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Analysis of the effects on the QT interval of a gatifloxacin-containing regimen versus standard treatment of pulmonary tuberculosis

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Running Head: QT interval prolongation and Gatifloxacin TB regimen

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Abstract

Background

The effects on ventricular repolarisation – recorded on the ECG as lengthening of the QT interval – of acute tuberculosis and those of standard and alternative anti-tuberculosis regimens are under-documented. A correction factor (QTc) is introduced to make the QT independent of the heart rate, translating into the slope of the regression line between QT and heart rate being close to zero.

Methods

ECGs were performed pre- and 1-5 hours post-dosing (month 1, 2, end of treatment) around drugs' peak concentration time in tuberculosis patients treated with either the standard 6-month treatment (rifampicin and isoniazid for 6 months, pyrazinamide and ethambutol for 2 months; "control") or a test regimen with gatifloxacin, rifampicin and isoniazid given for 4 months (pyrazinamide for the first 2 months) as part of the OFLOTUB study, a randomized controlled trial conducted in five African countries. Drug levels were measured at steady-state (month 1) in a subset of patients. We compared treatment effects on the QTc and modelled the effect of individual drugs' C_{max} on the Fredericia-corrected QT interval.

Results

1686 patients were eligible for the correction-factor analysis of QT at baseline (mean age 30.7 years, 27% female). Median heart rate decreased from 96/min at baseline to 71/min at end of treatment, and body temperature from 37.2 to 36.5 C. Pre-treatment, the non-linear model estimated the best correction factor at 0.4081 in-between Bazett's (0.5) and Fridericia's (0.33) corrections. On treatment, Fridericia (QTcF) was the best correction factor.

1602 patients contributed to the analysis of QTcF by treatment arm. The peak QTcF value during follow-up was >480ms for 21 patients (7 and 14 in the test and control arm) and >500ms for 9 (5 and 4, respectively), corresponding to a risk difference of -0.9% (95% CI: -2.0% to 2.3%, p=0.12) and 0.1% (95% CI: -0.6% to 0.9%, p=0.75), respectively between the test and control arms. 106 (6.6%) patients had a peak measurement change from baseline >60ms (adjusted between-arm difference 0.8%, 95% CI -1.4% to 3.1%, p=0.47). No evidence was found of an association between C_{max} of the anti-tuberculosis drugs 1 month into treatment and the length QTcF.

Conclusions

Neither a standard 6-month nor a 4-month gatifloxacin-based regimen appear to carry a sizeable risk of QT prolongation in patients with newly-diagnosed pulmonary tuberculosis. This is to-date the largest dataset studying the effects of anti-tuberculosis regimens on the QT, both for the standard regimen and for a fluoroquinolone-containing regimen.

Introduction

The time for ventricular depolarisation and repolarisation is measured on the surface electrocardiogram (ECG) as the time from the start of the Q wave to the end of the T wave. Prolonged repolarisation is recorded on ECG as lengthening of the QT interval (1). This condition is considered to increase the risk for ventricular arrhythmias and the potentially fatal 'Torsade de Pointe' (TdP). Ventricular repolarisation is mediated mostly by the outflow of potassium (K^+) from the myocytes. Attenuation of the voltage-dependent K^+ channels' ability to repolarize can prolong the QT interval and create the conditions for TdP.

There is very little knowledge about how acute tuberculosis affects the QT interval, or about the potential for anti-tuberculosis treatments to affect ventricular repolarisation. With prospects of having them added to the anti-tuberculosis armoury of drugs, drugs belonging to the fluoroquinolone (FQ) family have attracted attention, as they can variably affect ventricular repolarisation(2). These drugs have different affinities for binding to the rapid component of the delayed-rectifier current I_{Kr}, which is expressed by the human ether-a-go-go-related gene hERG(3). In particular, it has been suggested that compounds such as gatifloxacin and moxifloxacin, both considered in anti-tuberculosis regimens, which have a methoxy substitution at position C8, might inhibit hERG at therapeutically-achievable concentrations(4).

Establishing the risk for QT prolongation associated with the use of a drug is not straightforward. The length of the QT interval varies during the day and from day to day and with gender and age, and is influenced by potassium levels, body temperature, heart rate (HR), and factors such as disease and drugs. It is customary to introduce a correction factor to account for the effect of the heart rate (heart rate-corrected QT, or QTc). The correction factor is introduced to make the QT independent of the heart rate, hence the need for the slope of the regression line to be as close to zero when the QT is plotted against the heart rate. The QTc is calculated by dividing the QT by RR (calculated as 60 / heart rate). The

International Conference for Harmonisation (ICH) recommends analysing the QT using the Bazett and the Fridericia corrections (QTcB and QTcF), which use fixed exponents of 0.5 and 0.33, respectively, for the RR, and exploring other corrections whenever appropriate. The Bazett correction QTcB ($QT/RR^{0.5}$) is considered most suited for HR 60 – 100 bpm (it under-corrects if HR < 60 and over-corrects if HR > 100 bpm); the Fridericia formula QTcF ($QT/RR^{0.33}$) is generally regarded as more appropriate outside this range. Various other corrections exist. Population-based corrections are also recommended for specific conditions (5, 6). There is no information on the appropriateness of these corrections in patients with pulmonary tuberculosis (PTB) – i.e. how good they are in making the QT interval independent of the heart rate.

We analysed the QT of patients with PTB enrolled in a randomised trial with a non-inferiority design comparing the standard 6-month treatment to a gatifloxacin-containing 4-month regimen (the OFLOTUB trial) (7). We also evaluated the effect of exposure, expressed as C_{max} of the individual drugs of both treatment arms, in the patients who participated in a pharmacokinetic sub-study (nested pharmacokinetic/pharmacodynamic (PK/PD) study).

Materials and methods

Study design

The study was a non-inferiority randomized, open-label, controlled trial, conducted in five African countries: Benin, Guinea, Kenya, Senegal and South-Africa with a nested PK/PD study for subset of patients. Its objective was to assess the efficacy and safety of a gatifloxacin containing 4-month regimen for the treatment of drug-susceptible pulmonary tuberculosis compared to standard World Health Organisation recommended 6-month treatment (8). The protocol was approved by relevant ethics committee and regulatory authorities of all partner's institutions. This study was registered at Clinical-

Trials.gov under registration number NCT00216385. More details on study design have been published elsewhere (7).

Subjects

Male and female patients, aged 18 to 65 years, newly diagnosed with microscopically-proven pulmonary tuberculosis and providing informed consent for inclusion in the trial were considered for enrolment. Patients with congenital QTc interval prolongation >480 ms, clinically significant bradycardia (40 beats/minute), hypokalaemia grade 1 and above (i.e. < 3.0 mEq/l), and patients using drugs known to prolong QT interval, were excluded at enrolment.

Treatment arms

Patients were randomised, stratified by country, to one of two treatment arms. The control treatment regimen included isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) given daily for 2 months followed for 4 months with isoniazid and rifampicin (i.e. 2RHEZ/4RH). In the intervention arm (referred to as test), gatifloxacin (G) was substituted for ethambutol in the 2-month intensive phase and was maintained for the 2-month continuation phase (i.e. 2RHGZ/2GRH). Gatifloxacin was given at a dose of 400 mg per day, irrespective of body weight. The doses of HRZE followed World Health Organization (WHO) recommendations (8) and were provided as fixed dose combination tablets.

Measurements

Along with clinical and laboratory evaluations, twelve-lead electrocardiograms (ECGs) were performed at baseline (pre-treatment), at months 1 and 2 of TB treatment and at the end of the treatment. ECGs were obtained with a Shiller CP300 machine which was configured to report automatically QT intervals automatically and to calculate the corrected QT interval (QTc) by Bazett's formula. Exact heart rate at the time of ECG measurement was also automatically measured and recorded. This allowed us to calculate *a posteriori* QTc interval using other formulas such as Fredericia's. The following information

was also recorded for each patient: gender, age, medical history, vital signs (including body temperature), clinical examination and concomitant medication.

Plasma samples were taken for drug concentration measurements at baseline and month 1 as part of a population PK study. Patients were randomised to one of three sampling schedules (A, B and C), each with three sampling times: (A) Sample 1: within the hour before the treatment dose (-1 to 0 hours), Sample 2: between 1 and 2 hours after the treatment dose, Sample 3: between 2.5 and 3.5 hours after the treatment dose; (B) Sample 1: between 1 and 2 hours after the treatment dose, Sample 2: between 2.5 and 3.5 hours after the treatment dose, Sample 3: between 4 and 6 hours after the treatment dose; (C) Sample 1: between 1 and 2 hours after the treatment dose, Sample 2: between 2.5 and 3.5 hours after the treatment dose, Sample 3: between 8 and 10 hours after the treatment dose.

Population pharmacokinetic models were used to generate individual estimates of peak drug concentration (C_{max}) and time to C_{max} (T_{max}) at steady state. (9,10)

Drug safety was closely monitored during the course of the study in compliance with ICH/GCP guidelines.

Statistical methods

Review of the correction factor

The QT measurement at enrolment, combined across treatment arm, was used to assess the correction factor in this sample of TB patients. We calculated the linear regression coefficients of gradient and intercept for the Bazett corrected (correction factor $RR^{0.5}$) and Fridericia-corrected (correction factor $RR^{0.33}$) QT against 1-RR. These analyses were repeated for each measurement post randomisation: month 1 , month 2 and at the end of treatment (either month 4 or 6 for the test and control arms, respectively) combined across treatment arm for the purpose of assessing the adequacy and robustness of the correction factors.

In addition, a non-linear model was fitted to the uncorrected QT at baseline to estimate the population-specific correction factor for the pre-treatment patients with active pulmonary tuberculosis.

Definition of outcomes

According to ICH guidelines (6), QTc data are presented as both continuous and binary variables using the Fridericia correction (QTcF). Continuous measurements were summarised using the arithmetic mean, standard deviation (sd). Peak QTc was defined as the maximum QTc interval from up to a possible 3 follow-up recordings (week 4, 8 or end of treatment).

Between-treatment arm comparisons

Peak QTcF during follow-up and change of this measurement from baseline were compared between treatment arms using linear regression, adjusting for country where possible. Peak values were also classed as binary variables using cutpoints at >450ms >480ms, and >500ms, and change from baseline as >60ms; between-treatment comparisons were expressed as risk difference, adjusted for country. Patients with a baseline measurement and at least one follow-up measurement contribute to these analyses.

PKPD analysis

In the subset of patients who have drug concentrations measurements, the effect of C_{max}, for each drug separately, on QTcF at month 1 was assessed using linear regression, adjusting for country, sex, age and QTcF at enrolment, and study arm (only adjusting for study arm for the effect of C_{max} for isoniazid, rifampicin and pyrazinamide).

Results

Patients' characteristics

Of the 1692 patients in the ITT population, 1686 (99.6%) were eligible for the correction-factor analysis of QT at baseline (see flow diagram Figure 1). Mean age was 30.7 years, 27% were female, 18% HIV-positive, 51% had cavitation and 25% had a temperature >37.7^{o} C (Table 1).

Heart rate and Temperature

Median heart rate decreased progressively from 96/min at baseline throughout treatment to reach 71 at end of treatment. Median baseline body temperature was 37.2 and decreased to approximately 36.5 on treatment. The percentage of participants with temperature >37.7^{o} C fell over follow-up to 2.7% (43/1582) and 2.4 % (37/1539) at months 1 and 2 after the start of TB treatment, respectively, and to 0.7% (10/1445) at the end of treatment. (Table 2)

Correction factors

In these patients with active PTB about to initiate treatment, the uncorrected QT increased with the heart rate overall (coefficient -202.7 95% confidence interval [CI] -209.6 to -195.9, adjusted R^2 = 0.67) (Table 3).

At baseline, neither the Bazett and Fridericia corrections were optimal; QTcB tended to under-correct (gradient 51.8, 95% CI 43.5, 60.1) and QTcF over-correct (gradient -46.3, 95% CI -54.1, -38.5) the QT (Fig 2, Table 3). The non-linear model estimated the correction factor to be 0.4081 (95% CI 0.3949,

187 0.4213) (QTcTB), in between the Bazett and Fridericia correction factors. This correction factor was
188 independent of the country, sex and presence or absence of cavitation (Fig 3)

189 Applying the Bazett, Fridericia and the new correction factor to QT data measured 1 and 2
190 months after the start of TB treatment and at the end of treatment (month 4 in the test arm and month
191 6 in the control arm) showed the QTcF to be a better correction, with the gradient coefficient close to
192 zero (Table 3).

193 **Between-treatment comparison**

194 The QTcF was therefore applied for between-treatment comparisons. A total of 1602 patients
195 contribute to these analyses (Fig 1). Baseline characteristics were similar between the two treatment
196 arms (Table 1).

197 The peak QTcF value during follow-up was >480ms in 21 patients overall: 0.9% (7/804) and 1.8%
198 (14/798) in the test and control arms, respectively (Table 3). There were nine occasions of QTcF >500ms
199 (see Table 3 and Table 4). Five occurred in the test arm (0.6%) at month 1 (506 and 514ms), month 2
200 (518ms) and month 4 (502 and 511ms), and four in the standard treatment arm (0.5%) at month 2 (510
201 and 517ms) and month 6 (507 and 569ms). The risk difference for QTcF >480ms and >500 were -0.9%
202 (95% CI: -2.0% to 2.3%, p=0.12) and 0.1% (95% CI: -0.6% to 0.9%, p=0.75), respectively, between the test
203 and control arms. Overall 107 (6.7%) patients had a peak measurement change from baseline >60ms,
204 with no difference between the two treatment arms (adjusted difference 0.7%, 95% CI -1.5% to 3.0%,
205 p=0.53).

206 The overall mean peak QTc value was moderately higher in the test versus control arm; adjusted
207 mean difference 2.6ms (95%CI 0.2, 4.9)ms, p=0.030). The mean and 95%CI QTcF values at baseline,
208 month 1, month 2 and end of treatment were: 384.7ms (383.2-386.1), 394.2ms (392.6-395.7), 395.7ms
209 (394.1-397.3), and 395.9ms (394.2-397.5) for the test arm; and 385.1ms (383.6-386.6), 391.6ms (390.1-
210 393.2), 391.7ms (390.1-393.3), and 394.9ms (393.1-396.7) for the control arm, respectively. (Fig 4)

Drug levels

Pharmacokinetic measures were available for 291 patients at month 1 (144 and 147 respectively in the test and control arms). The C_{max}, T_{max} and AUC achieved by the individual drugs in the two treatment arms are summarised in Table 5. There was no evidence that C_{max} of any of the drugs individually were associated with QTc-F at month 1 (see Table 5).

Discussion

This study shows that the risk of QT prolongation with either a 4-month regimen including gatifloxacin or a standard 6-month treatment is low: only five (0.6%) and four (0.5%) subjects respectively had a value >500 ms, and 7% and 6.3% had a prolongation relative to their baseline value of >60 ms.

We also found that in this African population with active PTB, the Bazett formula QTcB ($QT/RR^{0.5}$) under-corrects, and the Fridericia formula QTcF ($QT/RR^{0.33}$) over-corrects QT as RR increases; the QTcTB ($QT/RR^{0.4081}$) fits best this population. For instance, screening patients for values >480 ms with the QTcF would have missed 1 of the 2 cases, and the QTcB would have excluded 3 more cases. While the TB correction factor appears to befit subjects of box sexes in all the countries of this study, it will be important to verify the appropriateness of this correction on larger and more diverse TB patient populations. This may have implications for entry criteria when recruiting into a TB treatment trial, as well as measuring relative changes in the QT after treatment. As patients on treatment recover, the Fridericia formula becomes more appropriate, and QTcB and QTcTB over-estimate the prolongation (with 11, 13 and 8 cases having QTcB, and 2, 3 and 3 cases having QTcTB, >480 msec at week 4, 8 and end of treatment, respectively). The correction factor is introduced to make the QT independent of the heart rate, which translates to the regression lines displayed in Figures 2 and 3 for corrected QTc; the slope is closest to zero (a horizontal line) when using the population-specific QTcTB.

ECGs were done before starting and during anti-tuberculosis treatment. During treatment the ECGs were done 1 – 5 hours post-dosing (corresponding to the interval when drug concentrations are expected to be highest in plasma) at month 1, 2 and at the end of treatment (month 4 for the gatifloxacin-containing regimen or month 6 for standard treatment). These measurements occurred when drug concentrations were at steady-state, and patients were improving or convalescent.

It is becoming increasingly clear that, while FQs are generally known to block the inward delayed rectifier current I_{Kr} through the potassium channel, QT prolongation and TdP risk cannot be considered as a class effect, as the individual FQ affinities for the hERG- I_{Kr} receptor (both in absolute terms and relative to plasma levels) vary widely.

In vitro, gatifloxacin had an IC_{50} of 130 µM (48.8 µg/ml) for the hERG channel I_{Kr} with blocking activities for other quinolones ranging from 18 µM (sparfloxacin) as the most active to 1420 µM (ofloxacin) as the least active quinolone(4). A similar range of blocking activities for I_{Kr} has been determined in the mouse tumour cell line AT-1, with IC_{50} values of 0.23 µM (sparfloxacin), 26.5 µM (gatifloxacin) and 27.2 µM (grepafloxacin)(11). The influence of a series of fluoroquinolones on action potential duration (APD) was also studied in isolated Guinea pig right ventricular myocardia: while some of the drugs tested did not influence APD, gatifloxacin increased the APD by 13% at a concentration of 100 µM (37.5 µg/ml); at the same concentration, sparfloxacin increased the APD by 41%, while grepafloxacin and moxifloxacin showed intermediate values of 24% and 25%, respectively(12).

All the FQ tested showed propensities for a prolongation of the QT and/or the QTc interval (Carlsson correction: QT – 0.175(RR – 300) in an *in vivo* anaesthetized rabbit model. The compounds were infused intravenously at a dose of 2 mg/kg/min for 30 minutes, with sparfloxacin producing the highest absolute QT prolongation (+129 ms from baseline); gatifloxacin showed a minimal prolongation of the QT interval (increase from baseline = 14 ms). Ventricular tachycardia and TdP were only elicited by sparfloxacin, and only when the infusion was extended to a duration of 60 minutes(11). A similar

model in rabbits using intravenous infusion doses of 4 mg/kg/min yielded QT and QTc interval prolongation values for gatifloxacin similar to those of sparfloxacin, with increases in interval times from about 160 ms at baseline to about 320 ms at 30 minutes after the start of the infusion(13).

In order to put the non-clinical data into perspective, these concentrations that evoke cardiac effects in experimental in-vitro and in-vivo models must be compared to plasma levels achieved in patients. According to the Tequin® (gatifloxacin) label, a 400 mg intravenous bolus given to healthy volunteers leads to a C_{max} of ~5.5 µg/ml, a concentration which is ~23-times lower than the IC_{50} for hERG inhibition and ~5-times lower than the IC_{50} for I_{Kr} blockade in AT-1 cells; in this phase 3 trial (oral treatment with 400 mg/d) the C_{max} was 3.9 µg/ml after the first dose and 3.8 µg/ml at steady state [IC_{50}/C_{max} ratio ~34 (95%CI 21 – 54)]. Both indicate a substantially lower risk than that inferred by Kang et al(4). In addition, when applying a scaling factor of 0.324 for the dose administered to extrapolate the *in vivo* rabbit data to humans, the intravenous infusion of 2 mg/kg/min, resulting in only a minimal prolongation of the QT interval, will then correspond to a human equivalent bolus dose of ~20 mg/kg, or 1000 mg for a 50 kg human. Similarly, the FDA data for Tequin® in mongrel dogs, where no influence on the ECG was seen at an intravenous infusion of 10 mg/kg/min, can be translated into a human equivalent bolus dose of ~162 mg/kg, or a dose of >8000 mg. All these data suggest a low risk for gatifloxacin to induce serious cardiovascular adverse events.

Furthermore, there is no clear correlation between hERG- I_{Kr} receptor affinity and risk of QT prolongation or risk of TdP. The risk of TdP with FQs is in actual facts very low, and is estimated to be at ~27 for 10 million prescriptions for gatifloxacin, including subjects with concomitant risk factors(14). The Uppsala Monitoring Centre database reports(15), as of 01/03/2014 a total of 13,556 cardiac adverse events with fluoroquinolones, of which 767 are QT prolongation and 451 TdP, 100 and 53 respectively with gatifloxacin, 207 and 166 with levofloxacin and 269 and 113 with moxifloxacin. Direct comparisons

282 are obviously not possible due to the absence of the denominator (number of people exposed to the
283 different FQs).

284 The main methodological limitation of this study is that there was no external review of QTc
285 measurement, but all were measured automatically with the same machine in all study sites, and all QTc
286 values reported in the CRF were reviewed by an external monitor; furthermore, there was only one QTc
287 measurement done at each time point. Another potential limitation is that, assuming that C_{max} is the
288 main determinant of the risk for QT prolongation, ECGs were done during treatment when all drugs
289 were at steady-state, but peak plasma concentrations might have been higher in the earlier phases of
290 treatment.

291 In summary, this study indicates that neither a standard 6-month TB treatment, nor a 4-month,
292 six-day-a-week regimen including gatifloxacin at 400 mg/d in combination with three (rifampicin,
293 isoniazid and pyrazinamide) other anti-tuberculosis drugs for the first two months, and two (rifampicin,
294 isoniazid) for the following two months, appear to carry a sizeable risk of QT prolongation.

295 These results are significant and novel for a number of reasons. To our knowledge, this is to-
296 date the largest dataset studying the QT interval during acute active tuberculosis itself, documenting
297 the effects on the QT interval of the standard regimen as well as a fluoroquinolone-containing regimen,
298 and investigating the relationship between drug levels and the QT. As such, they fill a knowledge gap,
299 and are useful for future studies. It will be important to verify in other sets of patients, including those
300 with other forms of tuberculosis, whether and how active disease affects the QT interval, and which
301 formula is best suited to correct it so as to make it independent of the heart rate. This knowledge will
302 improve also our understanding of treatment effects, as it will refine the classification of QT values as
303 being normal or prolonged – both for eligibility to treatment and for assessing risks. This study also
304 provides a reference point for other studies which will aim to evaluate the effects on ventricular

repolarisation of standard and alternative treatments on both newly-diagnosed and drug-resistant tuberculosis, as the latter in particular may include drugs with potential for QT prolongation.

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Disclaimer

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Table 1: Baseline demographics and clinical variables for patients in the (i) correction factor analysis (n=1686) and (ii) the comparison of QTc by treatment arm (n=1602)

		Correction factor analysis (i)				Between-arm comparison (ii)			
		Test (n=845)		Control (n=841)		Test (n=804)		Control (n=798)	
		n	%	n	%	n	%	n	%
Country	Benin	158	(18.7)	158	(18.8)	150	(18.7)	151	(18.9)
	Guinea	219	(25.9)	225	(26.7)	216	(26.9)	213	(26.7)
	Kenya	100	(11.8)	97	(11.5)	100	(12.4)	95	(11.9)
	Senegal	178	(21.1)	180	(21.4)	154	(19.1)	163	(20.4)
	South Africa	190	(22.5)	181	(21.5)	184	(22.9)	176	(22.1)
Age, years	Mean(sd)	30.8[1]	(9.1)	30.6	(9.0)	30.8	(9.1)	30.6	(8.9)
Sex	Female	229	(27.1)	232	(27.6)	215	(26.7)	224	(28.1)
HIV[2]	Positive	147	(17.5)	156	(18.8)	141	(17.6)	150	(18.9)
Cavitation[3]	Yes	438	(52.0)	417	(50.0)	413	(51.5)	394	(49.8)
Heart rate[4]	Mean (sd)	95.6	(17.4)	95.1	(17.8)	95.6	(17.5)	95.2	(17.5)
Temperature[5]	>37.7	216	(25.6)	198	(23.6)	201	(25.0)	187	(23.5)
BMI	Mean (sd)	17.4	(4.9)	17.5	(5.0)	17.3	(4.9)	17.5	(5.0)

[1]Age not known for n=1 in the test arm; [2] HIV status unknown in analysis (i) for n=11 (n=5 in the test arm, n=6 in the control arm) and in analysis (ii) for n=10 (n=5 in the test arm, n=5 in the control arm); [3] Cavitary status unknown in analysis (i) for n=10 (n=3 in the test arm, n=7 in the control arm) and in analysis (ii) for n=9 (n=2 in the test arm, n=7 in the control arm); [4] Heart rate unknown in analysis (ii) for n=4 (n=2 in the test arm, n=2 in the control arm); [5] Temperature unknown in analysis (i) for n=3 (n=1 in the test arm, n=3 in the control arm) and in analysis (ii) n=3 (n=1 in the test arm, n=2 in the control arm)

sd standard deviation; BMI body mass index

370 **Table 2:** Heart rate and Temperature during the treatment phase, restricted to samples with data

371 available for the correction analysis

		Baseline	Month 1	Month 2	End of treatment*
Heart rate	Median	96	81	78	71
	IQR	83-106	71-95	68-90	62-81
	n	1686	1562	1512	1402
Temperature	Median	37.2	36.6	36.5	36.4
	IQR	36.6-37.7	36-37	36-36.9	36-36.9
	n	1682	1582	1512	1445
	>37. 7^{o} C	24.6%	2.7%	2.4%	0.7%
	% (n/N)	(414/1682)	(43/1582)	(37/1539)	(10/1445)

372 * month 4 (gatifloxacin) or month 6 (control / IQR interquartile range

373

Table 3: Linear regression coefficients (gradient and intercept) for uncorrected QT, Bazett (QTcB), Fridericia (QTcF) and new correction (QTcTB) vs 1-RR at baseline (randomisation), 1 and 2 months from stat of treatment and at the end of treatment

		Baseline (n=1686)	**Month 1 (n=1560)**	**Month 2(n=1512)**	**End of treatment* (n=1402)**
Uncorrected QT	Gradient (95% CI)	-202.7 (-209.6, -195.9)	-162.3 (-168.8, -155.8)	-154.5 (-161.1, -148.0)	-134.4 (-141.3, -126.7)
	Intercept (95% CI)	403.8 (401.2,406.3)	396.3 (394.4, 398.3)	395.1 (393.4, 396.9)	395.1 (391.9, 395.0)
	R^2	0.67	0.61	0.59	0.48
QTcB	Gradient (95% CI)	51.8 (43.5,60.1)	80.8 (73.5, 88.1)	80.8 (73.6, 88.0)	90.0 (82.3, 97.7)
	Intercept (95% CI)	397.1 (394.1, 400.2)	394.1 (392.0, 396.3)	394.5 (392.5, 396.4)	394.7 (393.0, 396.3)
	R^2	0.08	0.23	0.24	0.27
QTcF	Gradient (95% CI)	-46.3 (-54.1, -38.5)	-9.8 (-16.8, -2.8)	-5.5 (-12.5, 1.4)	9.7 (2.2, 17.2)
	Intercept (95% CI)	401.0 (398.1, 403.9)	395.4 (393.3, 397.4)	394.9 (392.0, 396.7)	394.1 (392.5, 395.7)
	R^2	0.075	0.005	0.002	0.005
QTcTB**	Gradient (95% CI)	-2.9 (-10.9, 5.1)	30.7 (23.6, 37.8)	33.3 (26.2, 40.3)	46.0 (38.4, 53.6)
	Intercept (95% CI)	399.5 (396.5, 402.4)	394.9 (392.8, 397.0)	394.7 (392.8, 396.6)	394.3 (392.7, 395.9)
	R^2	0.000	0.044	0.053	0.092

QTcB	>450	5.5% (93)	7.0% (109)	6.7% (101)	6.3% (88)	374
	>480	0.3% (5)	1.22% (19)	1.2% (18)	1.1% (16)	375
	>500	0.1% (2)	0.7% (11)	0.5% (8)	0.2% (3)	376
QTcF	>450	0.24% (4)	1.7% (27)	1.3% (20)	2.2% (31)	377
	>480	0.06% (1)	0.5% (8)	0.3% (5)	0.6% (8)	378
	>500	0% (0)	0.1% (2)	0.2% (3)	0.3% (4)	379
QTcTB**	>450	0.89% (15)	2.4% (38)	2.7% (41)	3.3% (46)	380
	>480	0.12% (2)	0.6% (10)	0.5% (8)	0.78% (11)	381
	>500	0.06% (1)	0.51% (8)	0.20% (3)	0.29% (4)	382
						383

384 * month 4 (gatifloxacin) or month 6 (control) ** correction factor 0.4081 (95% CI 0.3949, 0.4213)

385

Table 4: Comparison of on-treatment Fredericia correction QT values by study arm

		Test (n=804)	Control (n=798)	difference (95% CI)	P-value
Peak value in follow-up	Mean (sd), ms	407.2 (23.3)	404.5 (25.3)	2.6 (0.2, 4.9)	0.030
Peak value in follow-up – change from baseline	Mean (sd), ms	22.9 (26.2)	19.1 (28.1)	3.8 (1.1, 6.4)	0.005
				Risk difference (95% CI)	
Peak value in follow-up	>450ms[1], % (n)	4.3% (35)	4.4% (35)	0.2% (-1.6%, 2.0%)	0.83
Peak value in follow-up	>480ms[2], % (n)	0.9% (7)	1.8% (14)	-0.9% (-2.0%, 2.3%)[4]	0.12
Peak value in follow-up	>500ms[3], % (n)	0.6% (5)	0.5% (4)	0.1% (-0.6%, 0.9%)[4]	0.75
Peak value in follow-up – change from baseline	>60ms, % (n)	7.0% (56)	6.4% (51)	0.7% (-1.5%, 3.0%)	0.53

[1]timing of peak value >450ms - test arm n=12, 10 and 13 at month 1,2 and end of treatment, control arm n=15, 9 and 24 at month 1,2 and end of treatment; [2]timing of peak value >480ms - test arm n=3, 1 and 3 at month 1,2 and end of treatment, control arm n=5, 4 and 5 at month 1,2 and end of treatment; [3]timing of peak value >500ms - test arm n=2, 1 and 2 at month 1,2 and end of treatment, control arm n=0, 2 and 2 at month 1,2 and end of treatment; [4] not adjusted for country; CI confidence interval; sd standard deviation

391

392 **Table 5**: C_{max}, T_{max} and AUC at steady state for each drug, by study arm (n=291)

Drug	At steady state	Test (n=144) Median (minimum, maximum)	Control (n=147) Median (minimum, maximum)	Estimated gradient (95% CI), P-value[1]
Gatifloxacin	C_{max}	3.8 (2.5-5.8)	NA	-3.82 (-11.78, 4.14), 0.34
	T_{max}	1.7 (0.8-3.6)	NA	NA
Ethambutol	C_{max}	NA	3.2 (1.5-5.5)	-1.99 (-5.96, 1.98), 0.32
	T_{max}	NA	2.5 (1.5-4.5)	NA
Isoniazid	C_{max}	3.1 (0.7-8.0)	3.1 (0.5-6.0)	0.86 (-1.11, 2.83), 0.39
	T_{max}	0.9 (0.6-3.2)	0.8 (0.3-3.6)	NA
Rifampicin	C_{max}	6.3 (1.4-13.2)	6.9 (2.0-15.6)	0.16 (-1.08, 1.39), 0.81
	T_{max}	2.2 (1.3-5.6)	1.9 (1.1-5.3)	NA
Pyrazinamide	C_{max}	35.9 (23.8-60.4)	35.0 (21.9-62.1)	-0.28 (-0.66, 0.10), 0.15
	T_{max}	1.7 (0.9-4.5)	1.5 (0.8-5.0)	NA

393 [1]for the association of each drug C_{max} individually on QTcF at month 1, adjusted for country, sex, age
394 and QTcF at enrolment, and study arm (only for Isoniazid, Rifampicin and Pyrazinamide). CI
395 confidence interval.

396

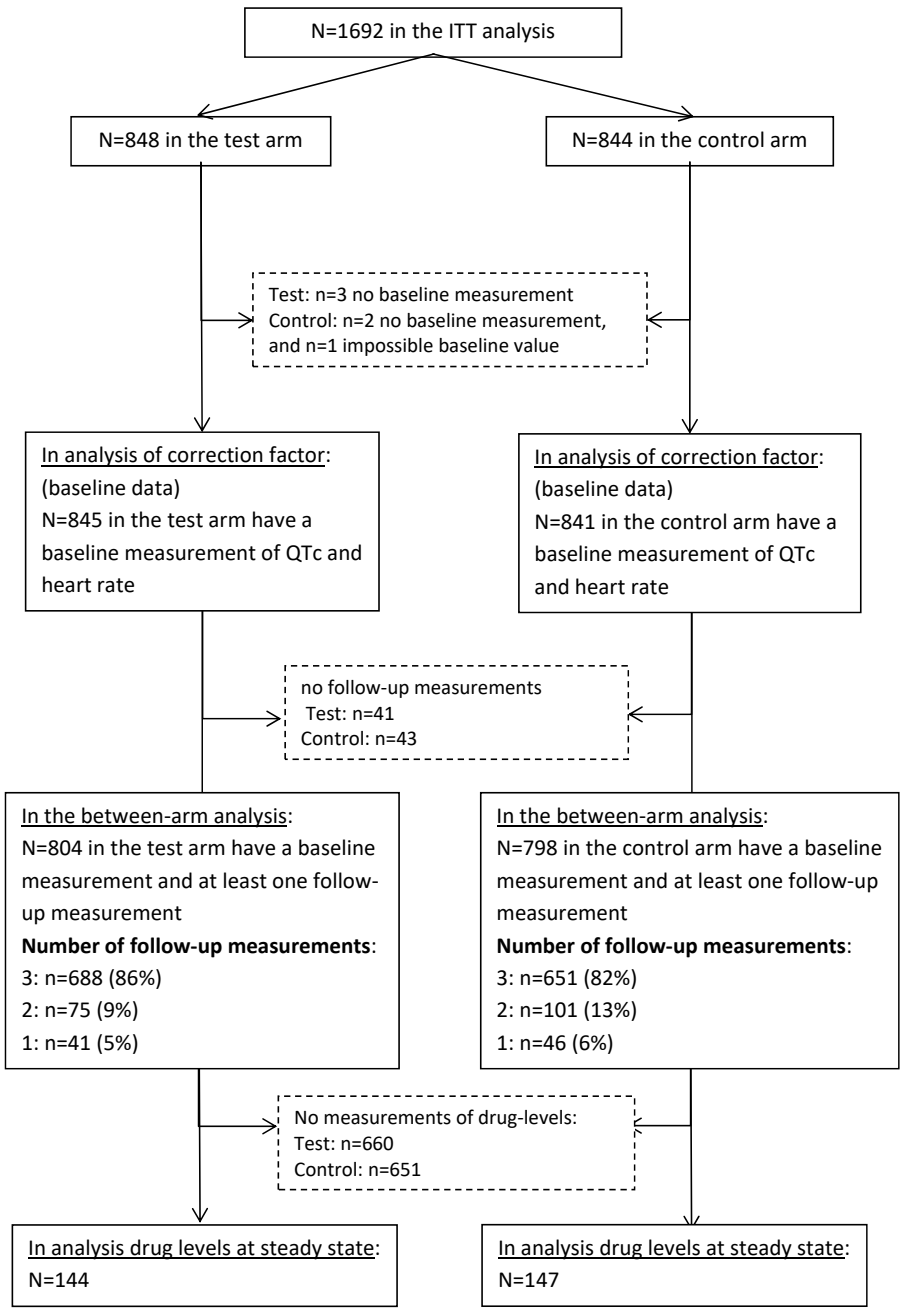
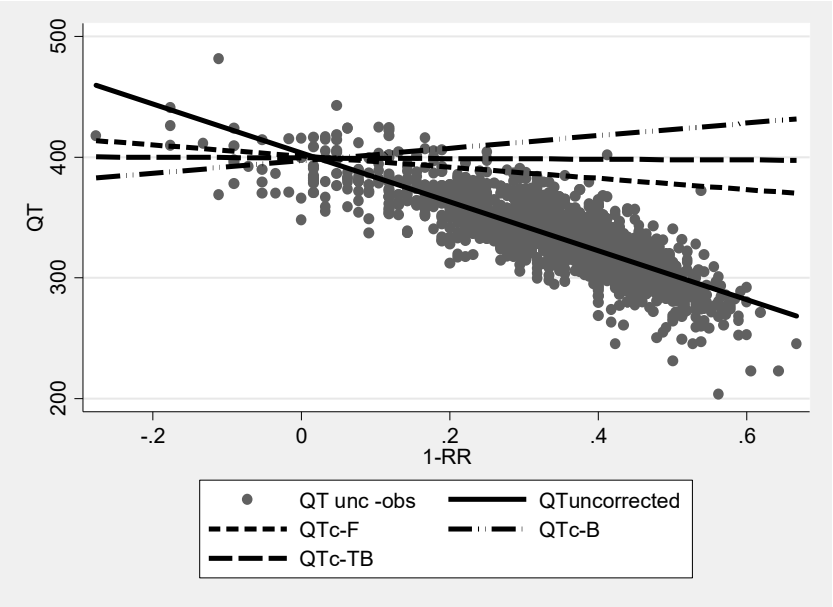


FIG 1 Study flow diagram



416

417 **FIG 2** Plot of uncorrected data and regression line; and regression lines for Bazett-corrected,

418 Fridericia-corrected and new-corrected QT (QTcTB), using data at baseline (n=1686)

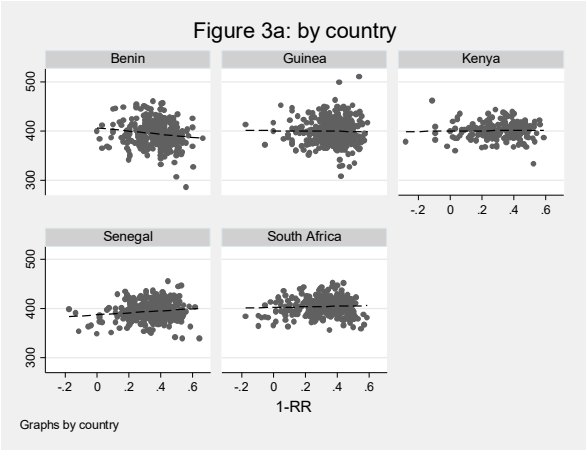
419

420 Footnote: QT unc-obs QT uncorrected observed data; QTuncorrected regression line; QTc-F

421 Fridericia corrected regression line; QTc-Bazett corrected regression line; QTc-TB corrected

422 regression line using correction factor of 0.4081.

423



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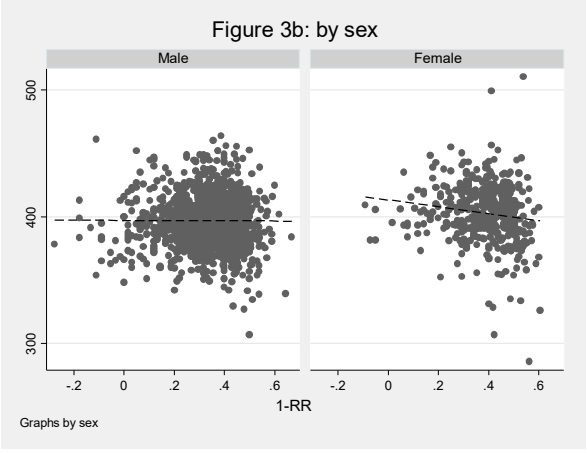

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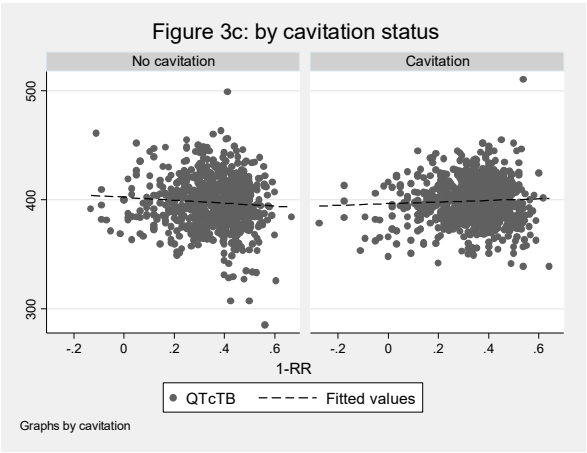
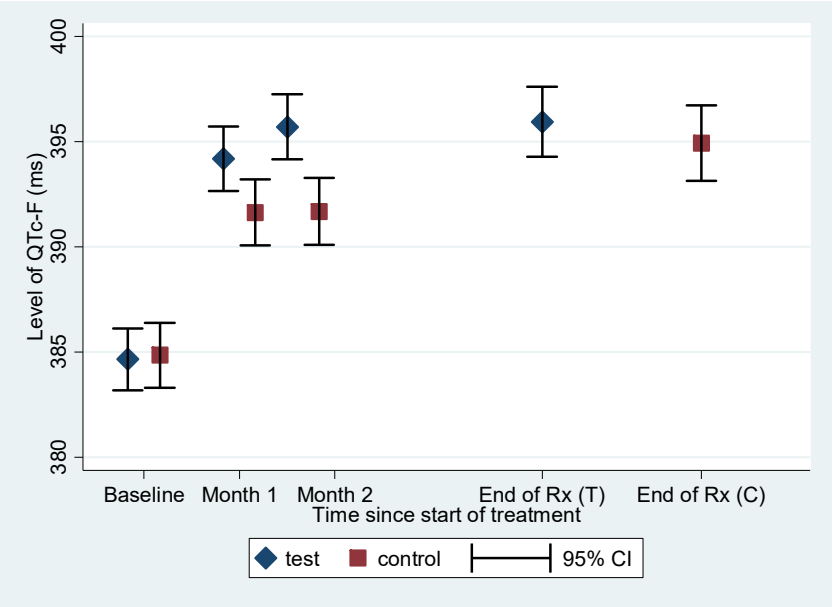


426

427 **FIG 3** Plot of QTcTB (0.4081) against 1-RR (where RR=60/heart rate), using data at baseline



428

429 **FIG 4.** Boxplots of QTcF values at baseline, months 1 and 2, and end of treatment (month 4 and 6,

430 respectively) for the gatifloxacin and standard treatment arm.

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432

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