St George's University of London

International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis (INTERTB)

Can we reduce treatment duration with currently used drugs?

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International Coordinator

Study A
Outcome at 12 months after stopping treatment

Regimen	Culture neg at 2 months(%)	Failures/Relapses %
2EHRZ/6EH	86	10
$2(EHRZ)_3$/6EH	77	14
2EHRZ/4HR	83	5

Jindani A, Nunn AJ, Enarson DA. 2004. Lancet;364:1244-1251

WHO recommended regimens

Regimen 1: 2EHRZ/4HR (US$ 18.34)

Regimen 2: 2EHRZ/6HE (US$ 22.01)

Reasons for further trials

- Annual mortality of 2,000,000
- 1 death every 15 seconds
- From a curable disease

New drugs

- Clinical trials are taking longer and costing more
- Competition for patients is heating up
- Time to develop a new drug:
  - 1960 : 8.1 years
  - 1990 : 15.3 years
- Cost of Phase III trial :
  - US$ 4 million – 20 million

Kittredge Clare. 2005. The Scientist; 19:46-49

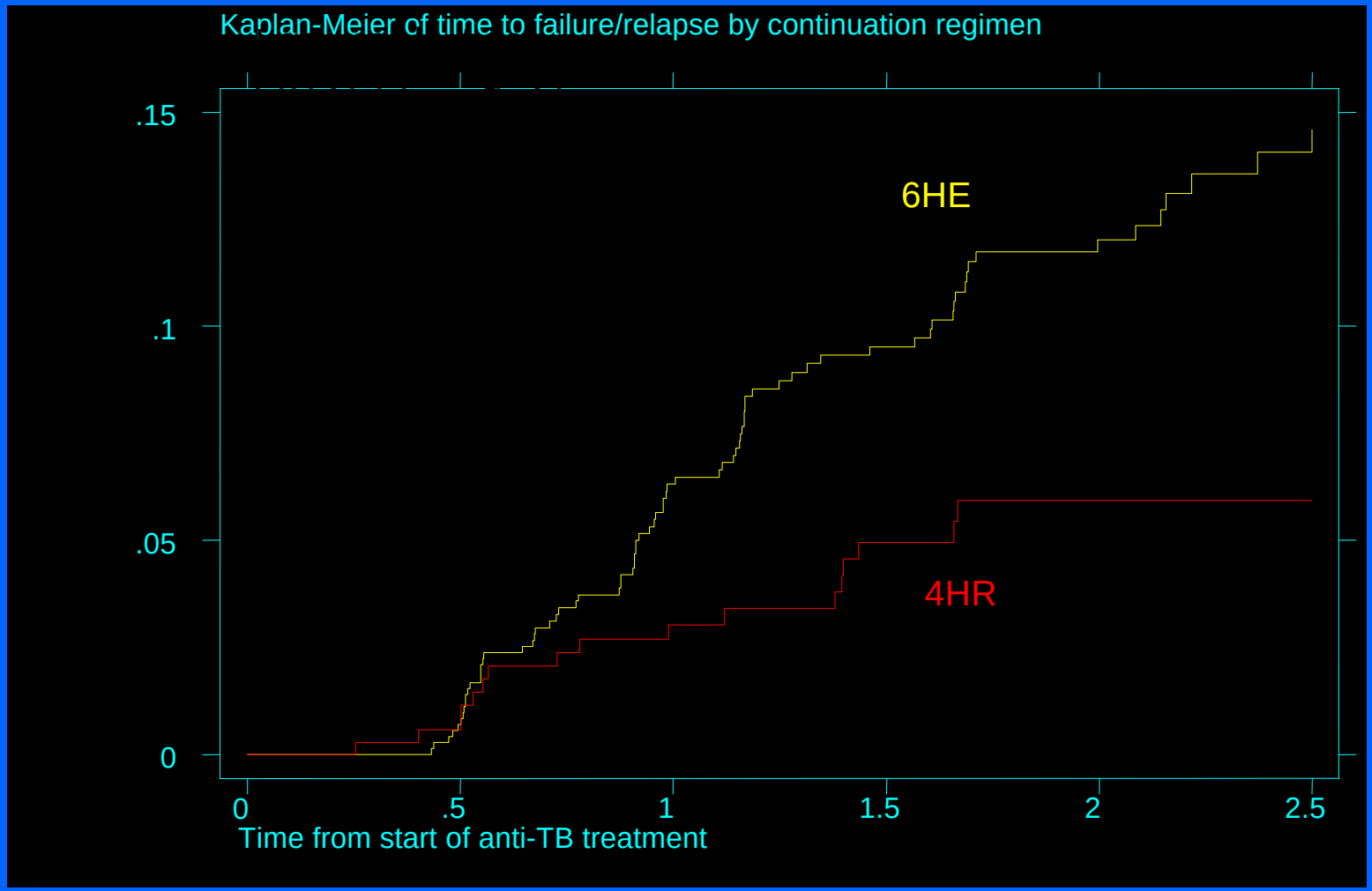
Existing Drugs

- Isoniazid
- Ethambutol
- Pyrazinamide
- Rifamycins : rifampicin
  rifapentine
  rifabutin
  others

- Quinolones : ofloxacin
  gatifloxacin
  moxifloxacin

IUATLD Study A

Jindani A, Nunn AJ, Enarson DA. 2004. Lancet;364:1244-1251



N: 8HE, 6HR	768, 365	714,346	567,292	451,240	334,175

Addition of rifampicin

Regimen	No. patients	Per cent patients	
		Cult +ve at 2 months	Relapses
6SH	154	*51*	*29*
6SHR	148	*31*	*2*
2SHZ/2(SHZ)$_2$	129	*28*	*6.2*
2SHRZ/2(SHZ)$_2$	261	*8*	*2.3*
3SHZ/2(SHZ)$_2$	236	*26*	*13*
3SHRZ/2(SHZ)$_2$ 3SHRZ	457	*9*	*4*

Rifampicin in the continuation phase

Regimen	Patient No.	Relapses	
		Number	Percent
2SHRZ/2HRZ	104	17	16
2SHRZ/2HR	104	11	11
2SHRZ/2HZ	98	31	32
2SHRZ/2H	105	32	30
2HRZ/2H	100	40	40

East African/British Medical Research Councils Study. 1981.
Controlled clinical trial of five short-course (4-Month) chemotherapy regimens in pulmonary tuberculosis
Second report of the 4th study. Am Rev Respir Dis; 123:165-170.

Addition of pyrazinamide

Regimen	No. of patients	Per cent patients: 2-month pos. cult.	Per cent patients: Relapse
6SH	154	*51*	*29*
6SHZ	150	*34*	*11*
2SHR/TH	194	*25*	*13*
2SHRZ/TH	179	*13*	*6*
6SHRE_2	129	*28*	*8*
6SHRZ_2	261	*8*	*1*
2SHRE_2/SHE_2	171	*19*	*23*
2SHRZ_2/SHZ_2	167	*5*	*7*
6SHR	169	*30*	
2SHRZ/4TH	347	*18*	
2EHR/7HR	157	*36*	
2EHRZ/4HR	141	*23*	
2SHRZ/4HR	146	*23*	

EFFECT OF PYRAZINAMIDE IN THE CONTINUATION PHASE

REGIMEN	TOTAL PATIENTS	RELAPSE RATE IN 2-YEAR FOLLOW UP (%)	CULTURE NEGATIVE AT 2 MONTHS (%)
2SHRZ/2HRZ	104	16	
2SHRZ/2HR	104	11	85
2SHRZ/2HZ	98	32	
2SHRZ/2H	105	30	

EA /BMRC.1981. Controlled clinical trial of five short-course (4-month) chemotherapy regimens in pulmonary tuberculosis. Second report of the 4th study.

Duration of treatment

Duration of chemotherapy (months)	Patients assessed	Bacteriological relapses	95% confidence limits
9	298	3 (1%)	0.2 – 2.9
6	422	4 (1%)	0.3 – 2.4
4½ - 5	465	16 (3%)	2 – 6
4	364	43 (12%)	9 – 16
3	307	41 (13%)	10 - 18

The six-month and shorter durations all contain streptomycin, isoniazid, rifampicin and pyrazinamide.

Fox Wallace. Whither short-course chemotherapy. Br J Dis Chest, 1981; 75: 331-357.

RCT

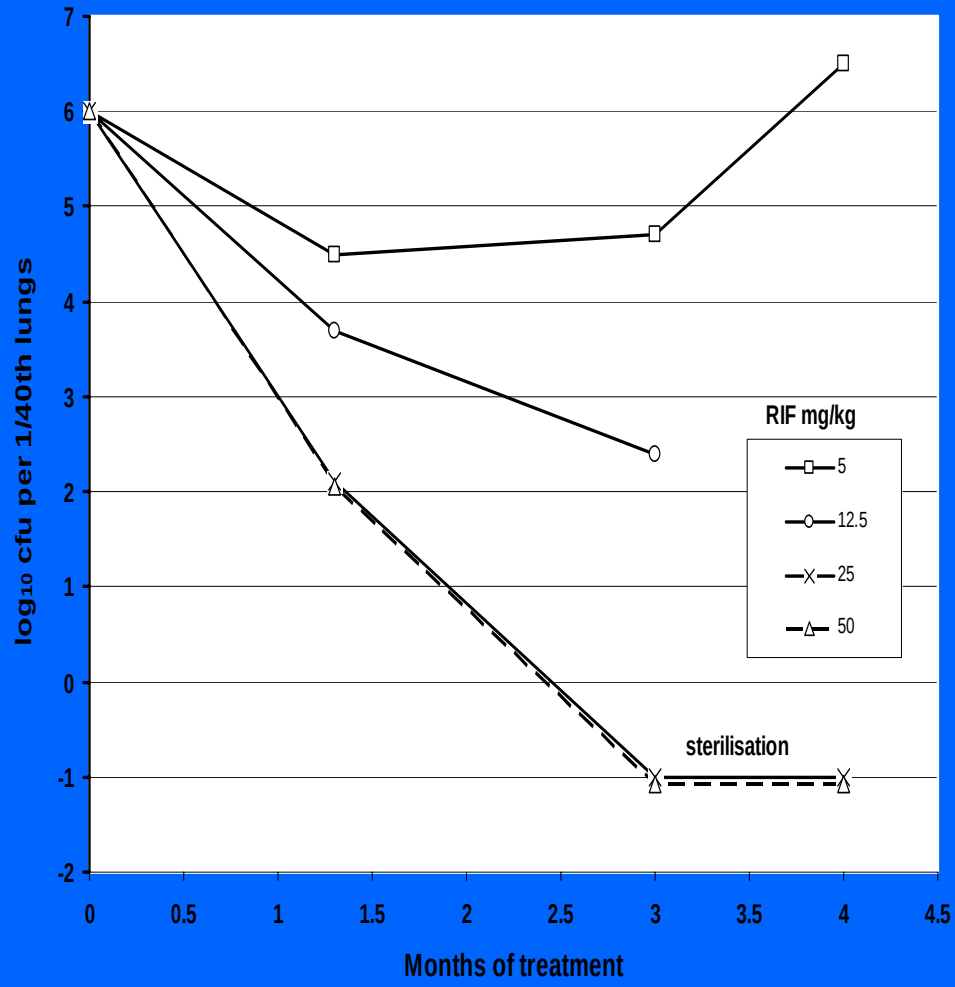
Regimen	R450	R600	R750
C+ at 12 weeks	**12%**	7%	6%
C+ at 20 weeks	7.7%	0.5%	0.9%
Failures	10	0	1
Relapses	1	2	0

Long MW, Snider JR. D, Farer LS. 1979. USPHS Cooperative Trial of Three Rifampicin-Isoniazid Regimens in Treatment of Pulomnary Tuberculosis. Am. Rev. Resp. Dis. 119:879-894.

Dosage effect

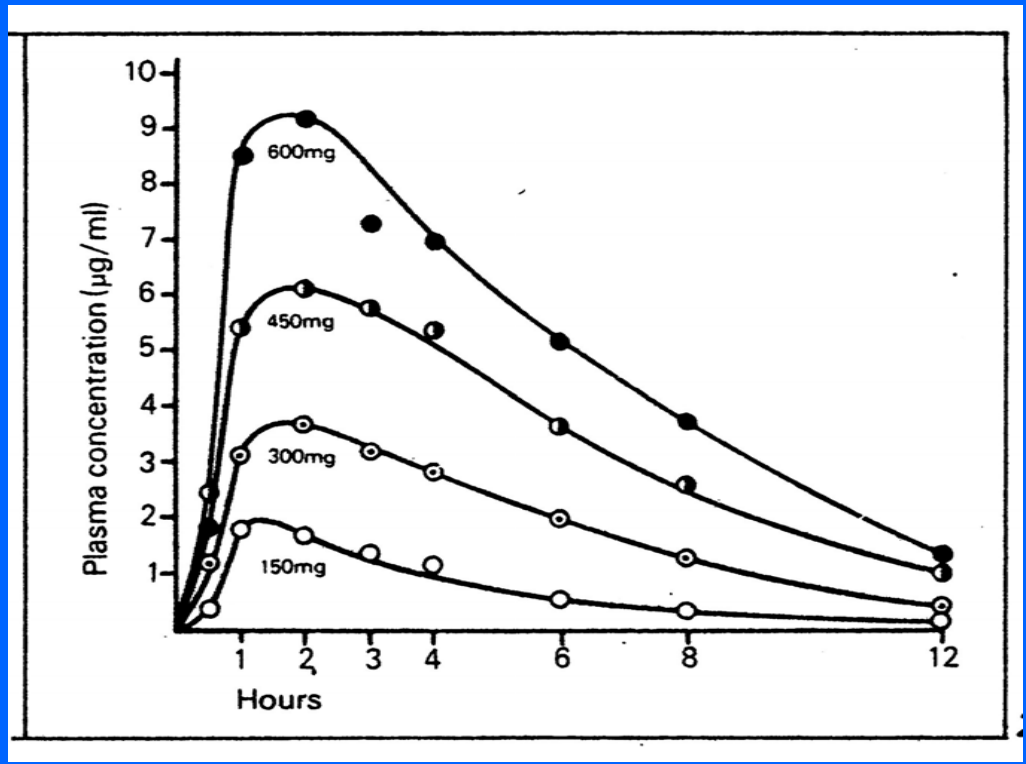
Medium	Publication
In vitro	**Dickinson JM, Jackett PS, and Mitchison DA. 1972. The effect of pulsed exposures to rifampicin on the uptake of uridine – C by *Mycobacterium tuberculosis*. Am Rev Respir Dis; 105:519-27**
Mice	**Verbist L and Gyselen A. 1968. Antituberculous activity of rifampicin *in vitro* and *in vivo* and the concentrations attained in human blood. Am Rev Respir Dis; 98:923-32**
Guinea pigs	**Dickinson JM and Mitchison DA. 1970. Suitability of rifampicin for intermittent administration in the treatment of tuberculosis. Tubercle; 51:82-94**

Studies in Mice



Grumbach F. L'activite de la rifampicine sur la tuberculose experimentale de la souris. Antibiotica et Chemotherapia, Kargel 1970; 16:392-405

Rifampicin PK Study



Acocella 1978. Clinical pharmacokinetics; 3:108-127

Rifampicin in the sputum

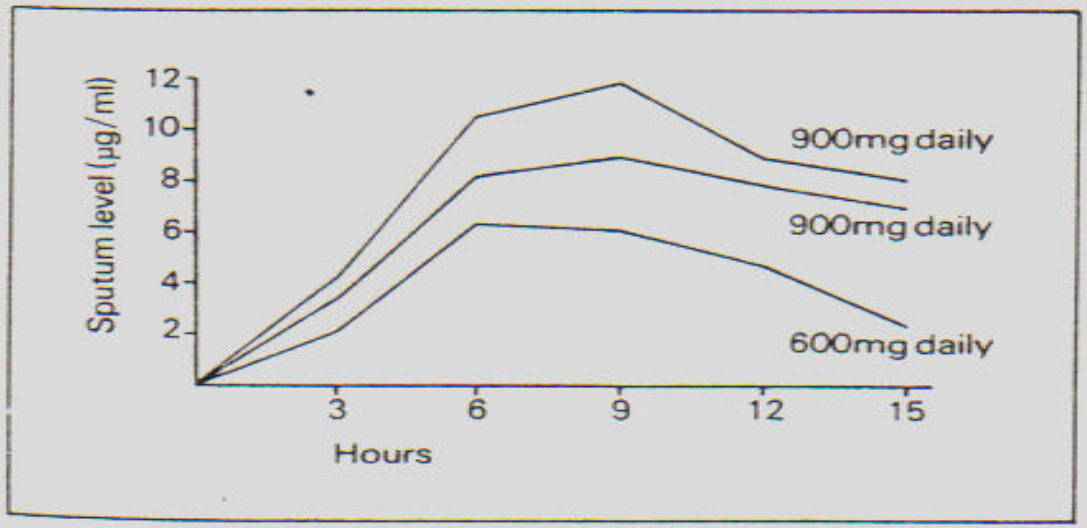


Fig. 7. Rifampicin concentrations (µg/ml) in the sputum of 3 tuberculosis patients treated with a daily dose of 600 and 900mg of the antibiotic (after Binda et al., 1971).

Acocella 1978. Clinical pharmacokinetics; 3:108-127

Jindani EBA Study

Regimen		Number	Fall in colony count (log10 cfu/day)		
			Days		
Drug	Dosage		0 to 2	2 to 14	0 to 14
R	5 mg/kg	3	0.06	0.08	0.09
R	10 mg/kg	8	0.19	0.1	0.110
R	15 mg/kg	8	0.41	0.15	0.180
	p		<0.05	NS	<0.05

Culture conversion

Dosage	1 month	2 month	3 month	Publication
600 mg	29%	73%	94%	East African/British Medical Research Councils. 1972. Controlled clinical trial of short-course (6-month) regimens of chemotherapy for treatment of pulmonary tuberculosis. Lancet;i:1079-1085.
1200 mg	72%	94%	98%	Kreis B, Pretet S, Birenbaum J, Guibot P, Hazeman JJ, Orin E, Perdrizet S and Weil J. 1976. Two three-month treatment regimens for pulmonary tuberculosis. Bull Int Un Tuberc; 51:71-75

Blood levels and response to treatment

Patient No.	R600 (µg/mL)	R900 (µg/mL)	R1500 (µg/mL)
1	1.5	9.2	
2	5.9	14.4	
3	<1.0	9.9	
4	<1.0	1.04	20.28
5	<1.0	13.8	
6	3.54	15.21	

Mehta et al. 2001. Chest: 120: 1520

Low Plasma Rifampicin and Failure of Culture Conversion

- Van Crevel R et al. 2002. Low plasma concentrations of rifampicin in tuberculosis patients in Indonesia. Int J Tuberc Lung Dis; 6:497-502

- Mehta JB, et al. 2001. Utility of rifampin blood levels in the treatment and follow-up of active pulmonary tuberculosis patients who were slow to respond to routine directly observed therapy. Chest; 120:1520-24

- Kimmerling ME, Phillips P, Patterson P, Hall M, Robinson CA and Dunlap NE. 1998. Low serum antimycobacterial drug levels in non-HIV-infected tuberculosis patients. Chest; 113:1178-83

Possible reasons for low Rif serum levels

- 85% is plasma bound
- Malabsorption
- HIV co-infection
- High fat meal

Study A
Reported side effects leading to interruption of treatment

Side effect	2EHRZ/6EH	2(EHRZ)$_3$/6EH	2EHRZ/4HR
Hepatic	7	1	4
Gastric	4	0	3
Cutaneous	2	2	1
Neurological	0	2	0
Ocular	2	1	1
T'cytopaenic purpura	0	1	0
Treatment interrupted	15	7	9
Total starting treatment	456	465	433

Adverse reactions

Regimen	Total	R450	R600	R750
ARs	27(3.3%)	4	10	13
SGOT	8	1	5	2
Jaundice	8	1	3	4

Long MW, Snider JR. D, Farer LS. 1979. USPHS Cooperative Trial of Three Rifampicin-Isoniazid Regimens in Treatment of Pulomnary Tuberculosis. Am. Rev. Resp. Dis. 119:879-894.

Association with hepatotoxicity

- Sarma GR, Immanuel C, Kailasam S, Narayana ASL and Venkatesan P. 1986. Rifampin-induced release of hydrazine from isoniazid. A possible cause of hepatitis during treatment of tuberculosis with regimens containing isoniazid and rifampin. Am Rev Respir Did; 133:1072-75.

  Hepatotoxicity linked to acetylator phenotype.

- Pande JN, Singh SPN, Khilnani GC and Tandon RK. 1996. Thorax;51: 132-36.

  Hepatotoxicity linked to acetylator phenotype, age and alcohol consumption.

Dosages of rifampicin

Disease	600mg	900mg	1200mg	1500mg	1800mg
Tuberculosis	✓	✓	✓	✓	✓
Brucellosis	✓	✓	✓		
Staph. spp.		✓			
Cutaneous Leishmaniasis			✓		

The problem of drug-drug interaction

- WHO recommendations
  - Alternative drugs
  - TB treatment first
- Advantages of shorten durations

An interesting 3-month regimen

Regimen 1g streptomycin 900mg isoniazid 1200mg rifampicin	Number of patients	Cult. Neg at end of treatment (%)	Relapses at the end of first year post treatment
Daily	47	100	14.9
Alternate days	44	97.9	11.4

Kreis B, Pretet S, Birenbaum J, Guibot P, Hazeman JJ, Orin E, Perdrizet S and Weil J. 1976. Two three-month treatment regimens for pulmonary tuberculosis. Bull Int Un Tuberc; 51:71-75

Increasing Doses of Rifampicin
Sequence of trials

- Phase IIa – EBA + toxicity
- Phase IIb – Culture conversion + toxicity + PK + interaction
- Phase III – Relapse + toxicity + PK

An interesting point of view

Experimental data that higher doses of rifampicin could realistically shorten therapy

TO ONE OR TWO MONTHS

would be much more compelling for investing in rifampicin than if the potential benefit appears to be limited to only shortening therapy

BY ONE OR TWO MONTHS

Gerald J. Siuta, Ph.D., Consultant, Business Development, Global Drug Alliance for TB Drug Development

The TRC Trial

REGIMEN	NUMBER	Relapsed	
		No.	(%)
3OHRZ	83	7	(8)
3OHRZ/1HRtw	81	3	(4)
3OHRZ/2HRtw	86	2	(2)
2OHRZ/2HRtw	91	12	(13)

Tuberculosis Research Centre. (Indian Council of Medical Research), Chennei. 2002. Ind J Tub; 49:27-38

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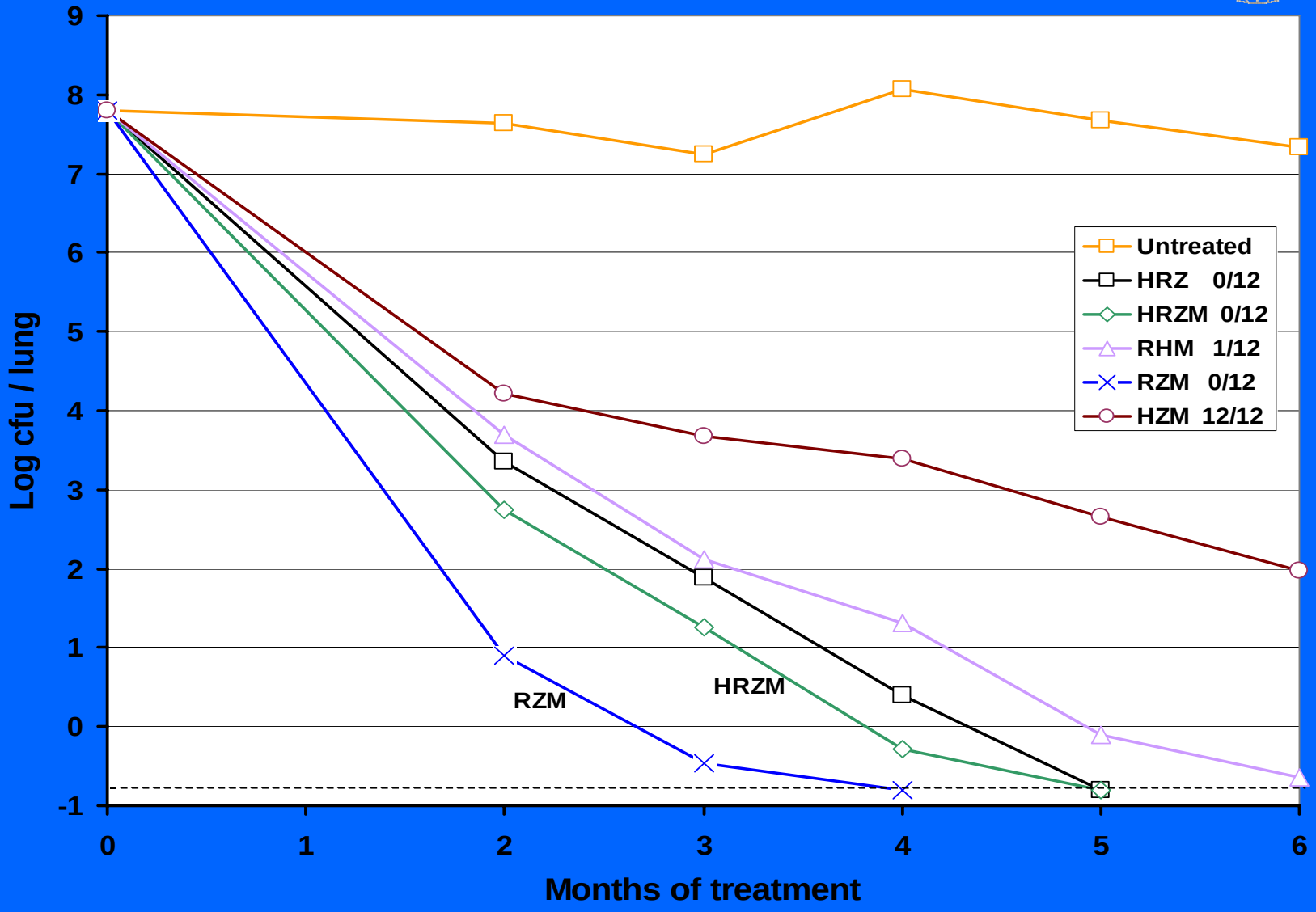
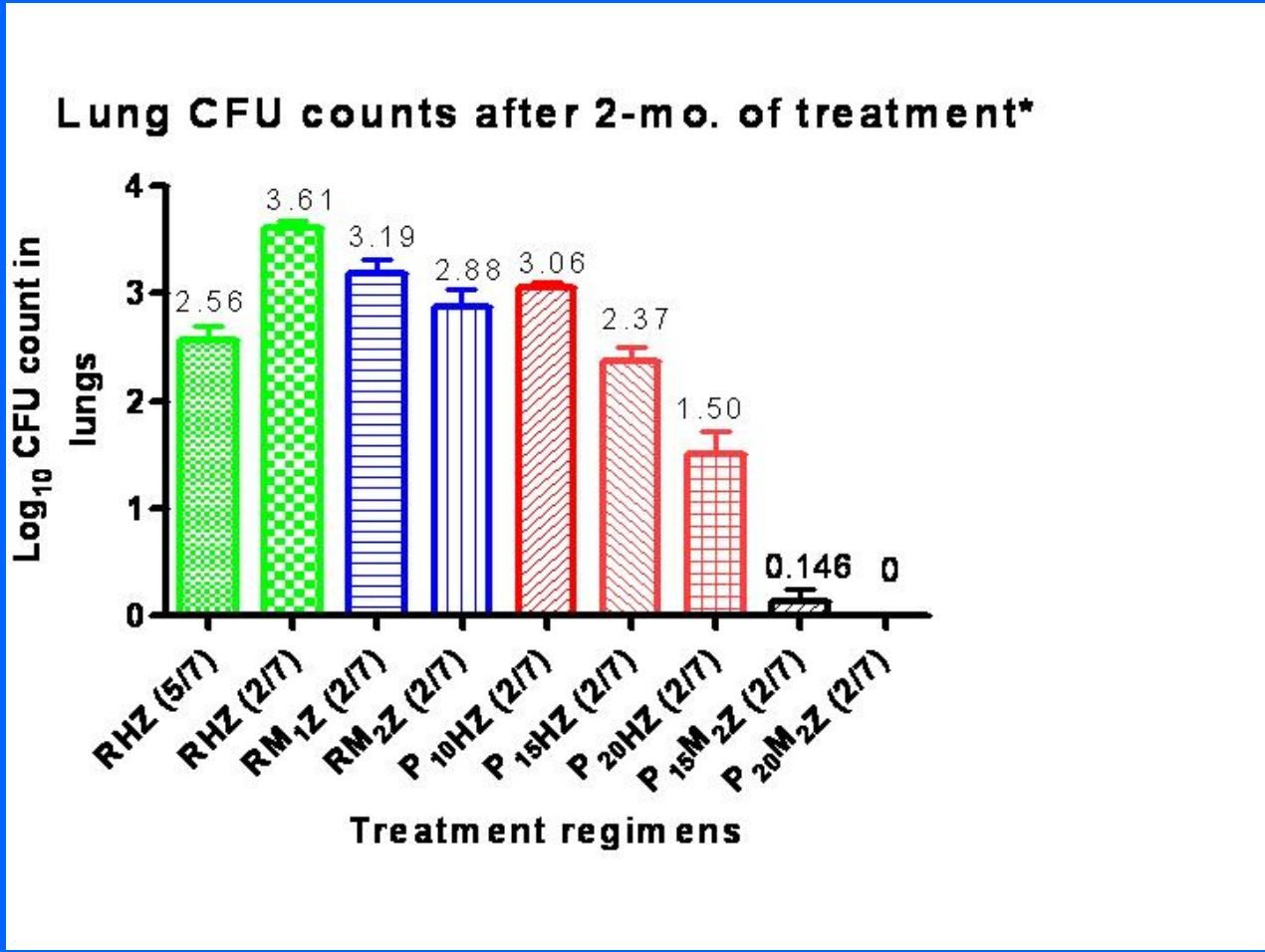
Grosset mouse experiment

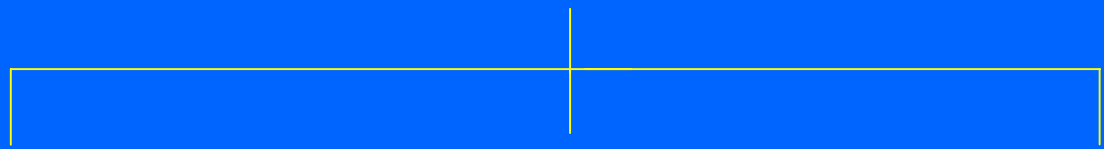


Grosset mouse experiments II



Trial Design

Randomisation



Test arm 1
$2EMRZ/2(PM)_2$

Test arm 2
$2EMRZ/4(PM)_1$

Control
2EHRZ/4RH

Rpe 15 mg/kg + Moxifloxacin 500 mg (TW)
Rpe 20/kg mg + Moxifloxacin 500 mg (OW)
Rifampicin 600 mg + INH 300 mg

Participating centres

CENTRE	Numbers allocated
Cape Town	210
Johannesburg	310
Harare	270
Marondera	150
Maputo	200
Macha	110
TOTAL	1250