Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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RIFAQUIN Online Supplementary Appendix

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2 Detailed Methods

2.1 Eligibility Criteria

2.1.1 Patient inclusion criteria

1. Newly diagnosed pulmonary tuberculosis.
2. Two sputum specimens positive for tubercle bacilli on direct smear microscopy.
3. Either no previous anti-tuberculosis chemotherapy, or less than 2 weeks of previous chemotherapy at enrolment.
4. Aged 18 years and over.
5. A firm home address that is readily accessible for visiting and be intending to remain there or within the recruitment area for the entire treatment and follow up period.
6. Willing to agree to participate in the study and to give a sample of blood for HIV testing (and in Botswana have their HIV status disclosed to them).
7. Pre-menopausal women must be using a barrier form of contraception or be surgically sterilised or have an IUCD in place for the duration of the treatment phase.

2.1.2 Patient exclusion criteria

A patient will not be eligible for entry to the study if he/she:

1. Has any condition (except HIV infection) that may prove fatal during the study period.
2. Has TB meningitis.
3. Has pre-existing non-tuberculous disease likely to prejudice the response to, or assessment of, treatment e.g. insulin-dependent diabetes, liver or kidney disease, blood disorders, peripheral neuritis.
4. Is female and known to be pregnant, or breast feeding.
5. Is suffering from a condition likely to lead to uncooperative behaviour such as psychiatric illness or alcoholism.
6. Has contraindications to any medications in the study regimens.
7. Has a history of prolonged QTc syndrome or current or planned therapy with quinidine, procainamide, amiodarone, sotalol, disopyramide, ziprasidone, or terfenadine during the intensive phase of TB therapy.
8. Haemoglobin <7g/l.
9. Either AST or ALT > 5 times the upper range.
10. Creatinine clearance of < 30mls/min.
11. Has a history of seizures.
12. *If HIV positive with a CD4 count of less than 200/mm^3
13. Weight < 35kg.
14. **Requires anti-retroviral treatment (ART) at diagnosis

*The CD4 cut-off was amended from 200/mm^3 to 150/mm^3 during the course of the trial to improve recruitment. In the event, only 2 patients co-infected with HIV and with CD4 count between 150 and 200/mm^3 were enrolled.
**This exclusion criteria was amended to 'Already receiving anti-retroviral therapy (ART)' during the course of the trial to allow for patients starting ART at screening to be eligible for the trial.

2.2 Treatment of Patients

The drugs were supplied in bulk from Sanofi-Aventis (rifapentine, isoniazid, rifampicin), Bayer Healthcare (moxifloxacin), Sandoz SA (pyrazinamide) and Genus Pharmaceuticals (ethambutol) and distributed by an approved international distributor in Johannesburg.

All drugs were given in single dose formulations. No combination formulations were used. The doses of drugs given to each patient in the intensive phase are shown in the tables below and were based on the weight of the patient at the time of starting treatment.

Intensive phase dosages: 4- and 6-month study regimens – daily for 2 months

MEDICATION	Number of tablets (total dose) for different weights (kg)			
	35-39	40-54	55-70	>70
ethambutol (400mg)	1 (400mg)	2 (800mg)	3 (1200mg)	3 (1200mg)
ethambutol (100mg)	2 (200mg)	-------	-------	2(200mg)
moxifloxacin (400mg)	1 (400mg)	1 (400mg)	1 (400mg)	1 (400mg)
rifampicin (150mg)	3 (450mg)	3 (450mg)	4 (600mg)	4 (600mg)
pyrazinamide (500mg)	2 (1000mg)	3 (1500mg)	3 (1500mg)	4 (2000mg)

Intensive phase dosages: Control regimen – daily for 2 months

MEDICATION	Number of tablets (total dose) for different weights (kg)			
	35-39	40-54	55-70	>70
ethambutol (400mg)	1 (400mg)	2 (800mg)	3 (1200mg)	3 (1200mg)
ethambutol (100mg)	2 (200mg)	--------	--------	2 (200mg)
isoniazid (300mg)	1 (300mg)	1 (300mg)	1 (300mg)	1 (300mg)
rifampicin (150mg)	3 (450mg)	3 (450mg)	4 (600mg)	4 (600mg)
pyrazinamide (500mg)	2 (1000mg)	3 (1500mg)	3 (1500mg)	4 (2000mg)
pyridoxine (25mg)	1 (25mg)	1 (25mg)	1 (25mg)	1 (25mg)

When patients had completed the 2-month initial intensive phase of treatment (8 weeks), they started the continuation phase, irrespective of the results of bacteriological examinations at 2 months. The frequency and doses were as follows:

4-month study regimen: Patients allocated to this arm received 900 mg of rifapentine and 400 mg of moxifloxacin twice a week for 2 months (9 weeks).

6-month study regimen: Patients allocated to this arm received 1200 mg of rifapentine and 400 mg of moxifloxacin once a week for 4 months (18 weeks).

Control regimen: Patients allocated to this arm received rifampicin, isoniazid and pyridoxine at the same doses based on the weight of the patient at enrolment for 4 months (18 weeks).

Patients were admitted to hospital or attended the treatment facility daily so that ingestion of the drugs could be directly observed for the first 2 months. Thereafter, patients on the control regimen were given a week or a month's supply of the drugs to be taken under the supervision of a relative or other person who was designated the Domiciliary Treatment

Monitor (DTM) and who had agreed to undertake this function. Patients randomised to receive the study arms attended the treatment facility once or twice weekly in the continuation phase, according to the allocated regimen, to receive their treatment, as well as the pre-dose meal, supervised by the clinic staff.

The treatment phase is defined as the period from randomization (the same day as first dose) during which a patient should have been on allocated trial treatment. This is 26 weeks for patients on the control or 6-month regimens and 17 weeks for patients on the 4-month regimen. The intensive phase of treatment is defined as the first 8 weeks of the 4-drug combination and the continuation phase of treatment is defined as the remaining treatment with the 2-drug combination.

Most patients (86%) were followed up for 18 months from randomisation. However, patients in South Africa and Botswana randomised in the final 6 month period of enrolment had their follow-up reduced to either 12 or 15 months, to permit prolongation of the enrolment period. A meta-analysis showed that such a strategy would result in only a modest reduction in power as 78% of relapses occurred within 6 months of stopping treatment[1] and a more recent trial has shown consistent results[2]. 50 (6%) of patients had scheduled follow-up duration between 12 and 15 months and 64 (8%) had scheduled follow-up between 15 and 18 months. Since blocked randomisation with stratification by site was used, patients with reduced scheduled follow-up were well balanced between treatment regimens.

2.3 Sample Size Calculations

2.3.1 Sample size for the primary endpoint

The original sample size calculations were based on the following assumptions:

1. The failure/relapse rate in the control and intervention arms will be 4%, consistent with finding in many randomised trials[3], most recently an international study conducted in African and Asian centres under less strictly controlled conditions[4].
2. A non-inferiority margin of 4% in failure/relapse rate between the control and either of the intervention regimens is acceptable.
3. Up to 24% of randomised patients may be not assessable on account of loss to follow-up, including death from non-tuberculous causes, or initial drug resistance.

Patients were randomised in equal proportions to the three regimens and a one-sided significance level of 5% is appropriate, since this is a non-inferiority trial, not an equivalence study.

Subsequent to determining the sample size for RIFAQUIN, a revision of the sample size assumptions in the REMoxTB trial (which were closely aligned to those in RIFAQUIN) took place. An FDA requirement was that the chosen level of the margin of non-inferiority should be justified on both statistical and clinical grounds.

A margin of non-inferiority of 6% was selected and the justification was based on a review of previous trials comparing a 6- and a 4-month regimen without the inclusion of any new drugs, the absolute difference in relapse rates was found to be approximately 10% with a lower bound of the 95% confidence interval around this estimate of 6%. A margin of non-

inferiority of 6% was therefore selected and this has been adopted in the REMoxTB trial and also the trial conducted by the OFLOTUB consortium[5]. A number of outcomes that were originally classified as not assessable have been reclassified as unfavourable. These include all-cause mortality during treatment, changes of treatment for any reason and failure to complete treatment with no further follow-up visits (see full definition of primary outcome below).

The definitions of the primary endpoint and the sample size calculations for RIFAQUIN were written in a similar fashion to those for the REMoxTB trial which was being conducted at the same time with a similar design but different regimens being evaluated. It was felt necessary and appropriate to make similar adjustments to the RIFAQUIN trial to allow for comparability.

These changes were implemented in version 1.6 of the protocol dated 1st December 2009 at which point only 302 (37%) of patients had been randomised and no patients had completed follow-up and therefore reached the final endpoint. The first patient randomised had been in the study for 15 months. The independent data monitoring committee (IDMC) had met on two occasions but had not reviewed any bacteriological or efficacy data. The IDMC were not involved in any way with the change in endpoint definition as this was a consequence of external factors and dictated by the FDA in the context of the REMoxTB trial.

The RIFAQUIN power calculations were revised as follows:

1. It is assumed that the rate of unfavourable outcome will be 10% on both the control and intervention arms.
2. The non-inferiority margin in the failure/relapse rate is 6%.
3. 15% of randomised patients will be not assessable as some patients previously classified as not assessable will now be classified as unfavourable.

Based on these assumptions, a total of 310 evaluable participants per arm was required to demonstrate non-inferiority with 80% power, corresponding to 365 participants per arm needing to be enrolled. The sample size was therefore revised from the original 1250 to 1095.

2.3.2 Power calculations for acquired rifamycin resistance

If two thirds of the patients are HIV-infected and the bacteriologically confirmed relapse rate in the rifapentine containing regimens is 4%, a total of 310 evaluable patients per arm would provide approximately 8 relapses per arm among HIV-infected patients in the two study regimens receiving rifapentine to assess the sensitivity of the relapse strains.

If there are no cases of acquired rifamycin resistance among 8 relapses, the one sided upper 90% confidence level for the proportion with resistance would be 25%, the corresponding upper 80% confidence level would be 18%. If both rifapentine arms can be combined and there are 16 relapses the corresponding one sided upper 90% and 80% confidence levels are 13% and 10% respectively. A relapse rate higher than 4% would result in smaller upper confidence limits.

2.4 Analysis Populations

2.4.1 Modified Intention to Treat (mITT)

All patients randomised are included in the mITT population with the following exclusions:

1. Patients without culture confirmation of tuberculosis either at screening or baseline or within 2 weeks from randomisation.
2. Patients with resistance to isoniazid, rifampicin or moxifloxacin at screening or baseline (late screening failure).
3. Patients who died during the treatment phase from violent cause or trauma (e.g. road traffic accident).
4. Women who become pregnant during the treatment phase and stop their allocated treatment where their last culture is negative.
5. Patients reinfected with a new strain different from that with which they were originally infected.
6. Patients who, having completed active treatment, do not complete scheduled follow-up, their last culture result being negative.
7. Patients who died during the follow-up phase with no evidence of failure or relapse of their TB (in the opinion of the investigator), their last culture result being negative.

Patients in categories 3-7 are only excluded if they have not previously been classified as having an unfavourable outcome.

2.4.2 Per Protocol (PP)

All patients in the mITT population are included in the PP population with the following exclusions:

1. Patients not meeting the definition of having received *adequate treatment* provided they have not already had an unfavourable response to treatment.
2. Patients whose treatment was modified or extended for reasons other than an unfavourable response to treatment, e.g. an adverse drug reaction.

2.4.3 Adequate Treatment

Adherence to treatment is a measure of the number of directly observed (DOT) doses of the allocated drugs the patient has taken whether doses were supervised at the clinic or by the domiciliary treatment monitor at home.

A patient is considered to have received *adequate treatment* if both of the following conditions are met:

- at least 40 doses of intensive phase treatment are taken with 70 days of starting treatment,
- at least 90 doses of continuation phase treatment are taken within 22 weeks of starting the continuation phase for patients on the control regimen and at least 16 doses are taken within 13 weeks of starting the continuation phase for patients on study regimen 1 or within 22 weeks for patients in study regimen 2.

2.5 Primary Efficacy Outcome Definitions

Assessable patients are classified as having a favourable or unfavourable status at the end of scheduled follow-up. For the primary analysis of the MITT population, the definitions of unfavourable and favourable status are as follows.

Any visits at 72 weeks or later after randomisation are included in the analysis as an 18 month visit (i.e. up to six weeks before the scheduled 18 month visit at 78 weeks).

For patients with scheduled follow-up reduced to 12 or 15 months, only the protocol-defined 7 day window is used for the analysis. Visits at or after 51 weeks is included as a '12 month visit' for patients with 12 months of scheduled follow-up and visits at or after 64 weeks is included as a '15 month visit' for patients with 15 months of scheduled follow-up.

For the mITT population, any of the following are be classified as an unfavourable outcome:

1. Patients requiring an extension, a restart, or a change of treatment for any reason other than to make up missed doses during the intensive or continuation phase or pregnancy.
2. Women who become pregnant during treatment whose last culture result was positive.
3. Patients who had a positive culture when last seen.
4. Patients who died during the treatment phase for reasons other than violent cause or trauma without having completed adequate treatment (see section 2.4.3 for a definition of adequate treatment).
5. Patients who died in the follow-up phase with evidence confirmed or suggestive of possible failure or relapse of their TB.
6. Patients failing to complete adequate treatment (see section 2.4.3 for a definition of adequate treatment), who did not have a negative culture at the end of scheduled follow-up.

Positive cultures identified as being non-tuberculous mycobacteria are considered as contaminated.

Patients with positive cultures in the follow-up phase (after completion of chemotherapy) which are identified by DNA finger printing as re-infections (i.e., with a distinguishable pattern) are excluded from the analysis population.

Patients with a negative culture at the end of scheduled follow-up, not otherwise classified as having an unfavourable status, are classified as having a favourable outcome.

The definition of treatment outcome is the same for the PP population with the exception of the additional exclusions.

A number of specimens were sent from the sites to the reference laboratory at St George's Medical School, London. Where available, culture and drug sensitivity results from the reference laboratory are used in preference to results done in site laboratory.

3 Secondary and Sensitivity Analyses

3.1 Statistical Analyses

The following sensitivity analyses were conducted on both PP and MITT populations to evaluate the sensitivity of the results of the primary outcome to changes in the outcome classification:

1. Repeating the primary analysis without adjustment for stratification factors (the results are in rows 2 and 8 of table S1)
2. Ignoring the MIRU results by classifying all reinfections as unfavourable (rows 3 and 11)
3. Classifying all deaths as unfavourable, apart from one death in a patient withdrawn as a late screening failure for baseline resistance (rows 4 and 12)
4. Restricting the patient population to the subgroup of HIV negative (rows 5 and 13) or HIV positive (rows 6 and 14) patients. The Wald test is used to test for an interaction between treatment and HIV status.

The following additional modified ITT analyses were conducted:

1. A second approach to modified ITT, termed mITT model 2, was also conducted (row 9). In this analysis patients that had changed treatment for reasons other than therapeutic outcomes were not necessarily classified as unfavourable but were classified according to their status at the end of follow-up. This follows the post hoc model 2 used in another recent randomised controlled trial[6].
2. A 'strict mITT' analysis was conducted where all exclusions for any reason apart from late screening failures are classified as unfavourable (row 10). In this analysis, only the 97 late screening failures are excluded.

Apart from the first unadjusted analyses and the subgroup analysis by HIV status, all other sensitivity analyses described here are adjusted for centre as the stratification factor.

The proportion of patients achieving culture negativity at 2 months is an important secondary outcome. A culture is included in the 2 month culture analysis if it is within 14 days of the scheduled 2 month visit after randomisation. If more than one result was available, a positive result takes precedence over a negative result.

MGIT was used for cultures from Botswana and South African sites and LJ slope was used for cultures from Zimbabwean sites. Cultures from Zambia were done on both LJ slope and MGIT. The analysis was repeated including LJ and MGIT results combined and positive results take precedence over negative results where both LJ and MGIT are available.

Adherence was summarised by treatment regimen and treatment phase as percentage of total allocated doses reported as received by the patient. Missing at least one tablet on a single day counts as a 'missed dose' on that day.

3.2 Results

3.2.1 Sensitivity Analyses

The results for each sensitivity analysis (Table S1) are similar and there is no evidence for an interaction between HIV status and treatment (all p-values > 0.14).

Of particular note is the strict mITT analysis (row 10) where all patients otherwise excluded from the primary mITT analysis apart from the 97 later screening failures are reclassified as unfavourable. As can be seen in Figure 1, fewer patients were excluded from the mITT analysis on the 6-month regimen (39) as compared to the 4-month (46) or control regimens (52). The main reason for the slight imbalance is fewer patients being lost to follow-up or attending their final follow-up visit too early. This is likely due to chance.

The strict mITT sensitivity analysis therefore shows a benefit in favour of the 6-month regimen, although the upper bound of the 90% confidence interval is greater than 0. This naïve analysis should be interpreted with great caution and illustrates the importance of considering both a mITT and PP, carefully defined, as primary analyses for a non-inferiority trial.

3.2.2 Culture results at 2 months

On each culture medium or combining results across LJ and MGIT (Table S2), there was a suggestion of a slight increase in the proportion culture negative at 2 months in the moxifloxacin group (an absolute difference ranging from 3% to 6%). There was marginal evidence that this difference was unlikely due to chance when LJ and MGIT were combined (p=0.058). These results are consistent with the only phase II trial to compare these intensive phases which showed a similar absolute difference of 5% (p=0.37)[7].

3.2.3 Safety endpoints

The primary safety endpoint was occurrence of grade 3 or 4 adverse events occurring on treatment or no more than 14 days after the last dose of trial medication. Table S3 shows a summary of these adverse events by treatment group and relatedness to trial medications. Among 827 patients eligible for the safety analysis, there were a total of 45 grade 3 or 4 adverse events on treatment among 38 patients. These events were approximately equally distribution across treatment groups (taking into account the shorter duration of the 4-month regimen) and there was no discernible pattern.

Table S4 shows a summary of deaths occurring during the trial. There were a total of 25 deaths with a slightly increased number in the 4-month regimen. This difference is likely to be a chance finding (p=0.291, χ^2 test for independence).

3.2.4 Adherence

Figure S1 shows percentage of patients in each adherence category by treatment phase and treatment regimen. Table S5 shows the number of doses corresponding to each adherence category.

In the intensive phase, at least 40 doses (71% of maximum of 56) are required for adequate treatment (see section 1.4.3). In the continuation phase, at least 90 doses (71% of maximum of 126) on the control regimen or at least 16 doses (89% of maximum 18) on the study regimens are required for adequate treatment.

The distributions of adherence categories were similar by treatment regimen within each treatment phase, even given the different number of total doses in the continuation phase between the control regimen (126 doses) and study regimens (18 doses).

Across both treatment phases, 221 (80%) of 275 randomised patients on the control regimen were classified as having adequate treatment compared to 216 (79%) of 275 patients on the 4-month regimen and 223 (81%) of 277 patients on the 6-month regimen.

3.2.5 Anti-retroviral treatment (ART) for patients co-infected with HIV

Patients requiring ART at diagnosis were ineligible for the trial (see section 1.1 for full eligibility criteria) and, although the eligibility criteria were amended during the trial to allow patients starting ART at screening to be eligible for the trial, no patients started on trial treatment while already receiving ART.

Of 233 randomised patients co-infected with HIV, a total of 85 patients started ART during the trial of whom 37 were still on trial treatment for TB. There was no evidence for a difference in numbers of patients starting on ART by treatment regimen (table S6).

3.3 Identifying Reinfections using MIRU-VNTR

There were a total of 51 treatment failures or recurrences across all three treatment arms. Of these, 4 patients were retreated on the basis of smear results and clinical signs and symptoms only. Heat killed organisms from baseline and failure/relapse sample pairs for all the remaining 47 patients were transferred to UCL Centre for Clinical Microbiology for DNA extraction and genotyping by the MIRU-VNTR method. Pairs were classified as failures/relapses if there were 12 or more matching MIRU loci pairs and no differences at any MIRU loci, possible failures/relapses if there were less than 12 matching MIRU loci pairs and no differences at any MIRU loci. Pairs were classified as reinfections if there were differences at 2 or more MIRU loci and possible reinfections if there were differences at only 1 MIRU loci. Possible reinfections were classified as relapses for the primary analysis.

Of 47 pairs, there were 2 for which there was insufficient DNA for a result. Of the remaining 45, there were 9 reinfections, 20 failures/relapses, 4 possible reinfections and 12 possible failures/relapses. Possible reinfections and possible failures/relapses were classified as failures/relapses for the primary analysis.

4 Supplementary Figures

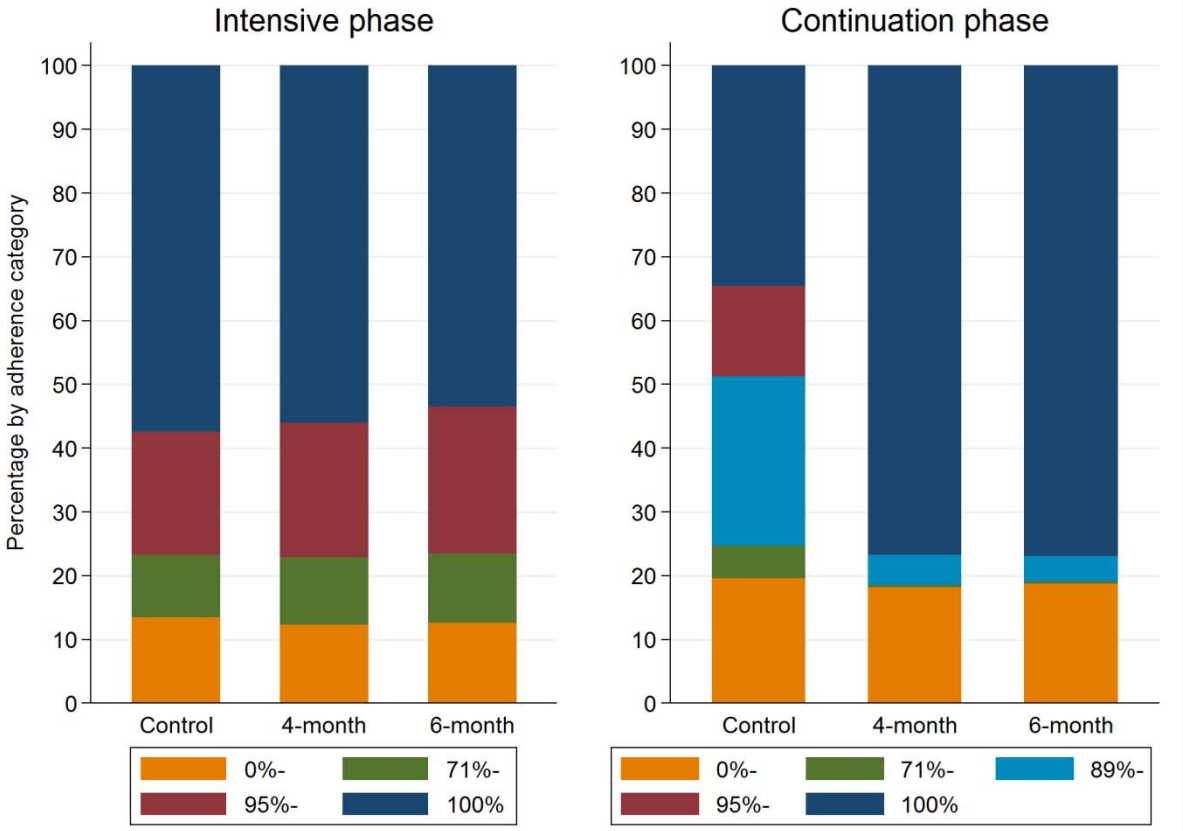

Figure S1. Percentage patients by adherence category, treatment phase and treatment regimen. Shaded bars indicate different adherence categories. Navy blue bars show patients that have taken all their medication. A maximum of 56 doses were given in the intensive phase, and a maximum of 126 doses for the control regimen and a maximum of 18 doses for the study regimens in the continuation phase. See table S5 for details of adherence categories.

5 Supplementary Tables

		Control	6-month regimen		4-month regimen	
	Analysis	**N (%) unfavourable / assessable**	**N (%) unfavourable / assessable**	**Difference from control (90% CI)**	**N (%) unfavourable / assessable**	**Difference from control (90% CI)**
	Per Protocol Analysis (PP)					
1.	Primary PP analysis as in Table 2	8 (4.9%) / 163	6 (3.2%) / 186	-1.8% (-6.1%, 2.4%)	30 (18.2%) / 165	13.6% (8.1%, 19.1%)
2.	Primary unadjusted PP analysis			-1.7% (-5.2%, 1.8%)		13.3% (7.6%, 18.9%)
3.	Classifying all reinfections as unfavourable	11 (6.6%) / 166	8 (4.3%) /188	-3.1% (-8.0%, 1.8%)	34 (20.1%) / 169	14.1% (8.4%, 19.9%)
4.	Classifying all deaths as unfavourable	13 (7.7%) / 168	11 (5.8%) / 191	-3.2% (-7.8%, 1.4%)	41 (23.3%) / 176	15.5% (9.3%, 21.7%)
5.	Subgroup of HIV negative patients	6 (5.2%) / 115	4 (2.8%) / 143	-2.4% (-6.5%, 1.7%)	24 (20.5%) / 117	15.3% (8.3%, 22.3%)
6.	Subgroup of HIV positive patients	2 (4.2%) /48	2 (4.7%) / 43	0.5% (-6.6%, 7.6%)	6 (12.5%) /48	8.3% (-0.8%, 17.5%)
	p-value for interaction by HIV status			p = 0.560		p = 0.322
	Modified Intention to Treat Analysis (mITT)					
7.	Primary mITT analysis as in Table 2	27 (14.4%) / 188	29 (13.7%) / 212	0.4% (-4.7%, 5.6%)	52 (26.9%) / 193	13.1% (6.8%, 19.4%)
8.	Primary unadjusted mITT analysis			-0.7% (-6.4%, 5.0%)		12.6% (5.9%, 19.3%)
9.	Alternative mITT analysis: mITT model 2	23 (12.2%) / 188	26 (11.9%) / 218	1.3% (-3.5%, 6.2%)	47 (24.1%) / 195	12.3% (6.3%, 18.3%)
10.	Strict mITT – all post-randomisation exclusions as unfavourable	79 (32.9%) / 240	68 (27.1%) / 251	-4.6% (-11.2%, 2.0%)	98 (41.0%) / 239	9.5% (2.4%, 16.5%)
11.	Classifying all reinfections as unfavourable	30 (15.7%) / 191	31 (14.5%) / 214	-0.3% (-5.5%, 5.0%)	56 (28.4%) / 197	13.8% (7.5%, 20.2%)
12.	Classifying all deaths as unfavourable	31 (16.1%) / 192	34 (15.7%) / 217	0.2% (-5.3%, 5.7%)	62 (30.5%) / 203	14.7% (8.1%, 21.3%)
13.	Subgroup of HIV negative patients	20 (14.9%) / 134	22 (13.5%) / 163	-1.4% (-8.1%, 5.3%)	41 (29.7%) / 138	14.8% (6.6%, 22.9%)
14.	Subgroup of HIV positive patients	7 (13.0%) / 54	7 (14.3%) / 49	1.3% (-9.8%, 12.5%)	11 (20.0%) / 55	7.0% (-4.6%, 18.7%)
	p-value for interaction by HIV status			p = 0.728		p = 0.370

Table S1. Summary of sensitivity analyses of the primary efficacy outcome under a per protocol or a modified intention to treat analysis.

Culture Medium	Culture Result	Drug added to rifampicin, pyrazinamide and ethambutol in the eight week intensive phase			χ^2 test for independence
		Isoniazid	Moxifloxacin	**Total**	
LJ Slope	Negative	85 (92%)	177 (95%)	**262 (94%)**	$\chi^2 = 0.55$
	Positive	7 (8%)	10 (5%)	**17 (6%)**	p = 0.458
	Total	**92**	**187**	**279**	
	Non-TB mycobacteria	0	0	**0**	
	Contaminated	0	0	**1**	
	Sputum not produced	0	0	**0**	
MGIT	Negative	108 (81%)	222 (87%)	**330 (85%)**	$\chi^2 = 2.67$
	Positive	25 (19%)	32 (13%)	**57 (15%)**	p = 0.102
	Total	**133**	**254**	**387**	
	Non-TB mycobacteria	0	7	**7**	
	Contaminated	7	13	**20**	
	Sputum not produced	4	4	**8**	
LJ and MGIT combined	Negative	187 (85%)	394 (90%)	**581 (89%)**	$\chi^2 = 3.61$
	Positive	32 (15%)	42 (10%)	**74 (11%)**	p = 0.058
	Total	**219**	**436**	**655**	
	Non-TB mycobacteria	0	7	**7**	
	Contaminated	7	13	**20**	
	Sputum not produced	4	4	**8**	

Table S2. Summary of culture results at 2 months. Percentages are of the total with a positive or negative result.

		Control regimen		4-month regimen		6-month regimen		Total
Total Patients Assessed		**275**		**275**		**277**		**827**
Related to study medications	**Definitely**	**0**		**0**		**0**		**0**
	Probably	**5**	1 Hepatic 1 Respiratory 1 Gastrointestinal 1 Neurological 1 IPT Purpura	**3**	1 Hepatic 1 Neurological 1 Cutaneous	**3**	1 Hepatic 1 Gastrointestinal 1 Renal	**11**
	Possibly	**1**	1 TB IRIS	**3**	1 Hepatic 1 Cardiovascular 1 Gynaecological/ Obstetrical	**1**	1 Hepatic	**5**
	Unlikely	**3**	1 Respiratory 1 Cutaneous 1 HIV Death	**3**	1 Gastrointestinal/Renal 1 Cardiovascular 1 Psychological	**10**	1 Respiratory 4 Neurological 2 Cardiovascular 1 Psychological 1 Cutaneous 1 Gynaecological/ Obstetrical	**16**
	Not related	**7**	3 Respiratory 2 Neurological 1 Gynaecological/ Obstetrical 1 Road traffic incident	**3**	1 Gastrointestinal 1 Kaposi's sarcoma 1 Bone fracture	**3**	1 Respiratory 1 Gastrointestinal 1 Gynaecological/ Obstetrical	**13**
Total number of events		**16**		**12**		**17**		**45**
Total number of patients		**12**		**11**		**15**		**38**

Table S3 Episodes of grade 3 or 4 adverse events reported during or up to 14 days after last dose of trial treatment. Analysis includes all patients randomised that had at least one dose of treatment. All of these adverse events were followed to resolution.

	Control regimen		4-month regimen		6-month regimen		Total
Total Randomised	**275**		**275**		**277**		**827**
<8 weeks	**1**	1 TB	**2**	1 TB 1 HIV	**1**	1 Gastrointestinal	**4**
8-<26 weeks	**1**	1 Unknown cause	**3**	1 HIV* 1 Stabbing* 1 Renal	**0**		**4**
26-<52 weeks	**3**	2 HIV 1 Cardiovascular	**5**	1 TB 2 HIV 1 Septicaemia 1 Unknown cause	**2**	1 Respiratory 1 Natural causes	**10**
≥52 weeks	**1**	1 Unknown cause	**2**	1 Natural causes 1 Unknown cause	**4**	1 TB 1 Gastrointestinal 2 Unknown cause	**7**
Total	**6**		**12**		**7**		**25**

Table S4 Summary of deaths during the trial by primary cause of death and number of weeks death occurred after randomisation.* These two deaths occurred 5.3 weeks (stabbing) and 9.3 weeks (HIV death) after the end of treatment. All other deaths occurring less than 26 weeks after randomisation were within 8 days of the last dose of trial medication.

Intensive phase		**Continuation phase**		
Adherence category	**Doses taken (maximum 56)**	**Adherence category**	**Control regimen doses taken (maximum 126)**	**Study regimen doses taken (maximum 18)**
0% -	0-39*	0% -	0-89*	0-12*
71% -	40-53	71% -	90-111	13-15*
95% -	54-55	89% -	112-119	16-17
100%	56	95% -	120-125	N/A
		100%	126	18

Table S5. Details of actual doses taken by adherence category as shown in Figure S1.
*Indicates inadequate treatment within treatment phase.

	Control regimen	**4-month regimen**	**6-month regimen**	**Total**
Total randomised	275	275	277	827
Co-infected with HIV (% of randomised)	87 (32%)	78 (28%)	68 (25%)	233 (28%)
Started ART while on trial treatment for TB (% of co-infected)	13 (15%)	11 (14%)	13 (19%)	37 (16%)
Started ART after trial treatment (% of co-infected)	14 (16%)	20 (26%)	14 (21%)	48 (21%)
Did not start ART (% of co-infected)	60 (69%)	47 (60%)	41 (60%)	148 (64%)

Table S6. Timing of starting ART for patients co-infected with HIV.

6 References

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7. Dorman SE, Johnson JL, Goldberg S, et al. Substitution of Moxifloxacin for Isoniazid during Intensive Phase Treatment of Pulmonary Tuberculosis. Am J Respir Crit Care Med 2009;180:273-80.