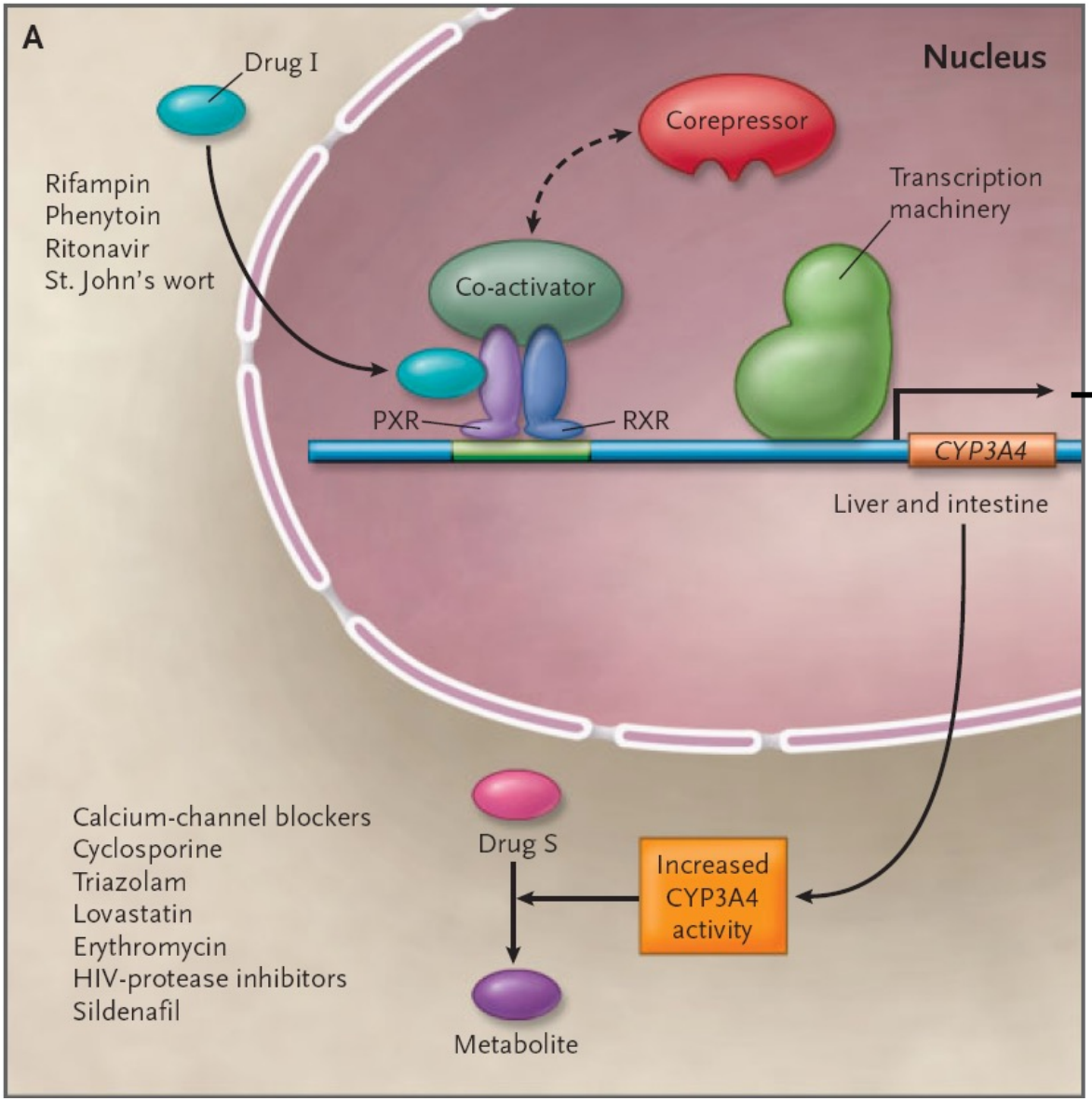
Drug-drug interactions ART & TB treatment

Gary Maartens

Division of Clinical Pharmacology
UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

PXR-RXR mechanism of enzyme induction



OTHERS ↑

Phase I
CYP2B6
CYP2C8/9

Phase II
UGT
GST

Transporters
P-glycoprotein
BCRP

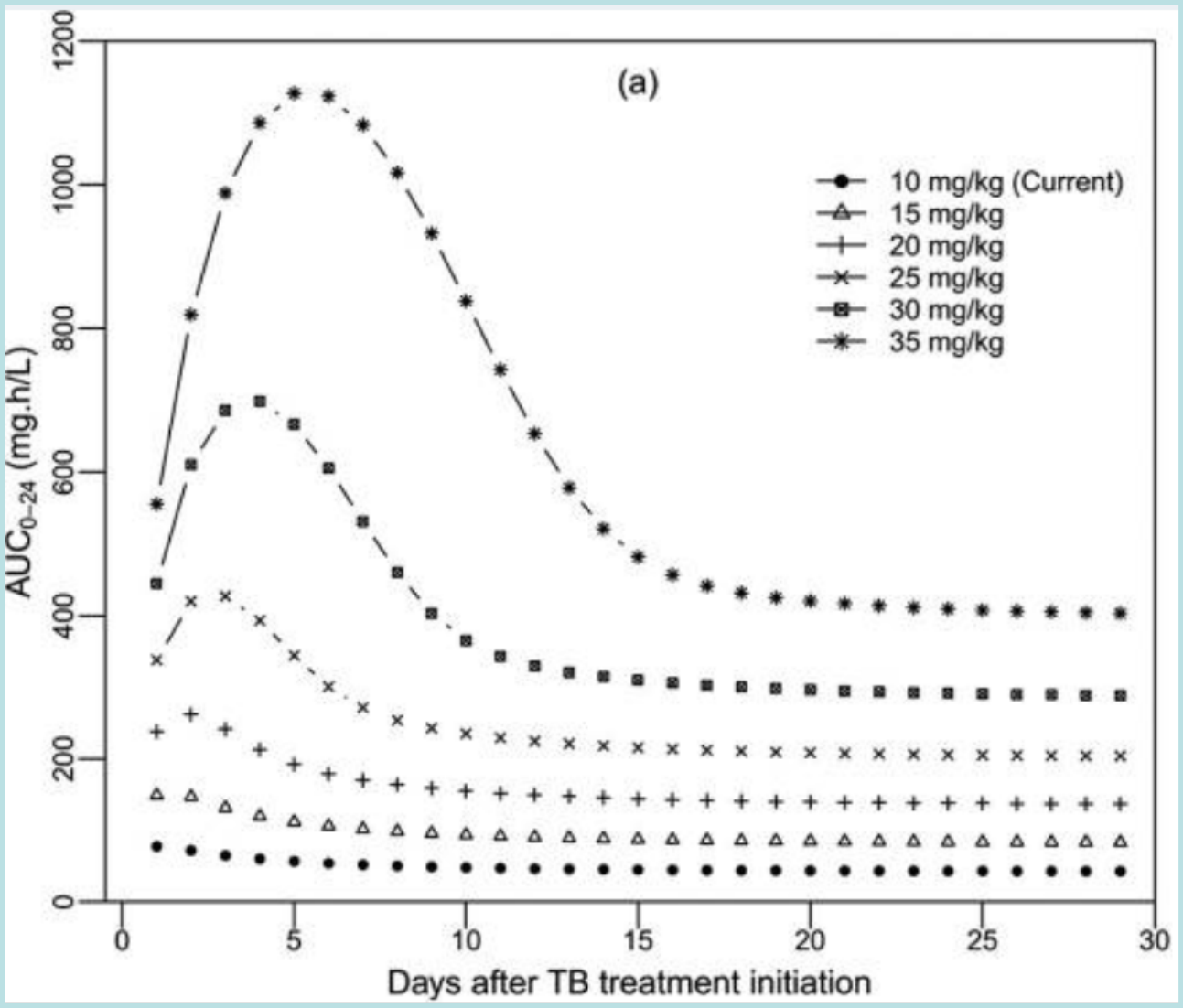
NEJM 2005;352:2211
Chen 2006

Rifampicin induction

Enzyme/transporter	**ARV substrate**
CYP3A4 (55.1-fold) CYP2B6 (8.8-fold)	PIs, NVP EFV, NVP
P glycoprotein	PIs
UGT1A1	Raltegravir Dolutegravir

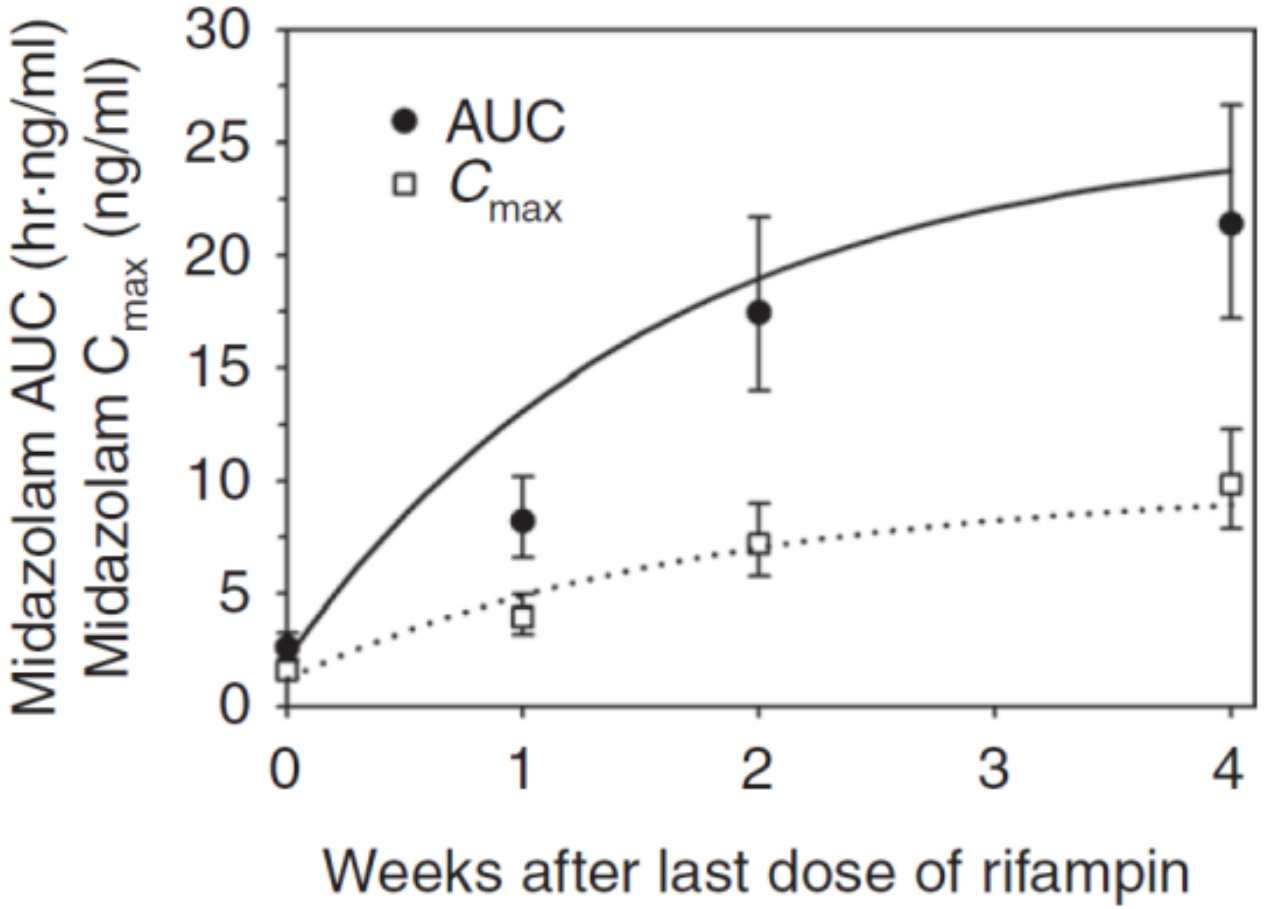
J Pharmacol Exp Ther 2001;299:849

Time course of rifampicin autoinduction



AAC 2015;50:487

Time course of rifampicin induction waning



Clin Pharmacol Ther. 2011;89(2):234-42

TB Rx effect on EFV PK

Studies in patients with TB show no significant effect on EFV concentrations:

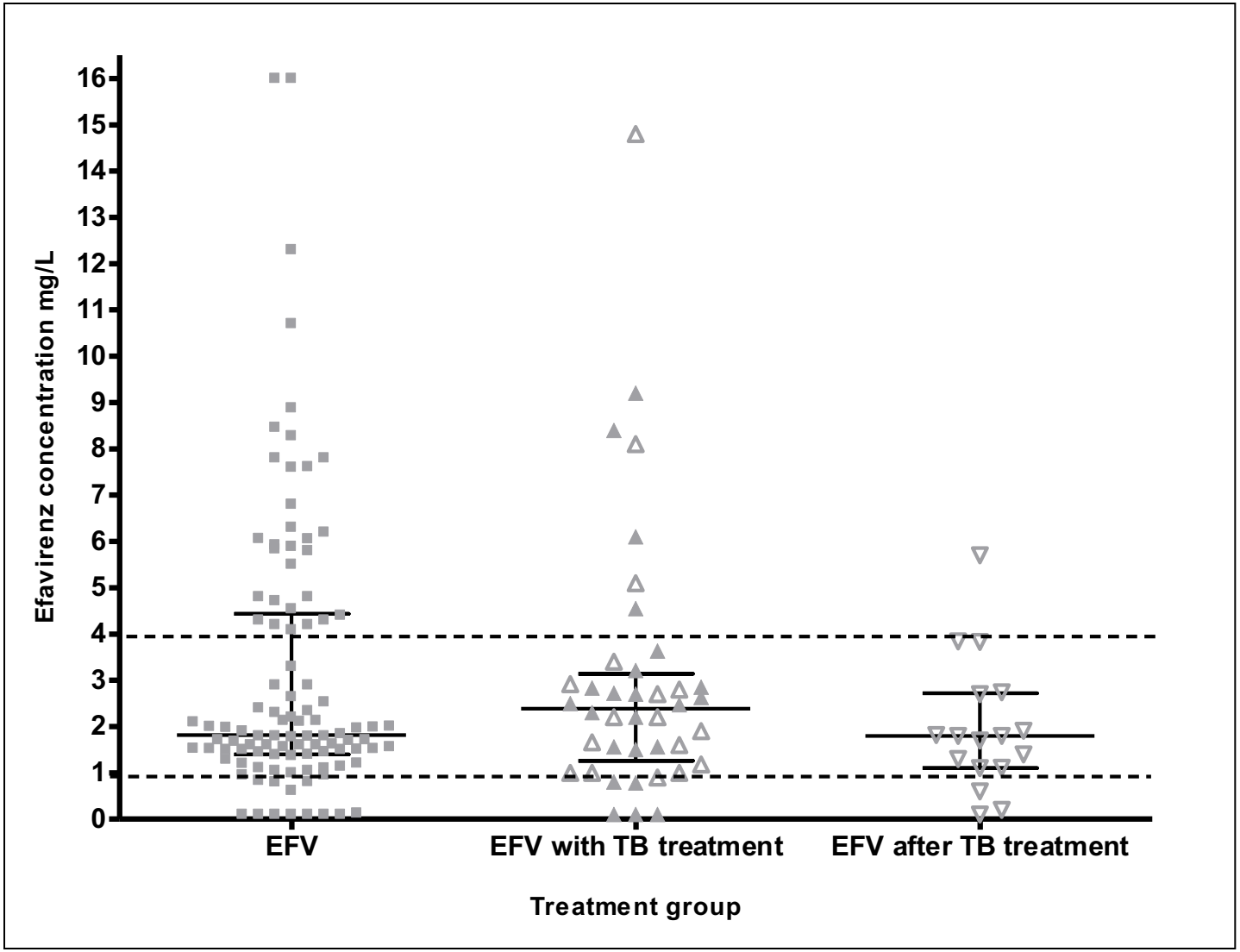
- Spain
- South African adults (2 studies) & children
- India
- STRIDE study

Package insert says AUC reduced 26% & recommends increase dose to 800 mg

- 12 healthy volunteers, only rifampicin, before maximal EFV autoinduction
- FDA recently reinforced this

Clin Pharmacokinet 2002;41:681
JAC 2006;58:1299
Antivir Ther 2009;14;687
JAIDS 2009;50:439
AAC 2009;53:863
Clin Infect Dis. 2013;57(4):586

Impact of rifampicin on efavirenz



Antivir Ther 2009;14;687

Eur J Clin Pharmacol (2012) 68:689–695
DOI 10.1007/s00228-011-1166-5

PHARMACOKINETICS AND DISPOSITION

The influence of tuberculosis treatment on efavirenz clearance in patients co-infected with HIV and tuberculosis

Tanuja N. Gengiah · Nicholas H. G. Holford · Julia H. Botha · Andrew L. Gray · Kogieleum Naidoo · Salim S. Abdool Karim

"Unexpectedly, concomitant rifampicin-containing tuberculosis treatment reduced apparent EFV clearance with a corresponding increase in EFV exposure."

EFV increases during TB Rx: pharmacogenomics

UCT PK study in children

- Genetic slow metabolisers in 20%
- EFV concentrations increased 49% on TB Rx in slow metabolisers
- Likely due to inhibition by INH of CYP2A6

STRIDE (ART @ 2 vs 8 weeks) substudy

- EFV concentrations increased 58% on TB Rx in slow metabolisers
- Exacerbated in NAT2 slow metabolisers

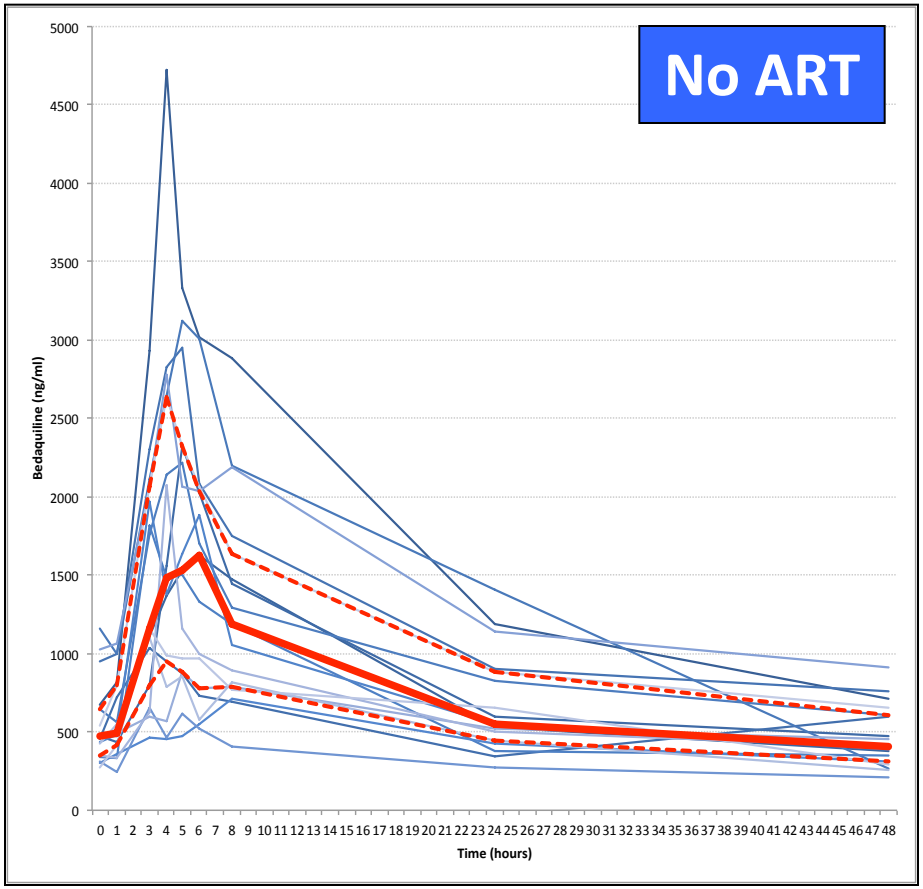
Clin Infect Dis. 2015;60:1860-3
AIDS. 2013 Jul 31;27(12):1933-40.

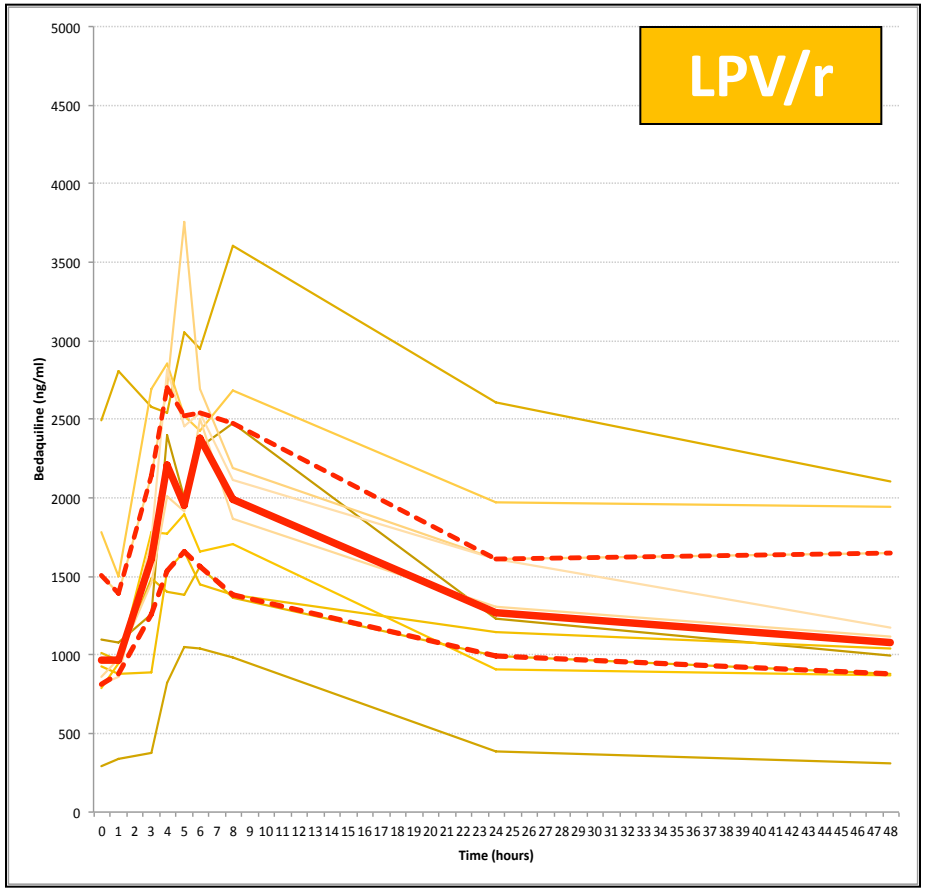
Bedaquiline

- Substrate of CYP3A4
- Lopinavir/r potent inhibitor CYP3A4
- Company did single dose drug-drug interaction study in healthy volunteers & concluded no significant effect
- Terminal half-life 5.5 months, so single dose studies misleading (pop-PK model estimated major interaction)

AAC 2014;58:6406

Bedaquiline	no ART	on LPV/r
Median Cmax in µg/ml (IQR)	1.97 (1.10–2.64)	2.49 (1.66 – 2.85) p=0.228
Median AUC_{48} in µg.hr/ml (IQR)	34.73 (27.47–52.83)	69.47 (54.68–88.26) **p=0.005**



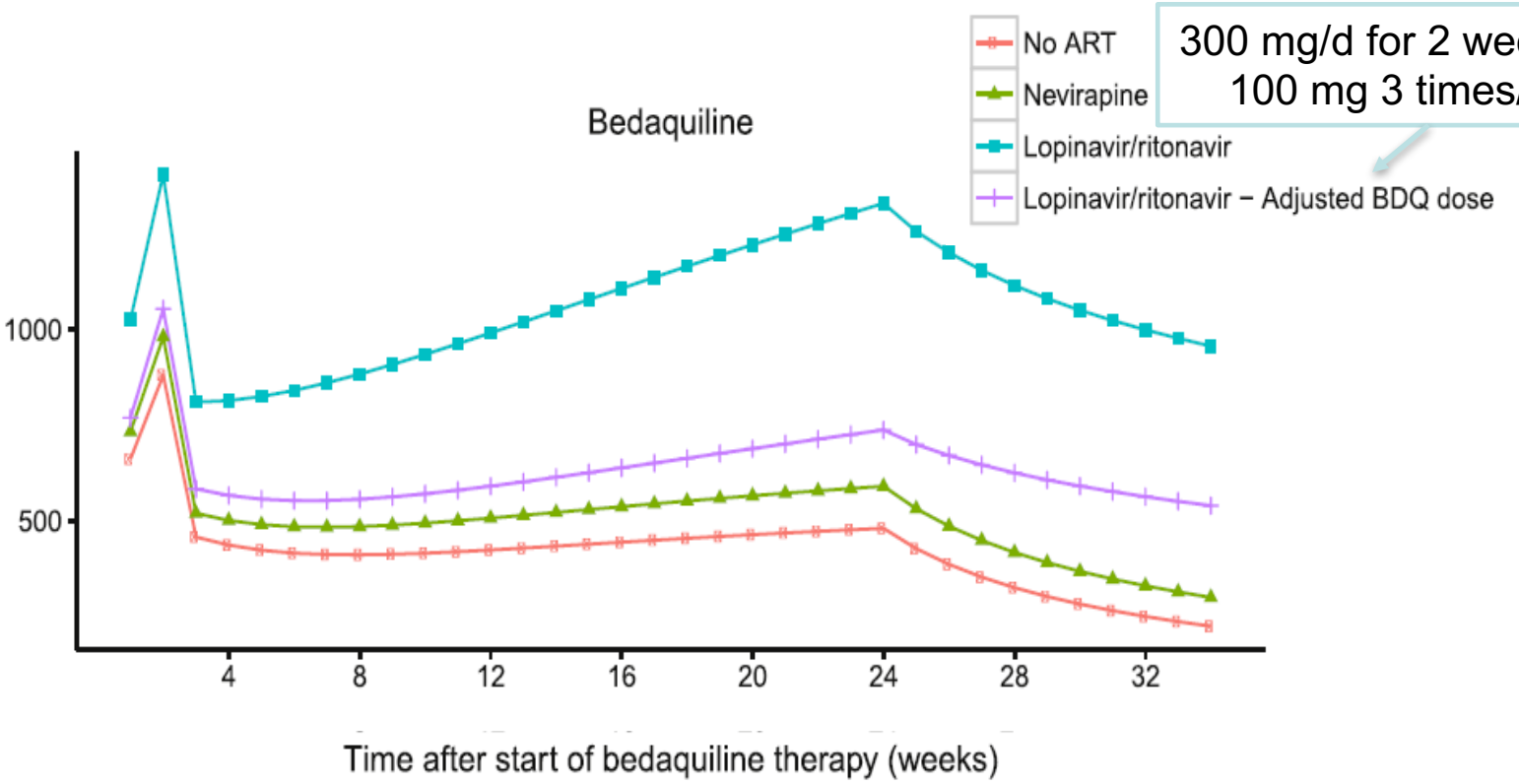


UCT Bedaquiline-LPV/r DDI study

- BDQ AUC increased 62% by LPV/r
- Participants sampled at different durations on BDQ
- Non-compartmental PK analysis unable to deal with this time effect
- Collaboration with group that developed the pop-PK model

JAC 2016;71:1037-40

Model using UCT data of BDQ concentrations with nevirapine & LPV/r



Confirmed model-predicted effects

Int J Antimicrob Agents 2017;49:212

Acknowledgements

Helen McIlleron design & analysis of DDI studies

Mishal Pandie did BDQ-ARV DDI study