# The relationship between pyrazinamide pharmacokinetics (PK) and microbiologic outcomes in patients with pulmonary TB receiving standard- or high-dose rifampicin: PK/PD results from TBTC trials 27 and 28 and PanACEA MAMS

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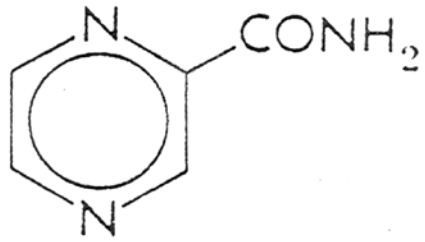
# Optimizing pyrazinamide (PZA) dosing (OpZAD)

## *Scientific questions*



Pyrazinamide

- What is the **right dose** of pyrazinamide?
  - Relationship between exposures and tolerability or toxicity?
  - Relationship between exposures and microbiologic activity?

- What is the **right duration** of pyrazinamide in combination therapy?
  - Would extending its use beyond 2 months improve outcomes when the total regimen duration is less than 6 months?
  - Relationship between duration of treatment and tolerability/toxicity

- If you already have a **high-dose rifamycin in the regimen, does PZA add anything**?

# A short walk back through history

# Knowledge about relationship between PZA dose and EFFICACY: *before rifampicin*

Patients previously unsuccessfully treated with PAS/SM, Rx 4-12 mos: Schwartz

| PZA Alone 2800 g | PZA 3g + SM | PZA 3g + PAS | PZA 3g + INH |
|---|---|---|---|
| Unsatisfactory | Unsatisfactory | Unsatisfactory | 83% culture conversion by 4 months |

Patients with advanced pulmonary TB: McDermott

| PZA 50 mg/kg plus INH 5 mg/kg |
|---|
| 93% culture conversion by 3 months, with sustained “reversal of infectiousness” |

Schwartz et al (1954) Am Rev Tuberc 70: 413
McDermott (1954) Am Rev Tuberc 70: 743
Muschenheim (1954) Am Rev Tuberc 1954 69: 319
Muschenheim, McDermott et al Am Rev Tuberc 70: 743

# Knowledge about relationship between PZA dose and EFFICACY: *before rifampicin*

***Are lower doses as effective?***

In patients with advanced disease, no previous treatment :

| PZA Dosage | Month 3 | Month 6 |
|---|---|---|
| 50 mg/kg | 49/53 (92%) | 48/53 (91%) |
| 20-30 mg/kg | 37/52 (71%) | 28/42 (66%) |

"Therapeutic inferiority was particularly evident at the lowest dosage level of 20 mg/kg"

Muschenheim (1955) Am Rev Tuberc Pulmon 72: 851

**Pyrazinamide has proven, significant sterilizing activity; dual therapy with INH at high doses results in cavity closure, protection against resistance, cure in most patients**

# Knowledge about relationship between PZA dose and EFFICACY: *PZA vs. rifampicin*

The Lancet · Saturday 20 May 1972

## CONTROLLED CLINICAL TRIAL OF SHORT-COURSE (6-MONTH) REGIMENS OF CHEMOTHERAPY FOR TREATMENT OF PULMONARY TUBERCULOSIS

EAST AFRICAN/BRITISH MEDICAL RESEARCH COUNCILS

***Summary*** A comparison has been made between four 6-month daily regimens, all containing streptomycin plus isoniazid, and 3 of them a third drug—rifampicin, pyrazinamide, or thiacetazone—and a standard 18-month regimen in the treatment of newly diagnosed extensive smear-positive pulmonary tuberculosis. At 6 months all except 2 of 450 patients (both of them on streptomycin plus isoniazid) had a favourable response. There was also very little drug toxicity. The bacteriological relapse-rates between 6 and 12 months were 18% of 94 patients on the two-drug combination, 4% of 99 on the rifampicin, 6% of 88 on the pyrazinamide, 21% of 84 on the thiacetazone, and 2% of 83 patients on the standard regimen. Most of the relapses occurred by 9 months and nearly every patient who relapsed did so with drug-sensitive organisms. It is concluded that both the rifampicin-containing and pyrazinamide-containing 6-month regimens are highly effective, especially considering the very severe disease under study, and that the prospects of developing effective and practicable short-course regimens are excellent.

***Compared to rifampicin:***
***Similar sterilizing activity at the tested doses***

TABLE II—CONDITION ON ADMISSION TO TREATMENT

| Factor on admission | Treatment series | | | | |
|---|---|---|---|---|---|
| | 6SHR | 6SHZ | 6SHT | 6SH | STH/TH |
| *Sex* | | | | | |
| Male .. .. | 65 (66) | 63 (72) | 59 (70) | 66 (69) | 56 (67) |
| Female .. .. | 34 (34) | 25 (28) | 25 (30) | 30 (31) | 27 (33) |
| *Age* (yr.) | | | | | |
| <35 .. .. | 55 (56) | 45 (51) | 43 (51) | 64 (67) | 46 (55) |
| 35–44 .. .. | 19 (19) | 17 (19) | 18 (21) | 19 (20) | 24 (29) |
| ≥45 .. .. | 25 (25) | 26 (30) | 23 (27) | 13 (14) | 13 (16) |
| *Average weight (kg.)* | 48·4 | 49·0 | 48·9 | 48·1 | 49·4 |
| *Radiographic extent of disease* *,† | | | | | |
| Nil, trivial, slight | 0 (0) | 0 (0) | 0 (0) | 1 (1) | 0 (0) |
| Limited .. | 14 (14) | 15 (17) | 14 (17) | 13 (14) | 10 (12) |
| Moderate .. | 36 (36) | 26 (30) | 30 (36) | 34 (35) | 37 (45) |
| Extensive .. | 39 (39) | 31 (35) | 29 (35) | 35 (36) | 25 (30) |
| Gross .. .. | 8 (8) | 15 (17) | 10 (12) | 11 (11) | 11 (13) |
| *Radiographic extent of cavitation*†,‡ | | | | | |
| Nil .. .. | 7 (7) | 8 (9) | 10 (12) | 6 (6) | 7 (8) |
| Slight .. .. | 3 (3) | 5 (6) | 1 (1) | 0 (0) | 1 (1) |
| Moderate .. | 26 (26) | 17 (19) | 27 (32) | 26 (27) | 23 (28) |
| Extensive .. | 61 (62) | 57 (65) | 45 (54) | 62 (65) | 52 (63) |

**Pyrazinamide dose**

2000 mg per day
(average 40 mg/kg)

***The studies demonstrating treatment-shortening potential of PZA used higher doses than we use currently***

Lancet (1972) EA/BMRC

# Knowledge about relationship between PZA dose and EFFICACY: *Pyrazinamide WITH rifampicin*

**Table 11—*Addition of Pyrazinamide to SHR: Results at 2 Months***

| Study | Regimens | No. patients | % culture negative at 2 months | P value |
|---|---|---|---|---|
| Second East African/ BMRC (1974)[27] | SHR | 169 | 70 | 0.006 |
| | SHRZ | 347 | 82 | |
| Third East African BMRC (1978)[28] | SHR | 194 | 75 | <0.01 |
| | SHRZ | 179 | 87 | |
| Second Hong Kong/ BMRC (1978)[26] | SHRE | 171 | 81 | <0.001 |
| | SHRZ | 167 | 95 | |

Average weight 46 kg

TABLE III—CULTURE RESULTS (BASED ON FIRST OR ONLY SPECIMEN AT EACH MONTH)

| Month | Treatment series | No. assessed | Culture negative | |
|---|---|---|---|---|
| | | | No. | % |
| 0 | SHR | 181 | 7 | 4 |
| | HR | 183 | 6 | 3 |
| | SHRZ/TH | 191 | 4 | 2 |
| | SHRZ/$S_2H_2Z_2$ | 179 | 5 | 3 |
| 1 | SHR | 161 | 54 | 34 |
| | HR | 159 | 36 | 23 |
| | SHRZ/TH | 170 | 63 | 37 |
| | SHRZ/$S_2H_2Z_2$ | 162 | 53 | 33 |
| 2 | SHR | 169 | 119 | 70 |
| | HR | 173 | 111 | 64 |
| | SHRZ/TH | 178 | 147 | 83 |
| | SHRZ/$S_2H_2Z_2$ | 169 | 136 | 80 |
| 3 | SHR | 177 | 169 | 95 |
| | HR | 175 | 168 | 96 |
| | SHRZ/TH | 185 | 174 | 94 |
| | SHRZ/$S_2H_2Z_2$ | 169 | 158 | 93 |

***Adding Z at dose of 1500-2000 mg (35-40 mg/kg) improves culture conversion at 2 months***

# Knowledge about relationship between PZA dose and EFFICACY: *Pyrazinamide WITH rifampicin*

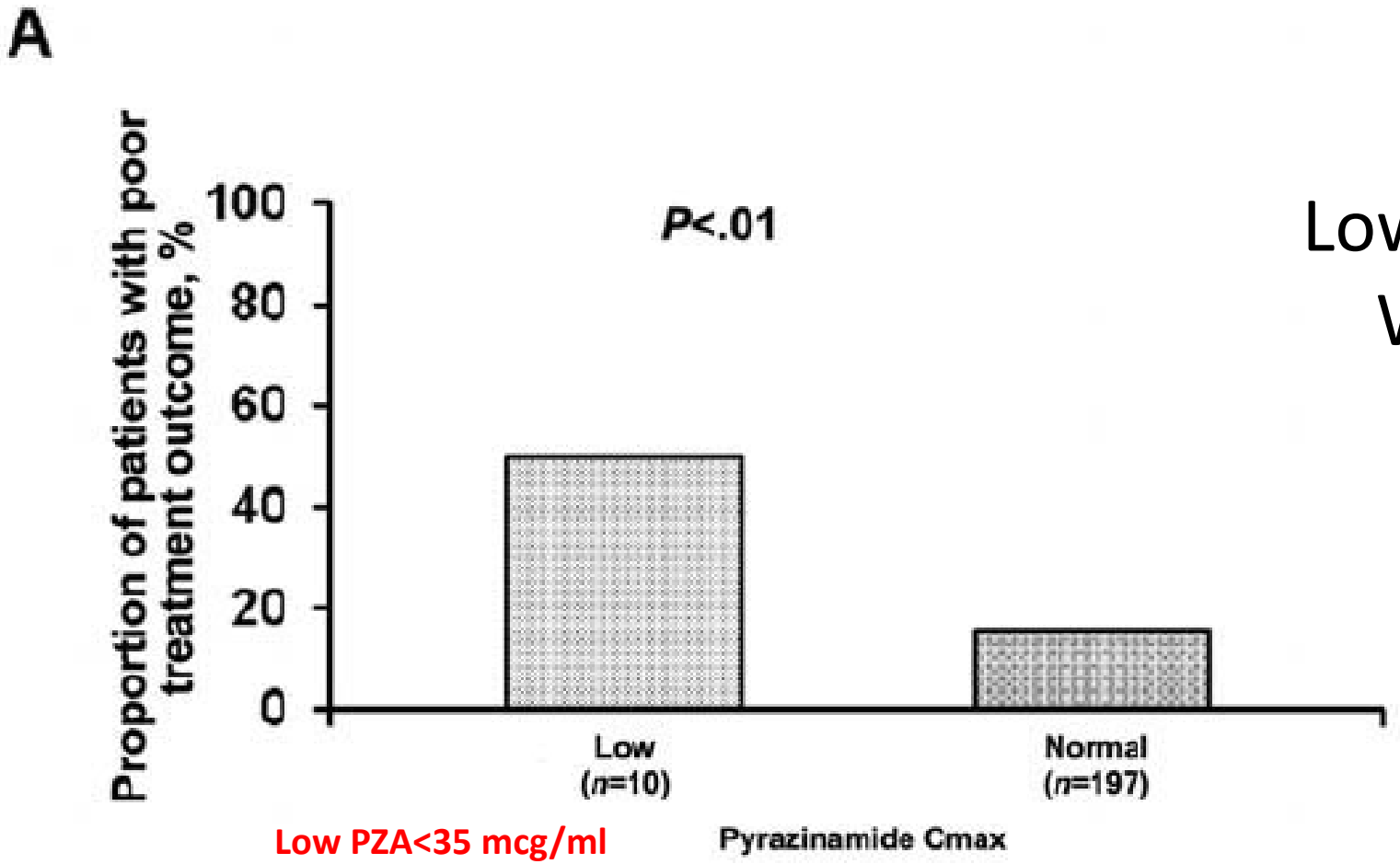
RELAPSES IN FIRST 6 MONTHS AFTER CHEMOTHERAPY AMONG PATIENTS WITH STRAINS OF TUBERCLE BACILLI DRUG-SUSCEPTIBLE BEFORE TREATMENT

| Duration of Chemotherapy (*months*) | Regimen | Patients Assessed (*no.*) | Relapses* | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Total | | Month after Chemotherapy | | | |
| | | | (*no.*) | (%) | 1 | 2 | 3 | 4 | 5 |
| 6 | SHR | 150 | 6 | 4 | 0 | 3 | 0 | 2 | 1 |
| | $SHRZ/S_2H_2Z_2$ | 90 | 3 | 3 | 0 | 2 | 1 | 0 | 0 |
| | $SHRE/S_2H_2E_2$ | 86 | 16 | 19 | 0 | 8 | 7 | 1 | 0 |
| | $S_3H_3R_3Z_3/S_2H_2Z_2$ | 74 | 4 | 5 | 0 | 0 | 3 | 0 | 1 |
| 8 | $SHRZ/S_2H_2Z_2$ | 88 | 2 | 2 | 0 | 1 | 0 | 1 | 0 |
| | $SHRE/S_2H_2E_2$ | 87 | 7 | 8 | 1 | 4 | 2 | 0 | 0 |
| | $S_3H_3R_3Z_3/S_2H_2Z_2$ | 89 | 1 | 1 | 0 | 0 | 0 | 0 | 1 |

***Adding Z at dose of 1500-2000 mg (35-40 mg/kg) in first two months allows for shortening to 6 months***

Hong Kong Chest Service/BMRC (1978) Am Rev Resp Dis: controlled trial of 6-month and 8-month regimens…

# Knowledge about relationship between PZA Exposures and EFFICACY: Evidence from modern regimens




Low PZA $C_{max}$ Associated with Worse Clinical Outcomes Among TB Patients in Botswana

Chideya S et al, Clinical Infectious Diseases 2009; 48: 1685

# Knowledge about relationship between PZA Exposures and EFFICACY: Evidence from modern regimens

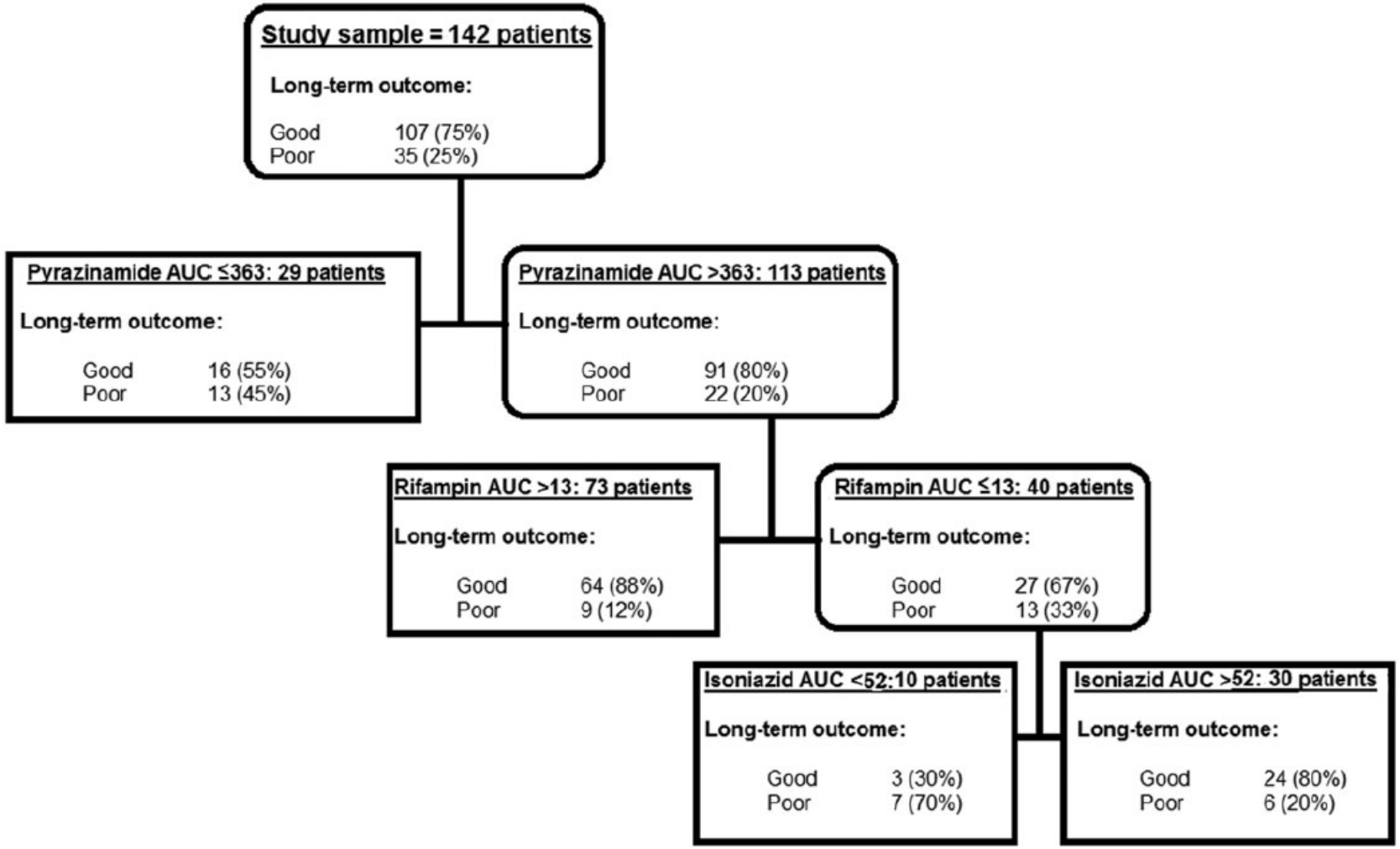



**Figure 3.** Variables predictive of poor long-term outcome in 142 patients. Pharmacokinetic parameters as well as patient demographic factors were examined in the initial models and the decision trees. The decision nodes demonstrate the primary node was for pyrazinamide 24-hour area under the concentration–time curve (AUC), followed by rifampin AUC. The AUC cutoff values that were identified as important predictive factors are shown.

Pasipanodya (2013)
AAC 208:1464.

# USPHS:
# *Study of hepatic toxicity* of PZA with Isoniazid

| Regimen | PZA dose | Duration (weeks) | N | Hepatotoxicity* |
|---|---|---|---|---|
| INH& PZA | 25 mg/kg | 24 | 160 | 4 (2.5%) |
| INH & PZA | 25 mg/kg | 12 | 101 | 3 (3.0%) |
| INH & PZA | 40 mg/kg | 24 | 167 | 11 (6.6%) |
| INH & PZA | 40 mg/kg | 12 | 91 | 2 (2.1%) |
| INH & PAS | n/a | 24 | 123 | 1 (0.8%) |

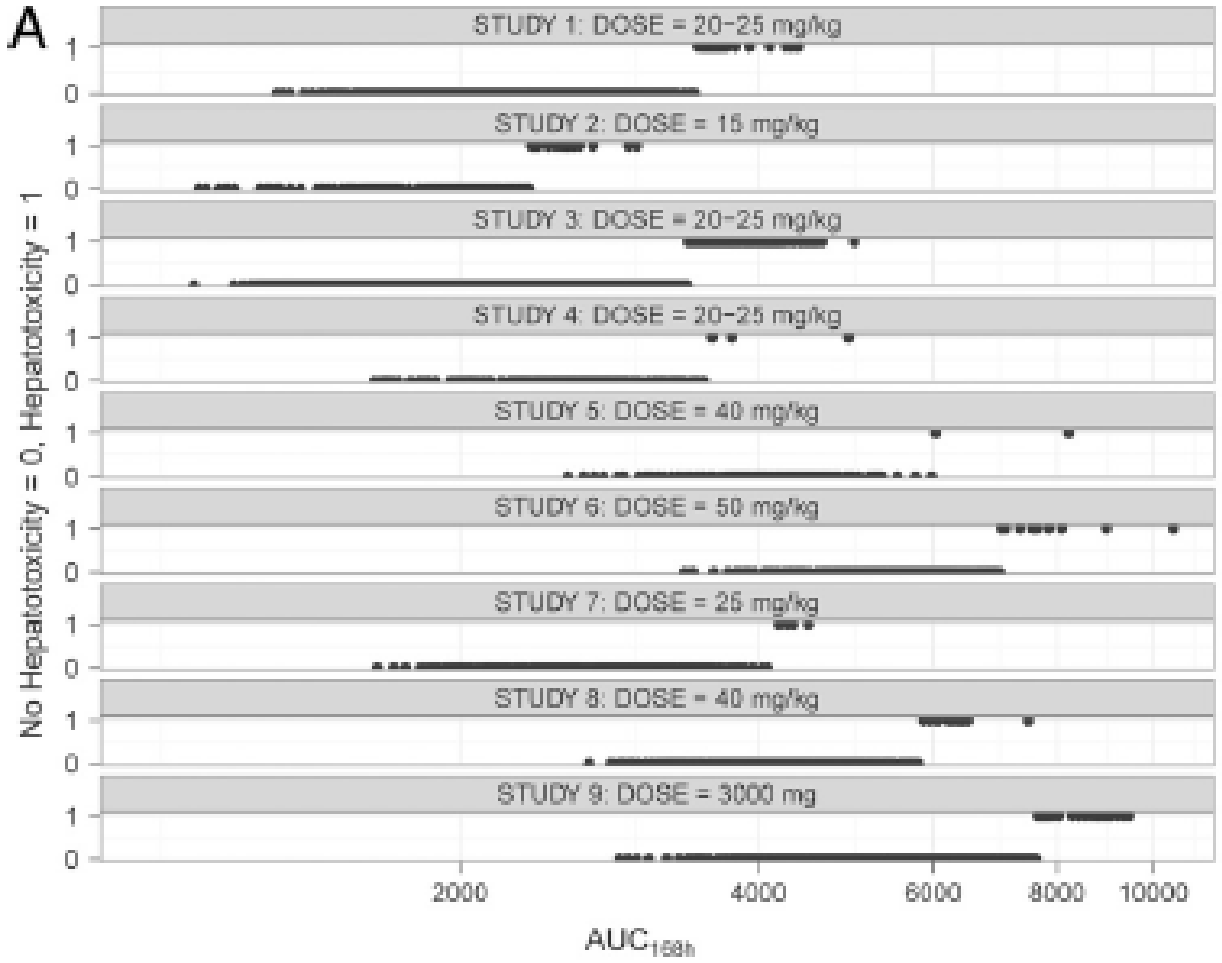
***Dose of 40 mg/kg for 6 months appears to have higher risk of hepatotoxicity than same dose for shorter duration or 25 mg/kg for similar or shorter duration***

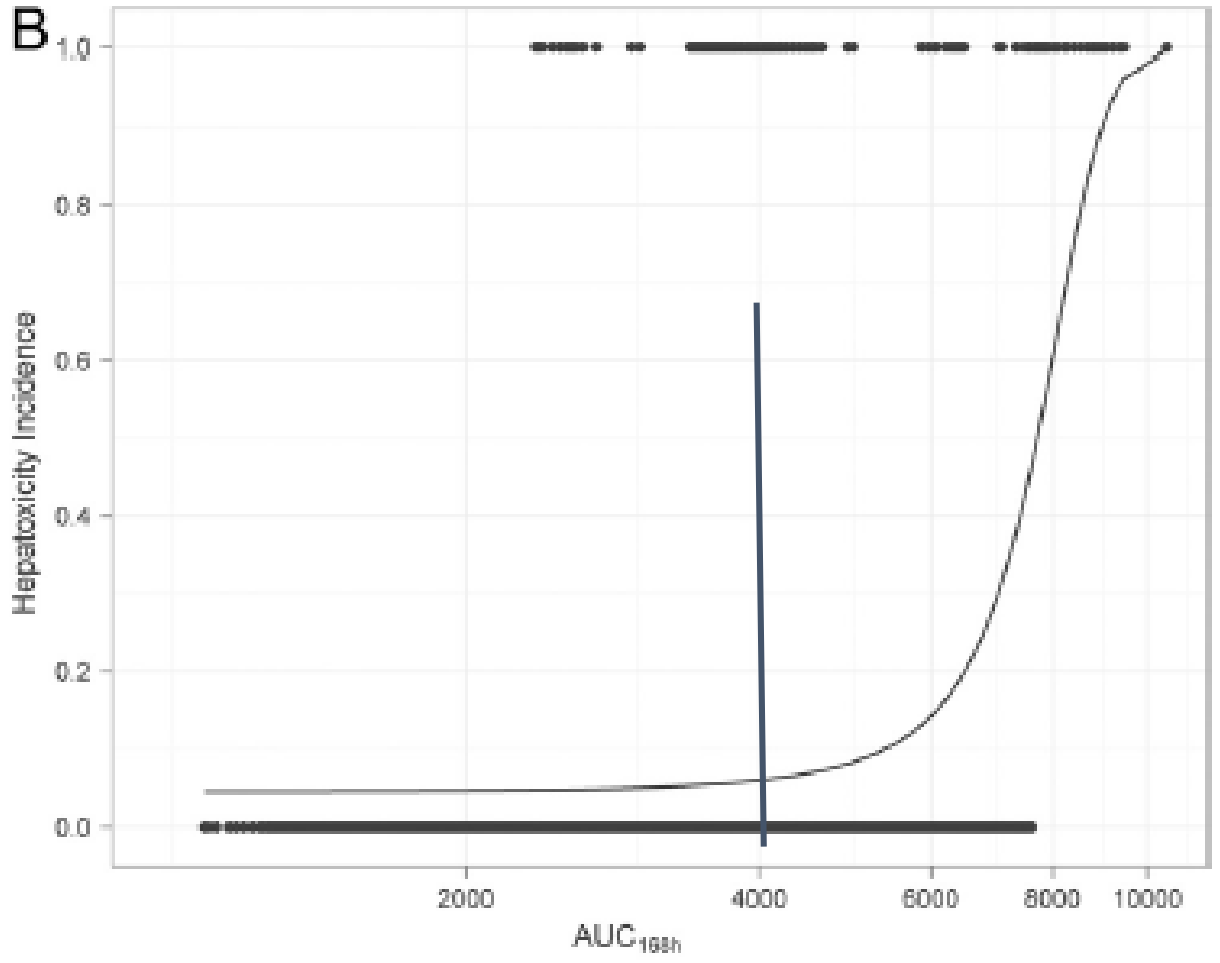
*Total serum bilirubin, cephalin cholesterol flocculation tests, bromsulphalein retention tests

**Of the 21 patients, 6 developed jaundice, 4 on 40 mg/kg dose at Weeks 19, 22, 23, 23

USPHS (1959) Am Rev Respir Dis 80: 371.

# PZA Exposure – Hepatotoxicity (Analysis based on n=4490 , studies from 1954 – 2010)




Sahota AAC 2012 56: 5442.

# Challenges with assessing dose-toxicity relationships from existing studies

- Measurement/definition of “hepatotoxicity”
- Doses in mg/kg vs. mg
- Variable durations
- Different companion drugs
- Comorbidities: alcohol, hepatitis

***Therapeutic margin for PZA remains poorly defined, suspect dose-limiting toxicity exists somewhere between the subtherapeutic dose of 20 mg/kg (given for 8 weeks) and 40-50 mg/kg given for 6 months***

# PZA PK-PD and PD-Toxicity Assessments Alternatively, Co-Optimizing RIF & PZA

Collaboration of TBTC and PanACEA

# Population PK of PZA: relevant learning

| | Pyrazinamide (RSE, %) Base | Pyrazinamide (RSE, %) Covariates |
|---|---|---|
| **CL (L/h)** | 4.03 (3) | 4.03 (3) |
| **V (L)** | 41.11 (3) | 44.25 (2) |
| **MTT (h)** | 1.23 (7) | 1.23 (7) |
| **Proportional error (%)** | 20 (6) | 20 (6) |
| **BSV CL, CV (%)** | 24 (8) | 25 (8) |
| **BSV V, CV(%)** | 17 (17) | 7 (39) |
| **BSV MTT (%)** | 59 (7) | 58 (8) |
| **WT on V* (V_WT)** | | 0.01596 (13) |
| **Sex on V (V_SEX)** | | -0.16 (19) |

Note: Weight has small effect on volume of distribution, no significant effect on clearance

# PZA Pharmacokinetics: What do current doses get you?

| Dose | n | AUC, Average (mg*h/L) | AUC, Ranges (mg*h/L) | Cmax, Average (mg/L) | Cmax, Ranges (mg/L) |
|---|---|---|---|---|---|
| **800 mg** | 1 | 204 | - | 33 | - |
| **1200 mg** | 49 | 316 | 200 - 581 | 35 | 29.6 - 48.5 |
| **1600 mg** | 33 | 393 | 258 - 573 | 40 | 32.8 – 50.1 |
| **2000 mg** | 3 | 461 | 263-674 | 45 | 37.4-51.1 |

# PK-efficacy relationships for PZA

# PZA Dose Optimization (UCSF): **TBTC** data
# Regimens containing *Standard-dose Rifampin*

- Background: TBTC trials
  - Studies 27 (HRZM vs. HRZE) and 28 (MRZE vs. HRZE)
  - PZA dose 20-25 mg/kg (1000-2000mg)
  - 72 patients
  - PZA MIC obtained (Posey)
  - PD outcome:  Time to first negative (on any culture) !
  - LFT results
- Challenges:
  - These were not dose-ranging studies
  - Range of PD outcomes

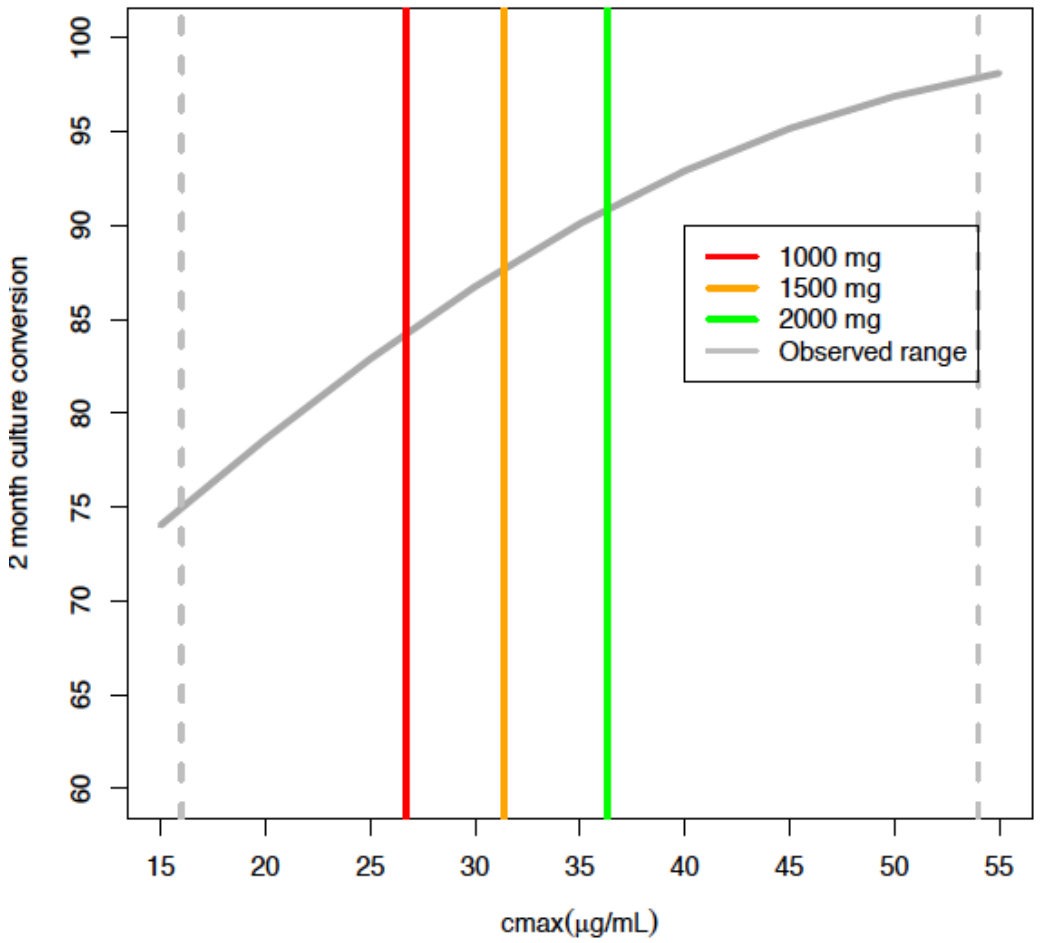
# PK based predictors (PZA)

| Predictor | Univariate | Multivariate |
|---|---|---|
| Cmax | **0.004** | 0.004 |
| AUC | **0.025** | 0.627 |
| MIC* | 0.179 | NA |
| AUC/MIC | 0.178 | NA |
| Cmax/MIC | 0.078 | NA |

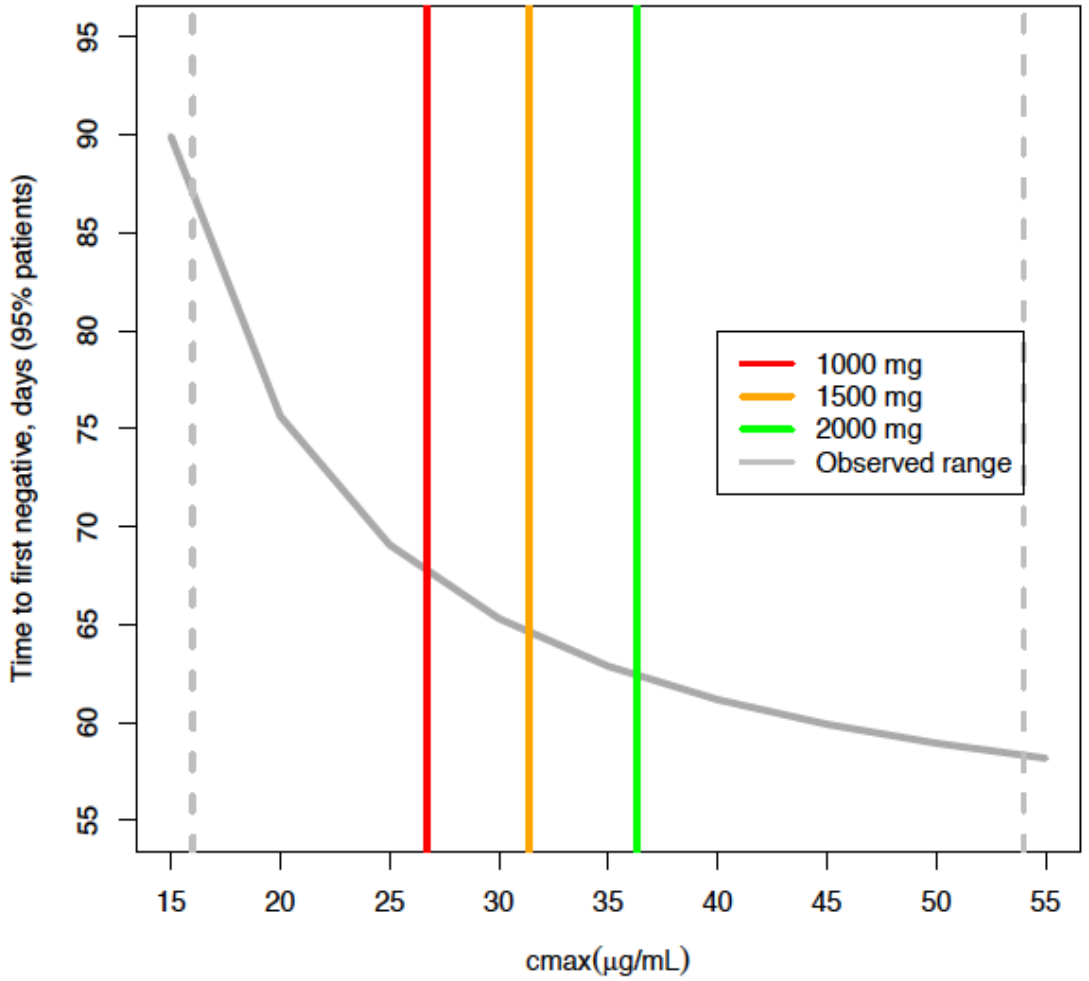
*low MIC range (25 (37 patients), 50 (29 patients) and 75 (4 patients), however enough signal to confirm that patients with MIC>25 need longer time to converge their culture

# TBTC Studies 27 & 28

## % with 2-month culture conversion




## Time to first negative

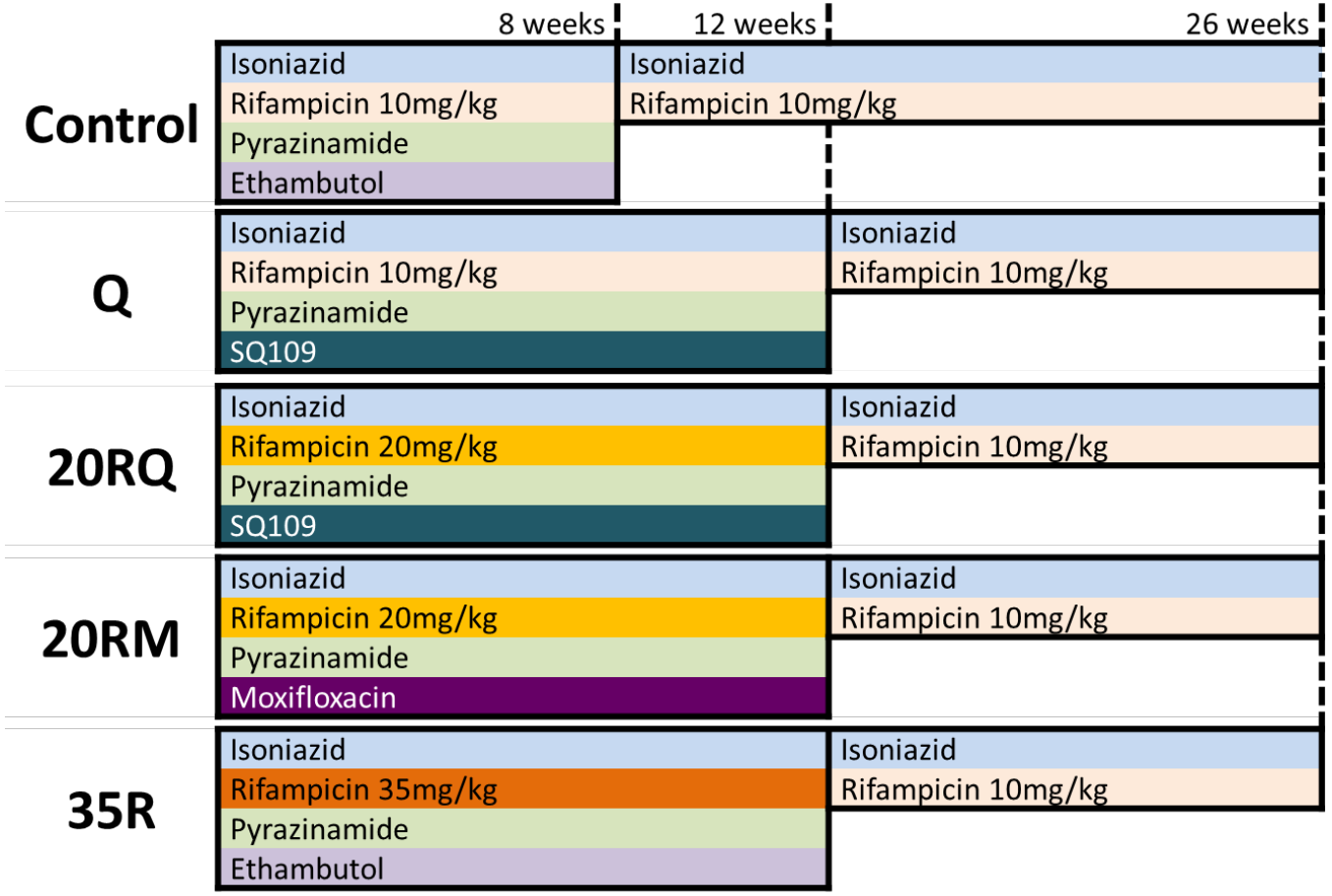



Modeling by Rada Savic

# PZA Dose Optimization (UCSF): **PanACEA** data
# Regimens containing *standard- or high-dose RIF*

- MAMS design, 5 arms:
  - $HR_{10}ZQ$, $HR_{20}ZQ$, $HR_{20}ZM$, $HR_{35}ZE$, $HR_{10}ZE$
- Total # participants=363 in MITT analysis
- Demographic, LFT data results on all 363 participants
- N=99 participants with PK sampling on D28, 10 samples/person
- Longitudinal cultures on MGIT
- PZA dose 25-30 mg/kg (actual 22-32)

# *PanACEA MAMS-TB*




- Covariate-adjusted hazard ratios (c/w control) over 8 weeks:
  - $HR_{20}ZM$ 1.69 (1.02-2.80)
  - $HR_{35}ZE$ 1.99 (1.21-3.29)

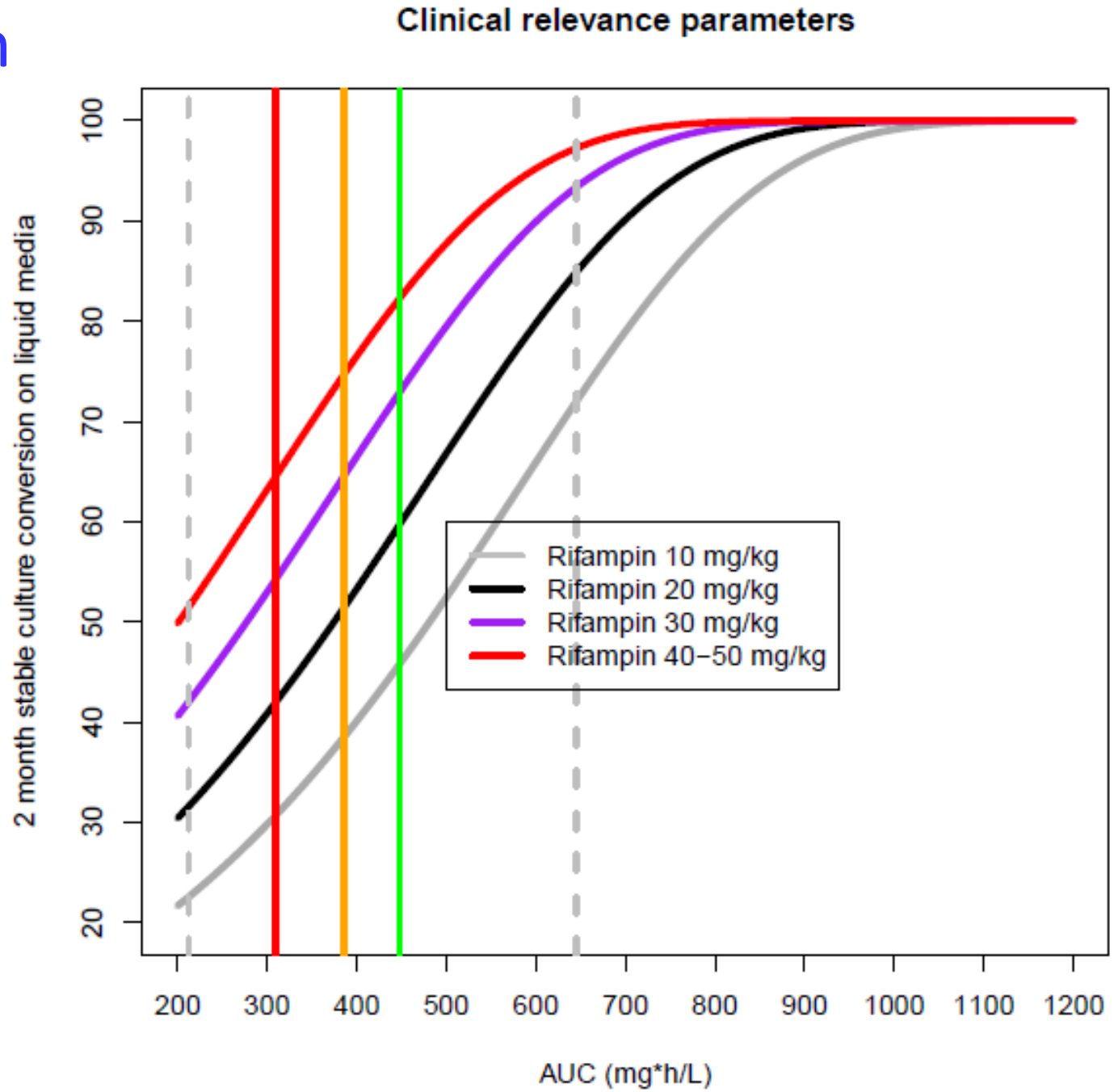
Slide from PanACEA

# Now RIF-PZA Co-Optimization Exposure-Response PanACEA MAMS data

PZA 1200 mg

PZA 1600 mg

PZA 2000 mg

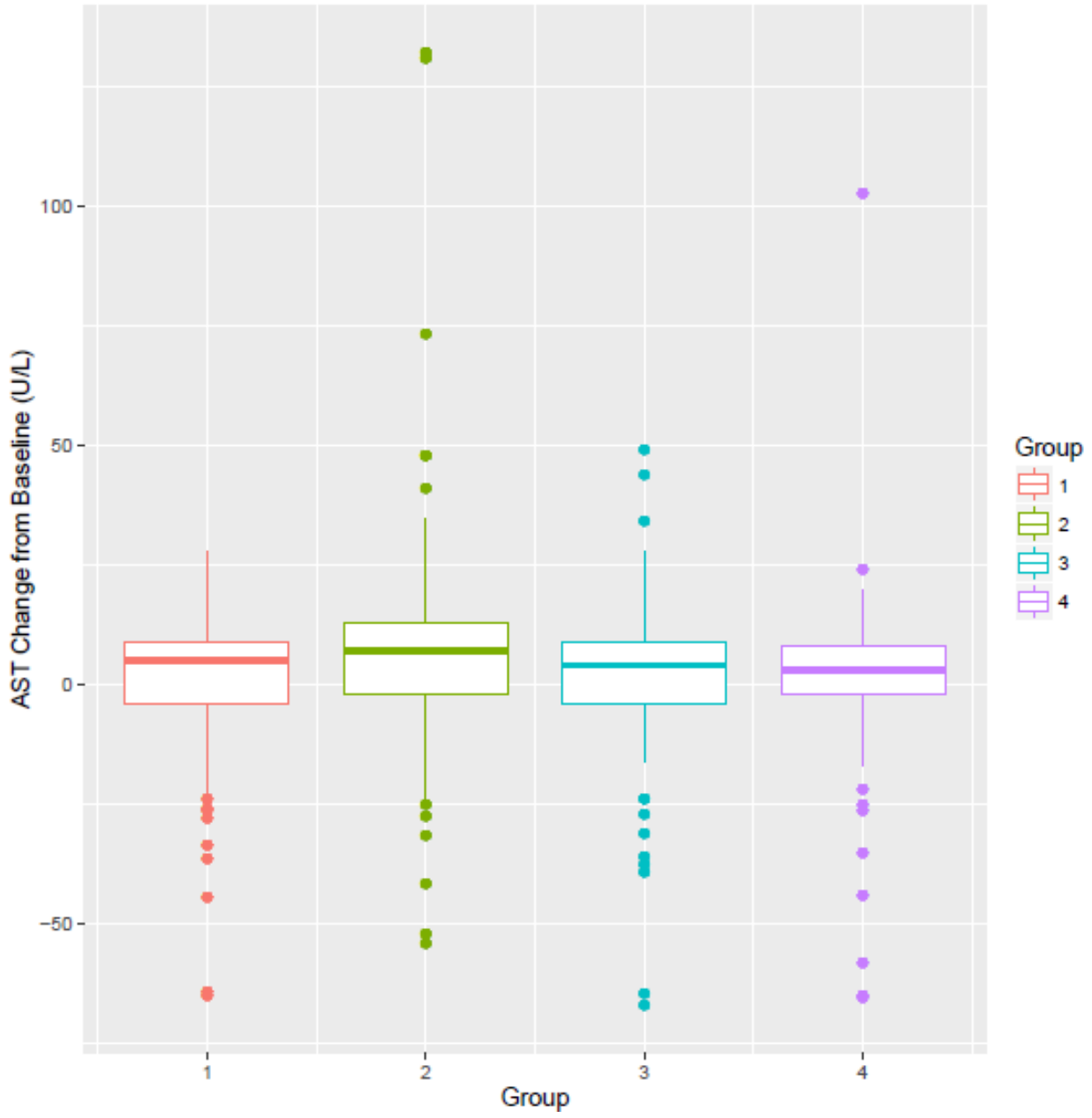



Modeling by Rada Savic

# Yes, but is it safe:  PK-toxicity assessments for PZA

# PZA summary concentration-toxicity relationships:

## AST change from baseline

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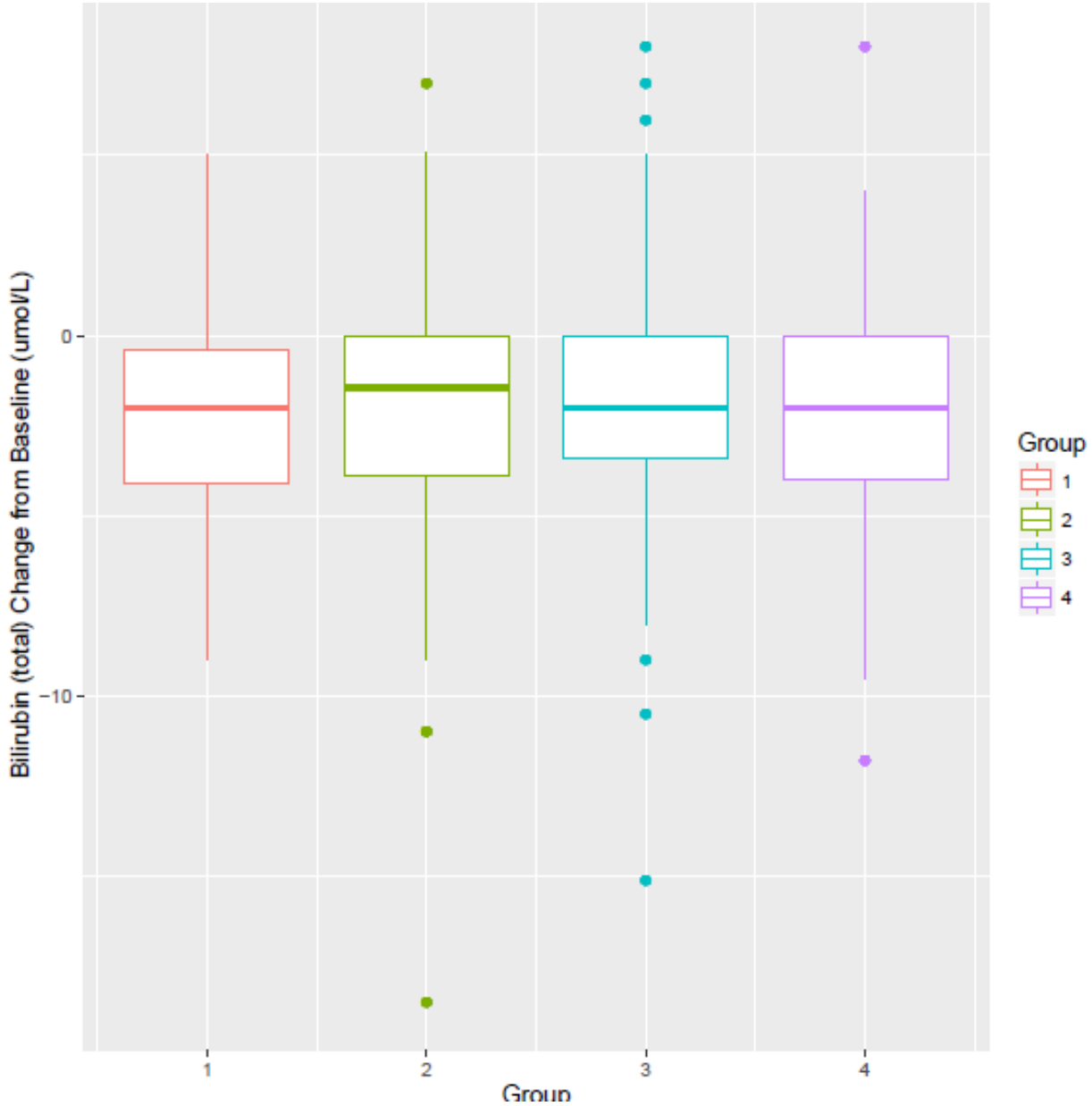
# PZA summary concentration-toxicity relationships:
## Total bilirubin change from baseline

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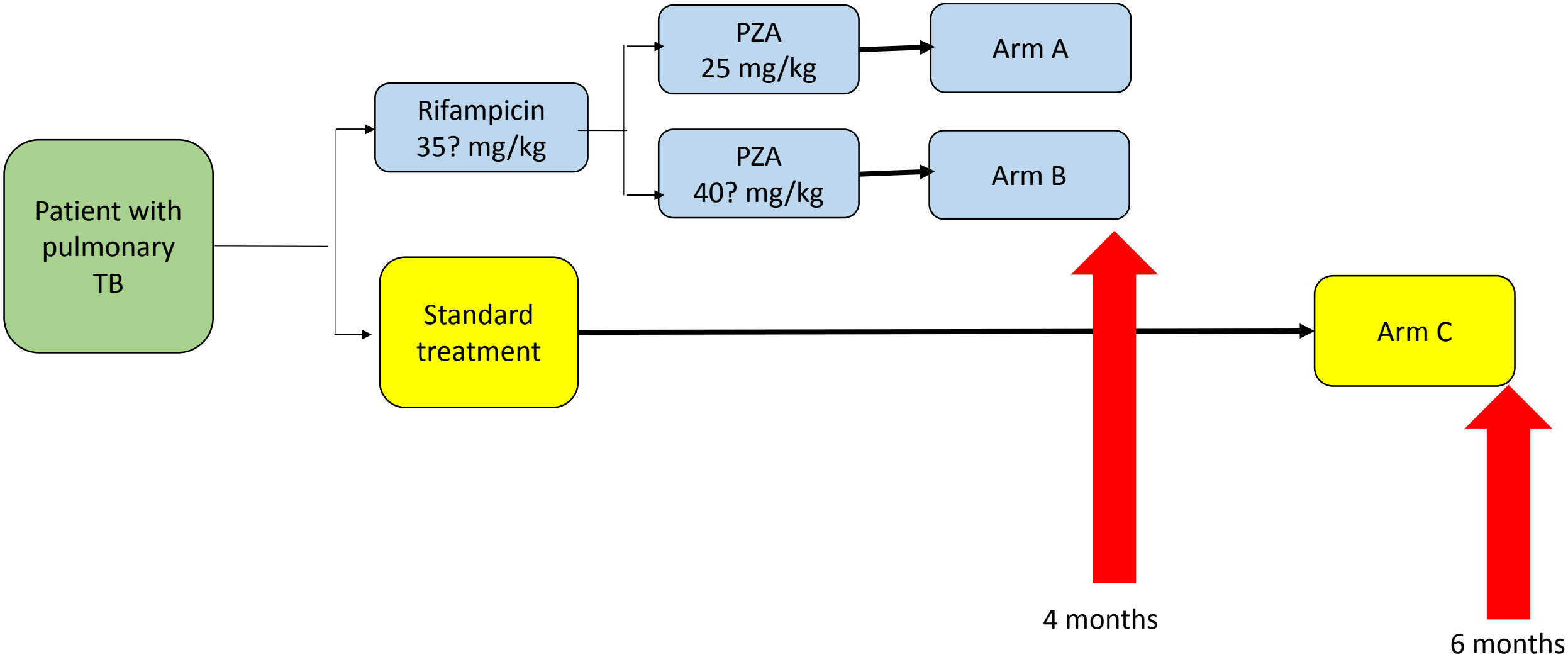
# *Taking lessons learned into a clinical trial?--*
# Higher-dose RIF, with or without Optimized PZA



# Summary

- The historical studies demonstrating treatment-shortening potential of PZA used higher doses (35-40 mg/kg) than we use currently
- At currently-used doses (20-25 mg), ‘target’ concentrations not achieved in many patients; low exposures associated with worse clinical outcomes in several recent studies
- Therapeutic margin for PZA remains poorly defined
- In recent TBTC and PanACEA multinational trials, microbiologic efficacy of pyrazinamide increased as exposure or concentration increased. This was true with regimens containing standard-dose or high-dose rifampicin
- Within the relatively narrow range of doses given, there was no relationship between dose and hepatotoxicity, and hepatotoxicity was rare
- These data support evaluation of high-dose rifampicin plus optimized pyrazinamide as a treatment-shortening strategy for drug-sensitive TB