretomanid (Pa). This is a new chemical entity, a nitroimidazo-oxazine, with significant anti-TB activity through a unique

mechanism of action [62]. It is active *in vitro* against drug-sensitive and MDR-TB strains, and *in vivo* in TB mouse models [75]. Physiochemical data suggest that the three drugs can easily be co-formulated in a fixed-dose preparation, which is an important consideration for future programmatic use. Both pre-clinical as well as phase II clinical data show the potential of the PaMZ regimen to reduce duration of therapy for TB infection susceptible to the three drugs, regardless of other resistance [76, 77]. The doses of pretomanid to be tested in STAND are based on data from two monotherapy trials and the phase II programme. In the monotherapy trials, a daily dose of 50 mg had lower bactericidal activity than higher doses, but there was no significant difference in bactericidal activity of daily doses from 100 to 1200 mg. The NC-001 trial demonstrated excellent bactericidal activity in the PaMZ combination at a daily dose of 200 mg [77, 78]. An 8-week phase IIb serial sputum colony counting trial demonstrated a greater time-dependent decline of viable bacteria in subjects with drug-sensitive pulmonary TB at 8 weeks (71.4% negative in liquid culture in comparison with only 37.8% of subjects treated with the standard HRZE control; $p < 0.05$) [7]. The phase II trial NC-002 evaluated this regimen at doses of pretomanid of both 100 and 200 mg with similar efficacy results, although for the primary end-point, *i.e.* reduction in colony-forming units of *M. tuberculosis* from sputum, only the 200 mg·day$^{-1}$ dose group was statistically significantly better than the HRZE control. Safety of this combination was also similar between the groups, although the 200 mg·day$^{-1}$ group had more grade 2 adverse events than either the 100 mg·day$^{-1}$ group or the HRZE control group [7]. Thus, the trial compares the standard HRZE regimen with a 4-month regimen of moxifloxacin, pyrazinamide and pretomanid at either 100 or 200 mg daily and with 6 months of pyrazinamide, moxifloxacin and pretomanid 200 mg daily. In addition, there is a MDR arm treated with pyrazinamide, moxifloxacin and pretomanid at 600 mg daily for 6 months. This trial is now recruiting with the results expected in 2018.

## Conclusion

The results of the three large-scale trials of fluoroquinolones are disappointing as it means that a short regimen cannot be recommended for drug-susceptible disease. However, many patients are not able to tolerate the standard HRZE regimen, and the physician is left with the challenge of constructing a regimen and deciding for how long to treat. The data presented above show that fluoroquinolones are at least as safe as standard regimen components and the higher bactericidal activity also suggests that moxifloxacin is a at least as bactericidal as the current standard of care. Thus, moxifloxacin should be considered for use as a key component of the treatment of MDR-TB and also those unable to tolerate the standard regimen.

This review summarises 15 years of research to repurpose an antibiotic for the treatment of TB. The data demonstrate that moxifloxacin is well absorbed orally and highly active against *M. tuberculosis*. A number of studies have been performed to determine how this drug could fit into a shorter regimen, but none has yet proved noninferior to standard chemotherapy. Moxifloxacin has an important role to play in the treatment of MDR-TB and in patients who are not able to tolerate the standard regimen. In new combinations, currently under trial, moxifloxacin may have a key role in shorter treatment for susceptible disease and in innovative short all-oral approaches for the management of MDR-TB.

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