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HIGHRIF2: a phase II trial comparing 10, 15 and 20 mg/kg rifampicin for two months

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APRIORI

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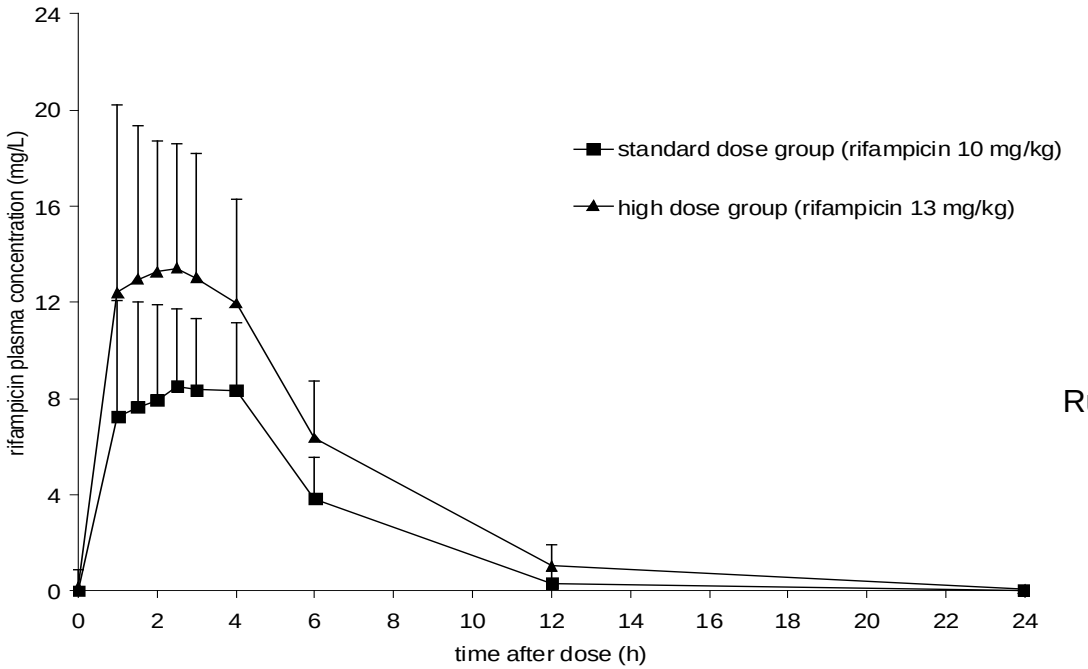
African PanACEA Partners:

Back in 2006 …..

- murine data (Jayaram et al, 2003)
- studies from 1970/80s (reviewed in Steingart et al, 2011)
- other diseases: brucellosis, leishmaniasis
- higher dose rifampicin in Indonesia



Ruslami et al, 2007

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Objectives

- effect of a higher dose of rifampicin on the PK of rifampicin in patients with smear-positive pulmonary tuberculosis in Tanzania
- effect of a higher dose of rifampicin on the occurrence of AEs
- to explore the effect of a higher dose of rifampicin on the bacteriological response of *M. tuberculosis*

Design

- double blinded, randomized, controlled, three arm, phase II clinical trial

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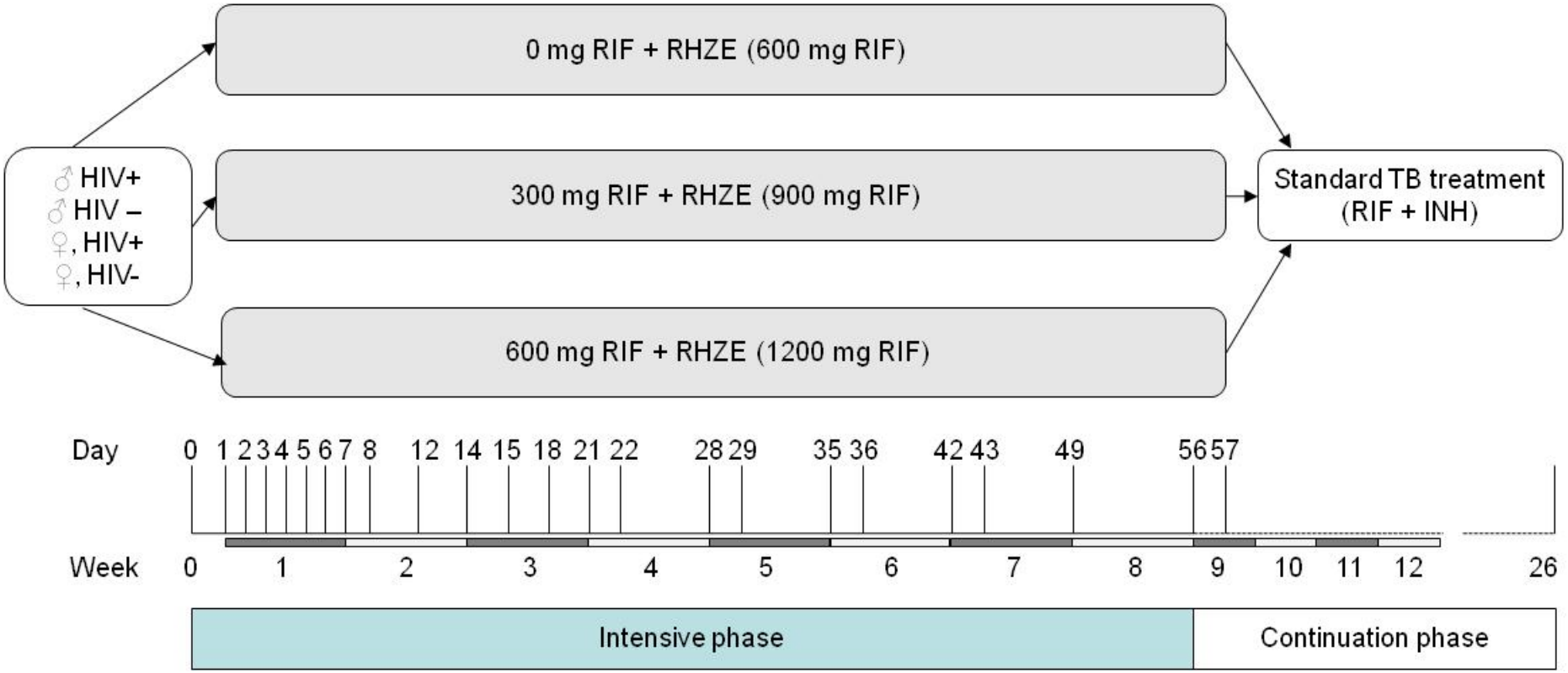
HighRIF2 – study design



Drugs: standard FDC + rifampicin /placebo

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Inclusion criteria

- a newly diagnosed pulmonary TB, confirmed by a positive smear of at least two sputum specimens with ZN staining
- 18-65 years

Exclusion criteria

- body weight less than 50 kg
- liver or kidney function disturbances
- on anti-retroviral treatment or expected to receive anti-retroviral treatment within 2 months

Pharmacokinetics

- Full PK curve: in 3 * 25 = 75 patients
- Sampling in week 6
- Before and at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 24 h post dose
- validated HPLC methods
- Non-compartmental PK techniques

Adverse effects

- questioning about AEs,

  physical examination

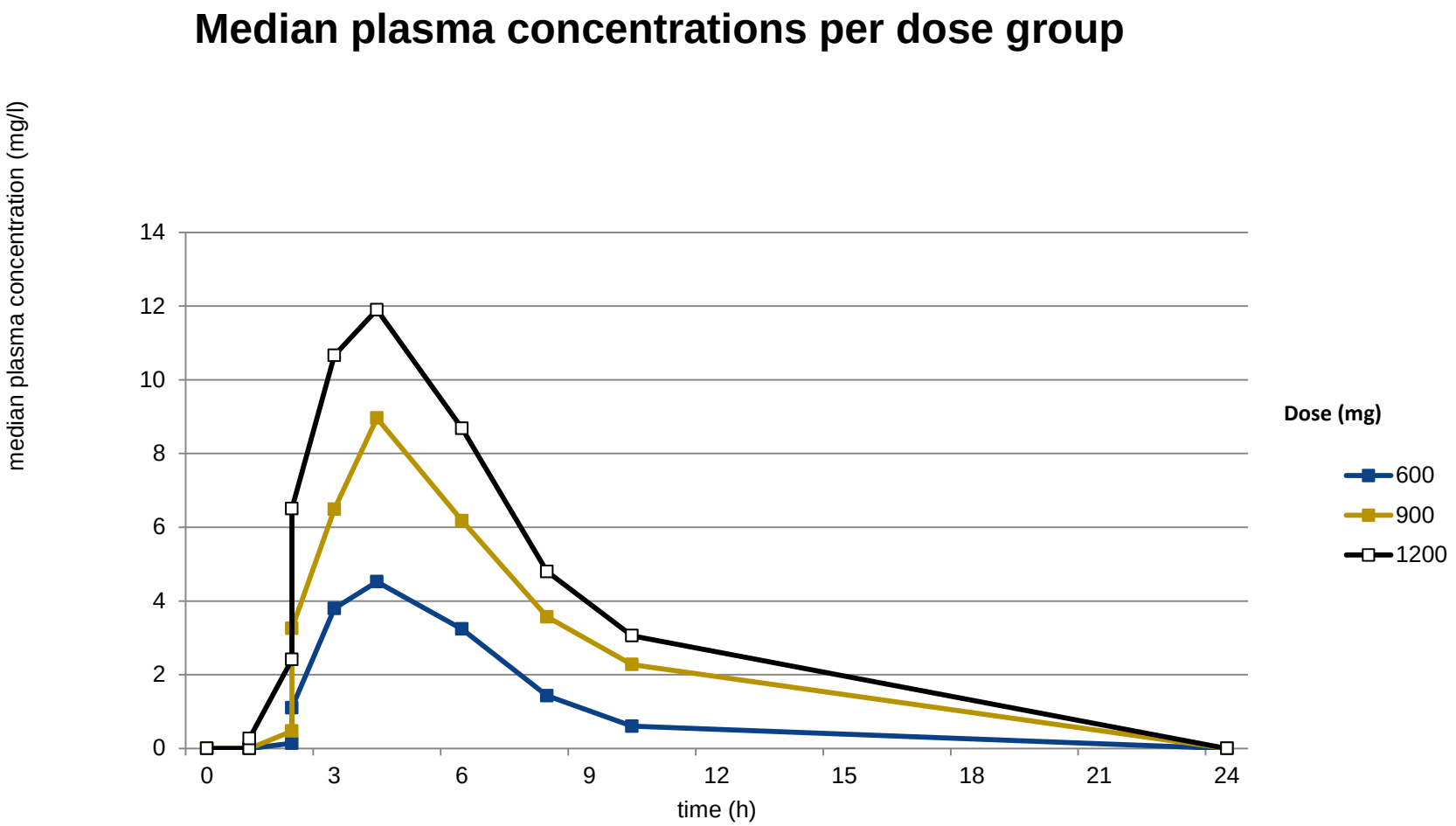
  biochemistry (ASAT, ALAT, γ-GT, alkaline phosphatase, creatinine)

  haematology (haemoglobin, haematocrit, red cell count, platelet count, total white cell count)
- at screening and after 1, 2, 3, 4, 6, 8, 10 and 12 weeks

Microbiology

- Colony forming units (CFU) of Mtb on solid medium and time to culture positivity (TTP) in liquid medium
- at baseline and at days 2, 4, 7, 14, 21, 28, 35, 42, 49, 56

Results - PK



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Results - PK

Parameter	Dose rifampicin (mg)			P-value (2-tailed)
	600	900	1200	
$AUC_{0\text{-}24h}$ (h*mg/l)[a]	23.9 (9.14-118)	48.4 (18.9-101)	73.8 (41.0-167)	< 0.001[c]
C_{max} (mg/l)[a]	5.32 (1.98-23.3)	9.27 (4.86-15.4)	13.6 (6.60-29.0)	< 0.001[d]
T_{max} (h)[b]	4.0 (2.0-6.1)	4.0 (2.0-6.1)	4.0 (2.5-6.2)	0.964[e]
CL (l/h)[a]	25.1 (5.06-65.6)	18.6 (8.89-47.7)	16.3 (7.19-29.3)	<0.05[c]
V_d (l)[a]	69.0 (17.6-213)	69.5 (41.8-131)	57.2 (34.0-129)	0.244[d]
$T_{1/2}$ (h)[a]	1.91 (1.07-4.48)	2.59 (1.39-3.77)	2.44 (1.38-3.42)	0.006[d]
No. patients with C_{max} > 8.0 mg/l (%)	5 (21.7)	14 (70.0)	19 (95.0)	< 0.001[f]

More than proportional increase in exposure with the dose

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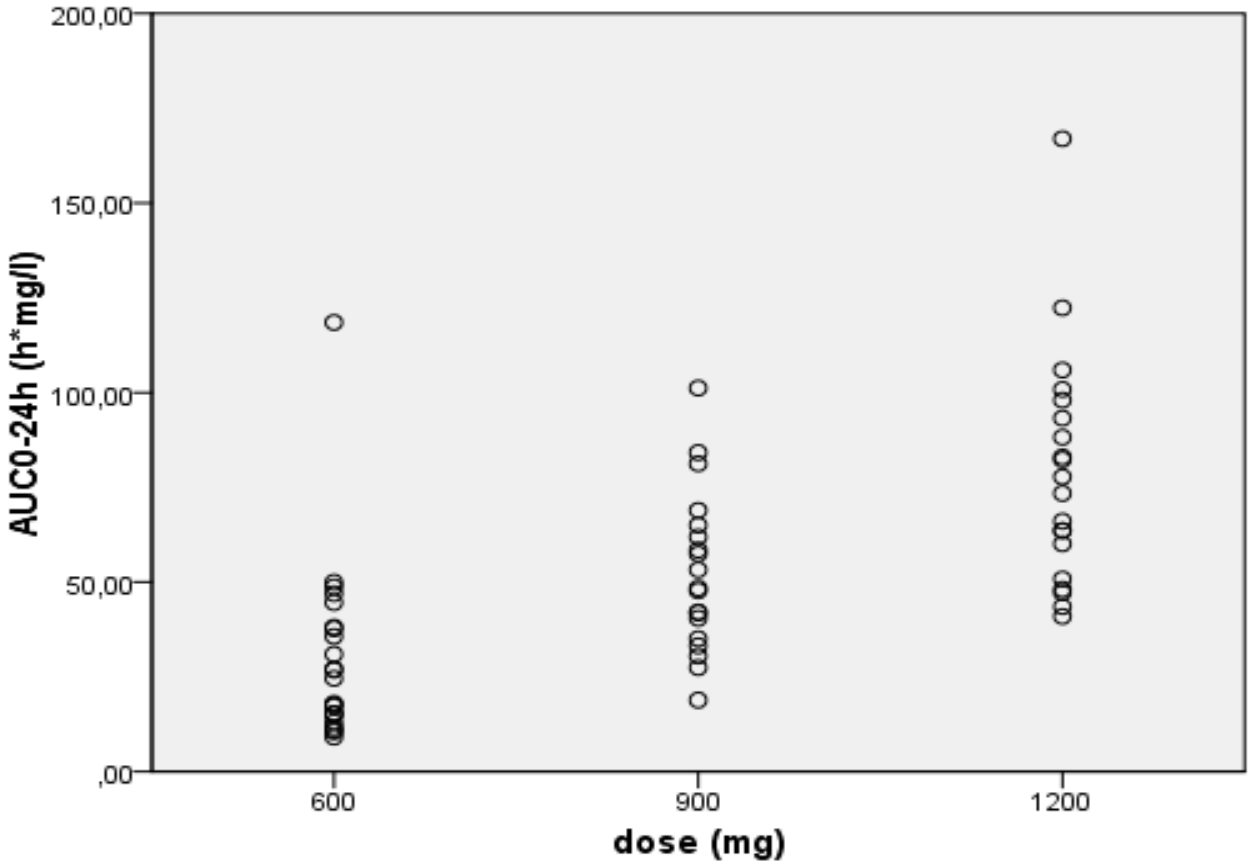
Results - PK



- Minimum exposure increases with the dose
- Large interindividual variability in PK !

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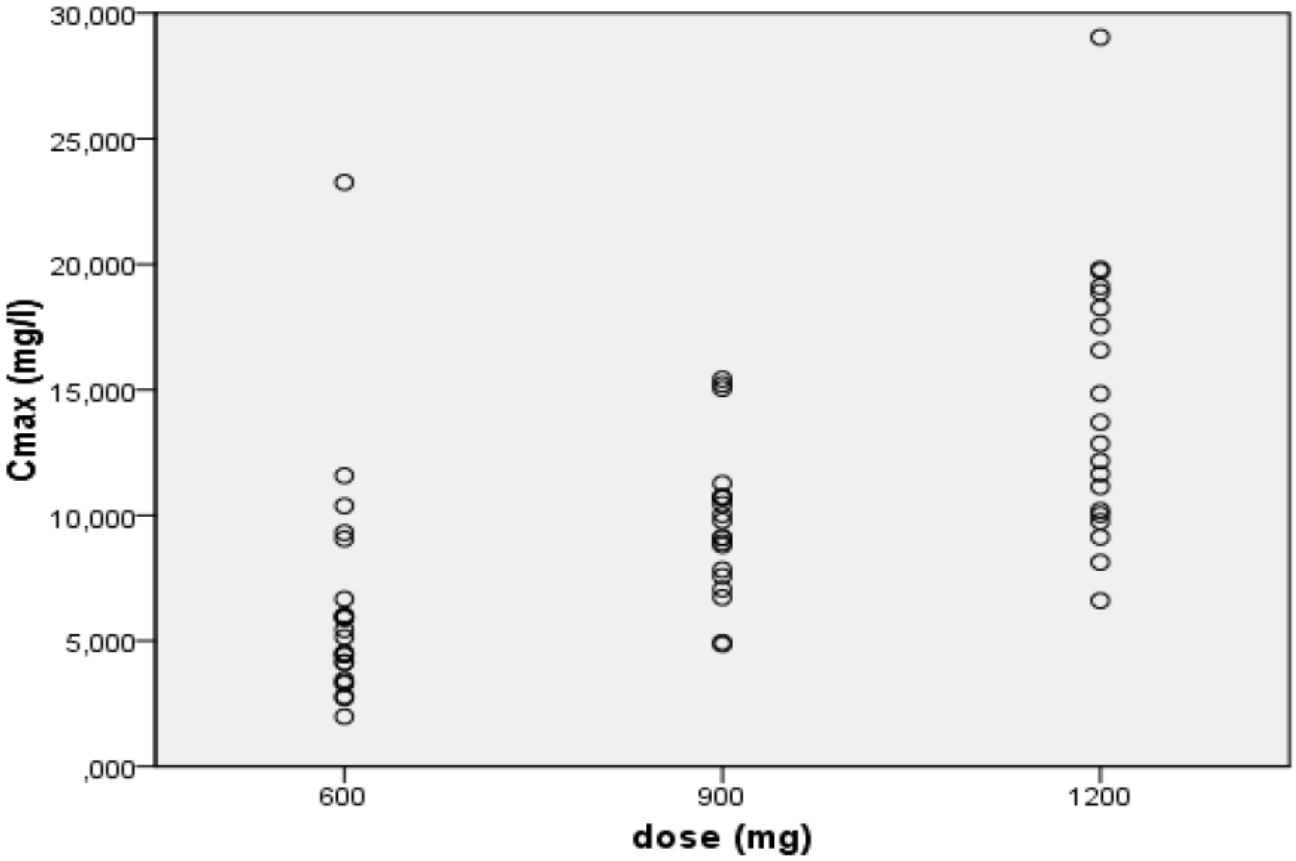
Results - PK



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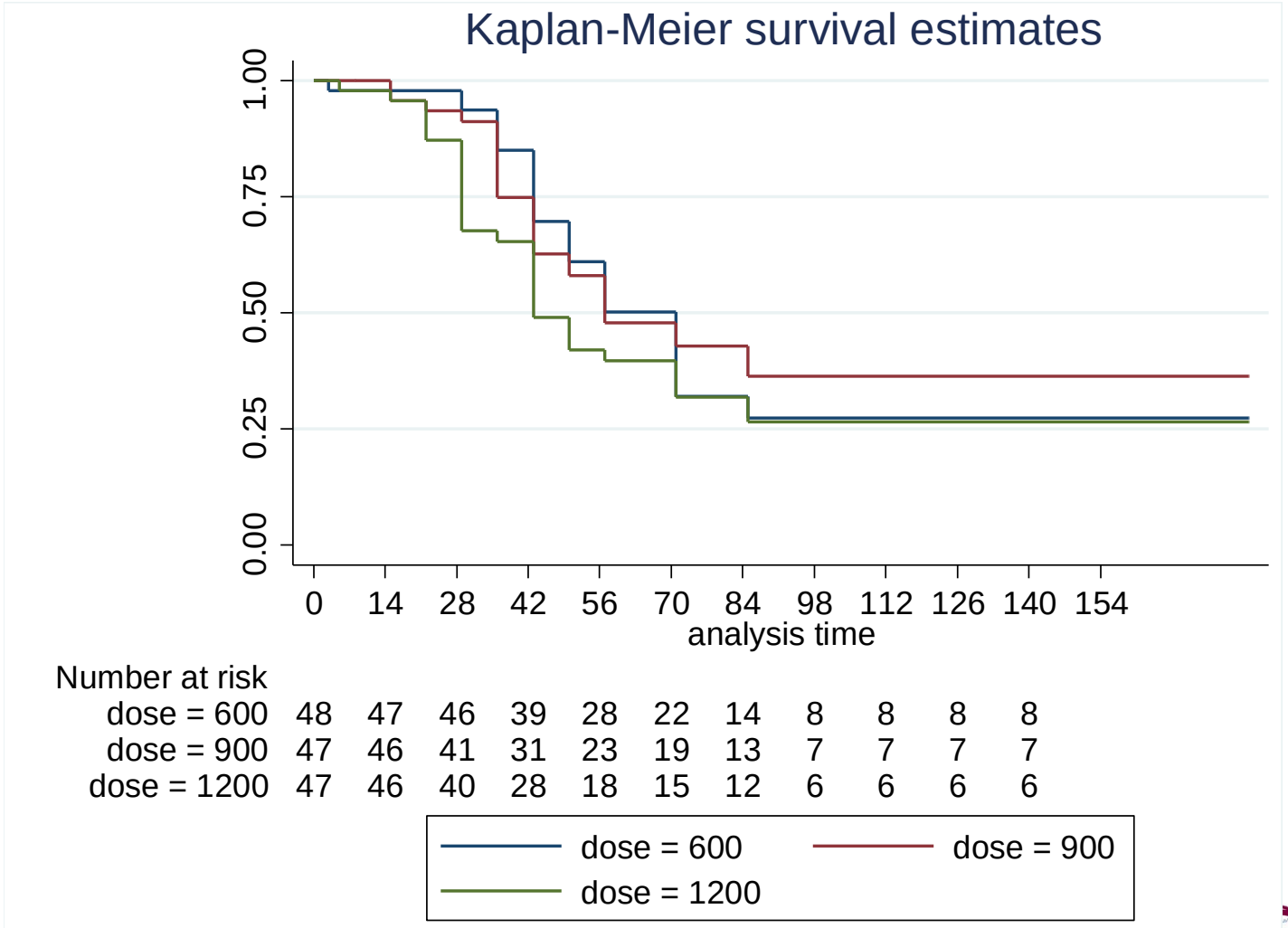
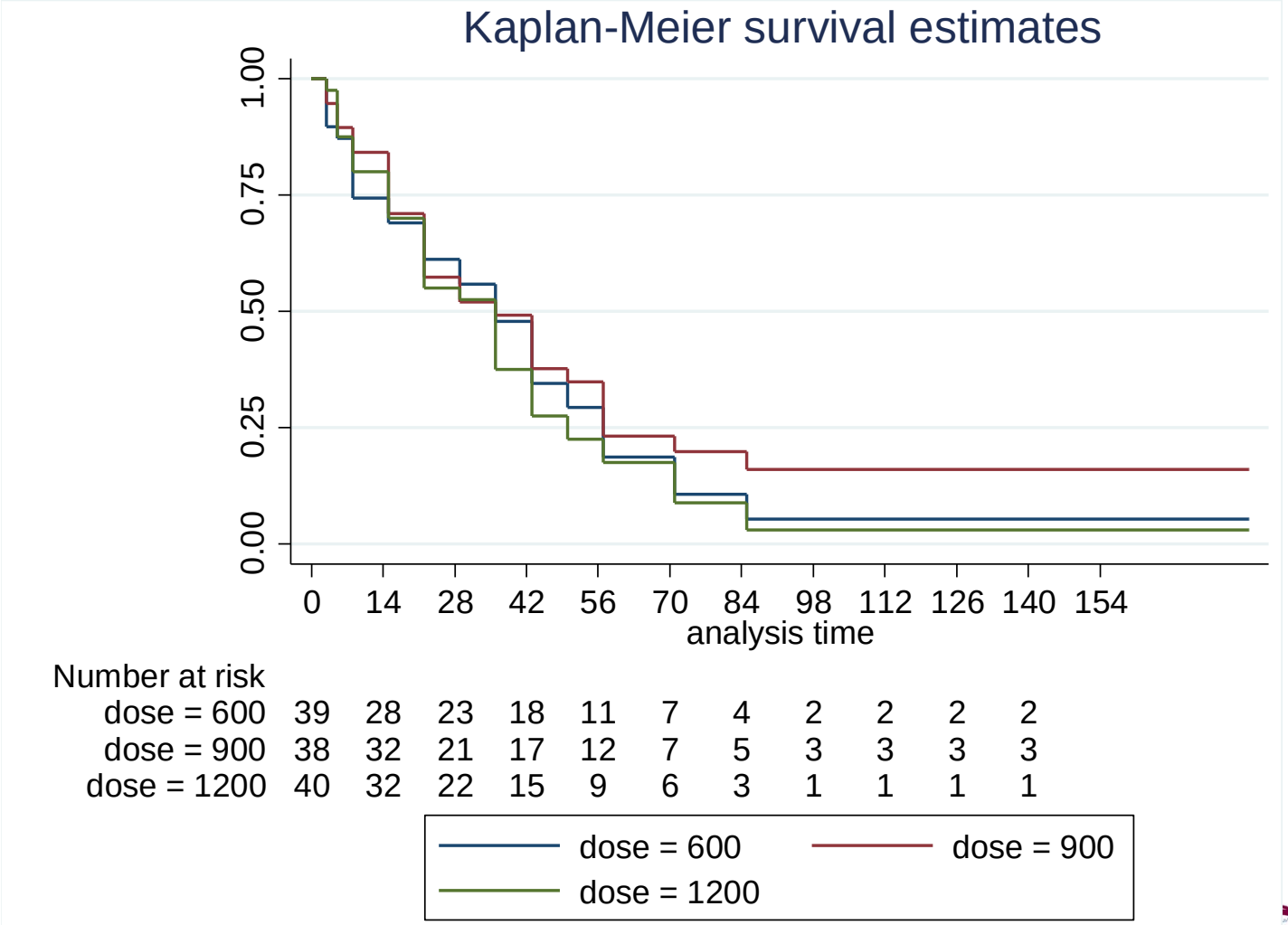
SAEs

- Grade 3: n=18, equally distributed over the arms
- Grade 4: none
- Grade 5: 3 deaths, one in each dose group, all had severe advanced disease

Time to culture conversion on MGIT



Time to culture conversion on LJ

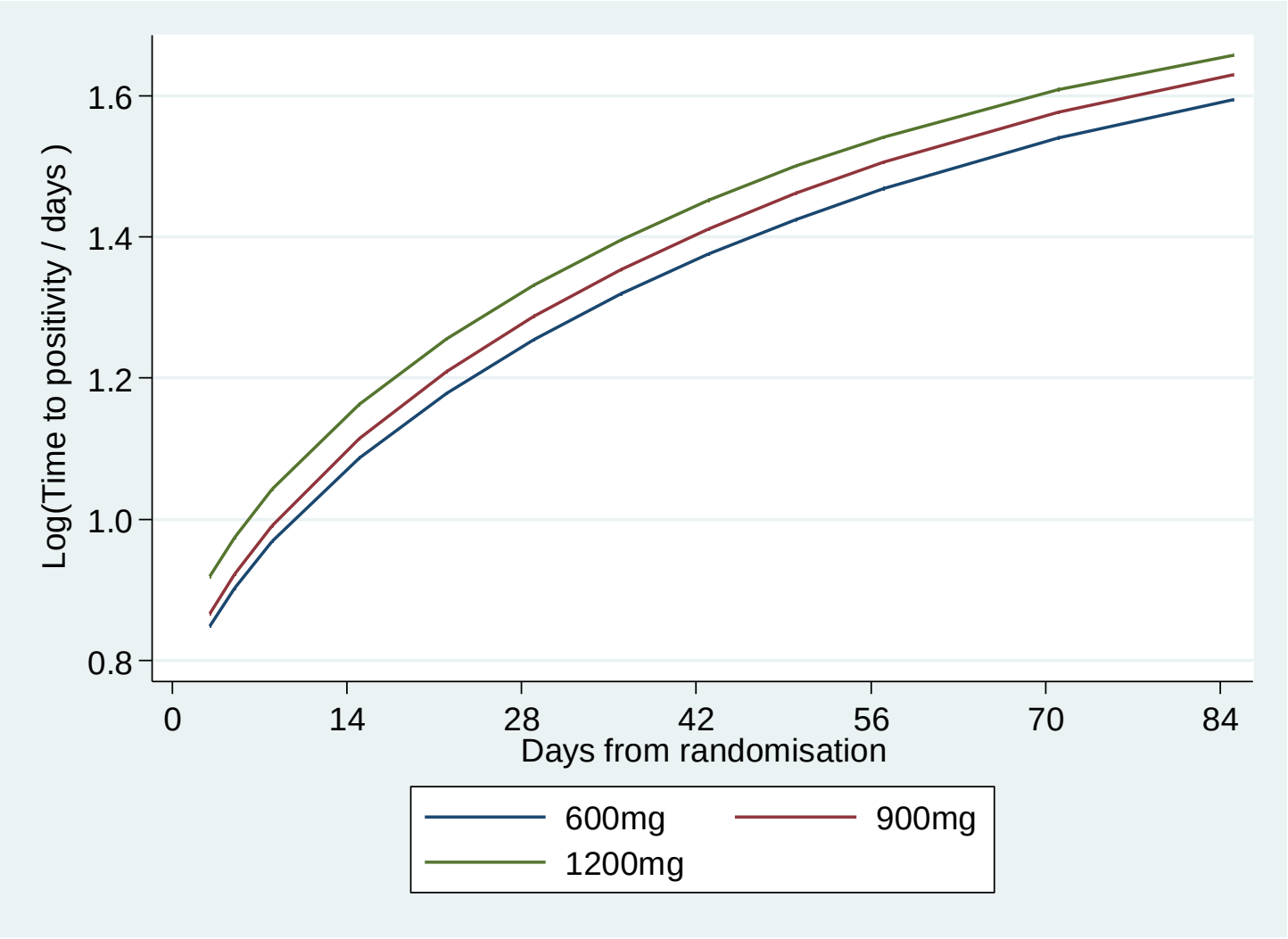


Modelling slopes of logCFU and logTTP over time

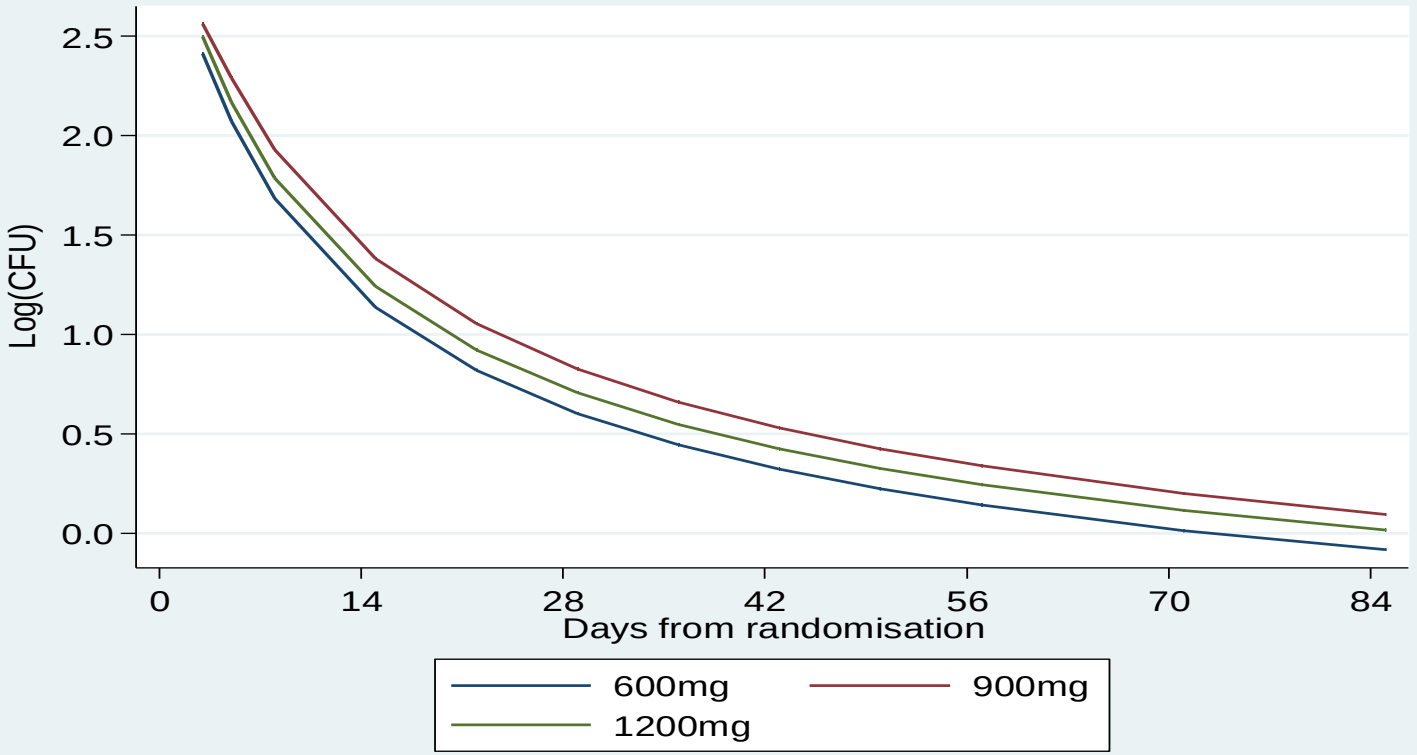
- Fractional polynomials in a mixed effects model
- Negative cultures imputed with limits of detection (TTP=42 days; CFU=1)

Work ongoing to properly account for censoring for limit of detection

Fitted Log(TTP) over time



Fitted Log(CFU) over time



- Not surprising in view of overlapping exposures
- Wait for PK-PD
- Evaluation of higher doses needed

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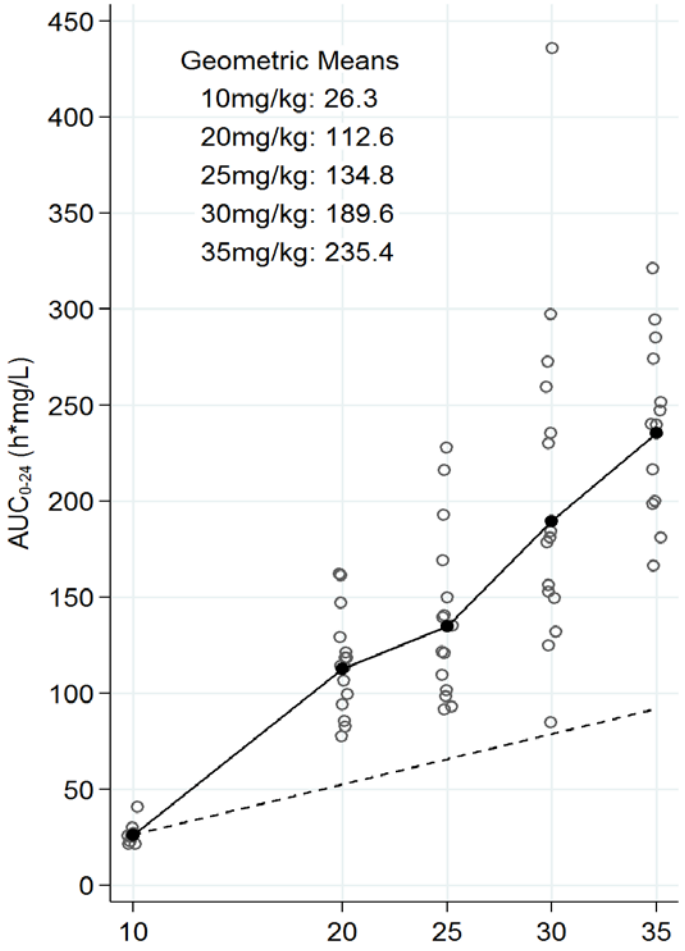
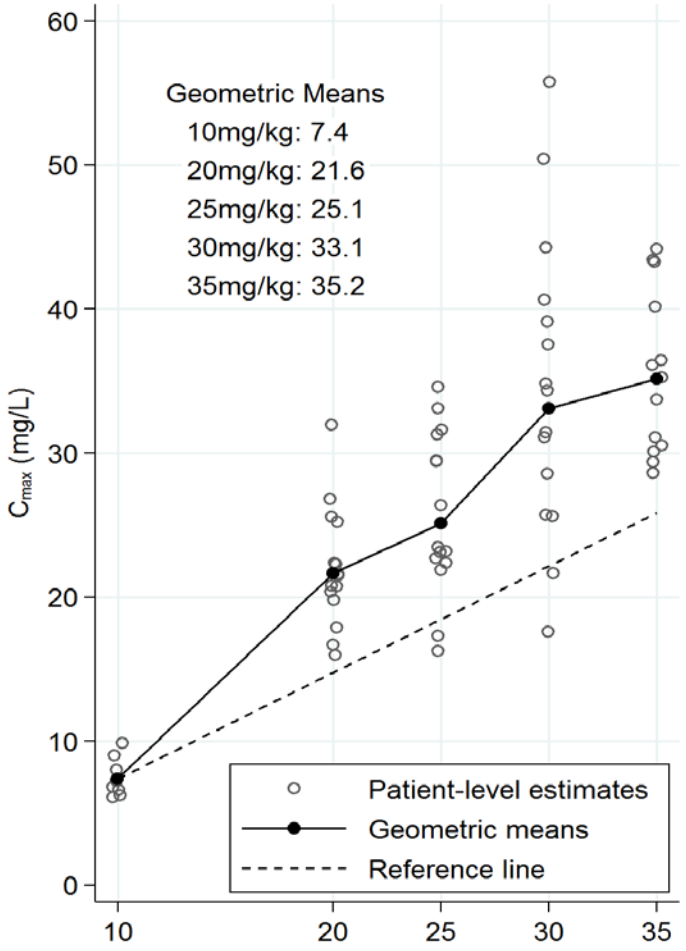
HIGHRIF1





MAMS in PanACEA

Control:	HRZE	isoniazid (H), rifampicin Std (R), pyrazinamide (Z), ethambutol (E)
Experimental Arm 1:	HRZQ	isoniazid (H), rifampicin 10 mg (R), pyrazinamide (Z), SQ109 300mg(Q)
Experimental Arm 2:	$HR_{20}ZQ$	isoniazid (H), **rifampicin 20 mg (R_{20}),** pyrazinamide (Z), SQ109 300mg (Q)
Experimental Arm 3:	$HR_{20}ZM$	isoniazid (H), **rifampicin 20 mg (R_{20}),** pyrazinamide (Z), moxifloxacin (M)
Experimental Arm 4:	$HR_{35}ZE$	isoniazid (H), **rifampicin 35 mg (R_{35})**, pyrazinamide (Z), ethambutol (E)

Preliminary conclusions HIGHRIF2

- nonlinear, superproportional increase in average AUC and Cmax, though less outspoken than in HIGHRIF1
- Large interindividual variability in PK
- 900 and 1200 mg rifampicin combined with standard TB drugs for 2 months are safe and equally well tolerated as standard dose rifampicin
- Modest, non-significant reduction in time to culture conversion on both MGIT and LJ with increasing dose
- Higher doses need to be evaluated

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Acknowledgements

- African Poverty Related Infection Oriented Research Initiative (APRIORI) / NACCAP and EDCTP for funding the trials

- Sanofi Aventis for providing rifampicin and placebo

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