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

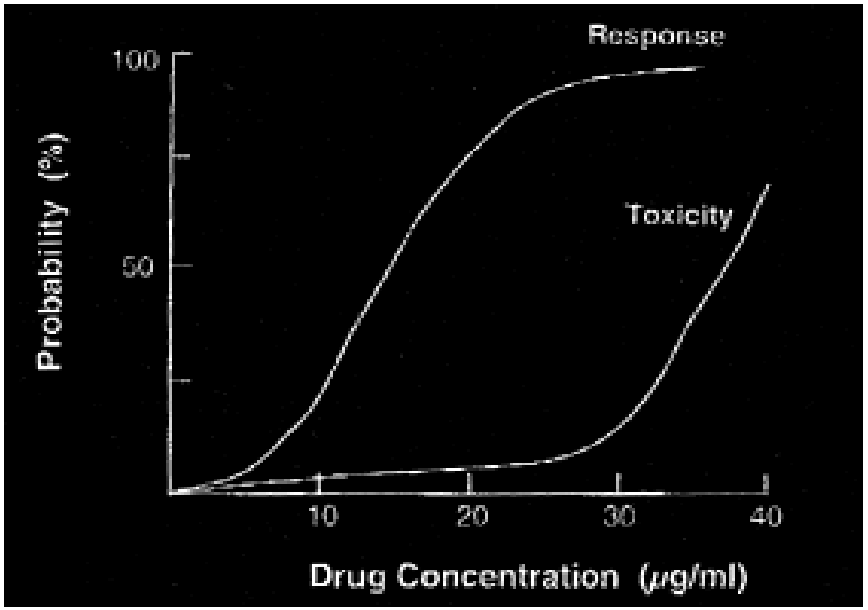
- Conclusions

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



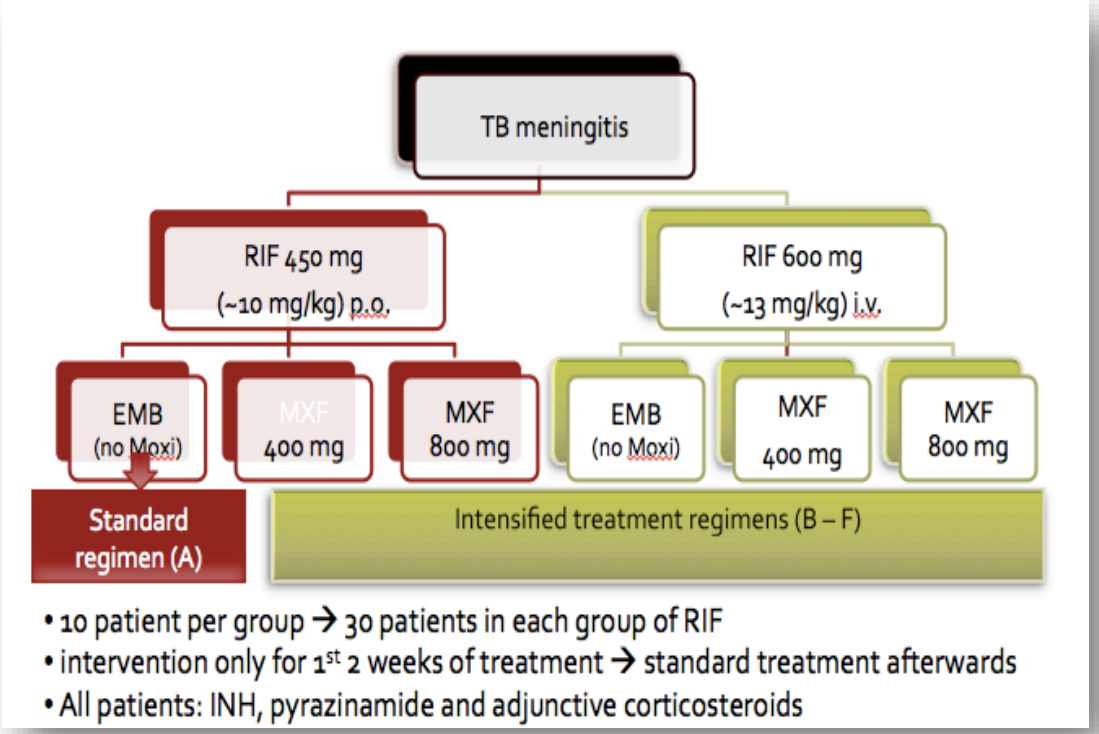
Peloquin, 2001

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



Ruslami et al. Lancet Infect Dis 2013;13:27-35

High dose rifampicin in Indonesian TBM patients

Pharmacokinetics of rifampicin:

	600 mg, intravenous (n=26)	450 mg, oral (n=26)	Ratio of intravenous to oral	p value
Plasma				
AUC_{0-6} (mg.h/L)	78·7 (71·0–87·3)	26·0 (19·0–35·6)	3·0 (2·2–4·2)	<0·0001*
C_{max} (mg/L)	22·1 (19·9–24·6)	6·3 (4·9–8·3)	3·5 (2·6–4·8)	<0·0001*
C_{max} (≥8 mg/L)	26 (100%)	13 (50%)	..	<0·0001†
T_{max} (h; median, range)	2 (1– 2)	2 (1–6)	..	0·048‡
CSF				
C_{max} (mg/L)§	0·60 (0·46–0·78)	0·21 (0·16–0·27)	2·92 (2·03–4·20)	<0·0001*

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

*) independent t- test after log transformation

T) chi-square

+) wilcoxon rank-sum test

High dose rifampicin in Indonesian TBM patients

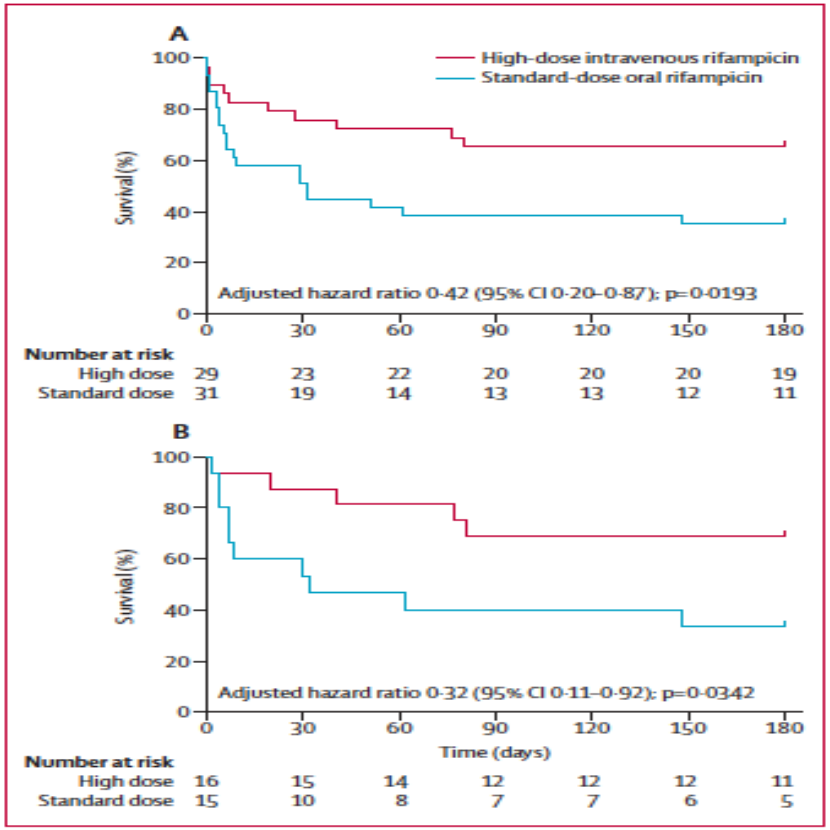
Survival:

- 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

International Journal of Antimicrobial Agents 45 (2015) 496–503

Contents lists available at ScienceDirect

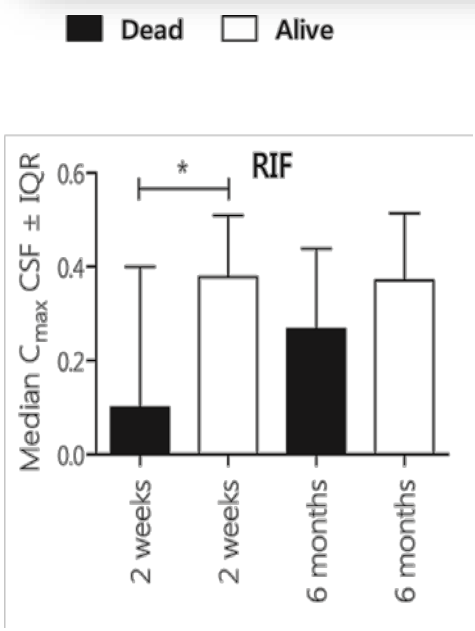
International Journal of Antimicrobial Agents

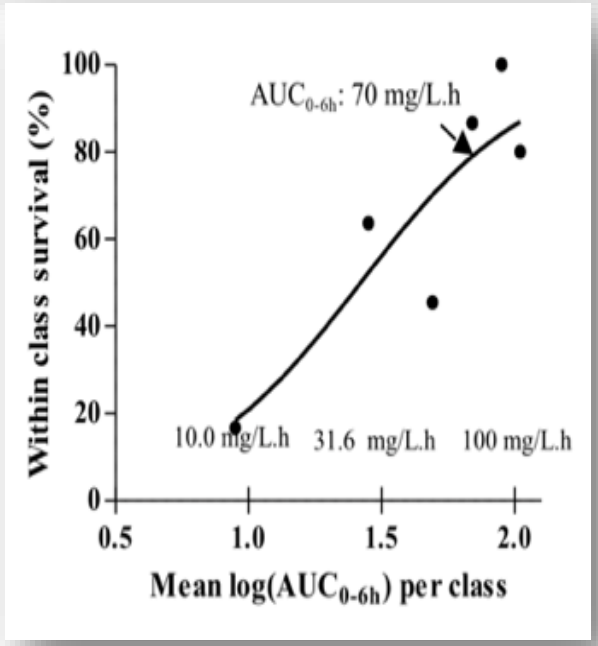
journal homepage: http://www.elsevier.com/locate/ijantimicag

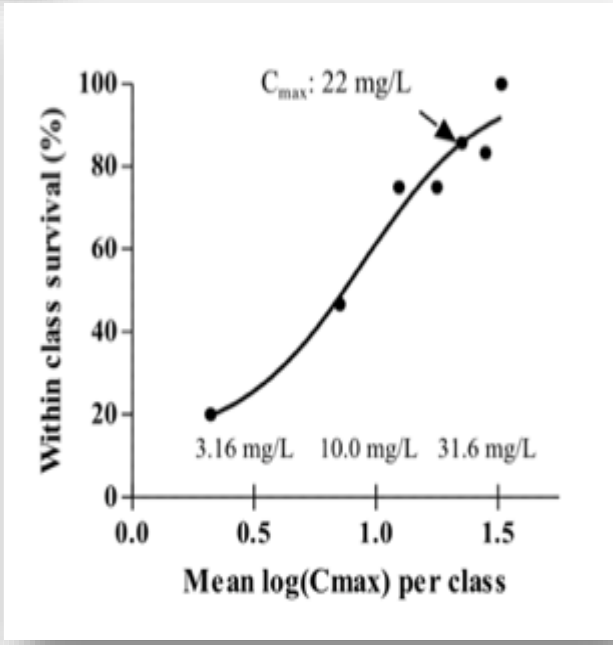
Pharmacokinetic/pharmacodynamic analysis of an intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis

Lindsey te Brake[a,*,1], Sofiati Dian[b,1], Ahmad Rizal Ganiem[b], Carolien Ruesen[c], David Burger[a], Rogier Donders[d], Rovina Ruslami[e], Reinout van Crevel[c], Rob Aarnoutse[a]

Te Brake et al.
IJAA 2015;45:496-503







High dose rifampicin in Indonesian TBM patients

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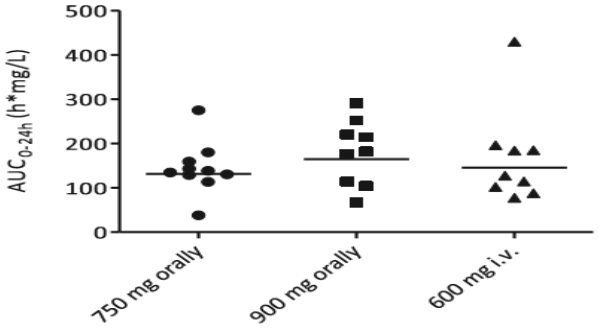
International Journal of Antimicrobial Agents

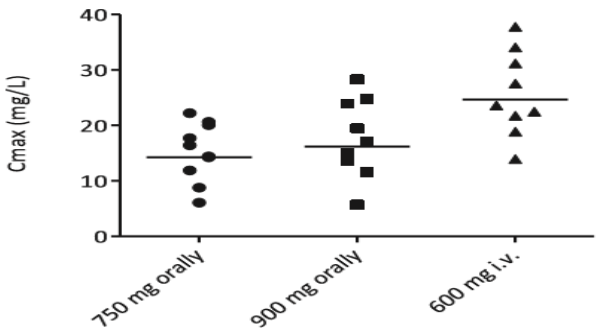
journal homepage: www.elsevier.com/locate/ijantimicag

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

Vycke Yunivita [a,1], Sofiati Dian [b,1], Ahmad Rizal Ganiem [b], Ela Hayati [b], Tri Hanggono Achmad [c], Atu Purnama Dewi [a], Marga Teulen [d], Petra Meijerhof-Jager [d], Reinout van Crevel [c], Rob Aarnoutse [d,*], Rovina Ruslami [a]

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

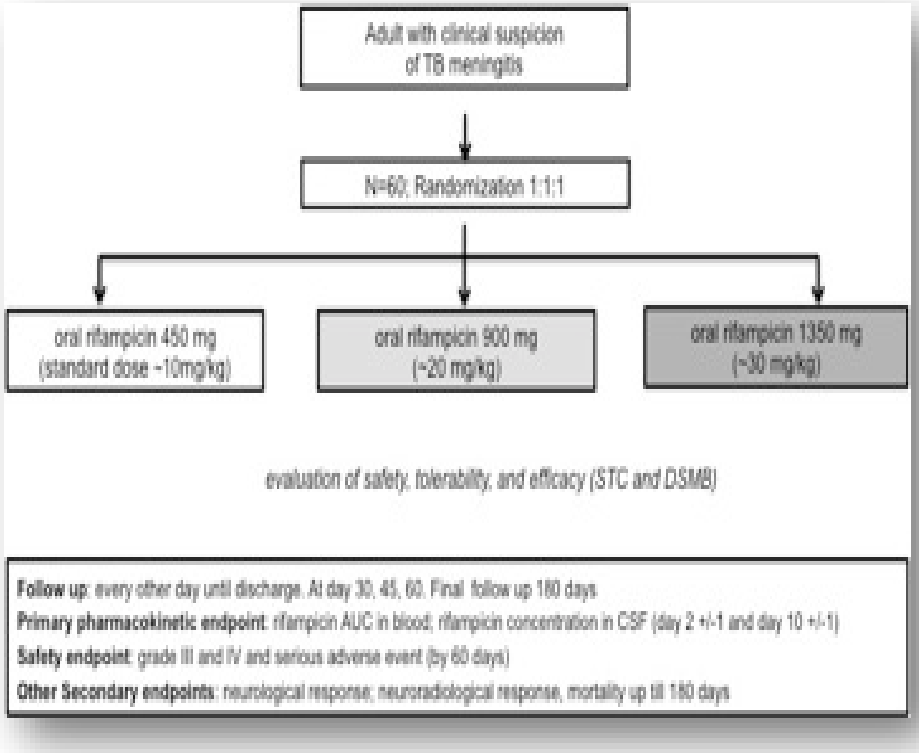
Radboudumc

High dose rifampicin in Indonesian TBM patients

ReDEFINe study

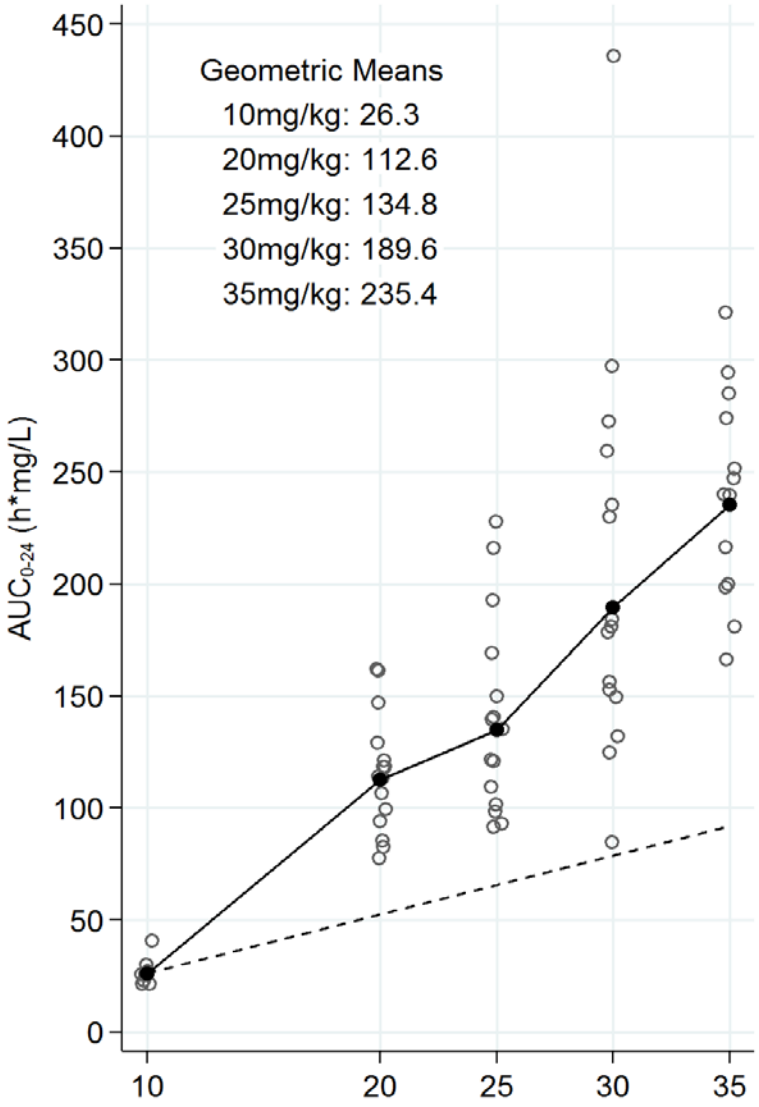
(funded by PEER Health project & PKSLN-DIKTI **)**

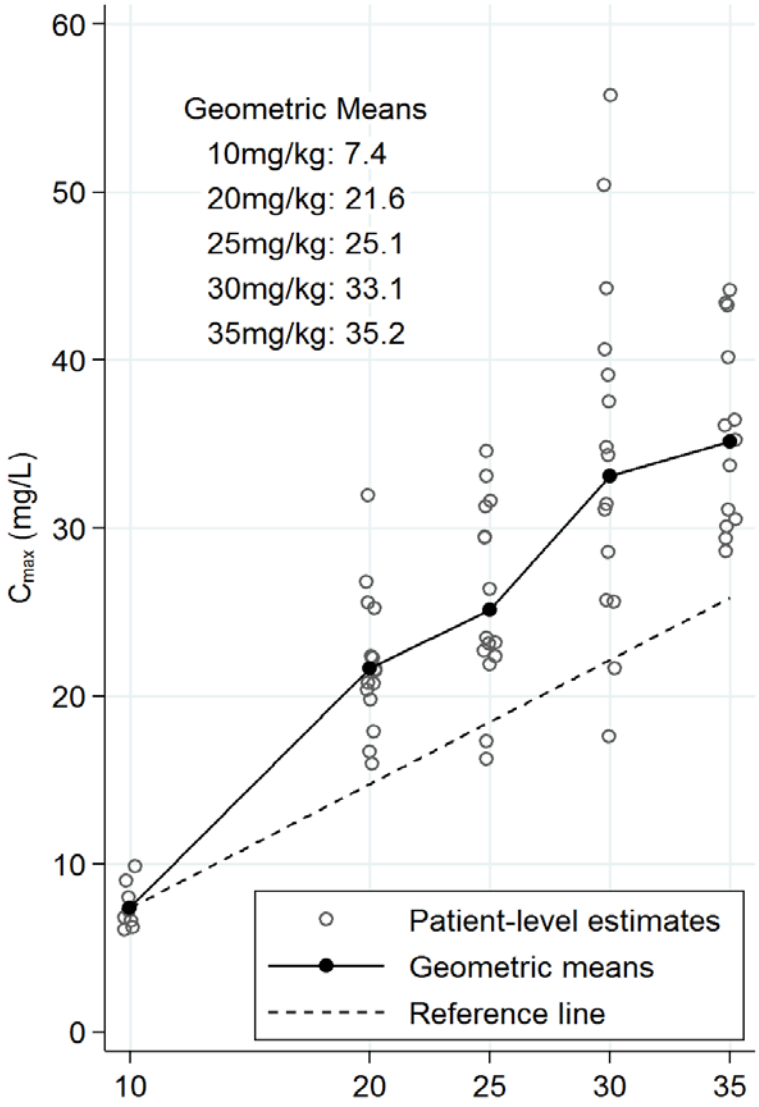
- Randomized double-blinded controlled phase 2 trial
- Primary objectives:
  - To generate PK data of higher oral dose of RIF in TBM patients
- Secondary objectives:
  - Safety and tolerability
  - Efficacy → clinical & neurological response
  - Inflammatory response
  - Gene-expert for TBM?
  - Bio-repository of blood, CSF for future research



PanACEA HIGHRIF1 study

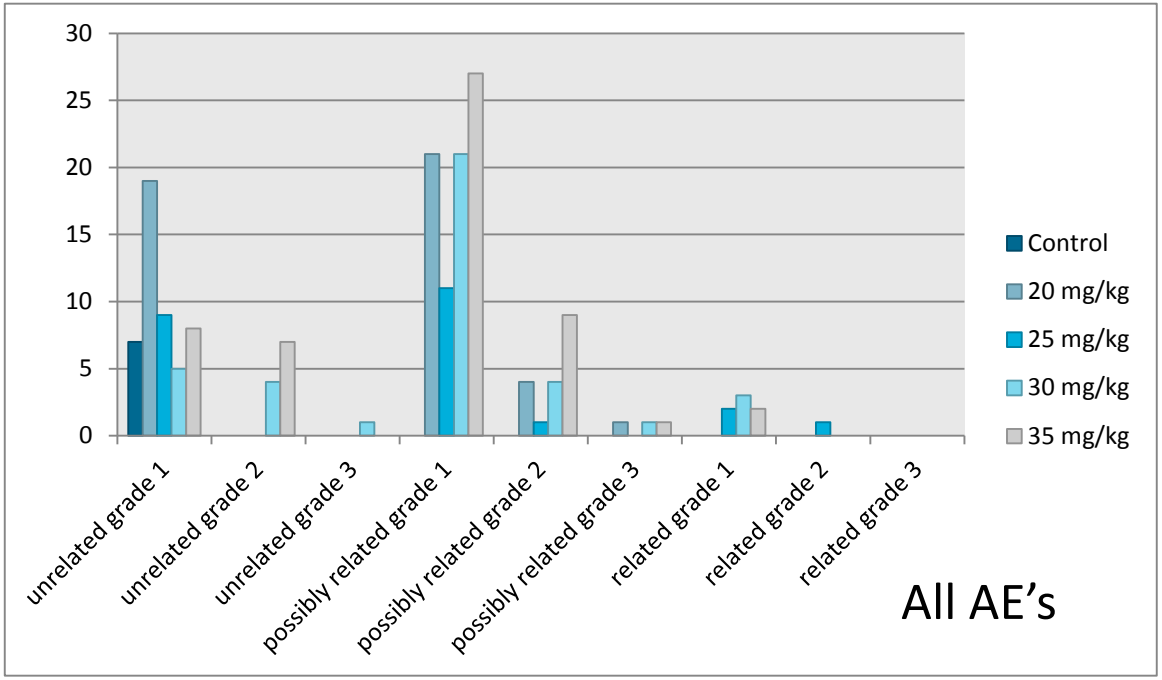
Am J Respir Crit Care Med 2015;191:1058-65





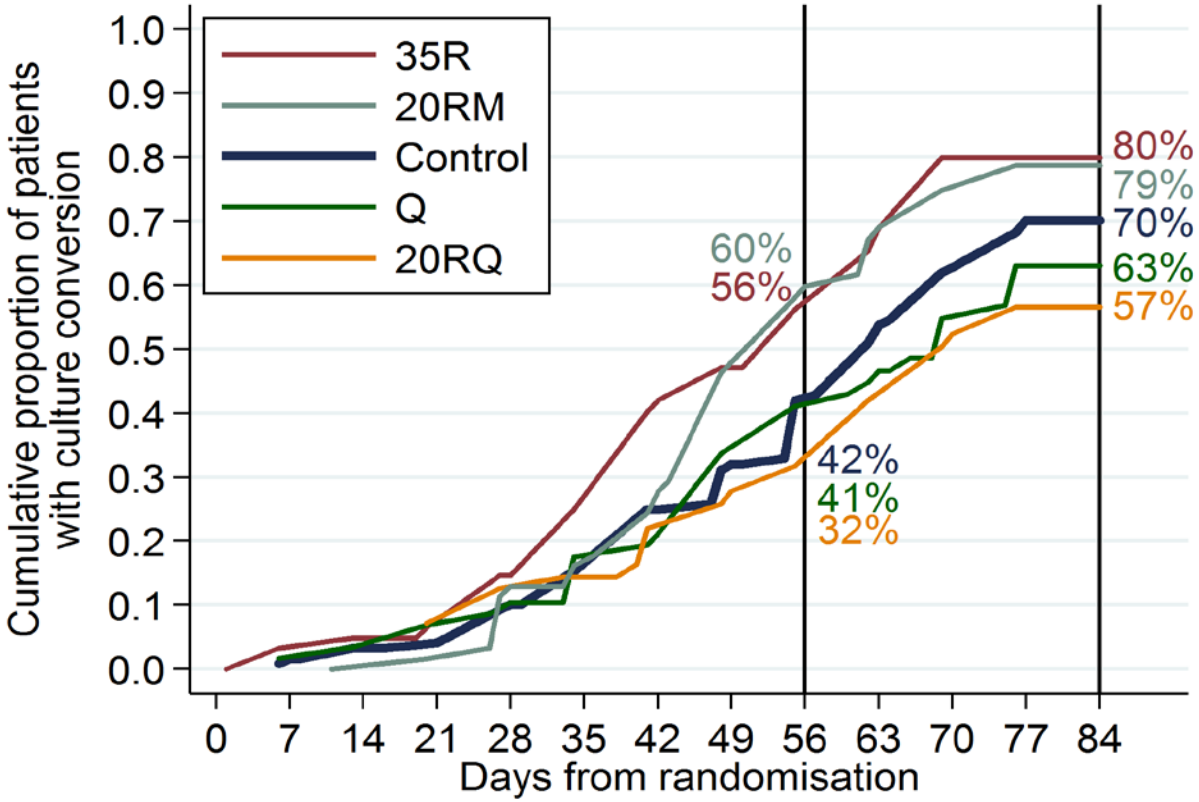
PanACEA HIGHRIF1 results: subjects with any adverse event

Arm	Total	Grade 1 AE	Grade 2 AE	Grade 3 AE	Grade 4 AE	Grade 5 AE
Control	**5**	5	0	0	0	0
20 mg RIF/kg	**17**	13	3	1	0	0
25 mg RIF/kg	**16**	14	2	0	0	0
30 mg RIF/kg	**20**	13	5	2	0	0
35 mg RIF/kg	**22**	15	6	1	0	0



PanACEA
Pan African Consortium for the Evaluation of Antituberculosis Antibiotics

PanACEA MAMS study in pulmonary TB



Lancet Infect Dis 2017;17:39-49

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High dose rifampicin in Vietnamese TBM patients

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensified Antituberculosis Therapy in Adults with Tuberculous Meningitis

A. Dorothee Heemskerk, M.D., Nguyen D. Bang, Ph.D., Nguyen T.H. Mai, Ph.D., Tran T.H. Chau, Ph.D., Nguyen H. Phu, Ph.D., Pham P. Loc, M.D., Nguyen V.V. Chau, Ph.D., Tran T. Hien, Ph.D., Nguyen H. Dung, Ph.D., Nguyen T.N. Lan, Ph.D., Nguyen H. Lan, M.D., Nguyen N. Lan, M.D., Le T. Phong, M.D., Nguyen N. Vien, M.D., Nguyen Q. Hien, M.D., Nguyen T.B. Yen, M.D., Dang T.M. Ha, Ph.D., Jeremy N. Day, F.R.C.P., Maxine Caws, Ph.D., Laura Merson, B.S., Tran T.V. Thinh, M.D, Marcel Wolbers, Ph.D., Guy E. Thwaites, F.R.C.P., and Jeremy J. Farrar, F.R.C.P.

ABSTRACT

N Eng J Med 2016;374;124-34

High dose rifampicin in Vietnamese TBM patients

Clinical Infectious Diseases

MAJOR ARTICLE

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

A. Dorothee Heemskerk,[1,2] Mai Thi Hoang Nguyen,[1] Ha Thi Minh Dang,[1,3] Chau Van Vinh Nguyen,[1,4] Lan Huu Nguyen,[3] Thu Dang Anh Do,[1] Thuong Thuy Thuong Nguyen,[1] Marcel Wolbers,[1,2] Jeremy Day,[1,2] Thao Thi Phuong Le,[1] Bang Duc Nguyen,[1,3] Maxine Caws,[1,5] and Guy E. Thwaites[1,2]

[1]Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam; [2]Nuffield Department of Medicine, University of Oxford, United Kingdom; [3]Pham Ngoc Thach Hospital for Tuberculosis and Lung Disease, and [4]Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam; and [5]Liverpool 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}, 3.00–11.6]), $P < .001$), 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

- Tools for evaluating and optimizing TB drugs for TBM

- Conclusions

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

Eur J Clin Pharmacol
DOI 10.1007/s00228-012-1429-9

PHARMACOGENETICS

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

Eur J Clin Pharmacol 2012

PanACEA Pan African Consortium for the Evaluation of Antituberculosis Antibiotics

Penetration of TB drugs into CSF

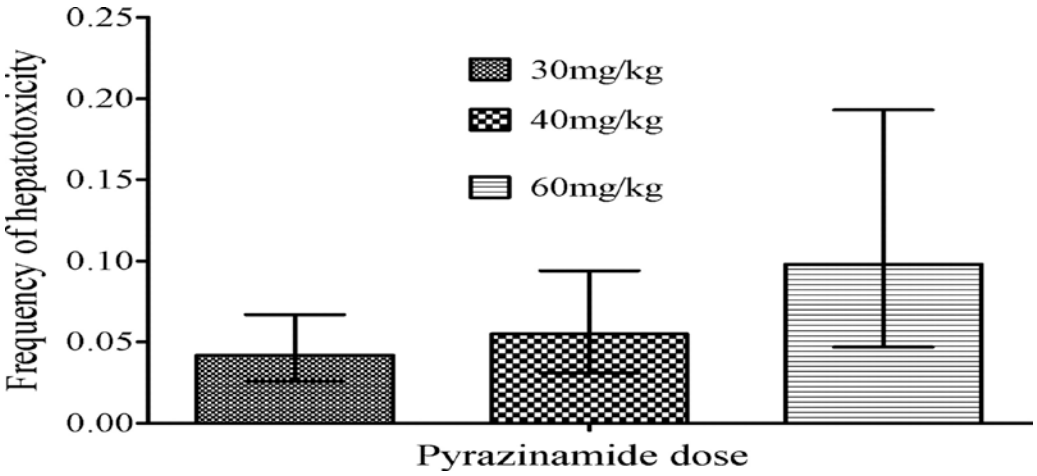
Pyrazinamide

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



Pasipanodya et al, Antimicrob. Agents Chemother. 2010

Pyrazinamide in Vietnamese TBM patients

ME Török, G Aljayyoussi, Waterhouse D, TTH Chau, NTH Mai, NH Phu, TT Hien, Hope W, JJ Farrar, Ward SA. Exposure to Anti-TB Drugs in a TBM/HIV+ Population is not Related to Anti-retroviral Therapy. Clin Pharmacol Ther 2017

'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

	800 mg (n=16)	400 mg (n=19)	Ratio of 800 mg to 400 mg	p value
Plasma				
AUC_{0-24} (mg.h/L)*	60·4 (45·4–80·3)	28·6 (24·2–33·8)	2·1 (1·6–2·9)	<0·0001†
AUC_{0-6} (mg.h/L)	31·5 (24·1–41·1)	15·1 (12·8–17·7)	2·1 (1·5–2·8)	<0·0001†
C_{max} (mg/L)	7·4 (5·6–9·6)	3·9 (3·2–4·8)	1·9 (1·4–2·6)	<0·0001†
T_{max} (h; median, range)	2 (1–6)	2 (1–6)	..	0·301‡
CSF			..	
C_{max} (mg/L)§	2·43 (1·81–3·27)	1·52 (1·28–1·82)	1·60 (0·34–2·20)	0·006†

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)**

Penetration of TB drugs into CSF

Ethionamide/ prothionamide	protein binding 30%
	limited studies point to penetration into CSF (low therapeutic conc. based on total conc.)
	gastro-intestinal AEs
Cycloserine	protein binding: none (0%)
	limited studies point to penetration into CSF (low therapeutic conc. based on total conc. or conc. similar to plasma conc.)
	neurological and psychiatric AEs
PAS	Protein binding: 50-60% limited data: low penetration into CSF

Penetration of TB drugs into CSF

Clofazimine
- protein binding ?
- penetration into CSF ?

Thioacetazone
- protein binding ?
- penetration into CSF ?

Linezolid
- protein binding 31%
- passes blood-brain barrier, CSF/plasma ratio at least 0.7 in various studies *(no data in TBM)*
- large PK variability
- PK study in TBM in preparation in Indonesia

Bedaquiline
- protein binding: >99%
- 'brain uptake was low in mice'
- case report: no uptake in CSF at week 11/6 of TB/BDQ treatment (Clin Infect Dis 2016;62:523-4)

Delamanid
- protein binding: >99%
- penetration into CSF ?

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Outline

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- Tools for evaluating and optimizing TB drugs for TBM

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Tool 1. Molecular pharmacological research

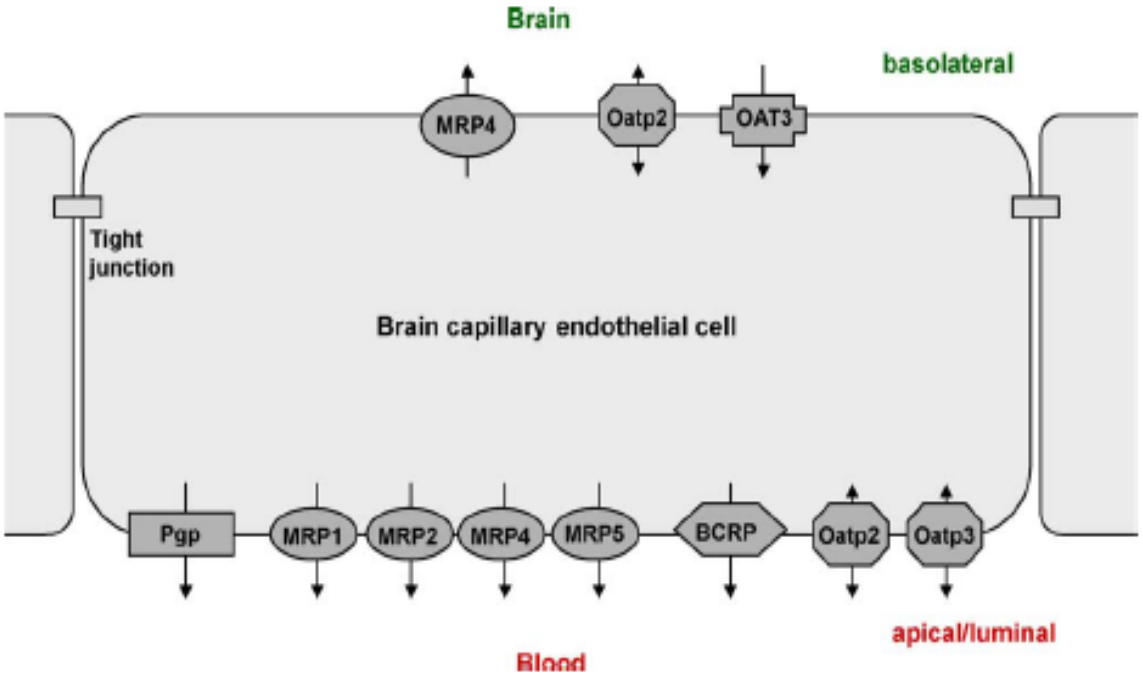


Fig. 4. Putative localization of drug efflux proteins on brain capillary endothelial cells that form the blood–brain barrier. Only those transporters are illustrated

Are TB drugs substrates to efflux pumps ?

- inside-out vesicles or HEK293 transfected cells
- In vitro BBB model

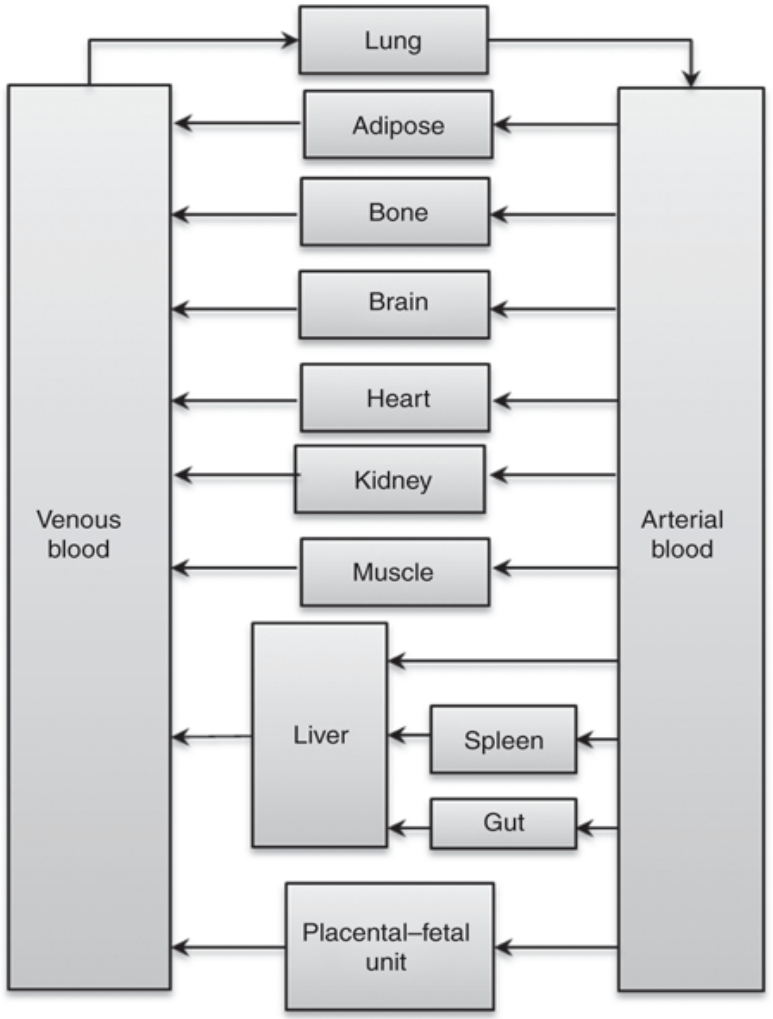
Tool 1. Molecular pharmacological research

	Pgp	BCRP	MRP1	MRP2	MRP3	MRP4	MRP5	BSEP
EMB								
INH								
PZA								
RIF	29.1	55.3	32.4	26.6	97.4	88.4	≥200[1]	24.8
AMK								
MXF								
CS								
PAS								
ETO		≥200[1]						
AMX			≥200[1]					
CLF	1.8	3.2	6.8	≥200[1]		≥200[1]		≥200[1]
LZD		≥200[1]						
SQ109	10.5	5.5	84.6	91.5	59.2	79.3	100-150[2]	
TRD	22.6	6.6	≥200[1]		≥200[1]	≥200[1]		
TIM	1.0	100-150[2]	4.3	≥200[1]		100-150[2]		3.0

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



Tool 3: improved PK analysis in CSF

1. CSF: plasma concentration ratio greatly depends on time post dose

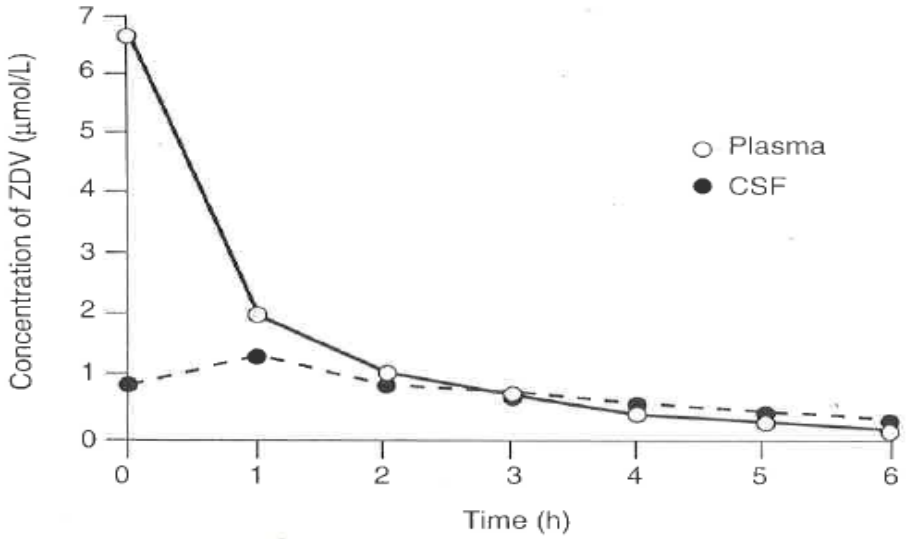
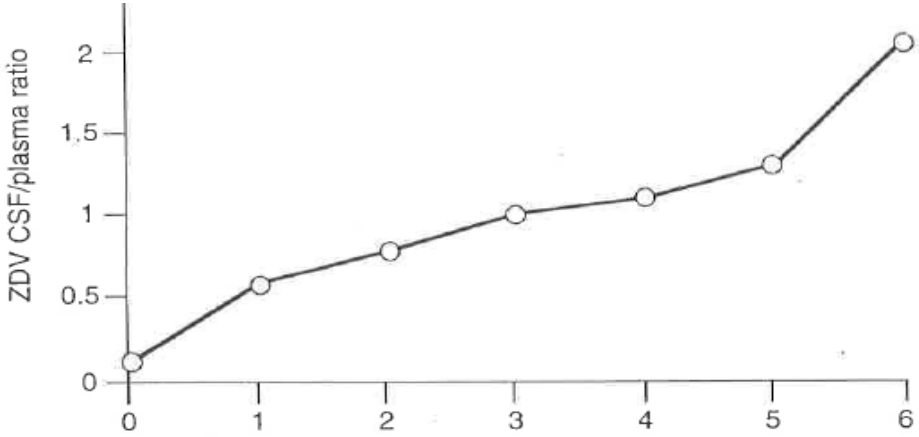


Figure 2
Profile of zidovudine concentrations in CSF and plasma after intravenous administration of the drug [6].



- 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

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

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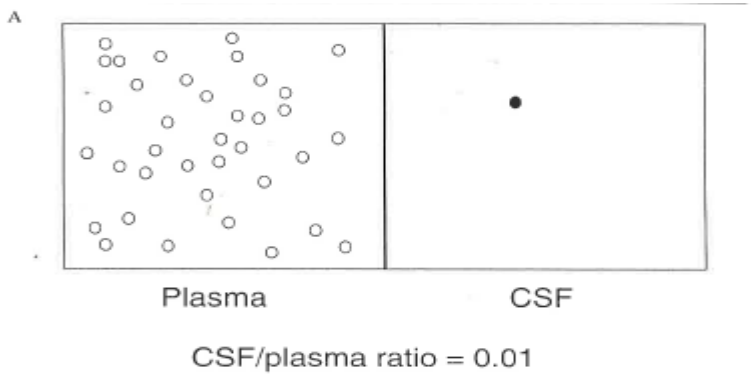
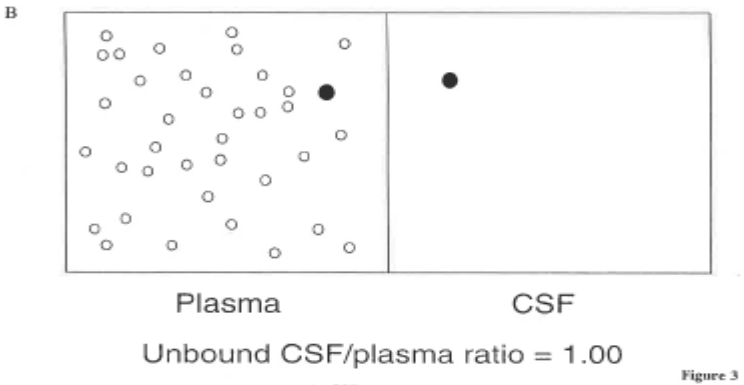


- CSF/plasma ratio based on *total* concentrations

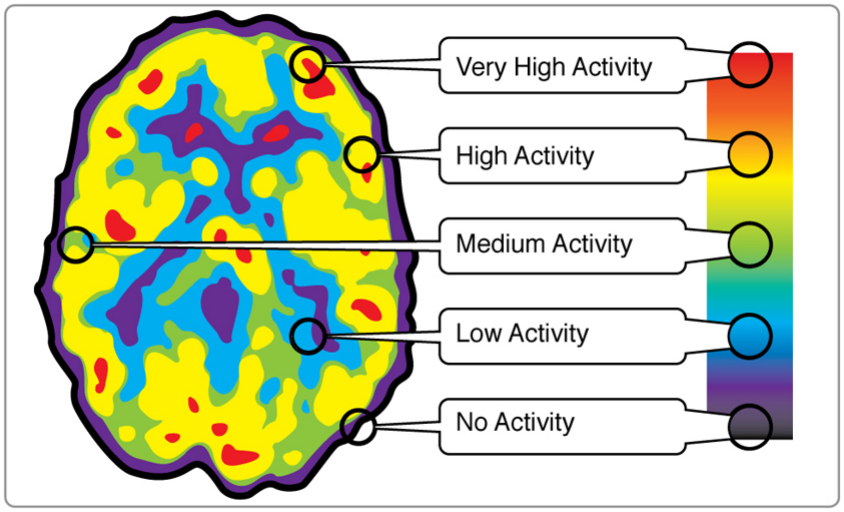


- CSF/plasma ratio based on *free* concentrations

Hoetelmans RM,
Antivir Ther. 1998

Tool 4: PET imaging and/or post mortem PK analysis

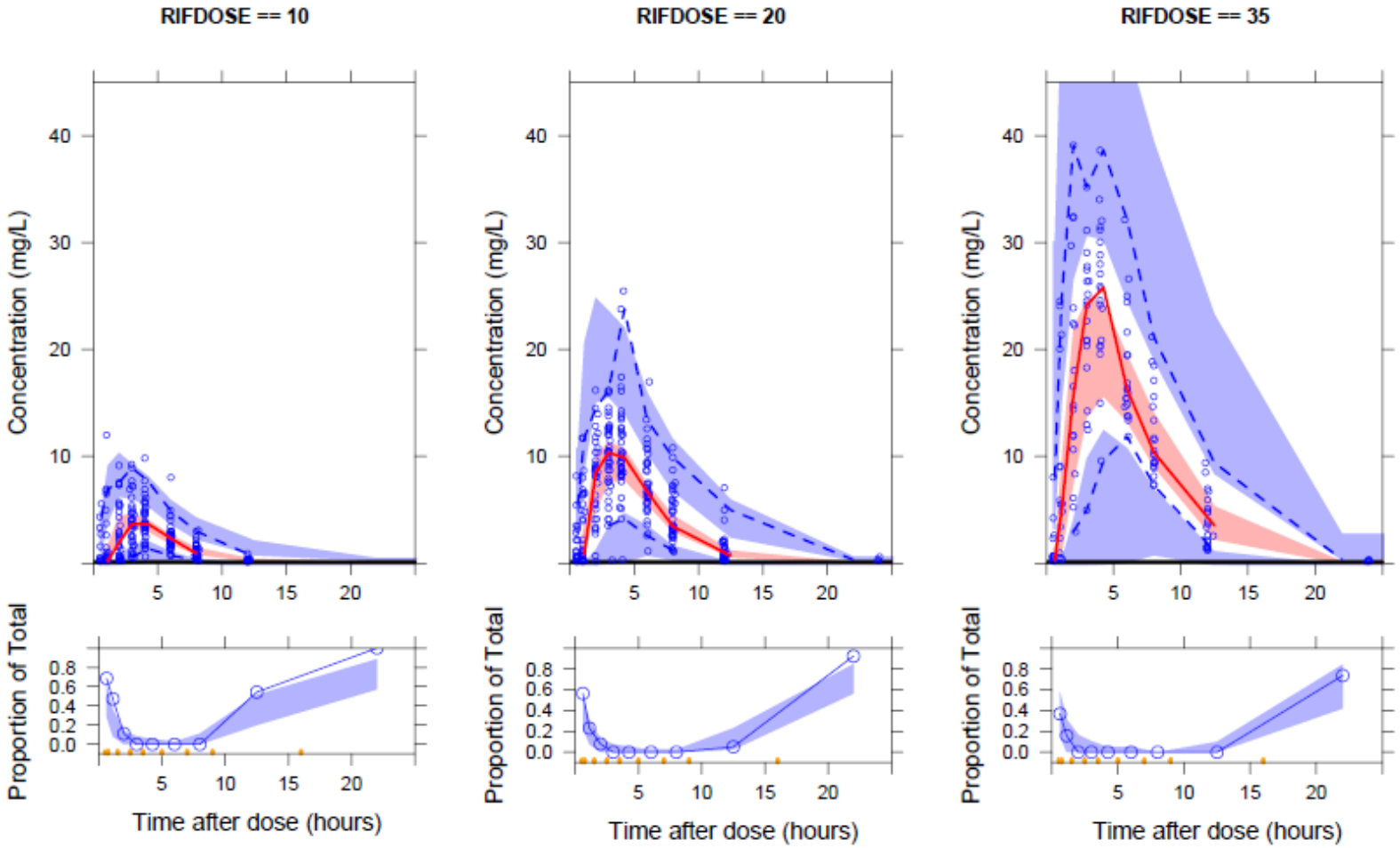
- Drugs labelled with positron emitting radionuclides
- Monitor whole-body distribution
- Correlate brain with plasma and
- CSF concentrations



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)



Tool 6. Smart phase II designs to find optimal TB drug REGIMEN

- 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)

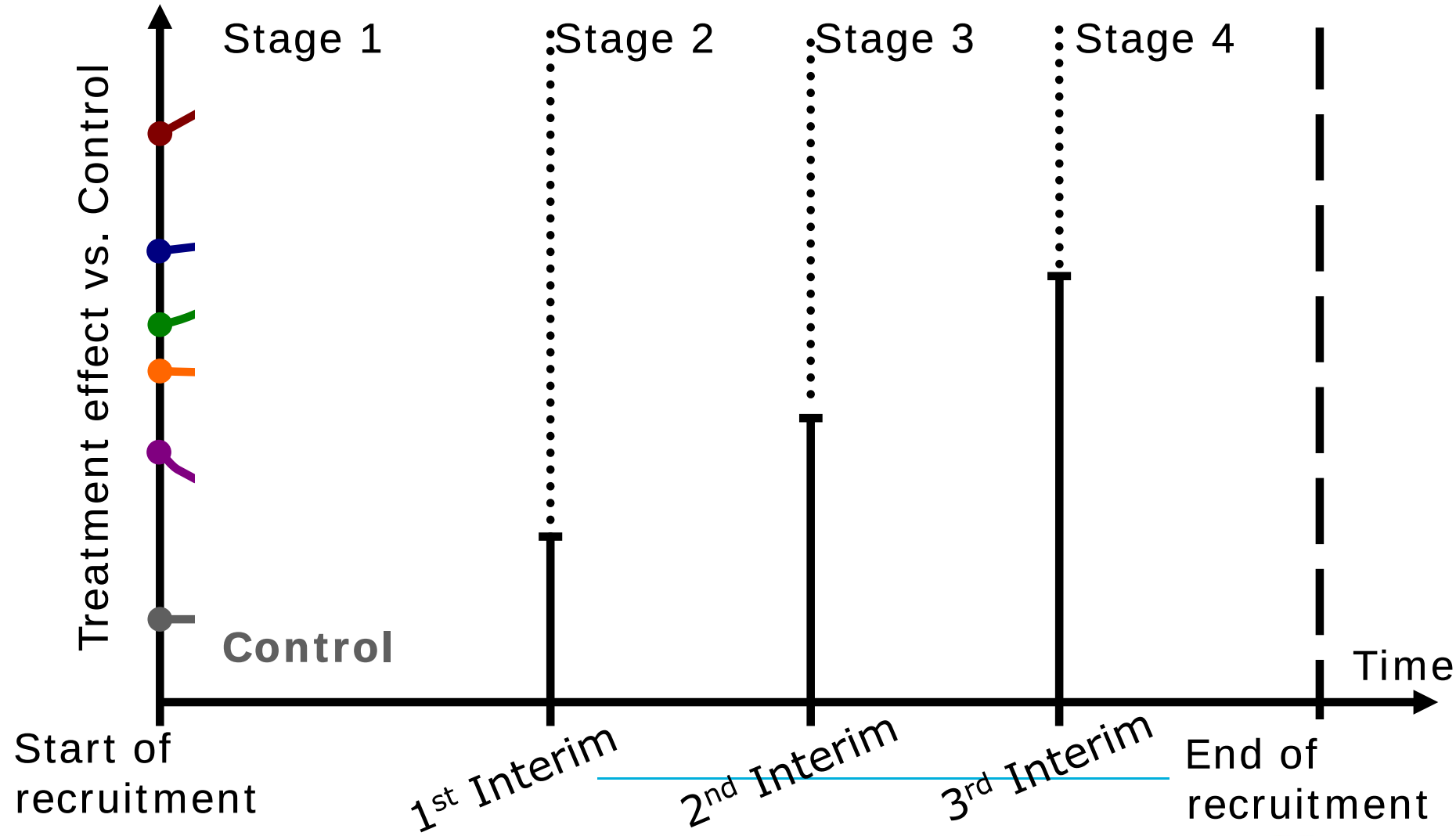
- Phase IIB
  - Collect efficacy data over longer durations
  - Of sufficient size to make decisions about which regimens to take forward to phase III
  - Very limited studies
  - Gap between phase IIa and III !

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

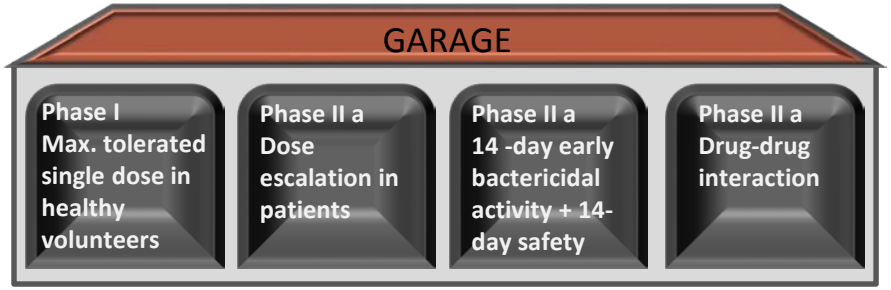
More information: Patrick Phillips, MRC, UCSF

MAMS design example for 6-arm TB trial (Patrick Phillips)



GARAGE

SETUP: 2-4 specialized sites participate
AIMS: Combine components for safety and synergy and establish proof-of-concept



Concept: PanACEA, Michael Hoelscher

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

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

- **Adaptive by design**

  • Pre-specified design feature in protocol and not a remedy for poor planning!

- 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

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

	Control	Q	20RQ	20RM	35R
Included in analysis	123	58	56	63	63
Median time	62 days	63 days	66 days	55 days	48 days
Adj. HR[1] (95% CI)		0.82 (0.55 - 1.24)	0.73 (0.48 - 1.13)	1.42 (0.98 - 2.05)	**1.75 (1.21 - 2.55)**
		p=0.35	p=0.16	p=0.07	**p=0.003**

[1] Analysis has been adjusted for: HIV status; baseline GeneXpert CT; centre; baseline culture (using TTP).

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Censoring data at 8 weeks (to mimic previous TB phase II trials)					
Adj. HR (95% CI)[1]		1.05 (0.60 - 1.83)	0.91 (0.50 - 1.68)	**1.69 (1.02 - 2.80)**	**1.99 (1.21 - 3.29)**
		p=0.88	p=0.78	**p=0.04**	**p=0.007**

[1] Analysis has been adjusted for: HIV status; baseline GeneXpert CT; centre; baseline culture (using TTP).

Concept of using EPIs to enhance CSF concentrations

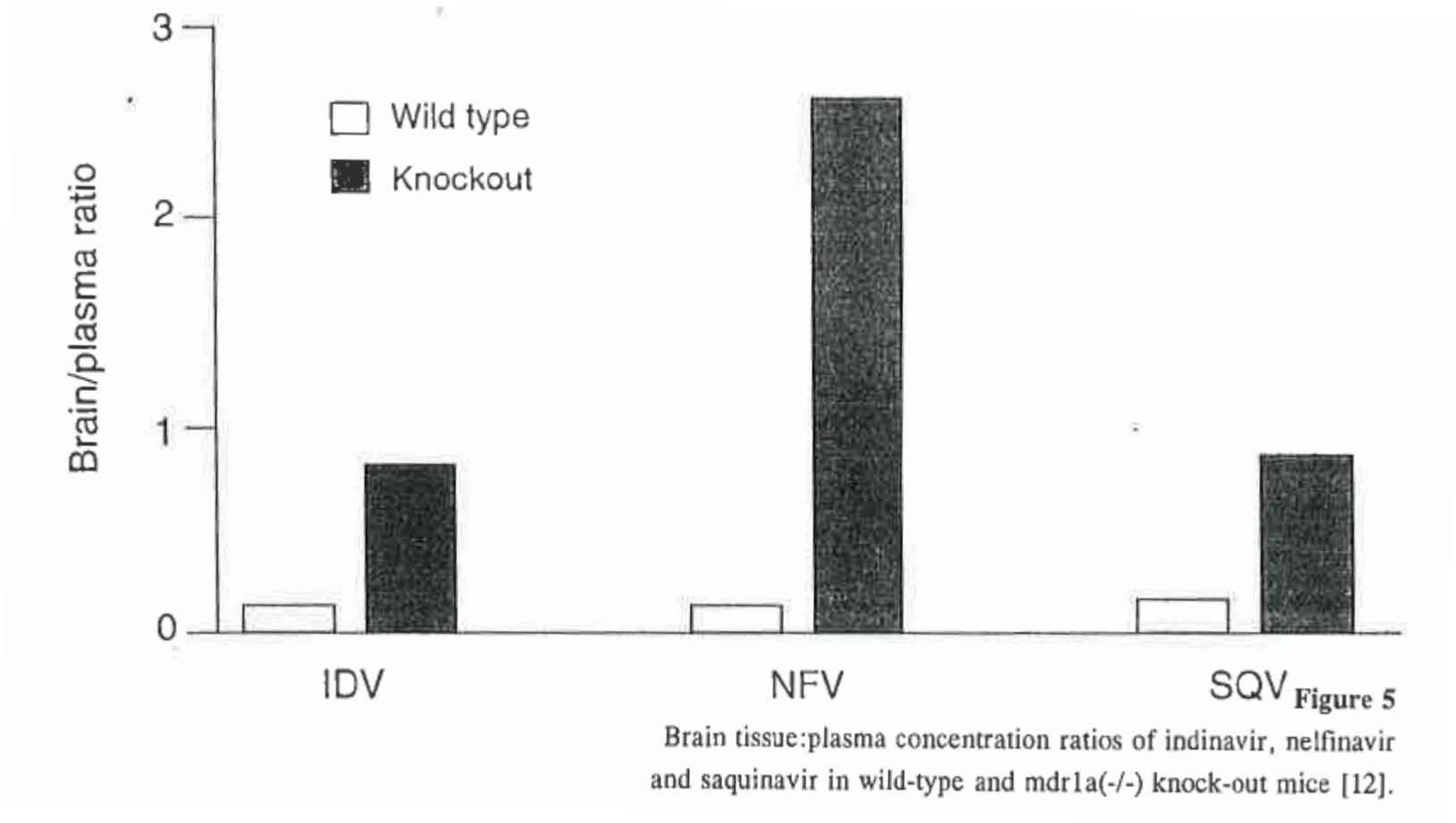

Figure 5

Brain tissue:plasma concentration ratios of indinavir, nelfinavir and saquinavir in wild-type and mdr1a(-/-) knock-out mice [12].