Evaluation and optimization of existing and new drugs for treatment of TBM

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Radboud university medical center, The Netherlands & Tuberculosis Research Group Bandung, Indonesia
Outline

• Penetration of TB drugs into CSF: an overview with focus on higher doses of rifampicin

• Tools for evaluating and optimizing TB drugs for TBM

• Conclusions
Penetration of TB drugs into CSF

**Rifampicin**

protein binding is circa 80-85%

Peter Donald: ‘18 papers, only 7 with individual or mean conc. > 1 mg/L’ (Tuberculosis 2010)

-> Need for higher doses in TBM

Peloquin, 2001
High dose rifampicin in Indonesian TBM patients

Open-label, randomized, phase 2, clinical trial (factorial design)

Subjects:

- 60 adult TBM patients
- 14 days intervention
- high dose iv rifampicin
- moxifloxacin

Pharmacokinetics of rifampicin:

<table>
<thead>
<tr>
<th></th>
<th>600 mg, intravenous (n=26)</th>
<th>450 mg, oral (n=26)</th>
<th>Ratio of intravenous to oral</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>AUC_{0-6} (mg.h/L)</td>
<td>78.7 (71.0–87.3)</td>
<td>26.0 (19.0–35.6)</td>
<td>3.0 (2.2–4.2)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>C_{max} (mg/L)</td>
<td>22.1 (19.9–24.6)</td>
<td>6.3 (4.9–8.3)</td>
<td>3.5 (2.6–4.8)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>C_{max} (≥8 mg/L)</td>
<td>26 (100%)</td>
<td>13 (50%)</td>
<td></td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>T_{max} (h; median, range)</td>
<td>2 (1–2)</td>
<td>2 (1–6)</td>
<td></td>
<td>0.048‡</td>
</tr>
<tr>
<td><strong>CSF</strong></td>
<td></td>
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</tr>
<tr>
<td>C_{max} (mg/L)</td>
<td>0.60 (0.46–0.78)</td>
<td>0.21 (0.16–0.27)</td>
<td>2.92 (2.03–4.20)</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

Data are no. (%) or Geometric mean (95% CI), unless otherwise indicated

*) independent t-test after log transformation
†) chi-square
‡) wilcoxon rank-sum test
High dose rifampicin in Indonesian TBM patients

Survival:

- 50% died within 6-m
- 22 (73%) in the first month

Main causes:
- respiratory failure (9)
- neurological deterioration (7)
- others (6)

Mortality was much lower in the high dose RIF group
- adjusted HR 0.42
  (95% CI 0.2-0.87), p=0.0193
High dose rifampicin in Indonesian TBM patients

Te Brake et al.
IJAA 2015;45:496-503
High dose rifampicin in Indonesian TBM patients

Yunivita et al.
IJAA 2016;48:415-21

17 vs 20 mg/kg orally vs 13 mg/kg i.v.
Large inter-individual variability in PK
ReDEFINe study

(funded by PEER Health project & PKSLN-DIKTI)

- Randomized double-blinded controlled phase 2 trial

- Primary objectives:
  - To generate PK data of higher oral dose of RIF in TBM patients

- Secondary objectives:
  - Safety and tolerability
  - Efficacy → clinical & neurological response
  - Inflammatory response
  - Gene-expert for TBM?
  - Bio-repository of blood, CSF for future research
PanACEA HIGHRIF1 study

Am J Respir Crit Care Med 2015;191:1058-65
PanACEA HIGHRIF1 results: subjects with any adverse event

<table>
<thead>
<tr>
<th>Arm</th>
<th>Total</th>
<th>Grade 1 AE</th>
<th>Grade 2 AE</th>
<th>Grade 3 AE</th>
<th>Grade 4 AE</th>
<th>Grade 5 AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>20 mg RIF/kg</td>
<td>17</td>
<td>13</td>
<td>3</td>
<td>1</td>
<td>0</td>
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<tr>
<td>25 mg RIF/kg</td>
<td>16</td>
<td>14</td>
<td>2</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>30 mg RIF/kg</td>
<td>20</td>
<td>13</td>
<td>5</td>
<td>2</td>
<td>0</td>
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</tr>
<tr>
<td>35 mg RIF/kg</td>
<td>22</td>
<td>15</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

All AE’s
PanACEA MAMS study in pulmonary TB

Lancet Infect Dis 2017;17:39-49
High dose rifampicin in Vietnamese TBM patients

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensified Antituberculosis Therapy in Adults with Tuberculous Meningitis


ABSTRACT

N Eng J Med 2016;374;124-34
High dose rifampicin in Vietnamese TBM patients

Clinical Outcomes of Patients With Drug-Resistant Tuberculous Meningitis Treated With an Intensified Antituberculosis Regimen

A. Dorothee Heamskerk,12 Mai Thi Hoang Nguyen,1 Ho Thi Minh Dang,13 Chau Van Vinh Nguyen,14 Lan Hue Nguyen,3 Thu Dong Anh Do,1 Thuong Thuy Thuong Nguyen,1 Marcel Weibors,12 Jeremy Day,12 Thao Thi Phuong Lo,1 Bang Duc Nguyen,12 Maxine Caws,13 and Guy E. Thwaites1,2

1Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam; 2Nuffield Department of Medicine, University of Oxford, United Kingdom; 3Pham Ngoc Thach Hospital for Tuberculosis and Lung Disease, and 4Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam; and 5Liverpool School of Tropical Medicine, United Kingdom

Background. Drug-resistant tuberculous meningitis (TBM) is difficult to diagnose and treat. Mortality is high and optimal treatment is unknown. We compared clinical outcomes of drug-resistant and -susceptible TBM treated with either standard or intensified antituberculosis treatment.

Methods. We analyzed the influence of Mycobacterium tuberculosis drug resistance on the outcomes of patients with TBM enrolled into a randomized controlled trial comparing a standard, 9-month antituberculosis regimen (containing rifampicin 10 mg/kg/day) with an intensified regimen with higher-dose rifampicin (15 mg/kg/day) and levofloxacin (20 mg/kg/day) for the first 8 weeks. The primary endpoint of the trial was 9-month survival. In this subgroup analysis, resistance categories were predefined as multidrug resistant (MDR), isoniazid resistant, rifampicin susceptible (INH-R), and susceptible to rifampicin and isoniazid (INH-S + Rif-S). Outcome by resistance categories and response to intensified treatment were compared and estimated by Cox regression.

Results. Of 817 randomized patients, 322 had a known drug resistance profile. INH-R was found in 86 (26.7%) patients, MDR in 15 (4.7%) patients, rifampicin monoresistance in 1 patient (0.3%), and INH-S + Rif-S in 220 (68.3%) patients. Multivariable regression showed that MDR (hazard ratio [HR], 5.91 [95% confidence interval [CI]], 3.00–11.61), P < .001), was an independent predictor of death. INH-R had a significant association with the combined outcome of new neurological events or death (HR, 1.58 [95% CI, 1.11–2.23]). Adjusted Cox regression, corrected for treatment adjustments, showed that intensified treatment was significantly associated with improved survival (HR, 0.34 [95% CI, .15–.76], P = .01) in INH-R TBM.

Conclusions. Early intensified treatment improved survival in patients with INH-R TBM. Targeted regimens for drug-resistant TBM should be further explored.

Keywords. tuberculous meningitis; tuberculosis; drug-resistance; isoniazid; levofloxacin.
Outline

• Penetration of TB drugs into CSF: an overview with focus on higher doses of rifampicin

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Penetration of TB drugs into CSF

REVIEW
Cerebrospinal fluid concentrations of antituberculosis agents in adults and children
P.R. Donald

Tuberculosis 2010

**Isoniazid**
- Protein binding is very low
- Excellent penetration into CSF

Higher dose needed to achieve similar exposures in CSF vs plasma?

Lower exposures in CSF in fast vs slow acetylators
NAT2 genotype guided regimen reduces isoniazid-induced liver injury and early treatment failure in the 6-month four-drug standard treatment of tuberculosis: A randomized controlled trial for pharmacogenetics-based therapy

Junichi Azuma • Masako Ohno • Ryuji Kubota • Soichiro Yokota • Takayuki Nagai • Kazunari Tsuyuguchi • Yasuhisa Okuda • Tetsuya Takashima • Sayaka Kamimura • Yasushi Fujio • Ichiro Kawase • Pharmacogenetics-based tuberculosis therapy research group
Penetration of TB drugs into CSF

**Pyrazinamide**  protein binding: 50%?

passes freely into CSF

Higher doses suggested for pulmonary TB based on
- hollow fiber model (Gumbo 2009)
- mice and guinea pigs (Ahmad 2011)
- PK-PD study in humans (Pasipanodya, 2013)

Risk of increased hepatotoxicity with higher doses

Pyrazinamide in Vietnamese TBM patients


‘Elevated CSF concentrations of pyrazinamide on the other hand were strongly and independently correlated with increased mortality and neurological toxicity.’
Penetration of TB drugs into CSF

**Ethambutol**
- protein binding 20-30%
- poor penetration into CSF

**Aminoglycosides**
- protein binding: 35%
- poor penetration into CSF, but also conflicting data
- ‘inflamed meninges only’
- adjunctive intrathecal administration was still needed in monotherapy SM

**Fluoroquinolones**

<table>
<thead>
<tr>
<th></th>
<th>Plasma</th>
<th>CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>800 mg (n=16)</td>
<td>400 mg (n=19)</td>
</tr>
<tr>
<td><strong>AUC$_{0-24}$</strong>&lt;sup&gt;mg.h/l&lt;/sup&gt;</td>
<td>60.4 (45.4-80.3)</td>
<td>28.6 (24.2-33.8)</td>
</tr>
<tr>
<td><strong>AUC$_{0-6}$</strong>&lt;sup&gt;mg.h/l&lt;/sup&gt;</td>
<td>31.5 (24.1-41.1)</td>
<td>15.1 (12.8-17.7)</td>
</tr>
<tr>
<td><strong>C$_{max}$</strong>&lt;sup&gt;mg/L&lt;/sup&gt;</td>
<td>7.4 (5.6-9.6)</td>
<td>3.9 (3.2-4.8)</td>
</tr>
<tr>
<td><strong>T$_{max}$</strong>&lt;sub&gt;h, median, range&lt;/sub&gt;</td>
<td>2 (1-6)</td>
<td>2 (1-6)</td>
</tr>
<tr>
<td><strong>C$_{max}$</strong>&lt;sup&gt;mg/L&lt;/sup&gt;</td>
<td>2.43 (1.81-3.27)</td>
<td>1.52 (1.28-1.82)</td>
</tr>
</tbody>
</table>

Data are number (%) or geometric mean (95% CI), unless otherwise indicated. Moxifloxacin concentrations were measured for plasma AUC$_{0-24}$ and AUC$_{0-6}$ and CSF C$_{max}$ in samples obtained during the first 3 days of treatment. AUC$_{0-24}$=area under the time-concentration curve up to 24 h after dose. AUC$_{0-6}$=area under the time-concentration curve up to 6 h after dose. C$_{max}$=maximum plasma concentration. T$_{max}$=time to C$_{max}$. CSF=cerebrospinal fluid. “Could be assessed in 24 patients. †Independent samples t test after log transformation. ‡Wilcoxon rank-sum test. ¶CSF samples were obtained in 15 patients on moxifloxacin 800 mg and 17 patients on 400 mg. All concentrations were above the limit of quantification of the assay.

*Table 3: Pharmacokinetic data for moxifloxacin (n=35)*
<table>
<thead>
<tr>
<th>Drug</th>
<th>Protein Binding</th>
<th>Penetration into CSF</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethionamide/prothionamide</td>
<td>Protein binding 30%</td>
<td>limited studies point to penetration into CSF (low therapeutic conc. based on total conc.)</td>
<td>gastro-intestinal AEs</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Protein binding: none (0%)</td>
<td>limited studies point to penetration into CSF (low therapeutic conc. based on total conc. or conc. similar to plasma conc.)</td>
<td>neurological and psychiatric AEs</td>
</tr>
<tr>
<td>PAS</td>
<td>Protein binding: 50-60%</td>
<td>limited data: low penetration into CSF</td>
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</table>
## Penetration of TB drugs into CSF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Protein Binding</th>
<th>Penetration into CSF?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clofazimine</td>
<td>- protein binding?</td>
<td>- penetration into CSF?</td>
</tr>
<tr>
<td>Thioacetazone</td>
<td>- protein binding?</td>
<td>- penetration into CSF?</td>
</tr>
<tr>
<td>Linezolid</td>
<td>- protein binding 31%</td>
<td>- passes blood-brain barrier, CSF/plasma ratio at least 0.7 in various studies (<em>no data in TBM</em>)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- large PK variability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- PK study in TBM in preparation in Indonesia</td>
</tr>
<tr>
<td>Bedaquiline</td>
<td>- protein binding: &gt;99%</td>
<td>- ‘brain uptake was low in mice’</td>
</tr>
<tr>
<td>Delamanid</td>
<td>- protein binding: &gt;99%</td>
<td>- penetration into CSF?</td>
</tr>
</tbody>
</table>
Penetration of TB drugs into CSF:
an overview with focus on higher doses of rifampicin

Tools for evaluating and optimizing TB drugs for TBM

Conclusions
Are TB drugs substrates to efflux pumps?

- inside-out vesicles or HEK293 transfected cells
- In vitro BBB model
### Tool 1. Molecular pharmacological research

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pgp</th>
<th>BCRP</th>
<th>MRP1</th>
<th>MRP2</th>
<th>MRP3</th>
<th>MRP4</th>
<th>MRP5</th>
<th>BSEP</th>
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<td>INH</td>
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<tr>
<td>RIF</td>
<td>29.1</td>
<td>55.3</td>
<td>32.4</td>
<td>26.6</td>
<td>97.4</td>
<td>88.4</td>
<td>≥200</td>
<td>24.8</td>
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<td>AMK</td>
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<td>PAS</td>
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<td>6.8</td>
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<td>SQ109</td>
<td>10.5</td>
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<td>91.5</td>
<td>79.3</td>
<td>100-150</td>
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<tr>
<td>TRD</td>
<td>22.6</td>
<td>6.6</td>
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<tr>
<td>TIM</td>
<td>1.0</td>
<td>100-150</td>
<td>4.3</td>
<td></td>
<td></td>
<td></td>
<td>100-150</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Te Brake et al. Overview of TB drug concentrations resulting in 50% inhibition (IC$_{50}$) of the ATP-dependent uptake of radio-labeled substrates.
Tool 2: PBPK modelling

- Combine *in vitro* data to simulate *in vivo* behaviour
- Predict PK based on ‘real’ populations
  - paediatric population
  - HIV population
- Evaluate drug-drug interactions
1. CSF: plasma concentration ratio greatly depends on time post dose

- Large fluctuation in plasma conc.
- Less dynamics in CSF conc.
- Ideally AUC ratio is used

Hoetelmans RM, Antivir Ther. 1998
Tool 3: improved PK analysis in CSF

2. CSF: plasma concentration ratios for the same drug greatly differ and mislead when total (free + protein-bound) concentrations are used

- suppose 99% protein binding = 1% free (active) in plasma
- only free drug penetrates into CSF
- drug in CSF is largely unbound due to low concentrations of protein
2. CSF: plasma concentration ratios for the same drug greatly differ and mislead when total (free + protein-bound) concentrations are used

• suppose 99% protein binding = 1% free (active) in plasma
• only free drug penetrates into CSF
• drug in CSF is largely unbound due to low concentrations of protein

• CSF/plasma ratio based on total concentrations

• CSF/plasma ratio based on free concentrations

Hoetelmans RM, Antivir Ther. 1998
Tool 4: PET imaging and/or post mortem PK analysis

- Drugs labelled with positron emitting radionuclides
- Monitor whole-body distribution
- Correlate brain with plasma and
- CSF concentrations
Tool 5. Advanced PK and PK-PD modeling (*pharmacometrics*)

- **A multi-disciplinary** field where statistics, mathematics and computational science meet pharmacology, physiology and biology

- Mathematical **models** to characterize, understand, and predict a drug’s pharmacokinetic (**PK**) and pharmacodynamic (**PD**) features in **populations**

- **Nonlinear mixed-effects** models describing the **typical** behavior and the stochastic **variability** in a system
High dose rifampicin model, in process (Elin Svensson)
Phase I
• First-in-man, dose-ranging for safety
• **Aim:**
  • Collect safety data with very little (or no) efficacy data

Phase II
• Exploratory, hypothesis-generating
• **Aim:**
  • Identify the most-promising regimen(s) to take forward to phase III

Phase III
• Confirmatory, proof-of-concept
• **Aim:**
  • Provide convincing evidence of regimen efficacy
Tool 6. Smart phase II designs to find optimal TB drug REGIMEN

- Phase IIA
  - Optimal dose, PK, drug-drug interactions
  - Collect safety data over longer durations than phase I
  - Generate preliminary efficacy data
  - Limited studies
  - Combination of classical drug treatment with host-directed therapy (factorial designs)

- Phase IIB
  - Collect efficacy data over longer durations
  - Of sufficient size to make decisions about which regimens to take forward to phase III
  - Very limited studies
  - Gap between phase IIa and III!
e.g. Multi-Arm Multi-Stage Design (MAMS)

- Multi-arm phase II/III trial with several planned interim analyses
- Intermediate endpoint used to compare each experimental arm with the common control
- Arms without sufficient evidence of benefit dropped, using a pre-specified critical value (‘hurdle’)
- The hurdles are raised at each interim analysis
- The analyses at the end of the trial is done on the definitive endpoint only on the ‘fittest’ arms that have not been dropped

More information: Patrick Phillips, MRC, UCSF
MAMS design example for 6-arm TB trial (Patrick Phillips)

Treatment effect vs. Control

Start of recruitment

Stage 1

Control

Stage 2

Stage 3

Stage 4

End of recruitment

1st Interim

2nd Interim

3rd Interim

Time
**Garage**

**Setup:** 2-4 specialized sites participate

**Aims:** Combine components for safety and synergy and establish proof-of-concept

---

**Garage Setup:**

- Phase I: Max. tolerated single dose in healthy volunteers
- Phase II a: Dose escalation in patients
- Phase II a: 14-day early bactericidal activity + 14-day safety
- Phase II a: Drug-drug interaction

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**Concept:** PanACEA, Michael Hoelscher
• Penetration of TB drugs into CSF:
  an overview with focus on higher doses of rifampicin

• Tools for evaluating and optimizing TB drugs for TBM

• Conclusions
Conclusions

- Drugs that warrant evaluation & optimization:
  - INH, rifampicin, pyrazinamide
  - FQs, cycloserine, ethionamide, linezolid
  - concept of efflux pump inhibition

- Pharmacological and methodological tools (current gaps):
  - molecular pharmacological research
  - PBPK modeling
  - optimized PK sampling and adequate bio-analysis
  - advanced PK and PK-PD modeling
  - PET scanning
  - innovative phase II designs:
    - combinations of antibiotics + anti-inflammatory treatment + HDT
    - factorial designs, phase III selection trials

- We need to develop regimens, not only drugs

- We need to collaborate
Acknowledgements

• Colleagues of Tuberculosis Research Group Bandung, Indonesia

• Colleagues at Radboudumc, The Netherlands
Enhancing delivery of drugs to the CNS (Beyley, 2004; Losher 2005)

1. Increasing the dose of drugs
   - rifampicin
   - isoniazid
   - pyrazinamide

2. Choosing other drugs
   - ethionamide/prothionamide
   - cycloserine
   - linezolid

3. Prodrugs

4. Local administration

5. Olfactory (nasal) administration

6. Modulation of blood-tissue barrier
   - osmotic opening: mannitol
   - bradykinin analogues
   - alkylglyceroles
   - ultrasound / electromagnetic radiation

7. Inhibition of efflux mechanisms

8. Others: liposome and nanoparticles, cell-penetrating vectors
Adaptive Clinical Trial Designs

- A trial that ‘uses accumulating data to decide on how to modify aspects of the study as it continues,... without undermining the validity and integrity of the trial’

  PhRMA Adaptive Designs Working Group, 2006

- Modification of eligibility criteria
- Selection of endpoint
- Sample size reassessment
- Group sequential designs
- Adaptive dose-ranging studies
- Early termination for lack of sufficient efficacy or overwhelming efficacy
- Seamless phase II/III designs
- Multi-arm treatment selection design

- Adaptive by design
  - Pre-specified design feature in protocol and not a remedy for poor planning!
Strengths of MAMS design

- Arms without evidence of sufficient efficacy are dropped early thereby reducing the sample size

- Pre-specified design and critical values - single trial protocol

- Answers more relevant public-health question:
  - Not: *Can this drug/regimen be used to treat TB?*
  - *What are the most effective regimens to treat TB?*
Weaknesses of MAMS design

- Slight risk of dropping an effective regimen
- Logistical complexity
- Unclear process for drug licensing
  - Less of a problem for Phase II trial
- Rapid data management systems are critical
- Efficiency is lessened due to long delay in culture endpoint – 8 weeks follow-up + 6 weeks growth
  - Biomarkers that are real-time and measured earlier in treatment will make the MAMS design much more efficient
    - GenXpert CT? Resuscitation-promoting factors? Molecular assays?
## Time to stable culture conversion on MGIT liquid

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Q</th>
<th>20RQ</th>
<th>20RM</th>
<th>35R</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Included in analysis</strong></td>
<td>123</td>
<td>58</td>
<td>56</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td><strong>Median time</strong></td>
<td>62 days</td>
<td>63 days</td>
<td>66 days</td>
<td>55 days</td>
<td>48 days</td>
</tr>
<tr>
<td><strong>Adj. HR(^1) (95% CI)</strong></td>
<td>0.82 (0.55 - 1.24)</td>
<td>0.73 (0.48 - 1.13)</td>
<td>1.42 (0.98 - 2.05)</td>
<td>1.75 (1.21 - 2.55)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p=0.35</td>
<td>p=0.16</td>
<td>p=0.07</td>
<td>p=0.003</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Analysis has been adjusted for: HIV status; baseline GeneXpert CT; centre; baseline culture (using TTP).
## Time to stable culture conversion on MGIT liquid

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Q</th>
<th>20RQ</th>
<th>20RM</th>
<th>35R</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Included in analysis</strong></td>
<td>123</td>
<td>58</td>
<td>56</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td><strong>Median time</strong></td>
<td>62 days</td>
<td>63 days</td>
<td>66 days</td>
<td>55 days</td>
<td>48 days</td>
</tr>
<tr>
<td><strong>Adj. HR</strong></td>
<td>0.82</td>
<td>0.73</td>
<td>1.42</td>
<td>1.75</td>
<td>(0.55 - 1.24)</td>
</tr>
<tr>
<td></td>
<td>p=0.35</td>
<td>p=0.16</td>
<td>p=0.07</td>
<td></td>
<td>p=0.003</td>
</tr>
</tbody>
</table>

**Censoring data at 8 weeks** (to mimic previous TB phase II trials)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Q</th>
<th>20RQ</th>
<th>20RM</th>
<th>35R</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adj. HR</strong></td>
<td>1.05</td>
<td>0.91</td>
<td>1.69</td>
<td>1.99</td>
<td>(0.60 - 1.83)</td>
</tr>
<tr>
<td></td>
<td>p=0.88</td>
<td>p=0.78</td>
<td>p=0.04</td>
<td></td>
<td>p=0.007</td>
</tr>
</tbody>
</table>

1 Analysis has been adjusted for: HIV status; baseline GeneXpert CT; centre; baseline culture (using TTP).
Brain tissue:plasma concentration ratios of indinavir, nelfinavir, and saquinavir in wild-type and mdr1a(-/-) knock-out mice [12].