Model-based meta-analysis of rifampicin exposure and mortality in phase II tuberculosis meningitis trials

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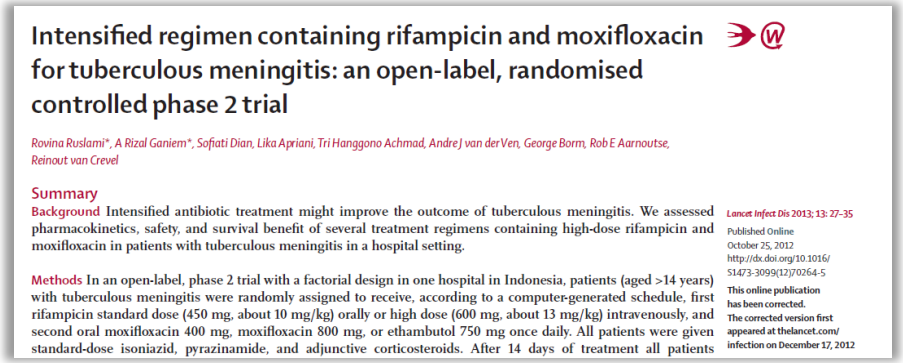
Radboudumc

Background

- Mortality of tuberculosis meningitis (TBM) often >40%
- Intensified rifampicin treatment → improved outcomes?



Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial

Rovina Ruslami*, A Rizal Ganiem*, Sofiati Dian, Lika Apriani, Tri Hanggono Achmad, Andre J van der Ven, George Borm, Rob E Aarnoutse, Reinout van Crevel

Summary

Background Intensified antibiotic treatment might improve the outcome of tuberculous meningitis. We assessed pharmacokinetics, safety, and survival benefit of several treatment regimens containing high-dose rifampicin and moxifloxacin in patients with tuberculous meningitis in a hospital setting.

Methods In an open-label, phase 2 trial with a factorial design in one hospital in Indonesia, patients (aged >14 years) with tuberculous meningitis were randomly assigned to receive, according to a computer-generated schedule, first rifampicin standard dose (450 mg, about 10 mg/kg) orally or high dose (600 mg, about 13 mg/kg) intravenously, and second oral moxifloxacin 400 mg, moxifloxacin 800 mg, or ethambutol 750 mg once daily. All patients were given standard-dose isoniazid, pyrazinamide, and adjunctive corticosteroids. After 14 days of treatment all patients

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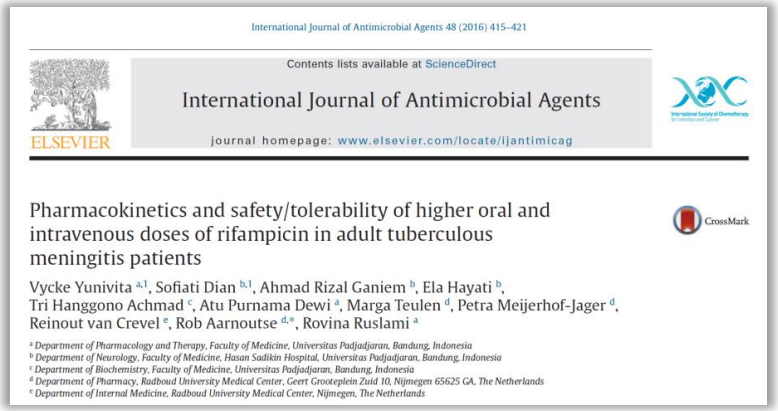

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Pharmacokinetics and safety/tolerability of higher oral and intravenous doses of rifampicin in adult tuberculous meningitis patients

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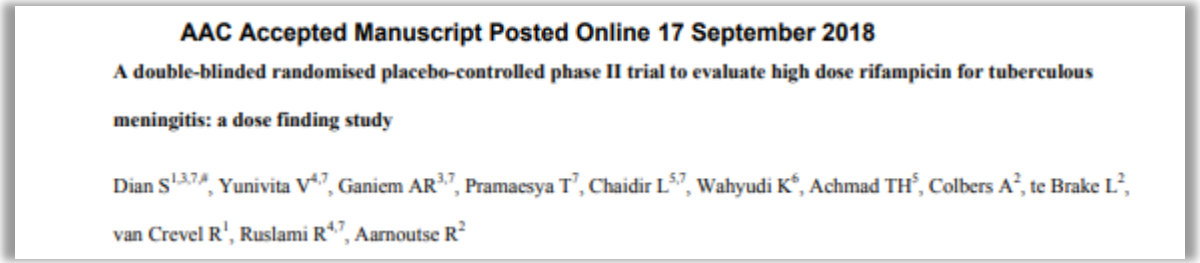


AAC Accepted Manuscript Posted Online 17 September 2018

A double-blinded randomised placebo-controlled phase II trial to evaluate high dose rifampicin for tuberculous meningitis: a dose finding study

Dian S[1,3,7,#], Yunivita V[4,7], Ganiem AR[3,7], Pramaesya T[7], Chaidir L[5,7], Wahyudi K[6], Achmad TH[5], Colbers A[2], te Brake L[2], van Crevel R[1], Ruslami R[4,7], Aarnoutse R[2]

Objectives

To characterize population pharmacokinetics of high-dose rifampicin in plasma and cerebrospinal fluid (CSF)

Evaluate the relationship between individual exposures and mortality

Investigate the need for weight-banded dosing

Data and methods

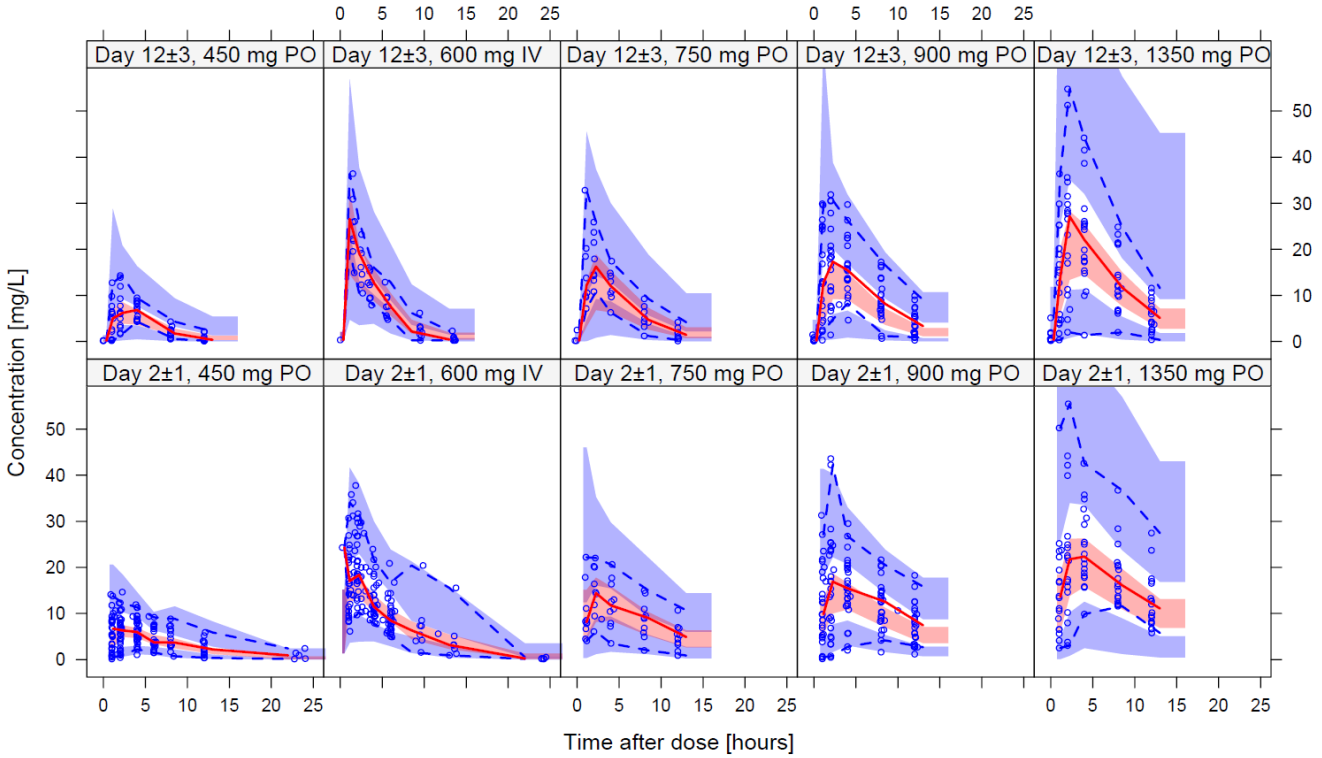
	Study 1	Study 2	Study 3
Rifampicin dose	450 mg PO, 600 mg IV	750 or 900 mg PO, 600 mg IV	450, 900 or 1350 mg PO
N subjects	60	30	60
PK sampling	Plasma: rich, day 2±1 CSF: two single samples (3-9h)	Plasma: rich, day 2±1 and 12±3 CSF: two singles sample (3-6h)	Plasma: rich, day 2±1 and 12±3 CSF: two single samples (3-9h)
Follow up (days)	180	180	180

- **PK:** Nonlinear mixed-effects models
- **Mortality:** Parametric time-to-event models

Plasma PK model in a nut shell

- Two disposition compartments
- Well-stirred liver model
- Saturable clearance
- Autoinduction

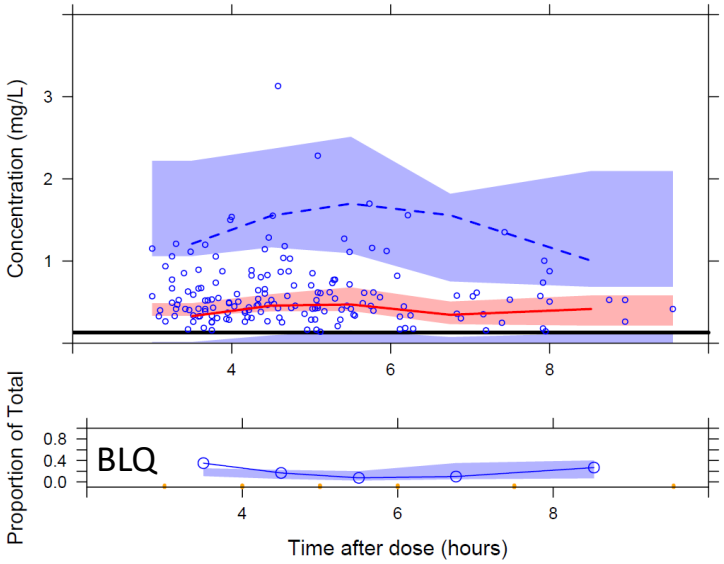
- Oral bioavailability 78% ($CI_{95\%}$ 71-84)
- Volume of distribution 19% ($CI_{95\%}$ 12-26) lower at late sampling days

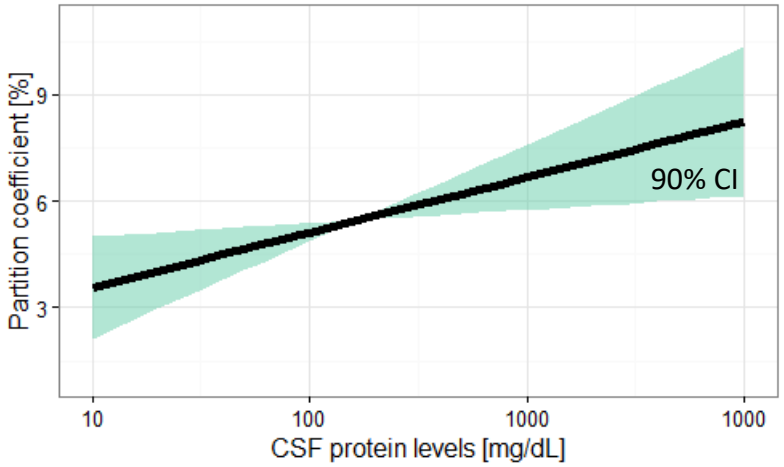


Details: Chirehwa et al., AAC 2016; Svensson et al., CPT, 2018; Savic et al., CPT, 2015

CSF PK model

- 170 observations
- Half-life for distribution 2.1 h ($CI_{95\%}$ 1.3-2.9)
- Partition coefficient 5.5% ($CI_{95\%}$ 4.4-6.4)
  - Higher CSF protein ➡ increased partition coefficient



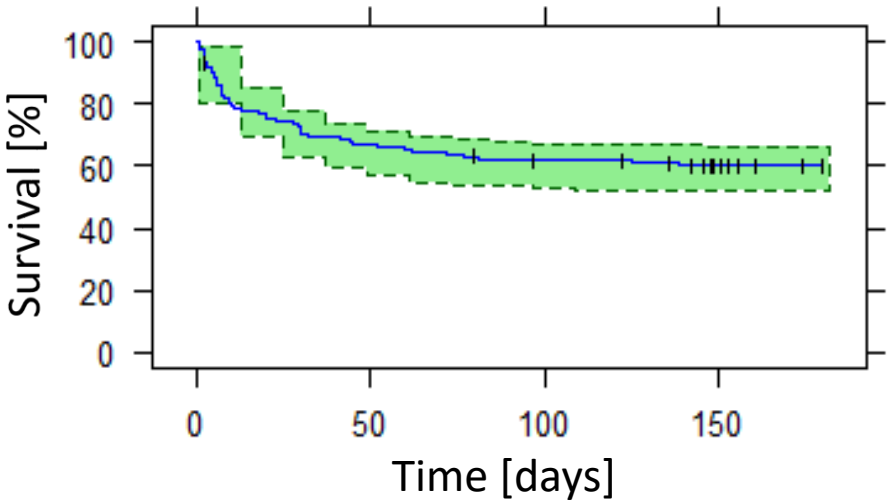


6-month mortality

- **148** individuals, **58** died, **15** dropped out

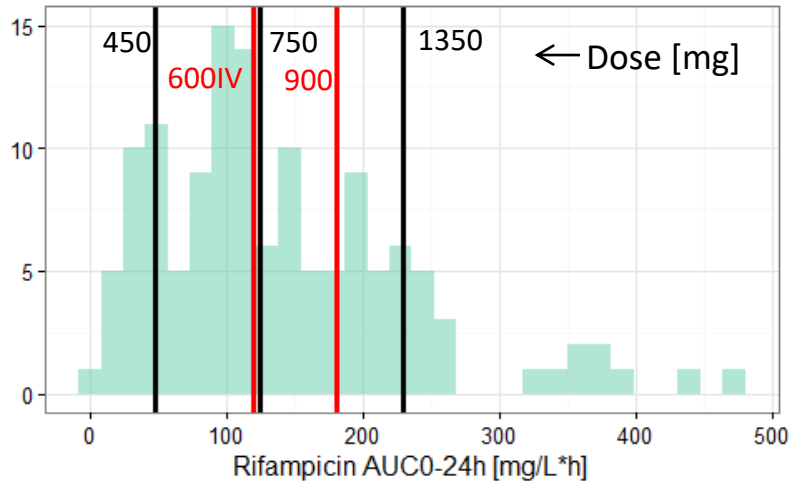
- Exponentially declining hazard
  - Lower age
  - Higher baseline Glasgow Coma Scale score
  - Higher rifampicin plasma $AUC_{0\text{-}24h}$

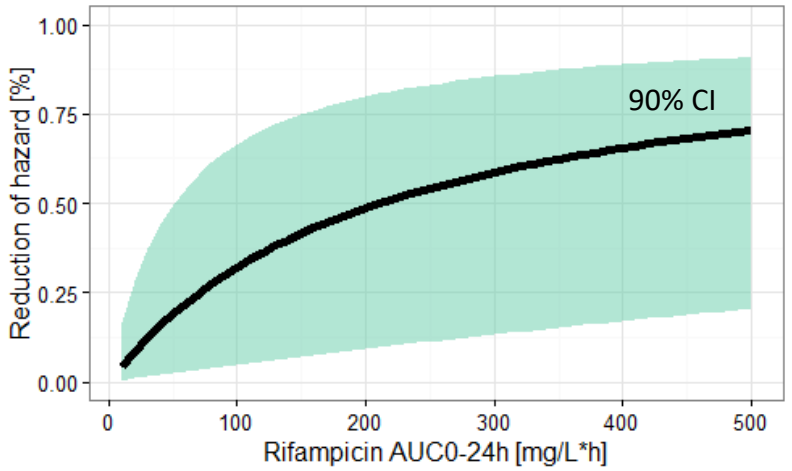
→ Reduced hazard



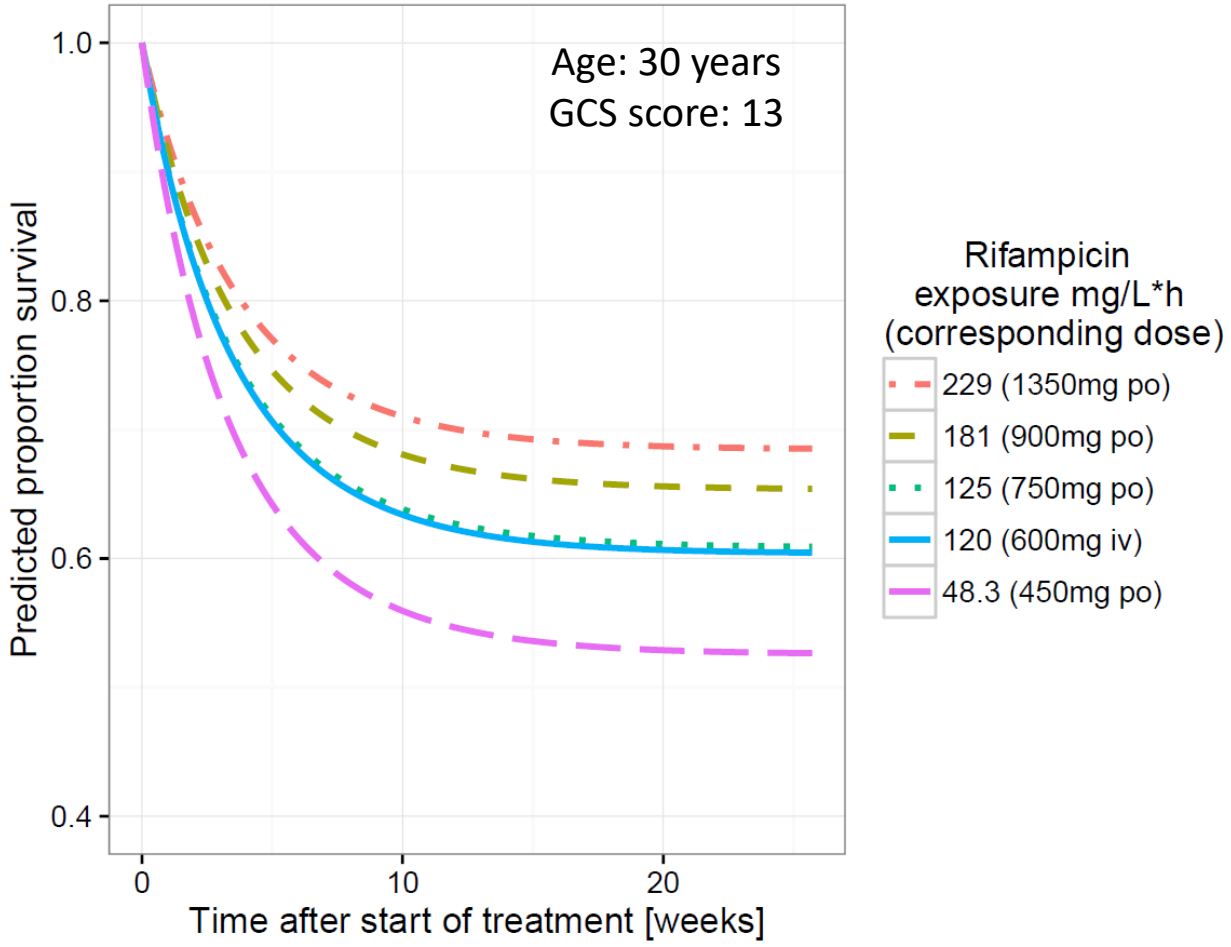
Influence of rifampicin on mortality

- Plasma $AUC_{0\text{-}24h}$ (day 2±1)
  - Stronger than C_{max} or CSF exposure
- Hill equation, maximal effect not estimable
- EC_{50} = 211 mg/L*h (RSE 94%)



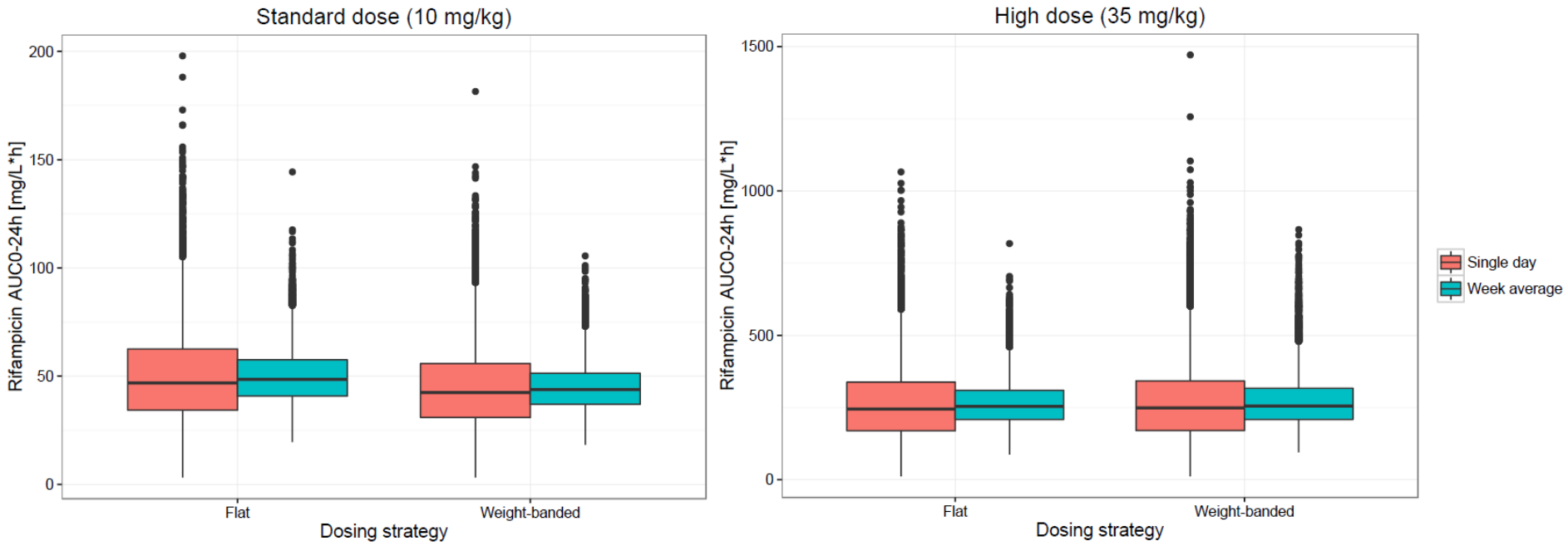


Influence of rifampicin on mortality



Simulations flat dosing

- Virtual population: 10,000 African and Indonesian TBM patients



Very little effect of dose-individualization on total body weight!

Conclusions

- Higher rifampicin exposure → substantially decreased the risk of death
- Maximal effect not reached → 1350 mg or higher
- Little effect of weight-banding → not necessary

The optimal dose of rifampicin in treatment of TBM should be further investigated in phase III type trials:

HARVEST

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- **Patients and staff participating in the trials**

- Co-investigators:

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  Radboudumc: *Lindsey te Brake, Reinout van Crevel, Rob Aarnoutse*

- Technical support: Uppsala Pharmacometrics Group

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Acknowledgments

Alva – 7 weeks tomorrow