

Beta-lactams Against TB: Teaching a New Trick to an Old Dog

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Require new anti-TB agents

- New or repurposed
 - No resistance
- Low potential for interactions
 - Rifampin, antiretrovirals
- Preferably no QT prolongation
- To partner with other novel drugs
 - New “universal” regimen

Beta-lactam Class: Carbapenems

- High intrinsic resistance against MTB blaC
- Active against resistant MTB in vitro
- Anecdotal success as part of XDR-TB regimens
- Many marketed compounds
 - Frequently used for bacterial infections
 - Excellent safety record

Hugonnet et al. *Science* 2009;323:1215. England et al. *AAC* 2012;56:3384. Gonzalo et al. *JAC* 2013;68:366. Dauby et al. *Pediatr Infect Dis J* 2011;30:812. Payen et al. *Int J Tuberc Lung Dis* 2012;16:558. De Lorenzo et al. *Eur Respir J* 2013;41:1386

Preclinical: Carbapenems and Amx/Clv

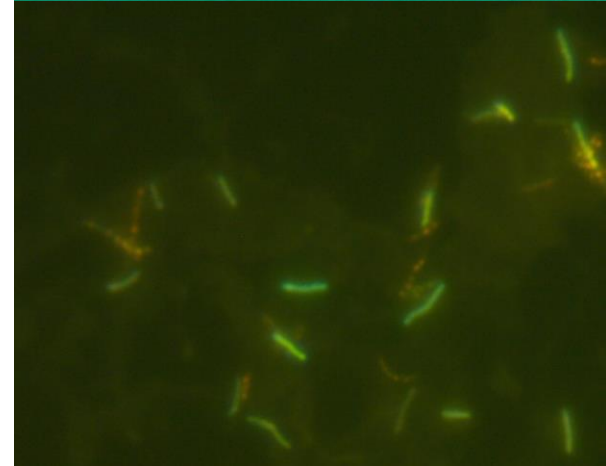
MIC against H37Rv

- intrinsically low in carbapenems
 - faropenem (orally available)
 - meropenem (only intravenous)
 - clavulanic acid decreases MIC
 - amoxicillin decreases MIC of combination
- No mouse model

	MIC H37Rv ug/ml	
	-	2.5ug/ml Clav
Faropenem	1.25	0.63
Meropenem	2.5	0.6
Amoxicilina	40	1.25

Proof of concept in TB patients

- Can beta-lactams be anti-TB drugs?
- 14-day early bactericidal activity study
 - Single site and laboratory in Cape Town
 - Sputum smear-positive, drug-sensitive TB patients
 - Untreated , no significant co-morbidities
 - Hospitalised for study
- 3 groups of 15 subjects
 - Faropenem 600mg po + A/CA 500/125 po tid
 - Meropenem 2g iv + A/CA 500/125 po tid
 - Control HRZE

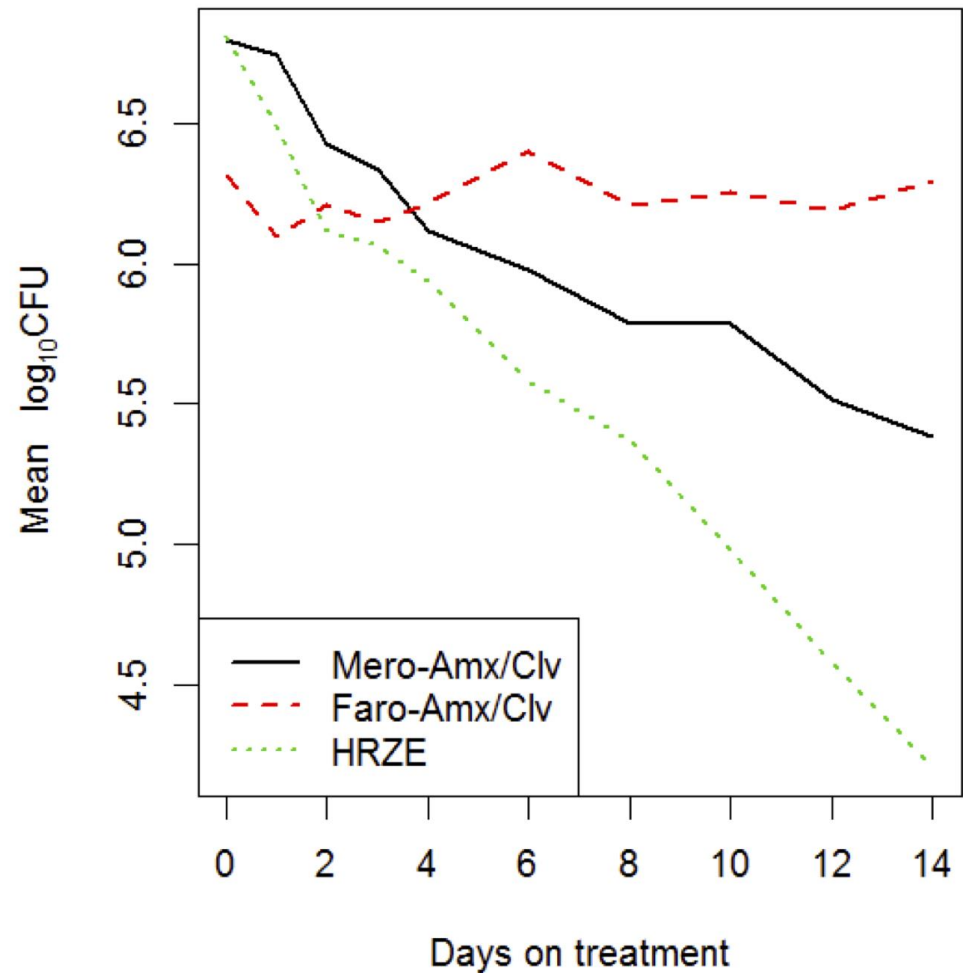


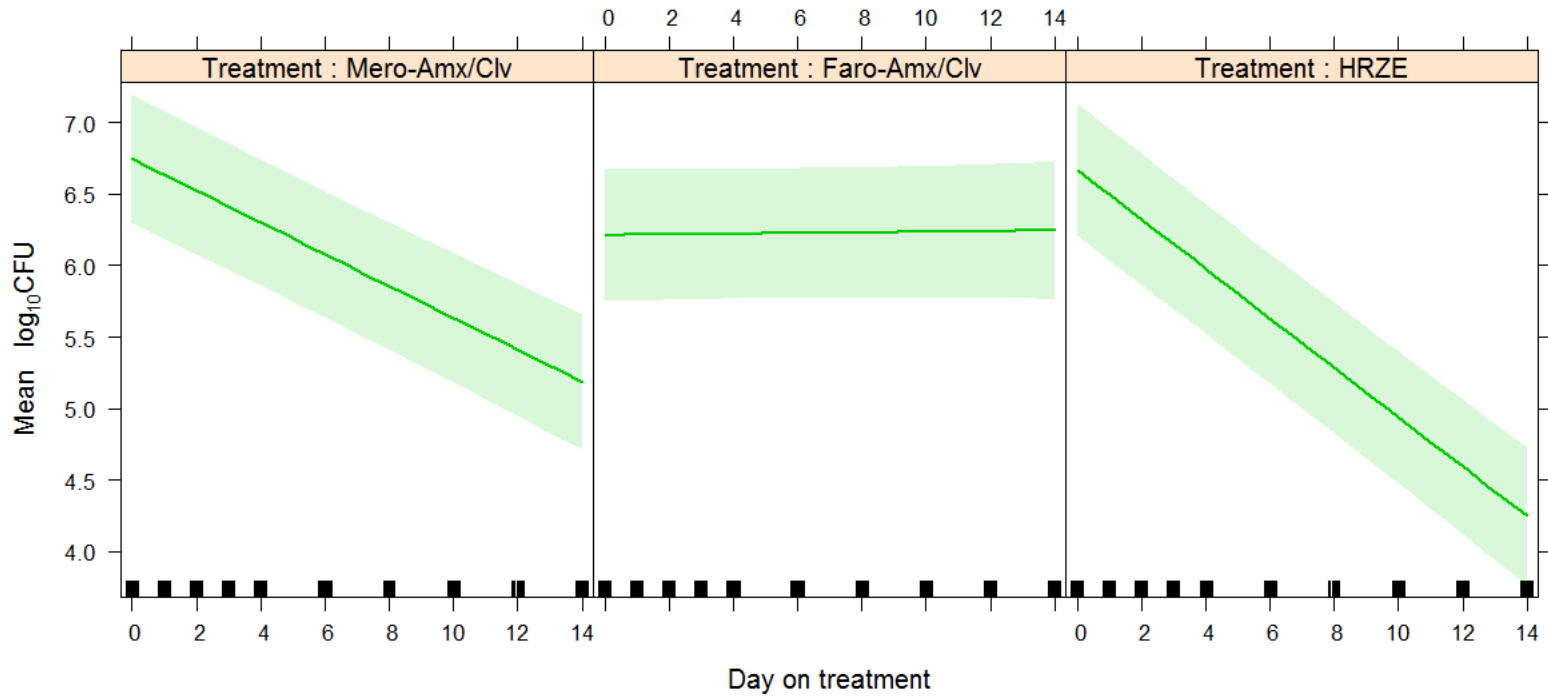
Demographics

	Control	Mero	Faro
Number	15	16	15
Age (yrs), median	31.0	29.5	27.0
Male, n (%)	11 (73%)	12 (75%)	13 (87%)
BMI (kg/m ²), median	18.7	19.0	19.2
HIV positive, n (%)	3 (20%)	1 (6%)	3 (20%)
Baseline log ₁₀ CFU, median	6.63	6.86	7.04
Baseline TTP (h), median	101.4	100.2	82.7

No significant differences between groups

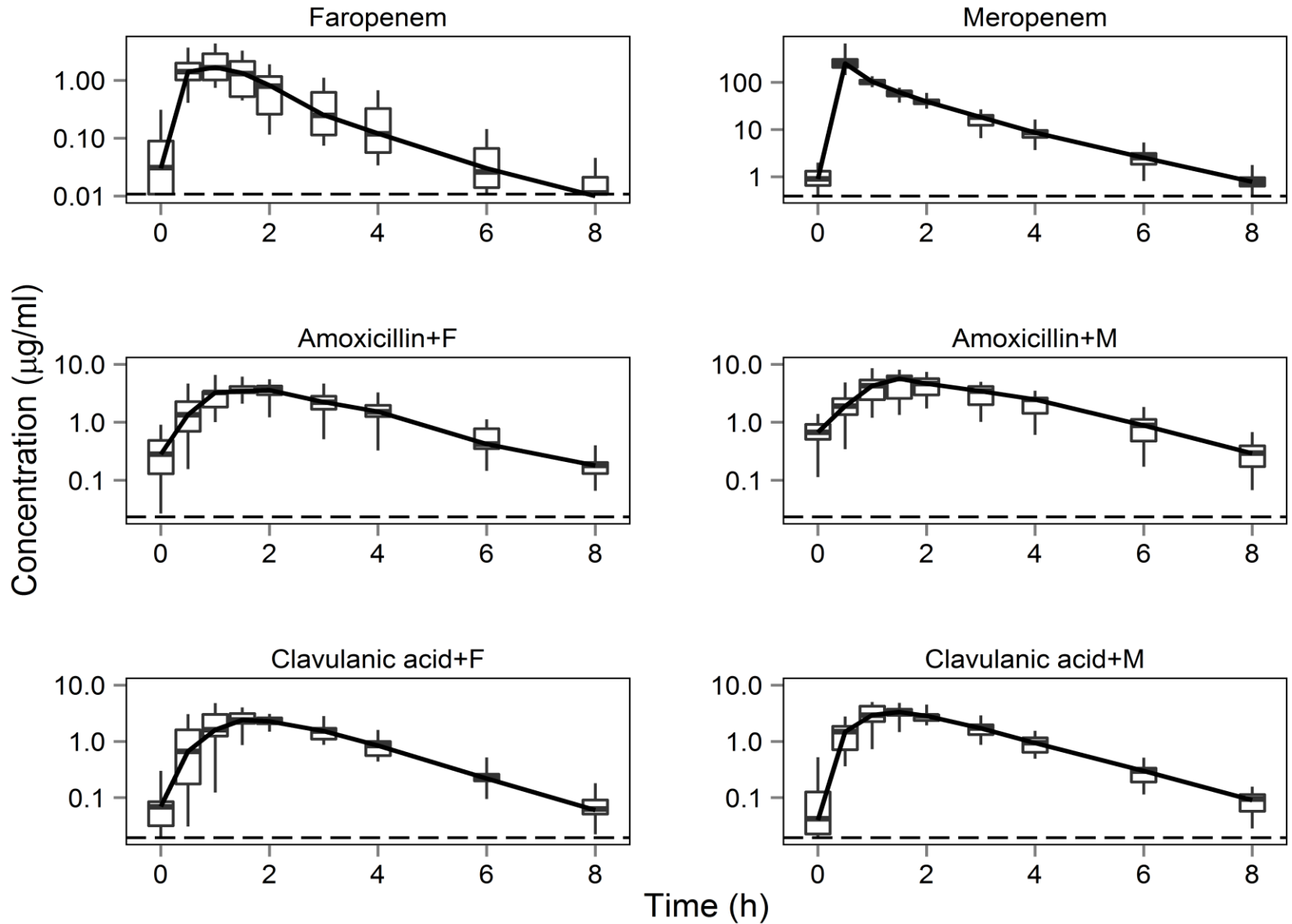
Observed means of \log_{10} CFU





Treatments	Estimated fall in log ₁₀ CFU (95% CI)	P-value vs no effect	P-value vs HRZE control
Mero Amx/Clv	0.11 (0.09 to 0.13)	< 0.001	< 0.001
Faro Amx/Clv	0.00 (-0.02 to 0.02)	0.799	< 0.001
HRZE	0.17 (0.15 to 0.19)	< 0.001	

Pharmacokinetic profiles on day 14



Adverse events

Events	HRZE	Mero A/CA	Faro A/CA
SAE (withdrawn)	2 (1)	0	1 (1)
Grade 3 and 4	2	0	2
Grade 1+2 events	32	53	26
- Diarrhea	1	9	11

Control: 1 patient: Acute liver failure on subsequent HRZE treatment
1 patient: DVT

Faro: 1 patient: Central nervous symptoms, withdrawn for exclusion of TB meningitis

Agents currently in use or in clinical development

	Year	EBA 0-14
RIF 35mg/kg	2015	0.26
INH 5mg/kg	1980	0.19
Meropenem iv Amx/Clv	2016	0.11
RIF 10mg/kg	1980	0.11
PZA 2g	1980	0.11
PA-824 200mg (pretomanid)	2010	0.11
BDQ 400mg (bedaquiline)	2013	0.10
PNU-100480 600mg bd (sutezolid)	2014	0.08
OPC-67683 50-200mg (delamanid)	2011	0.04
Faropenem po Amx/Clv	2015	0.00

Conclusions

- Beta-lactams are antituberculosis agents
 - Meropenem Amx/Clv iv tid for selected cases
 - Amx/Clv essential?
- Once daily treatment?
 - Ertapenem i.v. or i.m. ±Amx/Clv
 - Registered in SA
 - Proof of activity -> clinic
- Orally bioavailable agent
 - Faropenem medoxomil?
 - Not registered anywhere
 - Need investigator's brochure to persue further



- Grant participants
 - TASK/Stellenbosch University, South Africa
 - Diseases of the Developing World, GSK, Spain
 - Research Center Borstel, Germany
 - Manhica Health Research Centre, Mocambique
 - Barcelona Centre for International Health Research, Spain



