A moxifloxacin-based regimen for the treatment of recurrent, drug-sensitive pulmonary tuberculosis: An open-label, randomized, controlled trial

A moxifloxacin-based regimen for the treatment of recurrent drug-sensitive pulmonary tuberculosis: An open-label randomised controlled trial

Rubeshan Perumal [#,1,2,3], Nesri Padayatchi [#,1,3], Nonhlanhla Yende-Zuma[1,3], Anushka Naidoo[1,3], Dhineshree Govender[1,3], Kogieleum Naidoo[1,3]

[1] Centre for the AIDS Programme of Research in South Africa, Nelson R Mandela School of Medicine, College of Health Sciences, University of KwaZulu-Natal

[2] Department of Pulmonology and Critical Care, Groote Schuur Hospital, University of Cape Town, Western Cape, South Africa

[3] South African Medical Research Council-CAPRISA HIV-TB Pathogenesis and Treatment Research Unit, Doris Duke Medical Research Institute, University of KwaZulu-Natal

[#]RP and NP contributed equally to this manuscript

Corresponding author:

Rubeshan Perumal, MBChB, MPH, MMed, FCP(SA)

CAPRISA, Doris Duke Medical Research Institute, University of KwaZulu-Natal, Private Bag X7, Congella, 4013, South Africa. Telephone: (+27) 31 260 4550; Fax: (+27) 31 205 0329

rubeshanperumal@gmail.com

Summary of main point: Replacement of ethambutol with moxifloxacin for the treatment of recurrent TB did not improve culture conversion rates at the end of 8 weeks or treatment success compared with the standard regimen, and was associated with a higher incidence of adverse events.

Abstract

Background

The substitution of moxifloxacin for ethambutol produced promising results for improved tuberculosis (TB) treatment outcomes.

Method

We conducted an open-label randomized trial to test whether a moxifloxacin-containing treatment regimen was superior to the standard regimen for the treatment of recurrent TB. The primary and secondary outcomes were sputum culture conversion rate at the end of 8 weeks and the proportion of participants with a favourable outcome, respectively.

Results

We enrolled 196 participants; 69.9% were male and 70.4% were co-infected with HIV. There was no significant difference between the study groups in the proportion of patients achieving culture conversion at the end of 8 weeks [83.0% (Moxifloxacin) vs 78.5% (Control), p=0.463], however the median time to culture conversion was significantly shorter (6.0 weeks, IQR 4.0 – 8.3) in the moxifloxacin group than the control group (7.9 weeks, IQR 4.0–11.4) (p=0.018). A favourable end-of-treatment outcome was reported in 86 participants (87.8%) in the moxifloxacin group and 93 participants (94.9%) in the control group, for an adjusted absolute risk difference of -5.5 (95% CI -13.8 to 2.8, p=0.193) percentage points. There was a significantly higher proportion of participants with grade 3 or 4 adverse events [43.9% (43/98) vs 25.5% (25/98), p=0.011] and serious adverse events [27.6% (27/98) vs 12.2% (12/98), p=0.012] in the moxifloxacin group.

Conclusion

Replacement of ethambutol with moxifloxacin did not significantly improve culture conversion rates at the end of 8 weeks or treatment success, and was associated with a higher incidence of adverse events.

Keywords: moxifloxacin, tuberculosis, Recurrent tuberculosis, treatment outcomes

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Tuberculosis(TB) is the leading cause of death from a curable infectious disease globally[1]. Chemotherapeutic regimens for drug-sensitive pulmonary tuberculosis are associated with treatment success rates in excess of 95%[1]. However, there is considerable variability in treatment success across the world; only eight of the top 30 high TB burden countries reached or exceeded a 90% treatment success rate in 2015, over 1 million people experienced poor treatment outcomes globally[2, 3]. Recurrent TB remains a growing challenge in low and middle-income countries, where up to a third of patients present with previously treated TB[1]. In 2016, 300 000 of the 6.6 million people reported to have TB had previously been treated for the disease[1]. Treatment success rates in this vulnerable group range from 27% to 92%[4-6]. The WHO guidelines recommend that treatment of recurrent TB be based on drug susceptibility testing in individual patients, and advised against the use of the streptomycin-containing category II regimen[1]. There have been no randomized controlled trials to support the use of the existing WHO recommended treatment strategy for recurrent TB, and only a few observational studies have prospectively evaluated the present strategy[4-6].

Fluoroquinolones, including moxifloxacin, demonstrate high activity against *Mycobacterium tuberculosis*, have favourable pharmacokinetics, have limited drug-drug interaction potential, and have been shown to be safe[7-16]. Clinical trials have demonstrated improved time to culture conversion and non-inferior treatment outcomes compared to standard first-line treatment. However, fluoroquinolone-containing regimens have been associated with a higher incidence of relapse, albeit in the context of treatment shortening trials[10, 13, 17, 18].

As a step toward identifying a safe and effective treatment regimen for patients with previously treated TB in a high TB/HIV burden setting, who are at increased risk for treatment failure and acquired drug resistance, we designed the Improving Treatment Success (IMPRESS) Trial to determine whether replacement of ethambutol with moxifloxacin would improve treatment success compared with the standard regimen.

Methods

Study design and oversight

IMPRESS was an open-label randomized controlled trial to test whether a moxifloxacin-containing treatment regimen was superior to the standard regimen (Figure 1). The study was conducted under the oversight of the University of KwaZulu-Natal Biomedical Research Ethics Committee (BFC029/13) and the South African Medicines Control Council (MCC Ref:20130510). Standard TB drugs (rifampicin, isoniazid, pyrazinamide, and ethambutol) were procured from the Department of Health, and moxifloxacin was donated by Bayer Healthcare. Neither entity had any role in the study design, data accrual, data analysis or manuscript preparation.

Study participants

All participants recruited to the study were ≥18 years of age, had a history of completing prior TB treatment, and had been diagnosed with sputum smear-positive, rifampicin-susceptible *Mycobacterium tuberculosis* based on GeneXpert MTB/RIF®. All participants were required to agree to HIV testing, and both HIV-positive and HIV-negative participants were eligible. Written informed consent was obtained from all participants. The trial was

conducted at the eThekwini HIV-tuberculosis clinic, which is operated by the Centre for the AIDS Programme of Research in South Africa (CAPRISA) in Durban, South Africa.

Randomization and study treatments

Participants were randomized in a 1:1 ratio to the intervention or control arms using permuted block randomization, with blocks of size 4 and 6, stratified by HIV status. During randomization, participants were assigned a unique study number selected sequentially from the appropriate randomization list, generated by the study statistician that corresponded to the treatment arm. The standard treatment regimen (control group) consisted of daily doses of rifampicin, isoniazid, pyrazinamide and ethambutol for 8 weeks, followed by daily doses of rifampicin and isoniazid for 16 weeks; while the intervention arm substituted moxifloxacin for ethambutol (moxifloxacin group), and consisted of daily doses of moxifloxacin, rifampicin, isoniazid and pyrazinamide for 8 weeks, followed by daily doses of moxifloxacin, rifampicin and isoniazid for 16 weeks. During the first two months (intensive phase) of treatment, participants in the control arm received the following weight-based doses by fixed dose combination tablets: Participants who were 38 – 54kg received rifampicin 450mg, isoniazid 225mg, pyrazinamide 1200mg, ethambutol 825mg; participants who were 54 – 70kg received rifampicin 600mg, isoniazid 300mg, pyrazinamide 1600mg, ethambutol 1100mg; participants who were > 70 kg received rifampicin 750mg, isoniazid 375mg, pyrazinamide 2000mg, ethambutol 1375mg. During the subsequent four months (continuation phase), participants continued on the same weight-based doses of rifampicin and isoniazid. Participants in the moxifloxacin arm received 400 mg of moxifloxacin (Avelox®, Bayer Healthcare) daily for the entire duration of treatment.

Rifampicin, isoniazid, and pyrazinamide were dosed as for the control arm. Pill count reconciliation was performed at each visit, in addition to self-reported adherence.

Study procedures

After initial screening and baseline visits, participants were seen fortnightly for the first eight weeks, followed by monthly visits until 8 months after randomization, and then alternate month visits until 18 months after randomization. All participants underwent a baseline clinical evaluation which included physical examination, HIV testing, provision of contraception, screening of concomitant drug exposures, posteroanterior chest radiograph, electrocardiogram (with corrected QT interval estimation), tests of visual acuity (Ishihara and Snellen charts), and urinalysis. Safety monitoring, which included hepatic function assessment, kidney function assessment, electrolytes, and full blood count, was performed at baseline and every two-months until the end of treatment.

Sputum samples were collected for smears and culture at baseline, fortnightly for 8 weeks, monthly until the end of treatment, and then on alternate months until the end of 18 months after randomization. Sputum was decontaminated with *N*-acetyl-*L*-cysteine-sodium hydroxide (BBL Mycoprep- Becton Dickinson, Franklin Lakes, New Jersey), examined using Auramine O fluorescent microscopy, and cultured on Lowenstein-Jensen (Becton Dickinson, Franklin Lakes, New Jersey) solid medium and in a Mycobacteria Growth Indicator Tube (MGIT) containing Middlebrook 7H9 broth liquid medium (Becton Dickinson Franklin Lakes, New Jersey). At baseline, sputum was also evaluated by GeneXpert MTB/RIF (Cepheid Sunnyvale, California, United States) to exclude rifampicin-resistance. We performed mycobacterial speciation by MPT64 antigen detection and direct culture examination (Ziehl Neelsen microscopy).

Adverse events were graded according to the modified toxicity events criteria by the National Institute of Allergy and Infectious Diseases, Division of AIDS (DAIDS AE Grading Table, Version 1, August 2009).

Study outcomes

The primary efficacy outcome was the proportion of participants who had sputum culture conversion at the end of eight weeks of treatment, where culture conversion was defined as the first of two negative cultures at two different visits without an intervening positive culture. Time to culture conversion was the time from treatment onset to culture conversion. The secondary efficacy outcome was the proportion of participants with a favourable outcome, defined as having a negative culture at the end of treatment. An unfavourable outcome was defined as bacteriologically or clinically determined treatment failure or death before the end of scheduled treatment for reasons other than violence or trauma. Relapse after completion of treatment was defined as two positive cultures within a period of four months without an intervening negative culture.

Statistical analysis

We estimated that a total sample size of 330 participants would provide a power of 80% and alpha level of 0.05 to detect a 15% absolute difference in 8-week culture conversion rates between the moxifloxacin arm and control arm, assuming 75% and 60% culture conversion rates in the moxifloxacin and control arm, respectively. All analyses were performed according to the intention-to-treat principle. The primary and secondary outcomes were analysed with Fisher's exact test. To improve the precision of the treatment effect estimates, we used Poisson regression with robust variance. The multivariable models were adjusted for baseline characteristics such as HIV status, age, sex, the presence of cavitation

on chest radiograph, and time to initial sputum culture positivity. Baseline characteristics were summarised and compared using Fisher's exact test for the categorical data, and unpaired t-tests or the Wilcoxon two-sample test for continuous data. We used Kaplan–Meier curves and the Gehan-Breslow-Wilcoxon test to compare time to culture conversion. Moreover, we used a univariable proportional hazards model to measure the strength of the association between time to culture conversion and the study group. The proportions of participants who had at least one grade 3 or 4 adverse event, and those who reported at least one serious adverse event were compared across treatment groups using Fisher's exact test.

Results

A total of 244 participants were screened and 197 underwent randomisation at a single centre in Durban, South Africa, between 1 November 2013 and 31 October 2015 (Figure 1). The main reasons for ineligibility were inadmissible haematological or biochemical results, a low Karnofsky score, abnormal electrocardiography, or diabetes mellitus. One patient was excluded after randomisation due to a violation of entry criteria. Overall, retention until the end of follow-up was high (88.8%); 87.8% in the moxifloxacin arm and 89.8% in the control arm. The demographic and clinical characteristics of participants were similar in the study arms (Table 1). Males comprised 69.9% of the study population, and 18.4% of participants were over 45 years of age. Over two-thirds (70.4%) of participants were infected with HIV, and 39.5% had a CD4 count below 200 cells/mm^3. Cavitation was a radiological feature in 72% of participants. The time to a positive liquid culture result was greater than 5 days in the majority of participants in both study groups. Participants were followed for a median of

13 months (IQR 12 – 16); 13 (IQR 11 – 16) months and 13 (IQR 12 – 16) months in the moxifloxacin and control arms, respectively.

Culture conversion at the end of 8 weeks was reported in 78 participants (83%) in the moxifloxacin group and 73 participants (78.5%) in the control group (p=0.463) (Table 2). The median time to culture conversion was significantly shorter (6.0 weeks, IQR 4.0 – 8.3) in the moxifloxacin group than the control group (7.9 weeks, interquartile (IQR) 4.0 – 11.4) (Figure 2, Wilcoxon test p=0.018). Moreover, of those participants who achieved a favourable treatment outcome, participants in the moxifloxacin group had a significantly shorter time to culture conversion [Figure 3, Wilcoxon test p=0.005; hazard ratio (HR): 1.33 (95% confidence interval (CI): 0.98-1.80); p=0.065].

A favourable end-of-treatment outcome was reported in 86 participants (87.8%) in the moxifloxacin group and 93 participants (94.9%) in the control group (p=0.126), for an adjusted absolute risk difference of -5.5 (95% CI: -13.8 to 2.8) percentage points. The most common reasons for an unfavourable outcome at the end of treatment were treatment failure or death which occurred in 8 participants (8.2%) in the moxifloxacin arm and 3 participants (3%) in the control group. There were no unequivocal cases of acquired drug resistance in either group. We identified two cases of relapse in the 12-month follow-up period, one case of drug-susceptible pulmonary tuberculosis in each study arm, occurring 3 and 8 months after cure of the initial episode, respectively.

Although female sex [risk ratio (RR): 1.14 (95% CI: 1.0-1.31), p=0.056)], a longer time to culture positivity at baseline [RR: 1.29 (95% CI: 1.00-1.68), p=0.050] and the absence of cavitation [RR: 1.13 (95% CI: 0.99-1.29), p=0.076] had a non-statistically significant tendency toward an increased likelihood of culture conversion, we found no significant predictors of

culture conversion at 8 weeks in a multivariable model (Table 3). In an unadjusted model, HIV negative status was the only significant predictor of an improved likelihood of a favourable end-of-treatment outcome [RR: 1.08 (1.003-1.17), p=0.042] (Table 4).

In total, there were 164 adverse events from 72 participants during the trial; 110 adverse events occurred in 45 (45.9%) participants in the moxifloxacin group, and 54 adverse events occurred in 27 (27.6%) participants in the control group (p=0.012) (Table 5). There were 2 grade 1 events, 14 grade 2 events, 116 grade 3 events, and 32 grade 4 events (Supplementary material). Eighty-two serious adverse events were reported overall; 60 occurred in 27 (27.6%) participants in the moxifloxacin group and 22 occurred in 12 (12.2%) participants in the control group (p=0.012). There were 10 deaths (5 during TB treatment and 5 during follow-up); 2 of which were deemed to be tuberculosis-related; 6 deaths were reported in the moxifloxacin group and 4 deaths in the control group. Although there was a significantly increased risk of adverse events, specifically grade 3 or 4 events and serious adverse events, in the moxifloxacin group, there was no significant between-group differences in hospitalisation or death. In addition, we had no reported cases of adverse events of special interest, including tendinopathy, hypoglycaemia, peripheral neuropathy, or cardiac toxicity.

Discussion

This trial, conducted in a high TB/HIV burden setting, aimed to determine whether replacement of ethambutol with moxifloxacin would improve treatment success compared with the standard regimen, and demonstrated that substitution with moxifloxacin was not superior for the treatment of recurrent tuberculosis. The proportion of favourable

treatment outcomes were not significantly different between treatment groups; a finding which was consistent irrespective of HIV status. Although not statistically significant, a greater number of participants in the moxifloxacin group experienced treatment failure or death. Participants in the moxifloxacin group, however, had a significantly shorter median time to culture conversion; an observation which persisted in the HIV positive sub-group. This finding suggests that moxifloxacin may be a particularly useful therapeutic option in TB/HIV co-infected patients, who are generally at greater risk for delayed sputum culture conversion with standard treatment. Moreover, shortening the time to culture conversion is an important step toward reducing TB transmission[19]. In comparison with other trials that investigated fluoroquinolone substitution to improve treatment success, our study demonstrated lower rates of unfavourable outcomes in both treatment groups, although the proportion of participants who experienced culture-confirmed treatment failure in our study was higher than previously reported[10, 13, 17]. Additionally, the control regimen achieved a favourable outcome in 94.9% of patients, and as there is a paucity of trial data to support a retreatment regimen in patients with recurrent drug-susceptible TB, this study serves an important purpose of affirming the present WHO recommendation for retreatment.

This study showed that a moxifloxacin-containing regimen had significantly greater proportion of grade 3 or 4, and serious adverse events, but no increased risk of hospitalisation or death. In particular, we did not find evidence of hypoglycaemia, cardiac toxicity, tendinopathy, or hepatic dysfunction which have previously been raised as potential safety concerns[20-22]. Nonetheless, the moxifloxacin-containing regimen was associated with over twice the number of grade 3, grade 4, and serious adverse events compared with the control arm, and almost half (43/98) of all the participants in the

moxifloxacin group experienced at least one grade 3 or 4 adverse event. These are important findings for future studies which may seek to optimise the use of moxifloxacin in tuberculosis treatment regimens, as dose-dependent toxicities may pose a significant limitation to optimising pharmacokinetic/pharmacodynamic performance.

This trial joins other recent trials of fluoroquinolone substitution for the treatment of drug-susceptible tuberculosis in raising doubts about the benefit of such a therapeutic substitution[10, 13, 17]. Collectively, it does not appear that a fluoroquinolone-containing regimen is able to improve end-of-treatment outcomes, provide durable cure, or aid in the elusive goal of shortening treatment duration. While it is likely that the disappointing performance of moxifloxacin may be related to its inability to penetrate tuberculosis lesions where persistent mycobacteria can reside, suboptimal pharmacokinetics may also be partly responsible[23]. In a pharmacokinetic study nested within our trial, sub-optimal moxifloxacin pharmacokinetic parameters were common, and were likely driven by a combination of sub-optimal dosing, pharmacogenomic factors, and increased intrinsic clearance due to rifampicin and efavirenz co-administration[24]. It remains to be evaluated whether increased doses of moxifloxacin may realise the true potential of a fluoroquinolone-containing regimen. Evaluating the safety of higher dose moxifloxacin is likely to limit a rapid efficacy evaluation of such a strategy, and the concerning safety profile from this trial warrants a cautious approach to similar moxifloxacin-containing regimens in future. In comparison to other trials of moxifloxacin-containing regimens, we reported a higher proportion of patients with adverse events of all grades. However, this is the only trial in which participants received daily moxifloxacin for six months, resulting in a longer total duration of exposure and likely higher cumulative exposure. Notwithstanding the difference in duration of exposure, a recent re-analysis of the REMoxTB trial data revealed

that participants receiving a moxifloxacin-containing regimen had fewer 'drug-related' grade 3 or 4 adverse events compared to participants receiving the control regimen, despite the overall incidence of grade 3 or 4 adverse events being similar[25]. The relatedness of an adverse event to a drug exposure was determined by the treating clinicians in that trial as part of a subjective assessment. As we did not assess the relatedness of adverse events to drug exposure, it was not possible to determine whether the excess adverse events in the moxifloxacin group in our trial were indeed related to the drug exposure.

An important concern for the tuberculosis drug development pipeline is the evidence of discordance between 8-week culture outcomes and end-of-treatment outcomes. The lack of a highly predictive early biomarker of long-term treatment outcomes is a serious concern, and may have costly consequences for future candidate drug evaluation. Despite widespread optimism, and a profusion of evidence from early bactericidal activity studies demonstrating the efficacy of fluoroquinolone-containing regimens for the treatment of drug-susceptible tuberculosis, the results of large and costly randomised controlled trials have not delivered the anticipated results[26-31]. Nonetheless, effective, safe and shorter regimens are desperately needed to make meaningful progress towards tuberculosis eradication. Further evaluation of fluoroquinolone-containing regimens for the treatment of drug-susceptible tuberculosis will first require investigation of the pharmacokinetic-pharmacodynamic relationships, drug-drug interactions, and drug-gradients within mycobacterial sanctuaries[32, 33].

The trial had some limitations. The number of participants who underwent randomisation (197) fell short of the target sample size (330), due to a slower-than-expected recruitment. It is possible that the attained sample size was insufficient to detect a significant difference

between study arms which did demonstrate a trend toward improved 8-week culture conversion in the moxifloxacin arm. Nonetheless, the data still provide valuable information on the performance of the control regimen as a retreatment strategy, and provide a reliable estimate of the efficacy and safety of this moxifloxacin-containing regimen that can guide future research. Follow-up was truncated and may not have been sufficiently long to detect relapses.

In this trial, the substitution of ethambutol with moxifloxacin for the treatment of recurrent pulmonary tuberculosis did not improve treatment success in comparison to the standard regimen, despite a shorter median duration to culture conversion.

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Competing interests

All authors have none.

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Figure Legends:

Figure 1. Screening, randomisation and follow-up of the study populations

Figure 2. Kaplan–Meier estimates of time to culture conversion. Wilcoxon test p-value=0.018
Hazard ratio: 1.15 (95% CI: 0.85-1.54), p-value=0.356

Figure 3. Kaplan–Meier estimates of time to culture conversion among participants with favourable outcome. Wilcoxon test p-value =0.005
Hazard ratio: 1.33 (95% CI: 0.98-1.80), p-value=0.065

Table 1. Baseline characteristics of participants

Characteristic	Moxifloxacin group (N=98)	Control group (N=98)	p-value
Male sex	74 (75.5)	63 (64.3)	0.119
Age group, *years*			0.462
<25	7 (7.1)	14 (14.3)	
25-34	37 (37.8)	35 (35.7)	
35-45	35 (35.7)	32 (32.7)	
>45	19 (19.4)	17 (17.3)	
HIV positive	70 (71.4)	68 (69.4)	0.876
CD4 count[a]			0.721
≤200 cells/mm^3	27 (41.5)	24 (38.1)	
>200 cells/mm^3	38 (58.5)	39 (61.9)	
Weight group			
>40-50 kg	24 (24.5)	25 (25.5)	0.574
>50-60 kg	39 (39.8)	45 (45.9)	
>60 kg	35 (35.7)	28 (28.6)	
Smoking in past 3 months	37 (37.8)	27 (27.6)	0.17
Cavitation[b]	68 (71.6)	71 (72.4)	1.00
Time to positivity on MGIT sputum culture			
< 5days	20 (20.4)	15 (15.3)	0.605
>= 5days	73 (74.5)	79 (80.6)	
Not available/culture negative	5 (5.1)	4 (4.1)	

[a]10 participants have missing data, [b]3 participants have missing data

Table 2. Week 8 and end-of-treatment outcomes

Status and Outcome		**Moxifloxacin group (N=98)**	**Control group (N=98)**	**p-value**
Week 8 culture results, n (%) [a]				
All participants	Culture Negative	78 (83.0)	73 (78.5)	0.463
	Culture Positive	16 (17.0)	20 (21.5)	
HIV positive	Culture Negative	57 (85.1)	51 (79.7)	0.494
	Culture Positive	10 (14.9)	13 (20.3)	
HIV negative	Culture Negative	21 (77.8)	22 (75.9)	1.00
	Culture Positive	6 (22.2)	7 (24.1)	
Median time to culture conversion in weeks (IQR) for all participants		6.0 (4.0-8.3)	7.9 (4.0-11.4)	0.018
Median time to culture conversion in weeks (IQR) for HIV positive participants		6.0 (4.0-8.0)	7.9 (4.0-11.2)	0.016
Median time to culture conversion in weeks (IQR) for HIV negative participants		7.9 (6.0-11.6)	7.9 (7.1-11.6)	0.691
End-of-treatment outcome, n (%)				
Favourable outcomes		86 (87.8)	93 (94.9)	0.126
	Cure	*86 (87.8)*	*92 (93.9)*	
	Successful completion	*0*	*1 (1.0)*	
Risk difference (95% CI)		*-7.1% (-15% to 0.7%) p=0.073*		
Adjusted Risk difference (95% CI)		*-5.5% (-13.8% to 2.8%) p=0.193*		

Unfavourable outcomes		12 (12.2)	5 (5.1)	
	Treatment failure (culture-confirmed)	*4 (4.1)*	*2 (2.0)*	
	Died	*4 (4.1)*	*1 (1.0)*	
	Other non-specified TB outcome[b]	*2 (2.0)*	*0*	
	Treatment interruption	*2 (2.0)*	*0*	
	Moved away/Relocated	*0*	*1 (1.0)*	
	Transferred out	*0*	*1 (1.0)*	
HIV positive	Favourable outcomes	59 (84.3)	64 (94.1)	0.099
	Unfavourable outcomes	11 (15.7)	4 (5.9)	
HIV negative	Favourable outcomes	27 (96.4)	29 (96.7)	1.000
	Unfavourable outcomes	1 (3.6)	1 (3.3)	

[a]9 participants have missing data (4 in the moxifloxacin arm and 5 in the control arm): 4 missed visits (2 in each arm), 3 terminated before week 8 (1 in the moxifloxacin arm and 2 in the control arm), and 2 had MOTT cultured (1 in each arm)

[b]1 withdrew consent after a month of treatment and 1 had MDR-TB

Table 3: Predictors of negative culture results at week 8

	Univariate		Multivariate	
	RR (95% CI)	**p-value**	**aRR (95% CI)**	**p-value**
Moxifloxacin group (ref: control group)	1.06 (0.92-1.22)	0.438	1.09 (0.93-1.26)	0.288
HIV negative (ref: HIV positive)	0.93 (0.79-1.10)	0.407	1.02 (0.84-1.24)	0.825
Female gender (ref: male gender)	1.14 (1.00-1.31)	0.056	1.09 (0.94-1.28)	0.252
Age (per 5-year increase)	1.00 (0.96-1.04)	0.961	1.00 (0.95-1.04)	0.841
≥5 days to positivity (ref:<5 days)	1.29 (1.00-1.68)	0.050	1.28 (0.98-1.69)	0.075
No cavitation (ref: cavitation)	1.13 (0.99-1.29)	0.076	1.11 (0.96-1.28)	0.149

Table 4: Predictors of favourable end-of-treatment outcomes

	Univariate		Multivariate	
	RR (95% CI)	**p-value**	**aRR (95% CI)**	**p-value**
Moxifloxacin group (ref: control group)	0.92 (0.85-1.01)	0.078	0.93 (0.84-1.02)	0.11
HIV negative (ref: HIV positive)	1.08 (1.003-1.17)	0.042	1.09 (0.99-1.20)	0.065
Female gender (ref: male gender)	1.02 (0.93-1.11)	0.667	1.01 (0.91-1.13)	0.812
Age (per 5 year increase)	0.99 (0.96-1.01)	0.338	0.99 (0.96-1.01)	0.355
≥5 days to positivity (ref:<5 days)	0.99 (0.88-1.10)	0.801	1.02 (0.89-1.16)	0.787
No cavitation (ref: cavitation)	1.05 (0.97-1.14)	0.250	1.07 (0.97-1.18)	0.190

Table 5: Safety outcomes

Adverse event, n(%)	**Moxifloxacin group (N=98)**		**Control group (N=98)**		**p-value**
	No. of events	No. of participants (%)	No. of events	No. of participants (%)	Comparing no. of participants
Any event	110	45 (45.9)	54	27 (27.6)	0.012
Grade 3	77	40 (40.8)	39	23 (23.5)	0.014
Grade 4	22	12 (12.2)	10	7 (7.1)	0.335
Grade 3 or 4	99	43 (43.9)	49	25 (25.5)	0.011
Serious adverse event	60	27 (27.6)	22	12 (12.2)	0.012
Death		6 (6.1)		4(4.1)	0.747

Figure 1

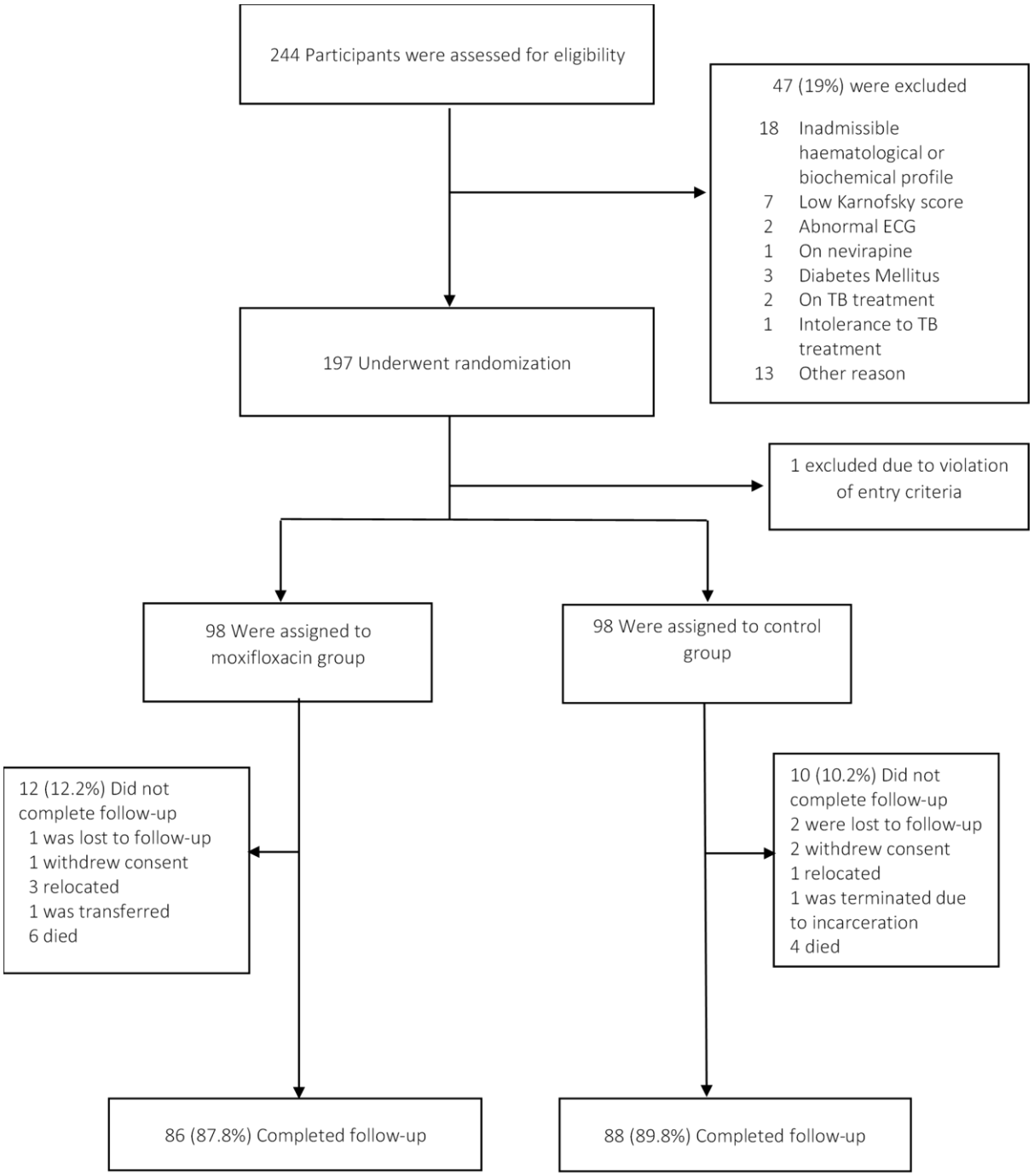
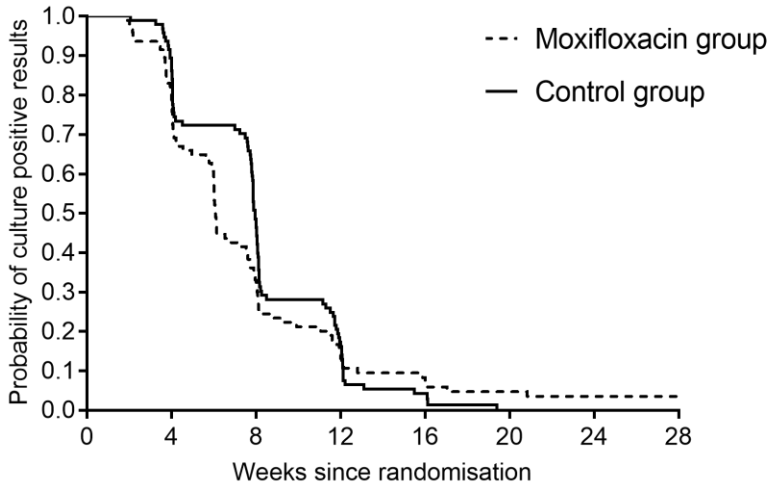
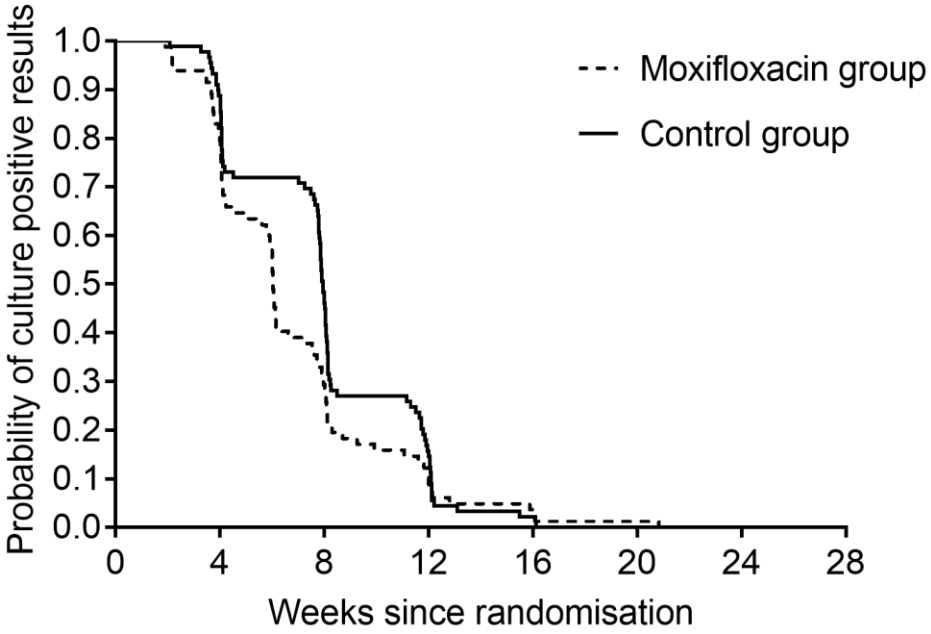


Figure 2



culture conversions/ at risk								
Moxifloxacin	0/98	18/76	63/31	79/13	84/8	88/4	89/3	89/3
Control	0/98	10/84	48/45	77/16	89/4	92/0	92/0	92/0

Figure 3



culture conversions/ at risk								
Moxifloxacin	0/86	16/66	58/24	73/9	79/3	81/1	82/0	82/0
Control	0/93	10/79	46/43	75/14	87/2	89/0	89/0	89/0