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A review of moxifloxacin for the treatment of drug-susceptible tuberculosis

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Abstract

Moxifloxacin, an 8-methoxy quinolone, is an important drug in the treatment of multidrug-resistant tuberculosis (MDR TB) and is being investigated in novel drug regimens with pretomanid, bedaquiline and pyrazinamide, or rifapentine, for the treatment of drug-susceptible tuberculosis. Early results of these studies are promising. Although current evidence does not support the use of moxifloxacin in treatment shortening regimens for drug-susceptible tuberculosis, it may be recommended in patients unable to tolerate standard first-line drug regimens or for isoniazid mono-resistance. Evidence suggests that the standard 400mg dose of moxifloxacin used in the treatment of tuberculosis may be suboptimal in some patients leading to worse tuberculosis treatment outcomes and emergence of drug resistance. Furthermore, a drug interaction with the rifamycins results in up to 31% reduced plasma concentrations of moxifloxacin when combined for treatment of drug-susceptible tuberculosis, although the clinical relevance of this interaction is unclear. Moxifloxacin exhibits extensive inter-individual pharmacokinetic variability. Higher doses of moxifloxacin may be needed to achieve drug exposures required for improved clinical outcomes. Further study is however needed, to determine the safety of proposed higher doses and clinically validated targets for drug exposure to moxifloxacin associated with improved tuberculosis treatment outcomes.

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We discuss in this review, the evidence for the use of moxifloxacin in drug-susceptible tuberculosis and explore the role of moxifloxacin pharmacokinetics, pharmacodynamics and drug interactions with rifamycins, on tuberculosis treatment outcomes when used in first-line tuberculosis drug regimens.

Keywords

moxifloxacin; tuberculosis; pharmacokinetics; pharmacodynamics

Introduction

Tuberculosis ranks alongside human immunodeficiency virus (HIV) as a leading cause of death worldwide.¹ There were an estimated 10.4 million cases of tuberculosis in 2015, approximately 1.1 million of whom were co-infected with HIV. The African Region had 26% of the world's tuberculosis cases in 2015.¹ South Africa is one of the highest tuberculosis-HIV burden countries in the world,¹ with HIV threatening tuberculosis treatment cure and completion rates, which in turn contributes to a high burden of multi-drug resistant tuberculosis (MDR TB).^{2–4}

The current standard six month drug regimens for drug-susceptible tuberculosis are highly effective, however, challenges such as increasing drug resistance, HIV co-infection, poor treatment adherence, drug interactions, toxicity or pharmacokinetic variability may result in suboptimal treatment outcomes.⁵ The development of safe and effective tuberculosis drug regimens that shorten the time to sputum culture conversion, improve cure and treatment completion rates, reduce morbidity, mortality and relapse is critical.⁵

Fluoroquinolones, including moxifloxacin, are highly active against *Mycobacterium tuberculosis* (MTB),⁶ and are currently recommended in World Health Organisation (WHO) and South African National Treatment guidelines for the treatment of multi-drug resistant tuberculosis.^{7,8} Furthermore, moxifloxacin, may be recommended for treatment in drug-susceptible tuberculosis, when one of the first line tuberculosis drugs are not tolerated or for isoniazid (INH) mono-resistance.^{8–10} Several drug regimens recently tested or currently in clinical trials for both drug-susceptible and MDR TB include moxifloxacin in treatment shortening or novel drug combinations.^{11–14} Moxifloxacin is being investigated in novel treatment shortening regimens in combination with pretomanid or bedaquiline and pyrazinamide for drug resistant and susceptible tuberculosis,^{5,11} and with high dose rifapentine in the tuberculosis trials consortium (TBTC) study 31(NCT02410772) for drug susceptible tuberculosis.

Evidence from mouse studies, suggesting that moxifloxacin-containing regimens may reduce time to eradication of MTB by 2 months^{15,16}, informed the design of phase II and III clinical trials investigating the ability of moxifloxacin-containing regimens to reduce the duration of tuberculosis treatment.^{12,13,17–21} The REMox and RIFAQUIN clinical trials testing moxifloxacin in drug regimens for drug-susceptible tuberculosis found that these regimens resulted in faster sputum culture conversion, but failed to improve clinical outcomes for relapse or treatment failure when treatment was shortened to 4 months in

sputum smear positive patients compared to standard 6 month regimens.^{12,13} Reasons for the disappointing outcomes of these studies have been explored in recent expert reviews, editorials and studies.^{22–28} The mouse model of tuberculosis and *MTB* cultured in the laboratory do not fully represent the course of human infection.^{29,30} Moreover, the eight week sputum culture conversion endpoint used in earlier studies is not as predictive of relapse as was thought previously.²³ Several other factors may have contributed to differences in patient outcomes. These include disease severity, HIV co-infection, poor adherence and reinfection. In addition, inadequate moxifloxacin concentrations, when the drug is given as part of treatment shortening regimens has been proposed as a contributing factor.^{22–25,27,28}

Accumulating evidence suggests that adequate drug concentrations in plasma and sites of infection are necessary for optimizing tuberculosis treatment outcomes.^{31–35} The optimal dose of moxifloxacin for the treatment of tuberculosis has not been clearly defined in humans. Firstly, there is evidence that the current dose of 400mg may lead to sub-therapeutic plasma and tissue concentrations,^{32,36} and the potential for an increased risk of treatment failure, relapse or acquired drug resistance in some patients based on a study using a pre-clinical model of tuberculosis.³² Secondly, plasma concentrations of moxifloxacin, are decreased by up to 31%, when co-administered with rifamycins.^{37–41} It is unclear whether this drug-drug interaction contributed to the clinical outcomes of the REMox and RIFAQUIN studies. Thirdly, recent studies using Matrix-assisted laser desorption/ionization (MALDI) mass spectrometry imaging found that moxifloxacin has heterogeneous distribution into lung tissues and granulomatous lesions with concentrations in these lesions higher than in plasma. Although moxifloxacin was shown to distribute well into the cellular regions of lesions, accumulation in the caseum, where persistent bacilli may be sequestered, is poor, particularly at lower than therapeutic concentrations.^{24,42} Therefore, higher doses of moxifloxacin at 600–800mg have been suggested to achieve optimal drug exposure for therapeutic efficacy in some patients.^{32,36,43} Safety data for these doses is however limited, although studies in patients with tuberculosis meningitis using 800mg doses of moxifloxacin did not report significant safety issues.^{44,45}

In this review, we discuss the use of moxifloxacin in the treatment of drug-susceptible tuberculosis, when, substituted for or added to standard first line drug regimens, or when used in novel treatment shortening regimens. In addition, we focus on the potential impact of pharmacokinetic, pharmacodynamic (PK-PD) and drug interaction studies investigating rifamycin co-administration, on moxifloxacin drug exposure and tuberculosis treatment outcomes.

Methods/Search Criteria

We conducted a literature search in PubMed, using “moxifloxacin” or “fluoroquinolone” as Medical Subject Headings (MeSH) terms in combination with, “tuberculosis/TB”, “pharmacokinetics/PK”, “pharmacodynamics/PD”, “minimum inhibitory concentration/MIC”, “resistance”, “early bactericidal activity/EBA” or “pharmacogenetics”. Randomized controlled trials investigating moxifloxacin for treatment of drug-susceptible *Mycobacterium tuberculosis*, where moxifloxacin was substituted in or added to standard

first line tuberculosis drug regimens, or was tested in shorter novel drug regimens, were considered. All studies including relevant animal or in vitro data that demonstrate moxifloxacin PK-PD or efficacy were included. Although this review focuses on drug-susceptible tuberculosis, studies that report on both drug-susceptible and MDR tuberculosis and those in MDR-tuberculosis that provide information on moxifloxacin pharmacokinetics, pharmacodynamics or efficacy were also included. We excluded studies testing moxifloxacin for infections other than *Mycobacterium tuberculosis*. The main outcomes of interest were; efficacy of moxifloxacin (time to sputum culture conversion at month two, relapse, treatment failure or death) in the treatment of drug-susceptible tuberculosis and the pharmacokinetics of moxifloxacin when used alone or in combination with other tuberculosis drug therapy in healthy volunteers or patients with tuberculosis.

Results

Pharmacokinetics, Pharmacodynamics and Efficacy of Moxifloxacin for treatment of drug-susceptible tuberculosis

Mechanism of Action and Activity of Moxifloxacin against *Mycobacterium tuberculosis*—Moxifloxacin, an 8-methoxy fluoroquinolone, is bactericidal with activity against Gram-positive and Gram-negative bacteria including *Mycobacterium tuberculosis*.^{46,47} The bactericidal action occurs by binding to the topoisomerase enzymes II (DNA gyrase) and thus preventing replication, transcription and repair of bacterial DNA.⁴⁸ Lethal action of the fluoroquinolones, including moxifloxacin, is suggested to occur through two steps, formation of bacteriostatic quinolone-gyrase-DNA complexes followed by chromosome fragmentation.^{49,50} A central feature of tuberculosis is the tendency of *Mycobacterium tuberculosis* to enter a dormant state in which the bacterium is likely to exhibit low susceptibility to chemotherapeutic agents.⁵¹ Moxifloxacin has been shown to have a unique ability to kill mycobacteria in the absence of ongoing protein synthesis or while in a dormant state, which is important for the eradication of the tuberculosis infection and prevention of relapse.^{49,50}

Pharmacokinetics

Absorption: Moxifloxacin is easily and rapidly absorbed after oral administration. Bioavailability of moxifloxacin following oral dosing exceeds 90%.⁵²

Drug distribution: Poor long term treatment outcomes in some patients despite clearance of *MTB* determined by negative sputum cultures suggests that the bacilli may persist in lung cavities, granulomas, caseum, abscesses and other lung or tissue lesions that may not be accessible to anti-tuberculosis drug therapy.^{12,13} It is clear that the efficacy of drugs used in the treatment tuberculosis may be affected by ability to distribute adequately to sites of action in lung tissue, epithelial lining fluid, macrophages, granulomas, caseum or necrotic lesions. Moxifloxacin is widely distributed, with some tissue concentrations reported in excess of plasma levels.^{24,42,53,54} Concentrations in epithelial lining fluid, lung tissue, alveolar macrophages (AM) and bronchial mucosa (BM) exceed the MIC values for activity against *MTB* and values for the WHO-defined critical concentration of 2.00 mg/L.²⁴ However, recent studies in a rabbit model of tuberculosis and patients undergoing lung

resection surgery, using mass spectrometer imaging (MALDI-MSI), found that although moxifloxacin concentrations in lesions are approximately three times higher than in plasma and distributes efficiently to lung tissue, lung epithelial fluid and periphery of granulomas, it does not accumulate as efficiently in the caseum where slowly replicating persistent *MTB* bacilli may be sequestered (Figure 1).^{24,42} Furthermore, the study in patients undergoing lung resection surgery, determined the concentrations of drugs and metabolites in homogenized lesions, relative to the aerobic minimum inhibitory concentration (MIC) and the minimum anaerobic cidal concentration (MAC), a measure of drug activity against bacilli persisting in necrotic lesions where anaerobic conditions prevail.²⁴ Moxifloxacin, in contrast to isoniazid, rifampicin and pyrazinamide was shown to be consistently present at significantly higher concentrations in lesions than in plasma, above the MIC in all lesion homogenates, and at or above the MAC in 38% of the lesions, indicating that it might reach non-growing persistent bacilli at therapeutic concentrations.²⁴ These factors may have contributed to the failure to shorten tuberculosis treatment especially the high relapse rate found in recent studies using moxifloxacin,^{12,13} further exacerbated by suboptimal drug concentrations achieved in some patients due to intra-individual variability in PK parameters, poor adherence or drug absorption, drug interactions (rifamycins) and or genetic variability. These studies also investigated the distribution of rifampicin and pyrazinamide into the caseous lesions and found that these drugs distributed evenly and achieved higher concentrations in the caseum when compared to moxifloxacin, findings that support treatment shortening ability of rifampicin and pyrazinamide.^{24,42} Moxifloxacin has good penetration into cerebrospinal fluid, and has been used effectively with rifampicin for the treatment of drug-susceptible tuberculosis meningitis at higher doses of 800mg, however, these higher doses were not found to be significantly associated with improved treatment outcomes.^{44,45}

Metabolism and Drug Transport: Moxifloxacin is metabolized in the liver via glucuronide and sulphate conjugation by cytosolic enzymes glucuronosyltransferase and sulphotransferase.⁵⁵ The major human uridine diphosphate (UDP)- glucuronosyltransferases (UGTs) responsible for formation M2 metabolite are UGT1A1, UGT1A3 and UGT1A9 (UGT1A1 being the main isoform). Moxifloxacin is a substrate of p-glycoprotein, and the drug transporter protein plays an important role in its absorption distribution and elimination.^{56,57} The cytochrome P450 (CYP450) enzyme system is not involved in the metabolism of moxifloxacin, nor is it affected by the drug.⁵⁸ Neither moxifloxacin nor its metabolites inhibit the CYP450 enzymes. Similarly, moxifloxacin was shown not to be an inhibitor of any of the major human UDP- glucuronosyltransferases. The sulphate conjugate (M1) accounts for 38% of the oral dose, and is excreted in faeces; about 14% of an oral dose is converted to the glucuronide conjugate (M2), and is excreted in urine.⁵⁹ Peak plasma levels of M1 and M2 are <10% and about 40% those of the parent drug, respectively. Overall, about 45% of an oral dose is excreted unchanged as parent drug, and about 51% as known metabolites, M1 and M2, which are biologically inactive.

Drug and food interactions: Co-administration with food may slightly prolong time to maximum concentration (T_{max}), and may reduce the maximum serum concentration (C_{max}) by 16%; these effects are thought to be insignificant, and moxifloxacin may therefore be

administered with or without food.⁶⁰ Few clinically significant interactions with other drugs have been described. Moxifloxacin may cause QTc interval prolongation and should be used with caution or avoided with other drugs or drug classes known to cause this effect. These include; antiarrhythmic, antifungals, antipsychotics, antidepressants and notably other tuberculosis drugs: bedaquiline, delamanid and clofazimine. However, moxifloxacin is being investigated for the treatment of MDR TB in combination with clofazimine in stage 1 of the *STREAM* trial and in the phase II NC005 study (NCT02193776) with bedaquiline, with careful monitoring.¹⁴ Safety data for the use of these drugs in combination may become available in 2018.¹⁴ All fluoroquinolones can bind to multivalent cations, including ferrous sulphate, aluminium hydroxide and magnesium sulphate, with resultant substantial (40–60%) decreases in absorption when taken concurrently.^{61,62} Iron or zinc containing multivitamin supplements magnesium or aluminum-based antacids and buffered didanosine should be dosed at least two hours before or after moxifloxacin. This may be challenging in patients with HIV co-infection, where multivitamin and iron supplements, in addition to antiretroviral therapy (ART), and drugs for tuberculosis and other treatment for opportunistic infections are prescribed. Drugs that inhibit or induce p-glycoprotein may also result in altered moxifloxacin pharmacokinetics.⁶³ These include; cotrimoxazole, phenytoin, nifedipine, rifampicin, midazolam, ketoconazole, erythromycin, amiodarone and mefloquine.

A recent study found a significant interaction with efavirenz, where oral clearance of moxifloxacin was increased by 42% resulting in an approximately 30% reduction in moxifloxacin drug concentrations, when co-administered with efavirenz.⁶⁴ The significant drug interaction found between moxifloxacin and efavirenz-based ART in HIV co-infected patients has not been previously described. Although this finding needs validation in other studies, it remains concerning, given the high HIV-tuberculosis co-infection rates in many tuberculosis endemic settings where the ART backbone remains efavirenz. These findings have direct implications for studies evaluating novel drug regimens containing moxifloxacin and for the use of moxifloxacin in non-standard treatment regimens for both drug-susceptible and drug resistant tuberculosis.

Interaction with Rifamycins: The rifamycins including rifampicin and rifapentine induce the activity of the phase II drug metabolizing enzymes glucuronosyltransferase and sulphotransferase and the drug transporter protein p-glycoprotein.^{65,66} Moxifloxacin is a substrate of these enzymes and drug transporter, and rifamycin induction results in altered moxifloxacin pharmacokinetics. The findings of several studies investigating the potential interaction between moxifloxacin and the rifamycins either in healthy individuals or in patients with tuberculosis^{37–41,64,67}, are summarized in Table 1. All these studies demonstrate decreased plasma concentrations of moxifloxacin at steady state, as a result of rifamycin co-administration. Area under the concentration time curve (AUC) and C_{max} reductions of 8–31% were reported. The variable results of these studies may be due to several factors; including dose, dosing frequency and type of rifamycin used, study design and PK variability in tuberculosis patients versus healthy individuals. Studies investigating the impact of rifapentine and moxifloxacin co-administration found lower differences in moxifloxacin drug concentrations (8–17%), likely due to rifapentine exhibiting less potent

induction of drug metabolizing enzymes than rifampicin with the doses used and less frequent dosing.^{41,67} It is however possible that high *daily* doses of rifapentine may result in higher enzyme induction and lower moxifloxacin concentrations. Bioavailability studies, conducted in healthy individuals and tuberculosis patients, using cross-over or sequential study designs to limit inter-patient variability, and intensive PK sampling, found higher reductions in moxifloxacin AUC 27–31%,^{38–40} in the presence of rifampicin compared to “real world” studies reporting high levels of heterogeneity between study groups compared and low sample sizes that may limit the generalizability of the findings.^{37,43}

Pharmacokinetics of moxifloxacin and other tuberculosis drugs may however differ in healthy individuals^{39,40} compared to patients with tuberculosis infection.^{43,68} Although the clinical relevance of the drug interaction between the rifamycins and moxifloxacin, and impact on tuberculosis treatment outcomes, needs further investigation, moxifloxacin is known to have concentration-dependant activity and lower concentrations will likely result in decreased drug activity and worse treatment outcomes in some patients.

Pharmacokinetic Data from Early Phase 1 studies in healthy volunteers: Moxifloxacin is well absorbed, with a bioavailability of approximately 90%.⁵² Pharmacokinetics are linear, with C_{max} and AUC increasing proportionally in the range of 50–800 mg for single doses and up to 600 mg once daily when dosing over 10 days.⁶⁹ Steady state is reached within 3 days. A single dose of 400 mg produces a C_{max} of 2.5–4.5 mg/L, half-life of 11–15 h, AUC_{0–24} of 25–40 ug.h/mL and volume of distribution of 2.5–3.5 L/kg. Protein binding is about 50%.⁷⁰ T_{max} is reached within approximately 1–3 hours.^{58,71}

Pharmacokinetics of Moxifloxacin in patients with tuberculosis (Table 1): The pharmacokinetic parameters of moxifloxacin from clinical trials done in patients with tuberculosis or healthy individuals using tuberculosis drug regimens is summarized in Table 1.^{37–41,43–45,67,68,72–77} The range of values for C_{max} , AUC and T_{max} for moxifloxacin are in keeping with data from studies in healthy individuals, although the ranges were wide and more variable (Table 1).^{59,70,71} Importantly, moxifloxacin concentrations are consistently lower when co-administered with rifamycins. Extensive inter-individual variability in moxifloxacin pharmacokinetic parameters is apparent and the ranges for AUC and C_{max} are wide. Doubling the moxifloxacin dose to 800mg results in proportional increases in AUC and C_{max} . Of note, most of the PK data from studies including moxifloxacin in tuberculosis treatment regimens, were in HIV uninfected individuals and in populations outside of Africa. While HIV co-infection itself may lead to altered pharmacokinetics and lower concentrations of tuberculosis drugs.⁷⁸, little data exists on the potential interactions of moxifloxacin with ART. One recent study reported a 42% reduction in oral clearance of moxifloxacin, resulting in a 30% decrease in moxifloxacin AUC, when co-administered with efavirenz-based ART in patients with HIV co-infection.⁶⁴ African populations have shown high levels of host genetic diversity resulting in differences in tuberculosis disease susceptibility.⁷⁹ Furthermore, genetic diversity in drug metabolising and drug transport enzymes in the host leads to lower tuberculosis drug concentrations and variation in drug response.^{80–82}

Pharmacogenetics—Genetic variation associated with single nucleotide polymorphisms, copy number variants, insertions or deletions in genes coding for drug metabolizing and transporter enzymes, are increasingly recognized as factors that may affect tuberculosis drug exposure and result in variable pharmacokinetic parameters.⁸³ Moxifloxacin is metabolized via glucuronide and sulphate conjugation by cytosolic enzymes glucuronosyltransferase and sulphotransferase. The major human UDP- glucuronosyltransferases (UGTs) responsible for formation M2 metabolite are UGT1A1, UGT1A3 and UGT1A9. Although there is no previous published data on the polymorphisms of genes coding for UGT enzymes, affecting moxifloxacin metabolism or pharmacokinetics in tuberculosis treatment, these are known to be highly polymorphic, leading to altered concentrations of other drugs and of moxifloxacin in healthy individuals.^{84,85} Moxifloxacin is a P-glycoprotein substrate, limited data from one study investigating polymorphisms in the ABCB1 (MDR1) gene coding for this transport protein, found that the MDR 3435 CC polymorphism may affect the absorption of moxifloxacin.⁴⁰ ABCB1 also exhibits high functional variance⁸⁶ and effects of polymorphisms in this drug transporter and genes coding for UGT enzymes on moxifloxacin pharmacokinetics need further investigation.

Pharmacodynamics—Many of the drugs currently being used in for the treatment of both drug-susceptible and MDR-tuberculosis were developed when pharmacokinetics and pharmacodynamics of drugs were not evaluated during the development of drugs or regimens. Consequently, more than 45 years after its introduction, several studies are only now underway to determine the optimal dose of rifampicin for the treatment of tuberculosis.^{87,88} The optimal dose of moxifloxacin for the treatment of tuberculosis in humans has not been clearly defined. The PK-PD marker suggested to predict the clinical efficacy of fluoroquinolones, including moxifloxacin is the total (protein bound and unbound) AUC/MIC ratio, and ratios >100–125 and $C_{\max}/MIC > 8-12$ or >10, have been demonstrated in laboratory based studies, to be associated with better treatment outcomes, greatest bacteriological activity against *MTB* and a decreased probability of resistance.^{48,89–91} A study using a novel PK infection model of tuberculosis reported doses of 800mg as likely to achieve PK-PD (free/unbound AUC/MIC ratio) target attainment levels of >53, excellent *MTB* microbial kill and complete suppression of the drug resistant mutants.³² The AUC/MIC target for moxifloxacin has however not yet been defined in humans with tuberculosis and drug exposures linked to optimal treatment outcomes need to still be determined. To attain the proposed AUC/MIC target ratios of > 100–125, AUC values 50 µg.h/mL and above must be achieved in patients where MIC's are 0.25–0.50 mg/L. This AUC target is clearly not achieved in many tuberculosis patients using 400mg doses, with AUC's as low as 8.5 and as high as 140µg.h/mL, most, ranging between approximately 15- 80µg.h/mL and mean or median AUC values of about 30µg.h/mL (Table 1). It is recognized that the effective treatment of tuberculosis requires drug regimens that include at least three or four effective drugs which work additively or synergistically to eradicate *MTB*, although that the activity of each of these drugs within the regimen should be optimized to achieve better treatment outcomes.

Drug resistance—Moxifloxacin, is a fourth generation fluoroquinolone, containing an 8-methoxy group and a hydrophobic diazabicyclononyl ring moiety with an S,S-configuration

at the 7-position, which may reduce the ability of *MTB* to efflux the drug across the cell wall, thus lowering risk of efflux-mediated resistance in comparison to earlier generation fluoroquinolones, with MIC's ranging between 0.12–0.50 mg/L.⁹² Resistance to moxifloxacin and other fluoroquinolones occurs mainly as a result of point mutations within the quinolone resistance determining region (QRDR) in DNA gyrase A (GyrA) and Gyrase B (GyrB) genes. Although, resistance to early generation fluoroquinolones such as ofloxacin may not confer cross-resistance to newer, more potent fluoroquinolones such as moxifloxacin and levofloxacin.^{93,94} The most frequent QRDR mutations are found at GyrA codons 90 (A90V), 91 (S91P), 94 (D94G, D94A, D94Y, D94N and D94H)^{48,92,95,96}, and double mutations in GyrA and GyrB have been reported.⁹² Studies investigating the association between presence of mutations in clinical *MTB* isolates and MIC's have shown variable results. Two studies in South Africa^{92,97} found that mutations at common codons 90 and 94 resulted in increases in MIC up to 2.00 mg/L, while studies in China and Thailand with similar findings, also reported much higher MIC's of up to 16.00 mg/L in a small percentage of patients with these and other mutations.^{98,99} A recent survey conducted in South Africa, Eastern Europe and Asia found that resistance was between 0.9–14.6% for moxifloxacin when tested at 0.50 mg/L and much lower in all countries when tested at 2.00 mg/L.⁹⁴ The study also determined resistance to moxifloxacin among patients with rifampicin-sensitive and rifampicin-resistant isolates. Among patients who were rifampicin-sensitive (910 of 951); 0.5% 95%CI (0.0–1.1) were resistant to moxifloxacin and among those with rifampicin resistant isolates (41 of 951), moxifloxacin resistance was 8.4% 95% CI (0.0–18.4), when tested at 0.50 mg/L. Drug susceptibility testing for moxifloxacin commonly uses phenotypic methods and critical concentrations, defined as the lowest concentration of a drug that inhibits approximately 99% of wildtype strains lacking mechanisms of acquired or mutational resistance to the specific drug.¹⁰⁰ The WHO defined critical concentrations for moxifloxacin as 0.25 mg/L using Mycobacterial Growth Inhibitor Tube (MGIT) or 0.50 mg/L using solid media,¹⁰¹ have recently been increased to 0.50 or 2.00 mg/L for both liquid and solid media,¹⁰² based on evidence that moxifloxacin may have clinical efficacy in patients given that plasma drug concentrations achieved in most tuberculosis patients may exceed 2 mg/L. This may not however be the case in all tuberculosis patients, or at all sites of action. The mutant prevention concentration or MPC, defined as the minimum concentration allowing no mutant recovery when $>10^{10}$ bacilli are applied to drug-containing agar,¹⁰³ is between 4.00–8.00mg/L for moxifloxacin. These levels are less achievable in most patients with tuberculosis, which may lead to increased risk of acquired resistance in patients with low drug concentrations in plasma or sites of action and MIC's 2.00 mg/L.¹⁰⁴ An additional concern is that the fluoroquinolones, including moxifloxacin, are used to treat a variety of bacterial infections¹⁰⁵ which presents the risk of pre-existing fluoroquinolone resistance and subsequent treatment failure if used in tuberculosis treatment. Moreover, in high tuberculosis burden countries such as South Africa the risk of treating undiagnosed tuberculosis with moxifloxacin monotherapy increases the risk of emergent resistance.

Safety—Moxifloxacin is generally well tolerated. Most common adverse events in adults include gastrointestinal (nausea, diarrhoea) and neurological (headache, dizziness) toxicities, or arthralgia. Serious adverse events are rare, and include tendon inflammation and rupture

(particularly in elderly patients and in those treated concurrently with corticosteroids), seizures, anaphylaxis, skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis and antibiotic associated colitis.^{58,106} Moxifloxacin has been shown to prolong the QT interval of the electrocardiogram in some patients by reversible and dose-dependent but weak blockage of the hERG potassium channels. For this reason higher doses of moxifloxacin should be used with caution. Some evidence from studies in tuberculosis meningitis where higher doses (600–800mg) may be justified suggest that these may be safe when carefully monitored.^{44,45,107} Moxifloxacin should be used with caution in patients on antiarrhythmic drugs and other drugs with known effects on QT prolongation, notably bedaquiline, also used in the treatment of tuberculosis.¹⁰⁸ A drug safety review of clinical data comparing safety and risk of adverse events in patients on moxifloxacin with similar comparator drugs found no significantly increased risk of adverse events with moxifloxacin.¹⁰⁹ Phase II or III studies conducted in patients with tuberculosis (Table 3) did not report any significant difference in the incidence of grade 3 or 4 adverse events between moxifloxacin containing arms of the study or standard treatment regimens.^{12,13,17–19,21,76,110} In keeping with other non-tuberculosis studies, moxifloxacin significantly increased rates of nausea and GI upset and arthralgia compared to standard tuberculosis therapy.^{17,21,110} The REMox study reported a nonsignificant reduction in incidence of hepatotoxicity for both of the experimental moxifloxacin-containing arms.¹² Moxifloxacin has been used as part of a “liver sparing” regimen, in treatment of patients with tuberculosis.^{12,26}

Activity *in vitro*, murine studies—Moxifloxacin is highly active against *Mycobacterium tuberculosis in vitro*. Minimum inhibitory concentrations (MIC₉₀), defined as the lowest concentration of drug required to inhibit 90 percent of bacterial growth, are in the range of 0.06–0.25 mg/L, with moxifloxacin exhibiting greater inhibitory activity in comparison to ciprofloxacin, levofloxacin and sparfloxacin⁶ and similar activity to rifampicin.⁴⁷

Moxifloxacin has bactericidal activity comparable to isoniazid¹¹¹ and exhibits dose dependant activity, post antibiotic effects and additive sterilizing potential when combined with isoniazid and rifapentine or rifampicin.^{112–114} Other fluoroquinolones such as gatifloxacin and high dose levofloxacin (1g) demonstrated similar findings with bactericidal activity comparable to isoniazid.¹¹⁵ Studies found, that addition of moxifloxacin to drug regimens containing rifampicin and pyrazinamide reduced the time to eradicate *MTB* from mouse lungs by up to two months¹⁵ and prevents relapse for up to six months.¹⁶ The six-month treatment study was conducted in a murine model to evaluate the sterilizing activity with different regimens. Treatment with rifampicin, moxifloxacin and pyrazinamide (RMZ) resulted in a 2.5-log greater reduction in colony forming units counts relative to rifampicin, isoniazid and pyrazinamide (RHZ) at 2 months ($p < 0.001$). After 3 months of RMZ/RM, only 2 of 5 mice had positive lung cultures. In contrast, all six mice given RHZ/RH were still culture-positive at 4 months. These data suggest that the combination RMZ has greater sterilizing activity than the standard regimen and may be able to shorten the duration of therapy for human tuberculosis by 2 months or more.¹⁶ Another study using four months of therapy with any of the RMZ-based regimens resulted in complete sterilization in all mice,

whereas four months of therapy with the standard RHZ-based regimen resulted in a relapse rate of 42%.¹⁵ These studies led to the design of phase II and III clinical trials investigating the ability of the fluoroquinolones to shorten the duration of tuberculosis treatment in patients with drug-susceptible TB.

Despite the improved bactericidal activity found in these studies it must be noted that when rifampicin and moxifloxacin in combination was compared to these drugs used alone, it was shown in both the hollow fibre and mouse model of tuberculosis to be that the combination was efficacious for suppressing resistant organisms but may be antagonistic for cell kill.^{116,117} Rifampicin and moxifloxacin in combination showed similar efficacy in reduction of colony forming unit count as moxifloxacin alone in the mouse model of infection.¹¹⁷ The investigators of this study note an important consideration, that to achieve the dual goals of shortening the duration of therapy and suppressing resistance, the combination therapy must increase the rate of kill as well as suppress resistance.¹¹⁷ This finding not been fully investigated in human studies, although it is possible that this may have contributed to the poor outcomes of some of the phase II and III studies investigating the treatment shortening ability of moxifloxacin for tuberculosis treatment.

Pyrazinamide contributes additional sterilizing activity beyond the first two months in moxifloxacin-containing regimens.¹¹⁸ Moxifloxacin has also been investigated in novel drug regimens with pretomanid (PA 824) and pyrazinamide for the treatment of tuberculosis.¹¹⁹ A study conducted in the murine model of tuberculosis found that the combination of moxifloxacin, pretomanid and pyrazinamide cured mice more rapidly than a standard regimen containing rifampicin, isoniazid and pyrazinamide.

Human studies

Early bactericidal activity (EBA) studies (summarized in Table 2): Moxifloxacin demonstrates early bactericidal activity, defined as the fall in log₁₀ colony forming units (cfu) of *M. tuberculosis* per ml sputum per day, comparable to isoniazid^{120–122} with one study reporting EBA of 0.53 log₁₀ cfu/day after 0.88 days for moxifloxacin compared to 0.77 log₁₀ cfu/day for isoniazid after 0.48 days.¹²² Studies testing moxifloxacin in combination with isoniazid, found no increase in bactericidal activity, although the combination was not antagonistic.¹²² Moxifloxacin demonstrates EBA similar to other newer generation fluoroquinolones, gatifloxacin and high dose levofloxacin.¹¹⁵ The mean 14-day EBA of pretomanid-moxifloxacin-pyrazinamide (n=13; 0.233 [SD 0.128]) was comparable with that of standard first line treatment (n=10; 0.140 [SD 0.094]).¹²³

Phase II and III Clinical trials: (Table 3): Studies investigating the efficacy of moxifloxacin for the treatment of drug-susceptible tuberculosis, are summarized in Table 3. Drug regimens used in these studies either replaced ethambutol or isoniazid with moxifloxacin, or added moxifloxacin to, the standard first line drug regimen or tested novel drugs, bedaquiline or pretomanid, with moxifloxacin and pyrazinamide. All studies included patients; with sputum smear positive tuberculosis, mainly HIV uninfected and most studies reported 60–70% or greater cavitation at baseline.^{11–13,17–21,76,110,124}

Studies reporting proportion of patients with negative sputum culture at 8 weeks

(Table 3): In studies where moxifloxacin replaced ethambutol or isoniazid in the standard drug regimen, no statistically significant difference was found in sputum culture conversion at eight weeks of treatment^{17,18,76,110,124} except in two studies conducted in Brazil and India, which reported favourable activity for the moxifloxacin-containing regimens.^{19,21} However, moxifloxacin-containing regimens resulted in significantly higher proportions of sputum culture conversion at time-points earlier than eight weeks.^{17,18,76,124} A Cochrane review and meta-analysis¹²⁵ assessing the use of fluoroquinolones in drug-susceptible tuberculosis, including these earlier studies^{17,76,110}, found insufficient evidence on whether addition or substitution of the fluoroquinolones (moxifloxacin, gatifloxacin and levofloxacin) for ethambutol or isoniazid in the first-line regimen reduces death or relapse, or increases culture conversion at eight weeks. One phase II study investigating the efficacy of levofloxacin in shortening time to culture conversion when added to standard drug regimens found no improvement in treatment outcomes and levofloxacin¹²⁵ was not moved forward into subsequent phase III treatment shortening trials testing efficacy of moxifloxacin and gatifloxacin regimens.

A study testing the novel combination of moxifloxacin, pretomanid, and pyrazinamide found this regimen to have superior bactericidal activity during the first 8 weeks of treatment compared with the standard of care of isoniazid, rifampicin, pyrazinamide, and ethambutol, when measured by the reduction in colony forming units of *Mycobacterium tuberculosis* per mL of sputum.¹¹ This regimen is now being tested in the phase III *STAND* trial (NCT02342886) and results of the study are expected in 2018.

Studies reporting tuberculosis treatment failure, relapse or death at 18 or 24 months

(Table 3): Three treatment shortening trials testing moxifloxacin-containing regimens of four months duration compared to standard six-month drug regimens for the treatment of drug-susceptible tuberculosis failed to demonstrate non-inferiority of four month moxifloxacin regimens.^{12,13,20} The findings of these studies were in keeping with previous reports of moxifloxacin regimens resulting in a more rapid decline in bacterial load and earlier sputum conversion, however rates of relapse, treatment failure or death were higher in the four month moxifloxacin arms compared to the standard six month regimens at 18 or 24 months of follow up. The RIFAQUIN trial found high dose rifapentine (1200mg) and moxifloxacin once weekly as part of a six month treatment regimen to be as effective as the standard six month regimen.¹³ This isoniazid-sparing regimen may have a role in settings with high levels of isoniazid resistance, although previous reports of impaired rifapentine efficacy and acquired drug resistance using lower doses in combination with isoniazid in HIV infected patients, may need further investigation when used in combination with moxifloxacin at higher doses.^{126,127} The disappointing results of these large, robust and expensive phase III studies has been extensively reviewed in other reports.^{23,26,27,29,30} In light of these findings questions have been raised regarding the reliability of the early mouse-model data that informed the design of the phase II and III treatment shortening studies, however one study that analysed the relapse data from the mouse studies concluded that researchers may have been over-estimated the findings of these studies as well as of the phase II clinical trials conducted.^{26,29} Inadequate moxifloxacin concentrations in plasma and

sites of action has also been suggested as a contributing factor for the poor outcomes shown.^{24,27}

Conclusions

Studies of moxifloxacin-containing regimens for treatment of drug-susceptible tuberculosis have reported earlier sputum culture conversion, although current evidence does not support the use of moxifloxacin in treatment shortening regimens. The RIFAQUIN trial found high dose rifapentine (1200mg) and moxifloxacin once weekly as part of a six month treatment regimen to be as effective as the standard six month regimens. Moxifloxacin may be used in drug-susceptible tuberculosis if toxicity develops to first line drugs or for INH mono-resistance, with no additional safety concerns when compared to current first line regimens, and remains an important drug for the treatment of MDR and XDR tuberculosis. Higher bactericidal activity also suggests that moxifloxacin-containing regimens are at least as bactericidal as the current standard first line regimens. Early results of studies using moxifloxacin in novel drug regimens are promising. Pharmacokinetics are highly variable and drug exposures achieved in plasma and sites of action, using standard 400mg dose, may not be optimal for clinical efficacy, preventing emergent resistance, or achieving the proposed PK-PD targets for clinical efficacy in all patients. Co-administration of rifamycins decrease moxifloxacin drug concentrations by up to 31%. Although the clinical relevance of this effect has not been evaluated, given moxifloxacin's concentration-dependant activity lower concentrations are expected to result in decreased activity and potentially worse treatment outcomes in some patients. The potential to improve clinical outcomes by adjusting drug dosages to achieve therapeutic targets presents an important opportunity to optimise the current treatment strategies used and reduce the risk of emergent resistance.

Knowledge gaps and future research

Clinically validated targets for drug exposure to moxifloxacin associated with improved tuberculosis treatment outcomes need to be defined. Despite limited resources for tuberculosis research, clinical trials testing the efficacy of new or repurposed tuberculosis drugs should include PK-PD studies that can fill knowledge gaps on effects of PK variability and drug interactions on drug exposures and treatment outcomes, in diverse patient populations and co-morbidities. Specifically, the impact of HIV co-infection and ART co-treatment on moxifloxacin pharmacokinetics in high HIV burden settings needs investigation. Little data is currently available on the effect of rifampicin co-administration in African patients. Safety data for dosing moxifloxacin at higher doses of 600–800mg is limited and some data will become available from the STREAM clinical trial testing moxifloxacin at 800mg for MDR-TB.¹⁴ The effects of pharmacogenetic variation in relevant drug metabolizing enzymes and drug transporter proteins on moxifloxacin PK parameters in tuberculosis treatment is an area for future research. Therapeutic drug monitoring (TDM) is a standard clinical technique using plasma drug concentrations to guide dosing. The use of drug concentration monitoring and adjustment of drug dosages in individual patients, has been employed in certain tuberculosis treatment centers to make informed dosing decisions, especially in patients with poor treatment responses. As more data becomes available on optimizing tuberculosis treatment outcomes using TDM, it may become more widely used

although its routine use in resource-constrained settings presents a challenge. Resources should be made available for future research in operational settings to include the use of cheaper innovative technology and less invasive methods in PK studies, such as dry blood spots which have been clinically validated for moxifloxacin¹²⁸ and may be stored at room temperature, as well as MIC testing plates¹²⁹ to determine PK-PD parameters.³⁴ Furthermore, well designed studies which will define clinically validated targets for moxifloxacin and other tuberculosis drug are necessary. One study by Pasipanodya et al, defined target thresholds of drug exposures for current first-line tuberculosis drugs that predicted poor treatment outcomes.³³ However, other similar studies that determine associations between drug exposures such as AUC adjusted for MIC (AUC/MIC ratio) and time to sputum culture conversion at 8 weeks, treatment failure, relapse or days to positivity, using modelling or statistical analysis methods that are able to capture the complex usually non-linear interactions between drug exposures, clinical and other factors predicting tuberculosis treatment outcomes, are needed.

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Figure 1.

Two-dimensional imaging of MXF and PZA by MALDI mass spectrometry. Reprinted by permission from Macmillan Publishers Ltd: [Nature medicine] (*Prideaux et al 2015*²³), copyright (2015)

(a) MALDI mass spectrometry imaging of small molecules in TB-infected lung tissue. The relative ion abundance of specific analytes in regions of interest delineated on the basis of histology staining can be measured to provide semiquantitative data. (b) Ion maps of PZA and MXF in representative (selected from more than 200 lesions) lung lesions sampled

throughout the dosing interval; signal intensity is fixed for each drug. Hematoxylin and eosin (H&E) staining of adjacent sections is also shown (bottom). Outlines highlight the necrotic center of each lesion. Scale bars, 5 mm. (c) Left, diffusion of MXF in caseum as a function of caseum cellularity. $**P < 0.05$, two-tailed unpaired t -test. Error bars, mean $\pm$ s.d. ($n = 3$). Right, a typical H&E example representative of each cellularity score.

Table 1

Pharmacokinetics of moxifloxacin in combination with, or without, rifamycins in healthy individuals or patients with tuberculosis

Reference	Study Location Population Type of TB Sample size HIV status	Study design	Daily dose (mg)	Moxifloxacin AUC ^h (µg.h/mL)	Cmax (µg/mL)	Tmax (hr)	Changes in MXF AUC when MXF dosed with RIF/RPT vs MXF alone
Nijland ³⁸ 2007	Indonesia Adults, DS-TB N=19, HIV -ve	PK, fixed order, 2-period	MXF: 400 RIF: 450	33.3 ^{a,i} (25.1–55.5)	3.2 ^{a,i} (2.5–4.5)	2.5 ^{a,i} (0.5–6.0)	31% decrease in MXF AUC when co-administered with RIF
			MXF: 400	48.2 ^{b,j} (37.2–60.5)	4.7 ^{b,j} (3.4–6.0)	1.00 ^{b,i} (0.5–3.0)	GMR= 0.69 (90% CI 0.65–0.74)
Weiner ⁴⁰ 2007	USA Healthy adults N=16, HIV -ve	PK, sequential, 2-period	MXF: 400 RIF: 600	29.2 ± 7.5 ^{a,j}	3.6 ± 1.1 ^{a,j}	1.56 ± 0.91 ^{a,j}	27% decrease in MXF AUC when co-administered with RIF
			MXF: 400	39.4 ± 7.7 ^{b,j}	3.8 ± 0.8 ^{b,j}	1.97 ± 0.97 ^{b,j}	GMR 73.3 (90% CI 64.3–83.5) P= < 0.0001
Dooley ⁶⁸ 2008	USA Healthy adults N=15, HIV -ve	PK, sequential 2-period	MXF: 400 RPT: 900 ^g	34.4 (7.3) ^{a,j}	3.33 (0.67) ^{a,j}	2.60 (1.5) ^{a,j}	17.2% decrease in MXF AUC when co-administered with RPT
			MXF: 400	41.9 (10.2) ^{b,j}	4.03 (1.5) ^{b,j}	2.37 (1.3) ^{b,j}	GMR 0.83 (90% CI 0.77–0.89) p=0.0006
Peloquin 2008 ⁷²	Brazil Adults, DS-TB N=29 (9 MXF PK) HIV -ve	Population PK	MXF: 400	60 ^{b,i} (24–140)	6.13 ^{b,i} (4.47–9.00)	1.0 ^{b,i} (1.0–2.0)	-
Alffenaar 2009 ⁴⁴	Netherlands Adult, DS-TBM N=4, HIV -ve	PK-PD	MXF: 400 RIF: 600	24.4 ^{a,i} (20.5–24.5)	2.57 ^{a,i} (1.79–3.47)	1.0 ^{a,i} (1.0–1.3)	
			MXF: 800 RIF: 600	38.3 ^{a,i} (32.2–42.4)	3.65 ^{a,i} (3.31–4.09)	2.0 ^{a,i} (2.0–2.5)	
Pranger 2011 ⁴⁰	Netherlands Adults, DS/DR-TB N=89 (16 MXF PK) HIV +ve (11%)	Retrospective PK-PD	MXF: 400 RIF: 450/600	21.3 ^{a,i} (8.5–72.2)	-	-	Not reported
			MXF: 400	36.8 ^{b,i} (12.7–50.4) 24.8 ^{b,i} (20.7–35.2)	2.5 ^{b,i} (2.0–2.9)	1 ^{b,i} (1–2)	RIF increased CL MXF (p=0.083)

Reference	Study Location Type of TB Sample size HIV status	Study design	Daily dose (mg)	Moxifloxacin AUC ^h (µg·h/mL)	Cmax (µg/mL)	Tmax (hr)	Changes in MXF AUC when MXF dosed with RIF/RPT vs MXF alone
			MXF overall alone/+RIF				
Ramachandran 2012 ³⁹	India Healthy Adults N=36, HIV -ve	PK, sequential, 2-period	MXF: 400 RIF: 450/600	34.26 ^{a,c,j} ± 6.37	4.66 ^{a,j} ± 0.74	1.72 ^{a,j} ± 0.96	29% decrease in MXF AUC when co-administered with RIF P<0.001
			MXF: 400	48.62 ^{b,c,j} ± 10.40	6.32 ^{b,j} ± 1.38	2.06 ^{b,j} ± 1.00	
Zvada 2012 ⁽⁴¹⁾	South Africa Adults, DS-TB N=28 HIV +ve (~27%)	PK	MXF: 400 RPT: 900 ^f	45.3 ^{a,d,i} (26.8–65.3)	2.8 ^{a,i} (2.0–4.5)	-	RPT increased MXF CL/F and decreased AUC by ~8% (weekly (1200)/ twice weekly 900mg dosing RPT)
			MXF: 400 RPT: 1200 ^e	46.2 ^{a,d,i} (29.5–60.6)	2.9 ^{a,i} (2.0–3.8)	-	
			MXF: 400	50.8 ^{b,d,i} (31.8–65.3)	3.8 ^{b,j} (2.1–4.6)	-	
Manika 2012 ⁽³⁵⁾	Greece Adults, DR-TB N=7, HIV -ve	Prospective PK	MXF: 400	37.96 ± 16.52 ^{b,j}	4.59 ^{b,j} ± 2.06	2.36 ^{b,j} ± 0.56	-
Rustami* 2013 ⁽⁴⁵⁾	Indonesia >14 years old DS/DR-TBM N=60 (35 MXF) HIV +ve (12%)	PK sub-study	MXF: 400 RIF: 450/600 IV	28.6 ^{a,j} (24.2–33.8)	3.9 ^{a,j} (3.2–4.8)	2 ^{a,i} (1–6)	
			MXF 800mg RIF: 450/600 IV	60.4 ^{a,j} (45.4–80.3)	7.4 ⁱ ^{a,j} (5.6–9.6)	2 ^{a,i} (1–6)	
Magis Escura 2014 ⁽⁷³⁾	Netherlands Adults, DS/DR-TB N=41 (12 MXF) HIV +ve (7%)	PK	MXF: 7 (5.7-9.3) mg/kg RIF: 9.3 (4.7-13.0) mg/kg	33.6 ^{a,j} (15.2–84.2)	3.3 ^{a,j} (2.4–5.8)	2.0 ^{a,i} (1.0–4.0)	-
Te Brake ^k 2015 ⁽⁷⁵⁾	Indonesia >14 years old DS-TB N=35, HIV +ve (12%)	PK-PD sub-analysis (exposure categories)	MXF: 400 RIF: 450/600IV	25 ^{a,j} (18–30)	2.7 ^{a,i} (1.3–3.7)	-	-
			MXF: 800 RIF: 450/600IV	78 ^{a,j} (53–120)	9.6 ^{a,i} (7.2–15.1)	-	-
Manika 2015 ³⁷	Greece Adults, DS/DR-TB N=22, HIV -ve	PK	MXF: 400 RIF: 450/600	29.1 ^{a,i} (10–47.4)	3.9 ^{a,i} (1.9–4.5)	1.3 ^{a,i} (1–2)	Decrease in MXF AUC in MXF+RIF group-effect lower than previously reported, p=0.644
			MXF: 400	36.5 ^{b,i} (14.6–54.2)	4.1 ^{b,i} (2–6.4)	2 ^{b,i} (1–3)	

Reference	Study Location Population Type of TB Sample size HIV status	Study design	Daily dose (mg)	Moxifloxacin AUC ^h (µg.h/mL)	Cmax (µg/mL)	Tmax (hr)	Changes in MXF AUC when MXF dosed with RIF/RPT vs MXF alone
							Tmax shorter in MXF+RIF group, p=0.046
Lee 2015 ⁷⁴	South Korea Adults, DR-TB N=24, HIV -ve	PK-PD Retrospective	MXF: 400	-	0.73^{b,i} (0.24–1.87) 2-3hr post dose 0.60^{b,i} (0.19–3.01) 3-4hr post dose 1.83^{b,i} (0.61–2.41) 4-6hr post dose	-	-
Thee 2015 ⁷⁷	South Africa Children, DR-TB N=23 (7-15yrs) HIV +ve (26%)	PK, PD	MXF: 10 mg/kg	23.31^{b,i} (19.24–42.30)	3.08^{b,i} (2.85–3.82)	2.0^{b,i} (1.0–8.0)	-
Conde 2016 ⁷⁶	Brazil Adults, DS-TB N=60, HIV -ve	PK sub-analysis	MXF: 400 RPT:300-450	28 ^{a,i} (19.9–64.2)	2.5 ^{a,i} (1.6–3.0)	-	-
Naidoo 2017 ⁶⁴	South Africa Adults, DS-TB N=58, HIV +ve (70%)	PK	MXF:400mg RIF: 600mg				MXF CL increased by 29% and AUC by 8% when co-administered with RIF EFV co-treatment increased MXF oral clearance by 42% and decreased AUC by 30%

All Moxifloxacin concentrations at steady state. Concentrations in bold =Moxifloxacin alone/without RIF co-administration

^aMXF+RIF/RPT

^bMXF alone

^cAUC (0-12) (µg.hr/mL)

^dAUC (0-∞) (µg.h/mL)

^eonce week dosing

^ftwice week dosing,

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g thrice week dosing

h Area under the concentration-time curve from 0–24hours unless otherwise indicated

i Median

j Mean

k Sub-analysis of Ruslami 2013

Abbreviations: AUC=Area under the concentration time curve, CL= Clearance, CL/F= Oral Clearance, C_{max}=Maximum concentration, DS=Drug sensitive, DR=Drug resistant, EFV= Efavirenz, GMR=Geometric mean ratio, HIV= Human Immunodeficiency Virus, hr=hours, IV=intravenous, L=Lite, MXF=Moxifloxacin, mg=milligram MDR=Multidrug-resistant, PD=Pharmacodynamic PK=Pharmacokinetic, RIF=Rifampicin, RPT=Rifapentine T_{max}= time to maximum concentration TB=Tuberculosis

Table 2

Early Bactericidal Activity (EBA) of moxifloxacin in patients with smear positive tuberculosis

Study (Ref)	Comparator Drugs ^d	Dose (mg)	EBA ^{a,b}
Gosling 2003 ¹²⁰			Mean EBA_{0.2}
	INH	300	0.77 (SD 0.37)
	RIF	600	0.28 (SD 0.21)
	MXF	400	0.53 (SD 0.31)
Pletz 2004 ¹²¹			Mean EBA_{0.5}
	MXF	400	0.21
	INH	6-8mg/kg	0.27 95% CI of difference (-0.337- 0.210)
Gillespie 2005 ¹²²			Mean EBA_{0.2}
	MXF+	400	0.60 (95% CI 0.23-0.97)
	INH	300	
Johnson 2006 ¹¹⁵			Mean EBA_{0.2}/ EBA_{2.7}
	INH	300	0.67 (SD 0.17)/ 0.08 (SD 0.09)
	LFX	1200	0.45 (SD 0.35)/ 0.18 (SD 0.13)
	GFX	400	0.35 (SD 0.27) /0.17 (SD 0.13)
	MXF	400	0.33 (SD 0.39)/ 0.17 (SD 0.09)
Diacon 2012 ¹²³			Mean EBA_{0.14}
	MXF+	400	0.233 (SD 0.128)
	PA824(Pa)+	200	
	PZA(Z)	1500	
	RHZE	275 ^c	0.140 (SD 0.094)

Abbreviations: CI= confidence interval, EBA= Early bactericidal activity, E=Ethambutol, GFX= Gatifloxacin, INH/H=Isoniazid, LFX=Levofloxacin, MXF=Moxifloxacin, PZA/Z=pyrazinamide, PA824/Pa= pretomanid, RIF/R=Rifampicin, SD= standard deviation

^a EBA defined as fall in log10 colony forming units (cfu)/ml sputum/day,

^b numbers in subscript refer to the number of days used to determine EBA

^c weight based,

^d plus sign (+) between drugs denotes drugs used in combination.

Table 3

Phase II and III clinical trials investigating the use of moxifloxacin in drug susceptible tuberculosis

Phase II or III RCT's: Proportion of patients with negative sputum culture after 8 weeks of treatment			
Study Population Total N	Participants	Drug Regimen Intensive Phase/Continuation Phase	Outcome (Proportion negative cultures after 8 weeks of treatment)
Burman 2006 ¹⁷ Africa, North America, N=336	74% cavitation, 22% HIV +ve Male 67%	Intervention Arms: 2RHZM, 4RH Control Arm: 2RHZE, 4RH	MXF Arm – 71% Control Arm – 71% (p=0.97) <i>MXF arm more negative cultures at week 4 and 6 (p=0.05, 0.06)</i>
Rustomjee 2008 ¹⁸ South Africa N=217	94% cavitation 59% HIV +ve Male 67%	Intervention Arms: 2RHZM, 4RH Control Arm: 2RHZE, 4RH	MXF Arm – 82% Control Arm – 64% (p=0.058) <i>MXF faster sputum conversion at earlier timepoints (p=0.009)</i>
Conde 2009 ¹⁹ Brazil N=170	69% cavitation 3% HIV +ve Male 62%	Intervention Arm: 2RHZM, 4RH Control Arm: 2RHZE, 4RH	MXF Arm – 80% Control Arm – 63% (p=0.03)
Dorman 2009 ¹¹⁰ Uganda, North America, South Africa, Brazil, Spain N=433	74% cavitation 11% HIV +ve Male 72%	Intervention Arm: 2RZEM/4RH Control Arm: 2RHZE, 4RH	MXF Arm – 60% Control Arm – 55% (p=0.37)
Wang 2010 ¹²⁴ Taiwan N=150 (*did not randomize)	41% cavitation 0% HIV +ve Male 66%	Intervention Arm: 2RHZEM, 4RH Control Arm: 2RHZE, 4RH	MXF Arm – 82% Control Arm – 83% (p=0.17) <i>MXF arm more negative cultures at week 6 (82% vs 61% p=0.011)</i>
Velayutham 2014 ²¹ India N=801 (Interim analysis at Week 8)	37% cavitation 0% HIV +ve Male 75%	Intervention Arms (MXF Arm): 3HRZEM; 2HRZEM, 2HRM(daily); 2HRZEM, 2HRM(thrice weekly) Control Arm: 2RHZE, 4RH (thrice weekly)	^h MXF Arm: 95% RHZE: 81% (p<0.001) <i>MXF arm more negative cultures at week 2, 4, 6 (p<0.05)</i>
Conde 2016 – RIOMAR ⁷⁶ Brazil N=121	76% Cavitation 0% HIV +ve Male 69%	Intervention Arm: 2RPT HZM, 4RH Control Arm: 2RHZE, 4RH	MXF Arm - 79% Control Arm- 66% (p = 0.23) ^e <i>MXF Arm-Earlier time to sputum culture conversion</i>
Moxifloxacin in Novel Drug Regimen with Pretomanid and Pyrazinamide-bactericidal activity at 8 weeks			
Study Population Total N	Participants	Drug Regimen	Outcome
Dawson 2015 ¹¹ South Africa, Tanzania N=207 HIV~ 20% <i>*Results of the ongoing phase III STAND trial testing these regimens expected in 2018</i>	20% HIV +ve Male 65%	Intervention Arms (DS-TB): MPa ^c Z MPa ^d Z Control Arm: RHZE	Mean change daily log¹⁰ CFU counts for days 0–56: (95% Bayesian credibility interval) MPa100Z arm 0-133 (0-109–0-155) MPa200Z arm 0-155 (0-133–0-178) Control Arm- 0-112 (0-093–0-131) MPaZ arms superior to control (higher bactericidal activity in DS-TB)
Phase III RCTs (Non-inferiority Studies): Proportion with treatment failure or relapse, at 18 or 24 months			
Study Population Total N	Participants	Drug Regimen Intensive Phase/ Continuation Phase	Outcome (Treatment failure, Relapse)
Gillespie 2014 – REMOX ¹² South Africa, Tanzania, Zambia, Kenya, China, Malaysia, Thailand, India Mexico N=1931	71% cavitation 7% HIV +ve Male 70%	Intervention Arms: 4RHZM (INH Arm) 4RZEM (EMB Arm) Control Arm: 2RHZE, 4RH	Proportion Favourable^f outcome at 18 months: MXF Arm (INH): 85% (-6.1 difference from control, 97.5% CI, 1.7 to 10.5) MXF Arm (EMB): 80% (-11.4 difference from control, 97.5% CI, 6.7 to 16.1) Control Arm - 92% Both MXF arms not non-inferior to Control

Phase III RCTs (Non-inferiority Studies): Proportion with treatment failure or relapse, at 18 or 24 months			
Study Population Total N	Participants	Drug Regimen Intensive Phase/ Continuation Phase	Outcome (Treatment failure, Relapse)
Jindani 2014–RIFAQUIN ¹³ South Africa, Zimbabwe Zambia, Botswana N=827	65% Cavitation 27% HIV +ve Male 64%	Intervention Arms: Four-month Arm 2RMZE, 2RPT ^a M (twice weekly) Six-month Arm 2RMZE, (4RPT ^b M (once weekly) Control Arm: 2RHZE, 4RH	Proportion Unfavourable ^g outcome at 18 months 4-month MXF Arm 18.2% (difference from control, 13.6; 90% CI, 8.1 to 19.1) 6-month MXF Arm: 3.2% (difference from control, –1.8; 90% CI, –6.1 to 2.4) Control Arm – 4.9% 4-Month MXF arm <i>not</i> non-inferior, but 6-month MXF arm as effective as control
Jawahar 2013 ²¹ India N=429 (<i>Trial stopped early due to higher recurrence rates in fluoroquinolone arms</i>)	79% cavitation 0% HIV +ve Male 74%	Intervention Arms: 2RHZM, 2RHM (thrice weekly) 2RHZG, 2RHG (thrice weekly) Control Arm: 2RHZE, 4RH	TB recurrence at 24 months: GFX Arm - 15% MXF Arm - 11% Control Arm - 6% (p = 0.02 GFX vs control)) MXF and GFX arms inferior to control

All patients were adults and sputum smear positive at baseline. Abbreviations: CI= confidence interval, DS=Drug-sensitive tuberculosis, EMB/E=Ethambutol, FQ=Fluoroquinolone, GFX/G=Gatifloxacin, HIV +ve= HIV positive, HIV-ve =HIV negative, INH/H=Isoniazid, MXF/M=Moxifloxacin, PZA/Z=Pyrazinamide, Pa=Pretomanid RIF=Rifampicin, RPT=Rifapentine, RCT=Randomized Controlled Trial.

^a 900mg,

^b 200mg,

^c 100mg,

^d 200mg,

^e results on MGIT,

^f favourable outcome defined as proportion of patients who had no bacteriologically or clinically defined failure or relapse within 18 months,

^g unfavourable outcome based on primary efficacy endpoints for composite treatment failure and relapse. Safety (Grade 3 or 4 Adverse Events) was not significantly different when compared across arms for all studies,

^h All patients allocated to the four moxifloxacin regimens received the same daily treatment (RHZEM) for the first 2 months, the study combined the results of these regimens and compared them with the control regimen