ECG monitoring in STREAM Stage 1:
Can we identify those at increased risk of QT prolongation?

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All authors report no conflicts of interest

Authors' contributions
GH and HB designed and led the analyses and wrote the first draft of the manuscript.
All authors provided input in study design, commented on analysis methods, and wrote the manuscript with GH and HB. AJN and SKM were chief investigators of the STREAM trial; IDR was the sponsor representative. All authors read and approved the final manuscript.

Running head: ECG monitoring to predict QT prolongation

Word count (abstract): 195

Word count (main text): 2569

References: 19

Tables: 2

Figures: 2

Key word: (3-5) Rifampicin-resistant tuberculosis, moxifloxacin, clofazimine, QTcF, electrocardiogram

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Background

STREAM Stage 1 was a randomised trial of a Short (9 month) regimen for rifampicin-resistant TB (RR-TB). QT or QTcF prolongation ≥500ms occurred in 31 (11%) of 282 Short regimen participants. The frequent ECG monitoring employed might be challenging for treatment programmes. This analysis aimed to determine whether those at higher risk of severe QT prolongation could be identified early for more targeted monitoring.

Methods

Data from the first month of treatment were used to investigate whether participants were at risk of developing QT/QTcF ≥500ms. QTcF increases from baseline at different time points were examined. Absolute QTcF measurements were categorised in 5ms increments at each time-point. The most discriminating time points and QTcF cut-offs were combined to optimise sensitivity and specificity.

Results

Absolute QTcF values were more discriminating than size of increase from baseline. More participants who developed QT/QTcF ≥500ms had a QTcF ≥425ms and ≥430ms at 4 hours and week 3 respectively ($p<0.05$) than those who did not. Combining QTcF values ≥425ms at 4 hours and ≥430ms at week 3 identified high-risk participants with 97% sensitivity and 99% negative predictive value.

Conclusion

Reduced ECG monitoring may be possible for many Short regimen participants.

Background

STREAM Stage 1 was a randomised phase 3 trial for participants with rifampicin-resistant TB (RR-TB) comparing a 9 month Short regimen to a Long (approximately 20 month) regimen based on 2011 WHO guidance.[1,2] In total 424 participants were randomised in a 2:1 ratio in favour of the Short regimen, which comprised moxifloxacin, clofazimine, ethambutol and pyrazinamide, supplemented with isoniazid, prothionamide and kanamycin for the 4-month intensive phase. Moxifloxacin dose was weight-based: 400mg if <33kg, 600mg (33-50kg) and 800mg (>50kg). Extension of the intensive phase by up to eight weeks was recommended for participants with smear positive sputum at week 16. The Long regimen included standard dose moxifloxacin or levofloxacin. Both may prolong the QT interval, although probably less than higher doses. As QT prolongation can lead to cardiac arrhythmia, particularly when ≥500 milliseconds (ms), regular electrocardiogram (ECG) monitoring occurred for all participants in the first year after randomisation.

Participants with a corrected QT (QTc) interval ≥500ms at screening were ineligible. A baseline ECG was performed before enrolment and repeated 4 hours after the first dose of medication. Initially ECGs were performed weekly to week 4 and then at 12, 24 and 36 weeks. The protocol was subsequently amended to require 4-weekly ECGs from weeks 4 to 52 to facilitate earlier detection of QT prolongation. The primary safety outcome was occurrence of a ≥Grade 3 adverse event; this included QT or QTc prolongation ≥500ms. Fredericia's correction formula (QTcF) was used.[3] For participants that received at least one dose of trial medication (safety population), QT or QTcF prolongation ≥500ms occurred in 11% (31/282) of Short regimen participants *versus* 6.4% (9/141) of participants allocated the Long regimen (P=0.14).

The higher frequency of QT prolongation on the Short regimen may be due to high-dose moxifloxacin and clofazimine in combination. We have previously presented analyses of predictive factors for QT prolongation in this population.[4] Most participants on the Short regimen did not develop a QT/QTcF ≥500ms and are unlikely to need the intensive ECG monitoring used in the trial. On the other hand, some "high-risk" participants benefited so treatment could be modified if needed.

Guidance on cardiac monitoring during RR-TB treatment varies. The TB drug monographs website recommends ECGs at baseline, 2 weeks and then every 3 months for participants taking clofazimine or moxifloxacin containing regimens.[5] The South African Department of Health recommends ECGs at baseline, monthly for the intensive phase and then 3 monthly in the continuation phase.[6] The frequency of monitoring has implications for both financial and staff resources and may negatively affect adherence. The cost of managing a RR-TB

patient in the UK is roughly ten times that of a drug susceptible TB patient.[7] Part of this cost is likely to be due to increased patient monitoring, which is more difficult in a resource-limited setting. Frequent visits to a health facility for ECG monitoring may affect adherence by increasing anxiety, frequency of clinic visits, waiting times and travel difficulties.[8]

The pharmacokinetics (PK) of moxifloxacin and clofazimine influence risk and timing of QT prolongation. Oral moxifloxacin is rapidly absorbed, reaching a maximum serum concentration (T_{max}) in 0.75–3.5 hours with a half-life of 6-12 hours.[9] Clofazimine has unusual PK properties being highly protein bound and lipophilic with a long half-life (approximately 25-34 days), reaching a steady plasma state after 18-21 weeks.[10,11] Several weeks of treatment may occur before participants reach a QT/QTcF ≥500ms. Previous analysis of STREAM Stage 1 found most participants who experienced QT or QTcF prolongation ≥500ms did so ≥12 weeks into treatment.[4] Predicting these participants from early QT readings would allow monitoring to be targeted to those most at risk.

Patients with higher baseline readings are more likely to experience QT prolongation ≥500ms.[12–14] Analysis of STREAM Stage 1 data showed participants on the Short regimen with a QT/QTcF ≥500ms were nearly six times more likely to have a baseline QTcF reading ≥400ms than <400ms.[4] However, most participants with baseline readings ≥400ms did not subsequently develop QT or QTcF ≥500ms. A monitoring strategy that separates patients into high and lower risk groups cannot rely on baseline readings alone.

The aim of this analysis was to determine whether QTcF measurements early on during treatment would distinguish between participants at “high” and “lower” risk of QT/QTcF prolongation and could be used as the basis for development of a simplified monitoring strategy for programmatic settings.

Methods

The data for this sub-study came from the STREAM Stage 1 trial.[1] Participants were included if they were randomised to the Short regimen and had at least four out of six ECG measurements between baseline and week 4. Participants with missing ECGs at particular time points were excluded from analyses at that time.

A series of exploratory analyses were undertaken to assess association with subsequent QT/QTcF prolongation:

1. Increase from baseline of 5, 10, 15, 20 and 40ms in participants' QTcF from 4 hours post first dose up to week 4.

2. Absolute QTcF values at baseline, 4 hours post first dose and weeks 1-4 were analysed to see whether a cut-off value could be identified below which no participants developed a QT/QTcF ≥500ms. The range of cut-off values considered (410ms up to 450ms in 5ms increments) reflected the Interquartile Range of QTcF readings from Short regimen participants during follow-up (409.7, 445.5).

3. The most discriminating absolute QTcF cut-off values from different time-points were combined to optimise sensitivity and specificity.

Participants allocated to the Short regimen were classified according to whether they had experienced QT/QTcF ≥500ms at any time up to week 52 ("high-risk") or not ("lower-risk").

The number and proportion of "high-risk" participants whose QTcF exceeded the cut-off value (either QTcF increase from baseline or absolute value) at each time-point were calculated. The proportions identified were compared across categories using Fisher's exact test. Sensitivity, specificity, and positive and negative predictive values (PPV, NPV) for QT prolongation ≥500ms, were calculated.

The optimal cut-off at each time point was selected based on the distance from the ideal scenario of 100% sensitivity and 100% specificity, with values closer to zero being best and to one being worst. Combinations of cut-off values and time points were amalgamated to assess the sensitivity and specificity of different combinations.

Receiver Operating Characteristic (ROC) curves, relating to QT/QTcF prolongation ≥500ms, were plotted based upon QTcF cut-off values ranging from 385 to 470ms, assessing sensitivity and specificity at each 5ms interval. Additionally, ROC curves were plotted for

time points from week 1 to 4, restricting the analysis to high and lower-risk participants with a QTcF below 425ms at their 4 hour reading (or were missing this result).

Statistical analyses were conducted using STATA v15.1.

Ethical considerations

The International Union Against Tuberculosis and Lung Disease (The Union, and its North American affiliate) was the sponsor of the STREAM trial and The Union's Ethics Advisory Group and all national and local ethics committees approved the trial. This study describes secondary analyses of trial data.

Results

Of 282 participants allocated to the Short regimen, seven were excluded as they had fewer than four ECG readings to week 4.

The size of increase in QTcF from baseline was a poor predictor of subsequent QT/QTcF ≥500ms; the best measure was ≥40ms at week 4, but twenty-two participants who went on to experience severe prolongation were missed and only eight correctly classified (Table 1). Absolute baseline values performed better than change from baseline, although the best cut-off (410ms) on its own missed a third of high-risk participants (Table S1).

ROC curves from 4 hours post-first dose to week 4 are displayed in Figures 1 and 2. The ROC curve analysis in Figure 1 shows how different time points (4 hours up to week 4) performed as a screening tool for high-risk participants using QTcF cut-off values of 410-450ms. Time points of 4 hours and week 3 appeared best when looking at the same population for each point (Fig 1, Table S4). The cut-off value of 425ms at 4 hours gave a sensitivity of 83.3% and missed only five high-risk participants with a false-positive rate to 32.8%. A cut-off value of 430ms at the later time point of week 3 was equally good with a sensitivity of 83.9% and false positive rate of 32% (Fig 1, Table S4).

Figure 2 shows ROC curves for time-points weeks 1-4 in the population whose QTcF at 4 hours was <425ms. The best time point appeared to be week 3 and using a cut-off QTcF of 430ms (the same second-best scenario as in the whole population). All five high-risk participants with 4-hour readings <425ms are identified, with a false-positivity rate of 21% (Table S5). The sensitivity was 83.3% as one high-risk patient was missed using this approach with a week 3 QTcF <430ms, though their 4-hour reading was unavailable, so they were not included in analysis at that time point.

Performance statistics of different QTcF cut-offs were calculated at 4 hours post first dose in the whole study population (Table S2), at week 3 amongst participants with a QTcF <425ms at 4 hours (Table S3)**,** and for the best scenarios from the two time points combined (Table 2). Using the combination of time points and cut-offs described, 47% of participants were correctly identified as lower risk, 11% correctly identified as high-risk, 41% incorrectly identified as high-risk and less than 1% incorrectly identified as lower risk. This equates to a 97% sensitivity, 53% specificity, 21% PPV and 99% NPV.

Discussion

In programmatic settings with limited resources and/or large catchment areas it would be useful for clinicians to know early on which patients are more likely to develop severe QT prolongation and which are at lower risk so that monitoring strategies can be adjusted, and better use be made of scarce resources. We analysed STREAM Stage 1 ECG data to see whether increases in QTcF from baseline or absolute QTcF values at different time-points in the first month of treatment identified participants with prolongation ≥500ms at any point during monitoring. At 4 hours after the first dose 95% (260/274) of participants had QTcF measurements within 40ms of their baseline reading; this includes 234 participants who never reached a QT/QTcF ≥500ms. However, this also includes 84% (26/31) of high-risk participants who did. At week 4, fewer of the lower-risk group had a QTcF increase ≥40ms from baseline value and more high-risk participants are captured, but 22/30 are still missed.

Absolute QTcF values performed better as a screening tool than increase from baseline as they discriminated high and lower risk participants to a greater degree. Our analysis showed using a low QTcF threshold of <410ms at 4 hours meant only one patient who later developed a QT/QTcF ≥500ms would be missed (Table S4). However, this comes at a cost of more intense monitoring for 61% of participants in the lower-risk group. Similarly picking a QTcF cut-off value of >450ms would mean only having to perform extra monitoring on 3% of lower-risk participants but would miss 22 high-risk participants, which is unsatisfactory. A cut-off value of 425ms at the 4-hour time point would allow reduced monitoring for 67% of lower-risk participants and capture 83.3% (25/30) high-risk participants. All but one of the high-risk participants were identified using a combination of QTcF cut-offs; 425ms at 4 hours and 430ms at week 3. Of the 162 lower-risk participants in the analysis at week 3, 79% could have had reduced monitoring, as they were below the 430ms threshold.

The high sensitivity of 97% and NPV of 99% demonstrates nearly all participants in our data set were correctly predicted to have reached a QT/QTcF ≥500ms during trial follow up and a QTcF <425ms at 4 hours and <430ms at week 3 was fairly reliable at excluding participants who subsequently developed QT/QTcF prolongation ≥500ms. The low specificity of 53% was disappointing and the PPV of 21% led to a relatively large number of false-positives. However, as the aim was to determine whether a reduction in monitoring for lower-risk participants could be achieved without missing high-risk participants, this trade-off is still reasonable. The combination of early time-points and cut-off values might permit a reduced ECG monitoring frequency in 47% of participants on the Short regimen from STREAM Stage 1. While 4 hours post first dose was used in the analysis as the first time-point, week 3 had similar sensitivity and false-positive rate (Table S4). As an ECG at a later time-point would be required to capture all higher-risk participants, we selected the 4-hour time point in

preference to week 3 as participants are more likely to be easily available and could stay in the clinic after their first dose for a repeat ECG 4 hours later. A second time point at week 4 may be more practical than week 3 but did not perform as well in our analysis.

In our data set a monitoring strategy based on the 4-hour reading alone would have led to missing five high-risk participants who went on to develop a QT/QTcF ≥500ms. Though if participants with a QTcF <425ms at 4 hours were brought back within the first month of treatment additional high-risk participants who would benefit from increased ECG monitoring would be identified.

Development of QT prolongation on treatment may be delayed. Torsades de Pointes developed >1 month after starting non-cardiac medication for 40% of participants in a large cohort.[15] Analysis of STREAM Stage 1 Short regimen participants found the median time to QT/QTcF prolongation ≥500ms was 20 [8, 28] weeks.[4] Although most participants did not develop severe QT prolongation until week 12 or later, we were able to predict nearly all these participants from values within the first month of treatment.

Anti-psychotics are well known for QT effects, but the range of agents available with different side effect profiles [16,17] allows clinicians to switch should clinical concerns arise.[18] This is less straightforward in the MDR-TB setting; a treatment regimen of several agents is required and four of the seven most effective drugs according to WHO guidelines [19] (moxifloxacin, levofloxacin, bedaquiline and clofazimine) can prolong the QT interval. Given their efficacy and the limited alternatives, QT prolongation needs to be monitored for and managed rather than being avoided altogether.

Our proposed strategy has some limitations. Firstly, it is based on data from a single trial and has yet to be validated in a different data set (though this is planned for STREAM Stage 2). Secondly, other risk factors for QT prolongation may affect its performance such as renal or hepatic impairment which could lead to vomiting and electrolyte disturbance. Concomitant medications that affect the QT interval or drug metabolism may also play a role. Thirdly, the strategy requires lower risk participants to return for an extra ECG and some high-risk participants may still be missed. Fourthly, some of the drugs will not have reached a steady state at 4 hours, though this is mitigated by the inclusion of a later time point at week 3.

The main strengths of this study are that STREAM Stage 1 is currently one of the largest trials in drug-resistant TB treatment and that regular ECG monitoring using a calibrated standardised machine was carried out for all participants, irrespective of regimen or QT interval.

Conclusion

Using the strategy described, it may be possible to limit the number of ECG monitoring visits required in almost half the participants receiving the Short regimen. Such a targeted monitoring strategy could be useful in programmatic settings, particularly with limited resources or a large geographic spread of participants.

Acknowledgements

This study is made possible by the United States Agency for International Development (USAID) through the TREAT TB Cooperative Agreement No. GHN-A-00-08-00004, with additional funding from the United Kingdom Medical Research Council (MRC) and the United Kingdom Department for International Development (DFID) under the MRC/DFID Concordat agreement. We would like to thank all the participants and collaborators without whom the STREAM study would not have been possible.

Conflicts of interest: none declared.

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Tables

Table 1. Increase from baseline QTcF in the first 4 weeks of treatment based on a 40ms threshold comparing participants who subsequently developed QT/QTcF prolongation ≥500ms and those who did not.

Time point	Increase from baseline	Total assessed[1] (n=275)	Prolongation ≥500ms (n=31)	P-value[2]
4 hours	<40ms	260	26 (86.7%)	0.054
	≥40ms	14	4 (13.3%)	
Week 1	<40ms	248	24 (77.4%)	0.017
	≥40ms	26	7 (22.6%)	
Week 2	<40ms	243	26 (83.9%)	0.368
	≥40ms	31	5 (16.1%)	
Week 3	<40ms	241	24 (77.4%)	0.064
	≥40ms	31	7 (22.6%)	
Week 4	<40ms	229	22 (73.3%)	0.103
	≥40ms	42	8 (26.7%)	

[1] *Participants with missing ECG results at a particular time point are excluded from that analysis.*

[2] *Fisher's exact test*

Table 2. Combined performance using a cut-off of 425ms at 4 hours and 430ms at week 3 to identify participants with a diagnosis of QT/QTcF prolongation ≥500ms during ECG monitoring

Sensitivity	Specificity	PPV	NPV	Distance
96.77%	52.89%	20.83%	99.22%	0.4722

Figures

Figure 1. Receiver operating characteristic curve analysis using QTcF cut-off at 4 hours and weeks 1- 4 to identify a diagnosis of QT/QTcF prolongation ≥500ms.

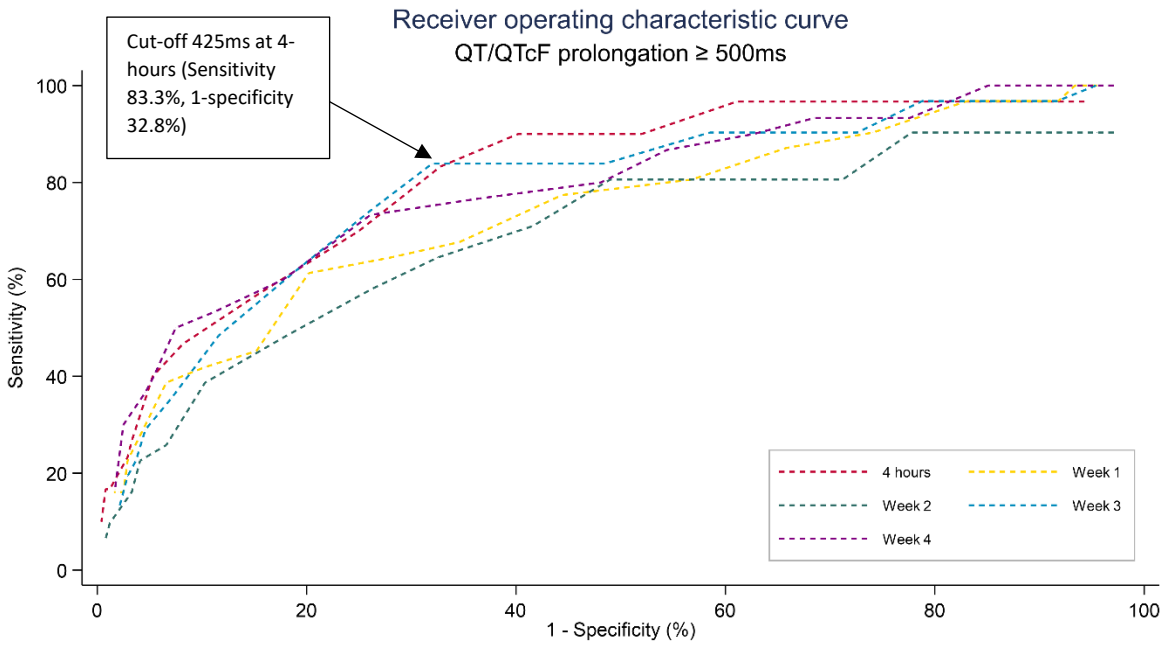

Figure 2. Receiver operating characteristic curve analysis for high and lower-risk participants with a 4-hour QTcF <425ms using QTcF cut-offs at weeks 1- 4 to identify a diagnosis of QT/QTcF prolongation ≥500ms