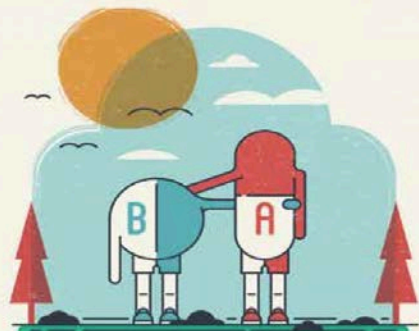
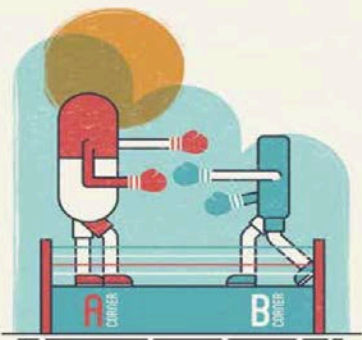


# Drug-drug interactions between Bedaquiline and the Antiretrovirals nevirapine and lopinavir/ritonavir in patients

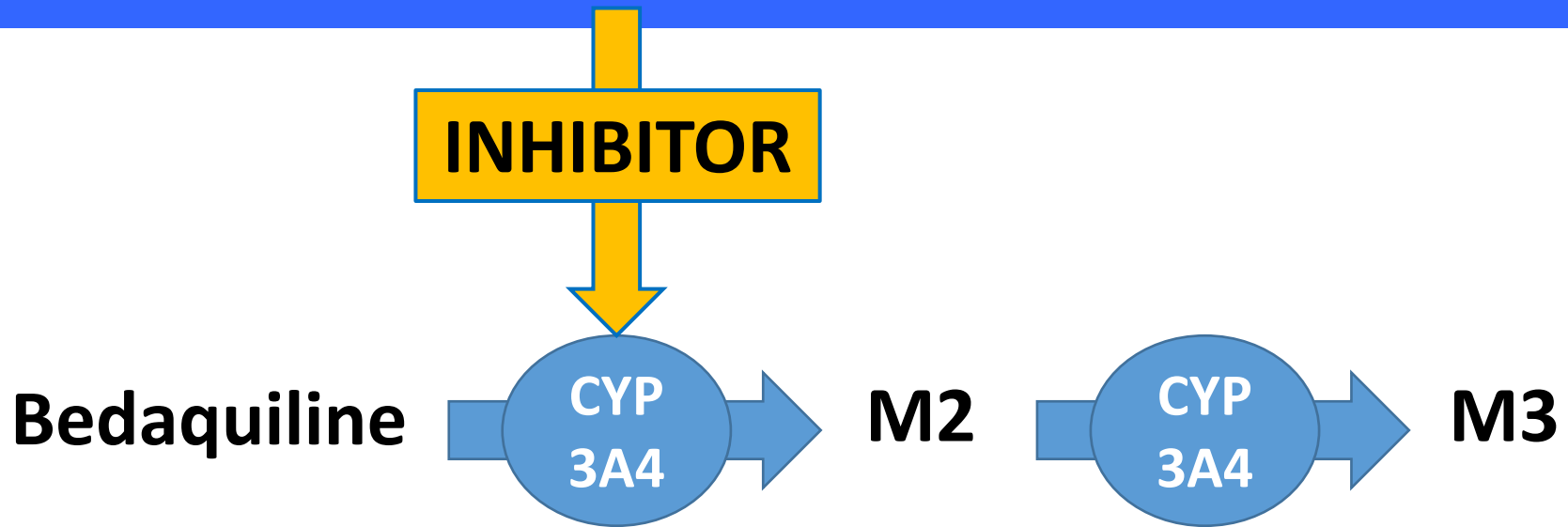
**Dr Mishal Pandie, Division of Clinical Pharmacology, University of Cape Town**  
**7th International Workshop on Clinical Pharmacology of Tuberculosis Drugs**  
**Washington DC, 2014**



# Bedaquiline (BDQ)

- First-in-class diarylquinoline antimycobacterial
- Terminal half-life: 5.5 months
- Bactericidal activity: Concentration dependent
- Toxicities: QT prolongation, phospholipidosis, raised hepatic enzymes

# Lopinavir/ritonavir (LPV/r)



Cross-over interaction study:

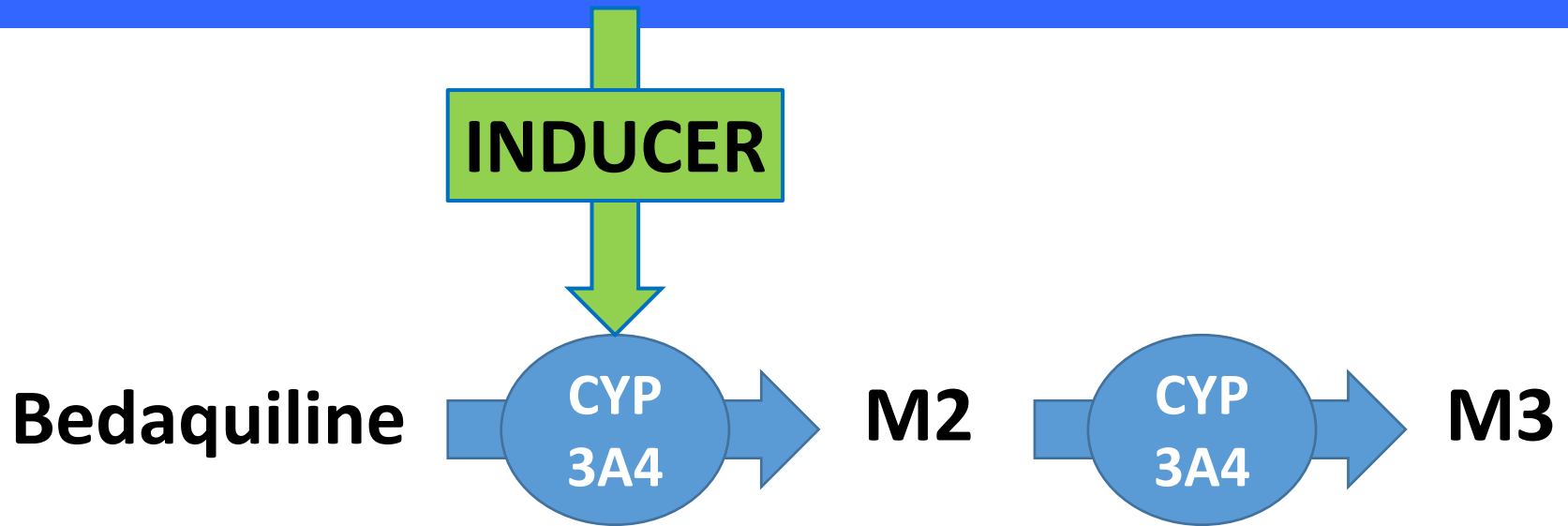
- 16 healthy adults
- Single-dose bedaquiline

→ **22% increase** BDQ AUC

Non-linear mixed effects  
population PK modelling:

→ decrease BDQ  
clearance by 35%

# Nevirapine



Cross-over interaction study:

- 16 HIV-1-infected adults
- Single-dose bedaquiline

→ **No change** in BDQ AUC

Van Heeswijk, et al. 2011

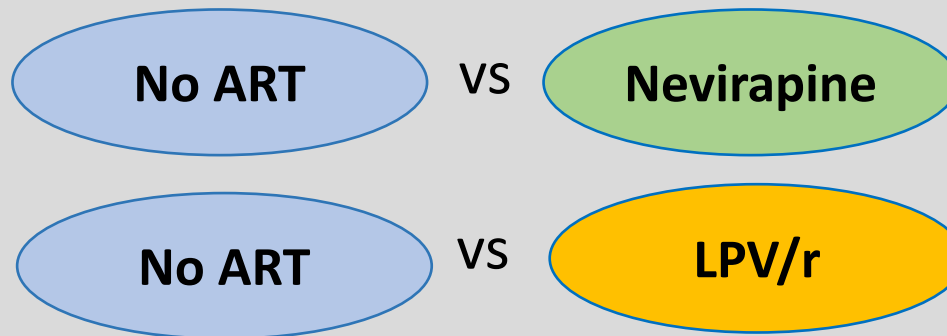
Non-linear mixed effects  
population PK modelling:

→ minimal impact on  
bedaquiline PK

Svensson, et al. 2013

# Study objective

Compare the pharmacokinetics (PK) of bedaquiline in patients not on antiretrovirals to patients on antiretrovirals (nevirapine and LPV/r) during the maintenance dose phase of bedaquiline treatment, in patients with drug-resistant tuberculosis.



# Study design

## Observational Pharmacokinetic study

### Inclusion:

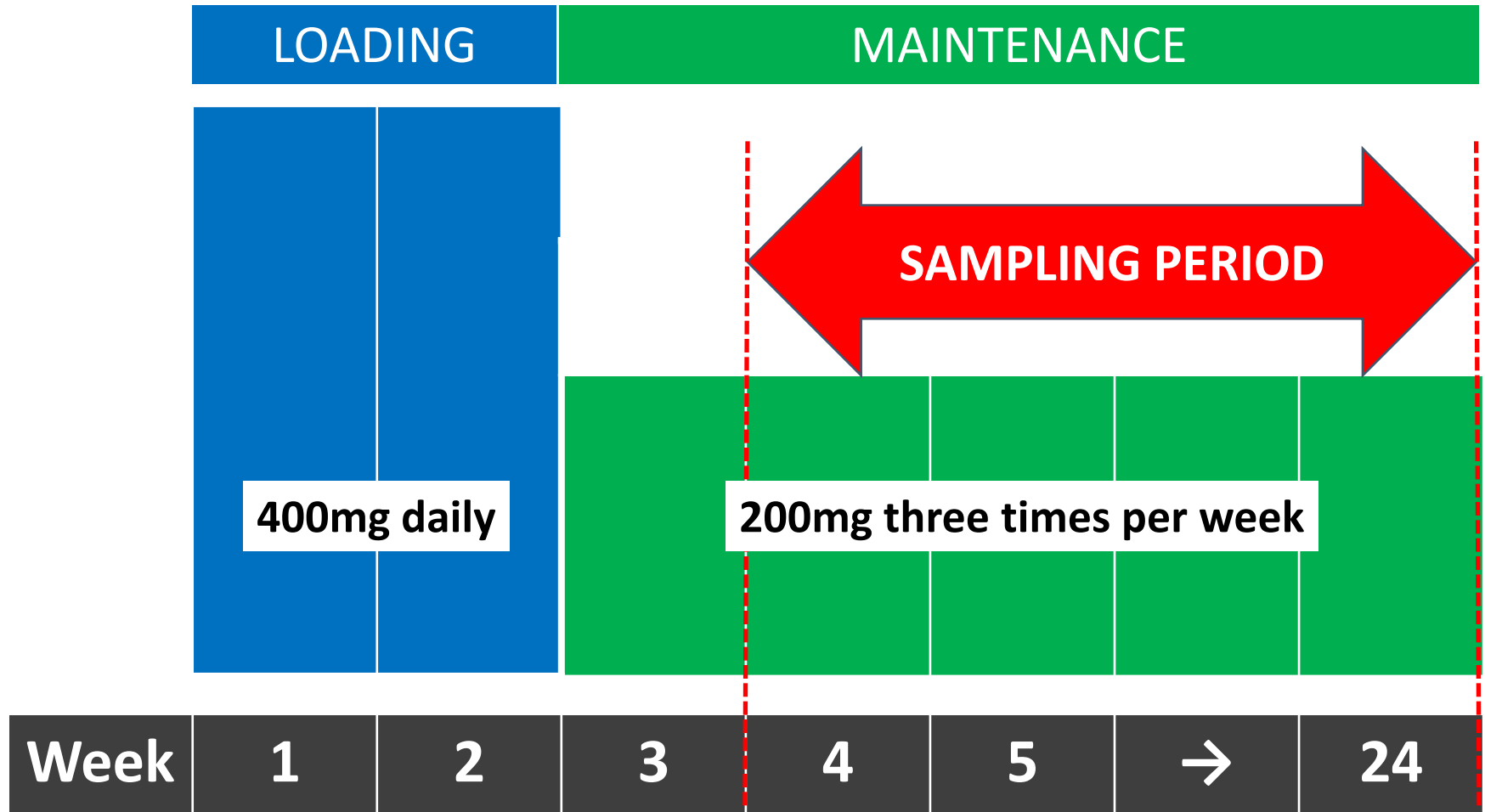
- Patients in SA Bedaquiline Clinical Access Program
  - bedaquiline for pre-XDR or XDR pulmonary TB
- On nevirapine > 2 weeks
- On LPV/r > 3 days

### Exclusion:

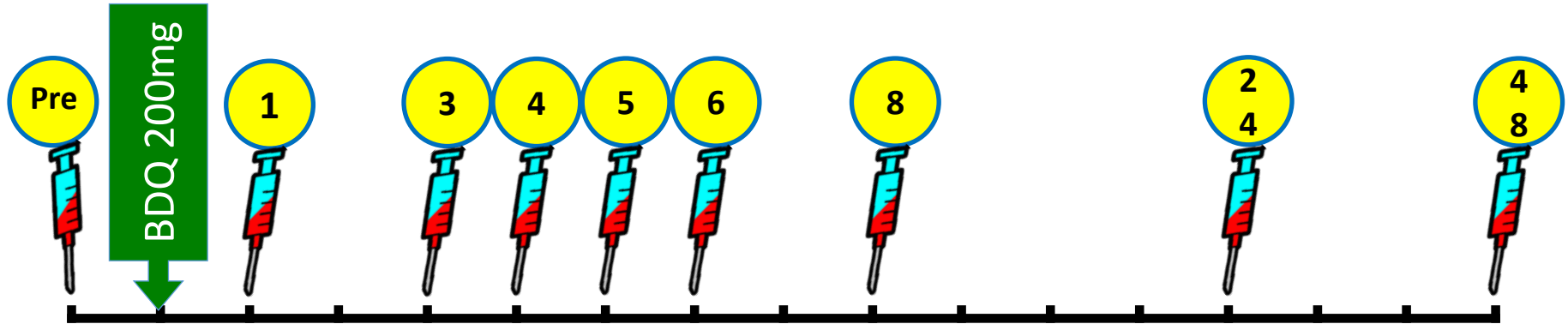
- Concomitant inducer or inhibitor of CYP3A4



# BDQ dosing and Sampling period



# Methods



Centrifugation and plasma storage at  $-70^{\circ}\text{C}$ .

Liquid chromatography – tandem mass spectroscopy.

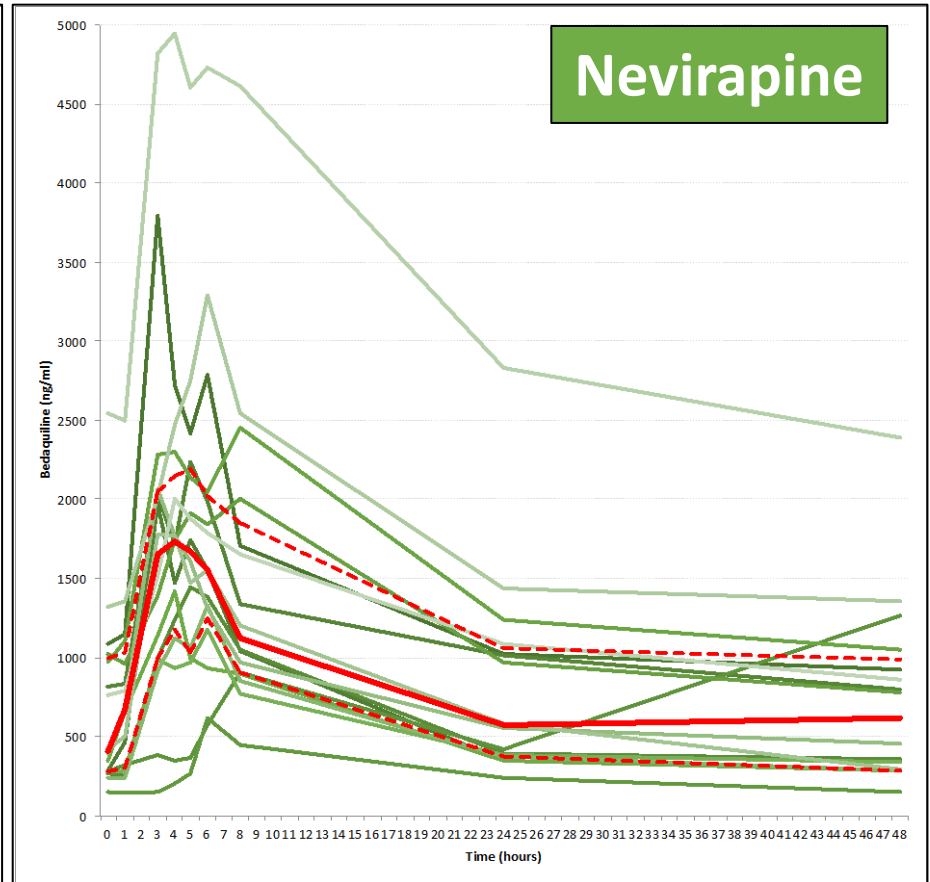
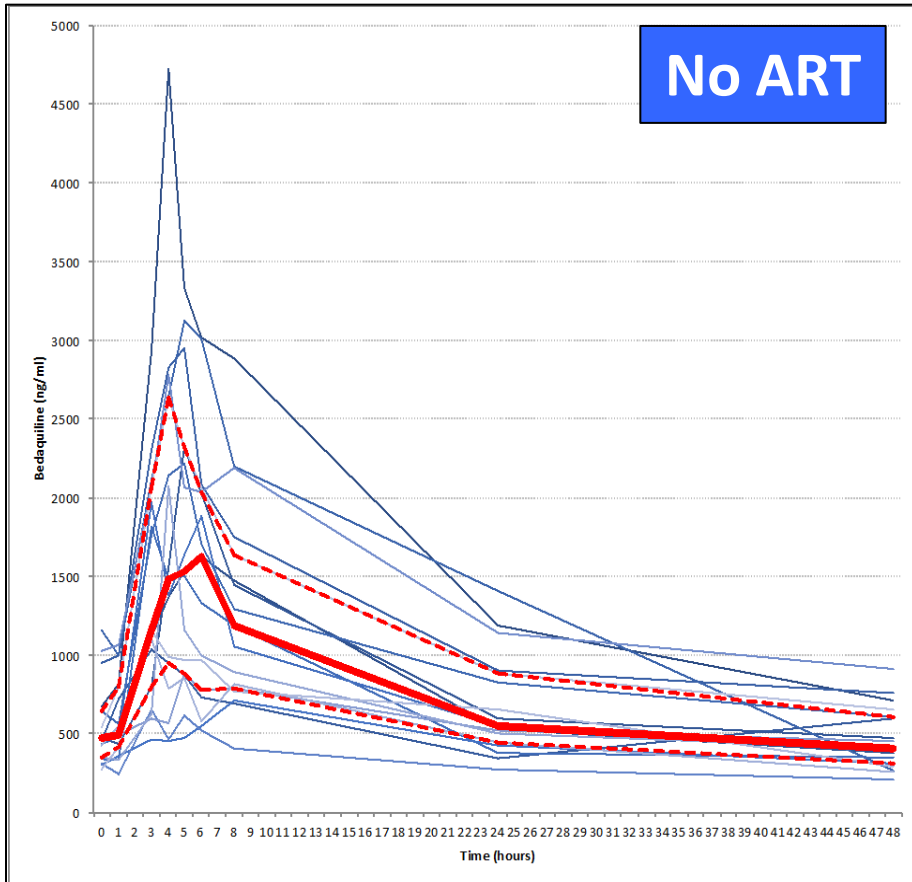
Non-compartmental analysis.  
Non-parametric tests.  
Multivariate Linear Regression.



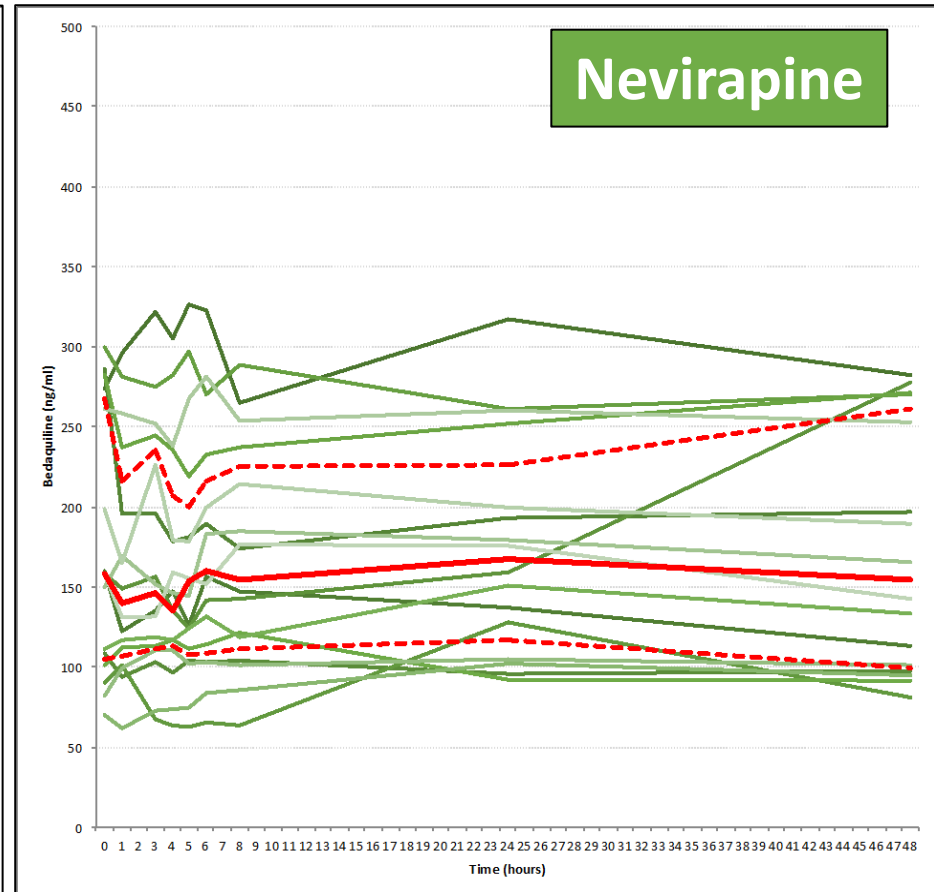
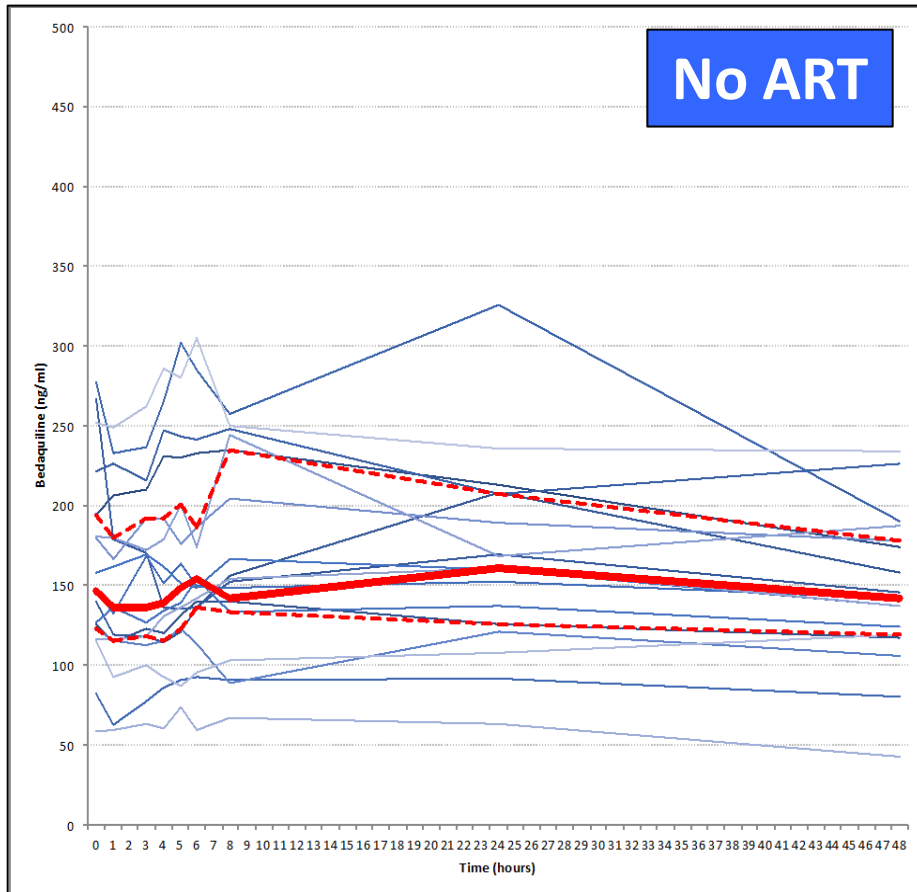
# Patient characteristics

	HIV negative	Nevirapine	LPV/r
n	17	16	10
Male sex	76%	56%	70%
Median age in yrs (IQR)	25 (22-38)	36.5 (28-45)	31 (24-36)
Median wt in kg (IQR)	57 (52-65)	58 (54-70)	55 (48-64)
Median days on BDQ (IQR)	43 (34-79)	70 (35-79)	57 (35-107)

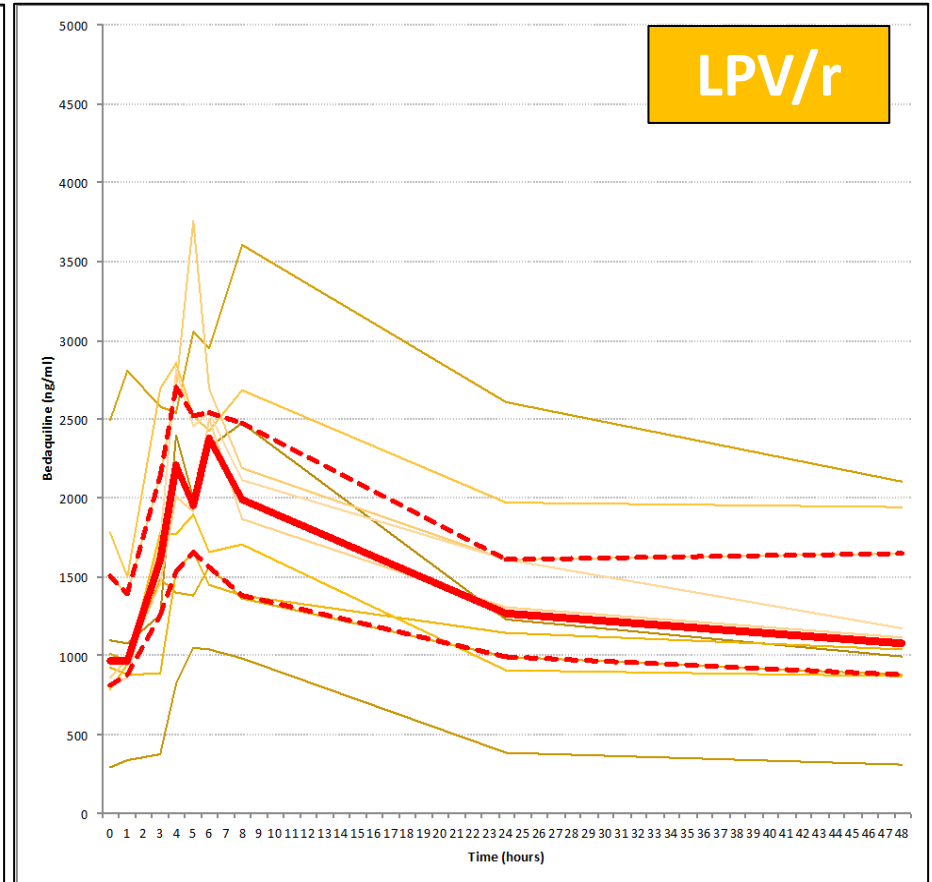
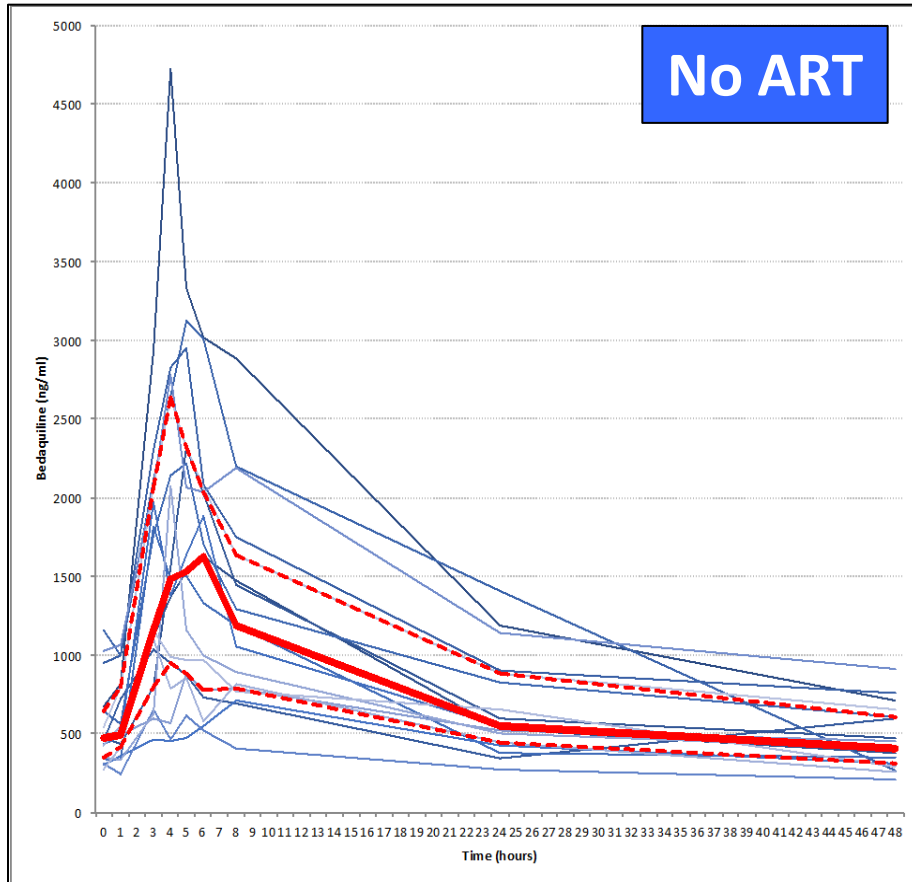
Bedaquiline	no ART	on Nevirapine
Median C <sub>max</sub> in µg/ml (IQR)	1.97 (1.10–2.64)	1.98 (1.38–2.35) p = 0.746
Median AUC <sub>48</sub> in µg.hr/ml (IQR)	34.73 (27.47–52.83)	35.11 (26.75–60.79) p = 0.666



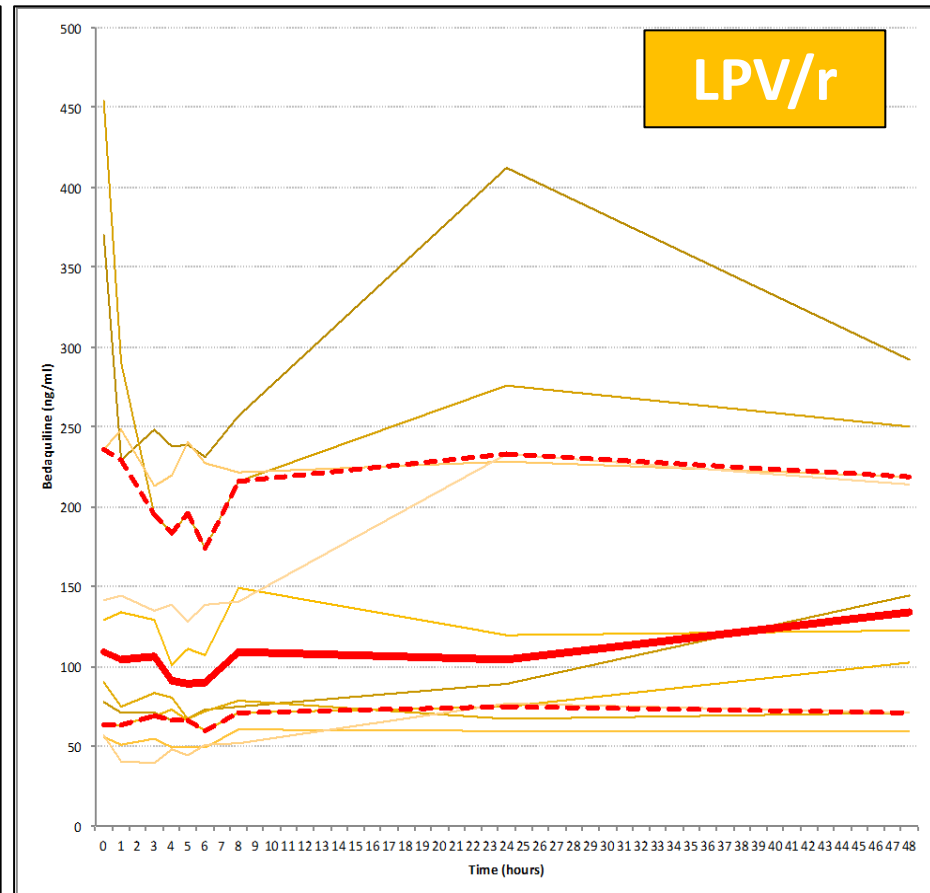
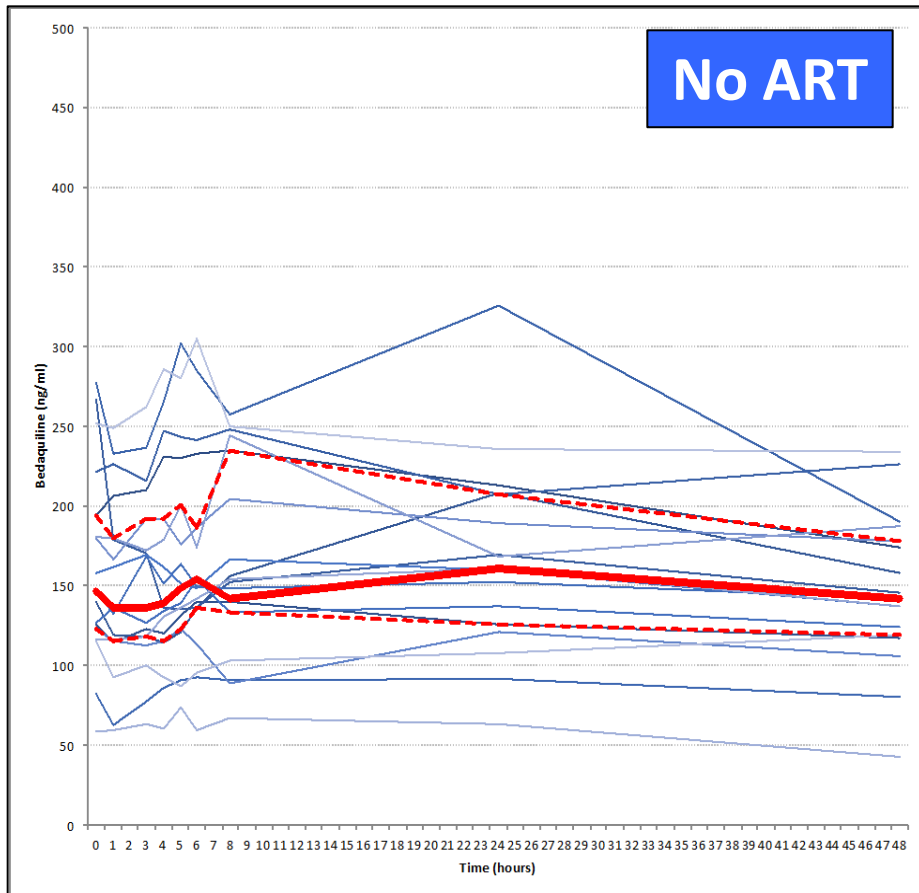
M2	no ART	on Nevirapine
Median Cmax in $\mu\text{g/ml}$ (IQR)	0.17 (0.14–0.24)	0.18 (0.13–0.28) $p = 0.760$
Median AUC <sub>48</sub> in $\mu\text{g}\cdot\text{hr/ml}$ (IQR)	7.45 (6.06–9.06)	8.10 (4.88–10.82) $p = 0.719$



Bedaquiline	no ART	on LPV/r
Median C <sub>max</sub> in µg/ml (IQR)	1.97 (1.10–2.64)	2.49 (1.66 – 2.49) p=0.228
Median AUC <sub>48</sub> in µg.hr/ml (IQR)	34.73 (27.47–52.83)	69.47 (54.68–88.26) p=0.005



M2	no ART	on LPV/r
Median Cmax in $\mu\text{g/ml}$ (IQR)	0.17 (0.14–0.24)	0.15 (0.90 – 0.25) $p = 0.530$
Median AUC <sub>48</sub> in $\mu\text{g}\cdot\text{hr/ml}$ (IQR)	7.45 (6.06–9.06)	5.38 (3.43–10.80) $p = 0.451$



# Covariate effects on bedaquiline AUC<sub>48</sub>

	Change in geometric mean	95% CI	P-value
Reference: No ART			
Nevirapine	15% increase	-20% to 65%	0.428
<b>LPV/r</b>	<b>72% increase</b>	<b>16% to 155%</b>	<b>0.009</b>
Male sex	40% increase	-1% to 97%	0.056
Days on BDQ	<0.01% increase	0% to 0.01%	0.104
10kg wt change	12% decrease	-24% to 97%	0.107
Age	<0.01% increase	-1% to 2%	0.186

# Conclusions

No ART  
vs  
Nevirapine

- No significant difference in bedaquiline and M2 PK parameters.

No ART  
vs  
LPV/r

- Median  $AUC_{48}$  of bedaquiline was 2 times higher in patients on LPV/r.
- No significant difference in M2 PK parameters.

Study  
Limitations

- Small sample size.
- Control group was HIV negative.
- Clinical relevance of BDQ-LPV/r interaction not determined.

# Acknowledgements

## Supervisors

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## Co-investigators

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Ebrahim Variava (Tshepong Hospital)

## Sponsors

