Prediction of pharmacokinetic interactions for drugs with a long half-life

Evidence for the need of model-based analysis

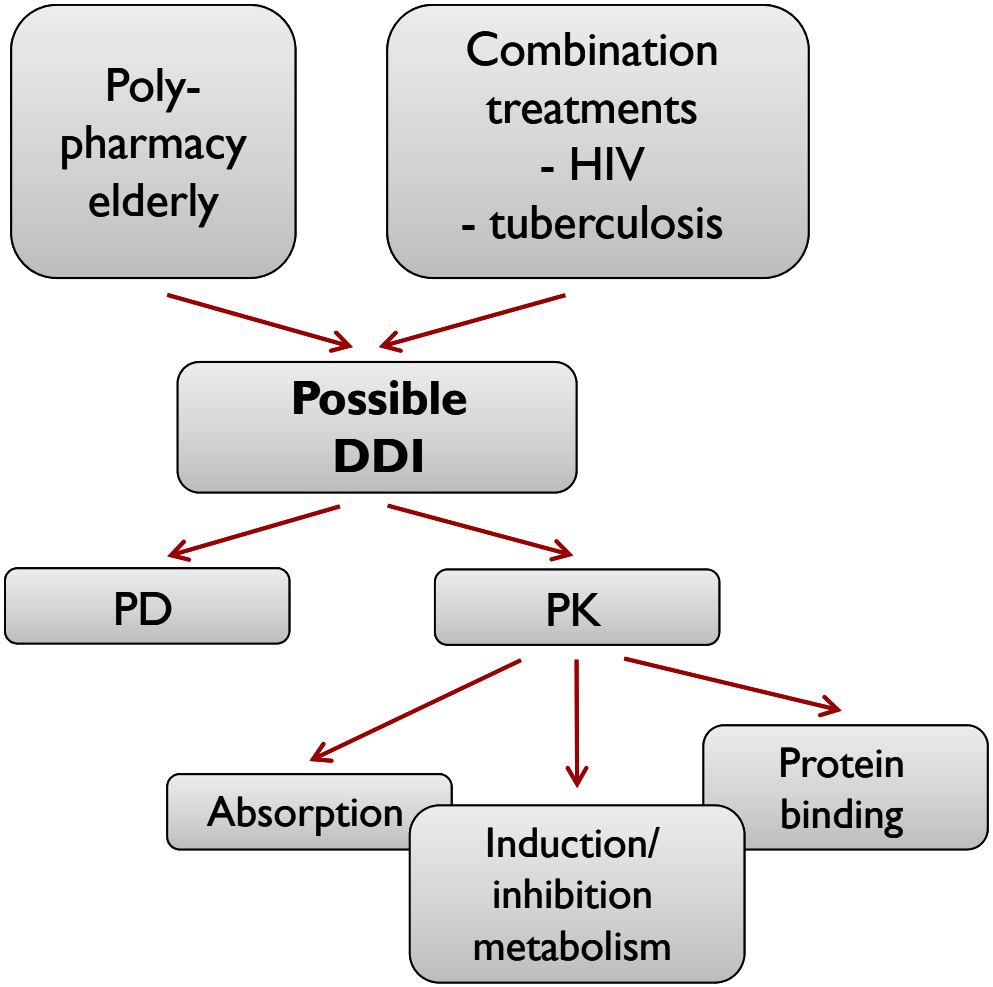
Elin M. Svensson[1]

Kelly E. Dooley[2], Mats O. Karlsson[1]

1. Pharmacometrics Research Group, Department of Pharmaceutical Biosciences, Uppsala University, Sweden

2. Department of Medicine, Divisions of Clinical Pharmacology and Infectious Diseases, Johns Hopkins University School of Medicine, USA

Importance of drug-drug interactions



Consequences

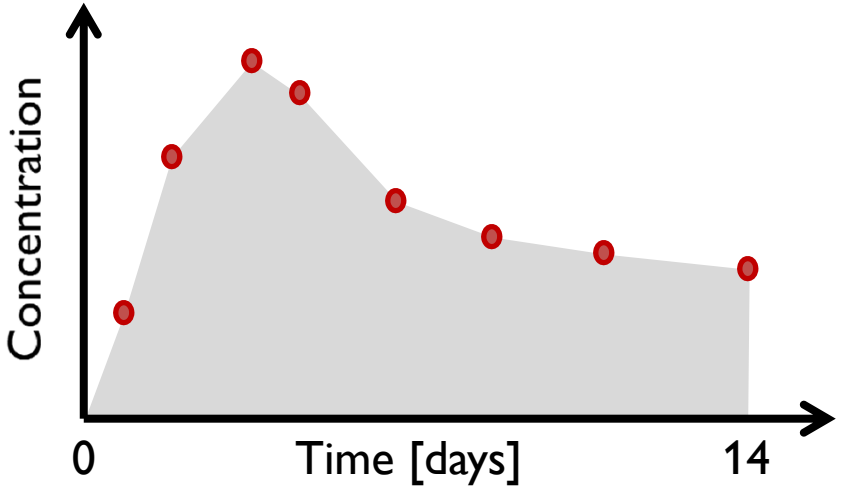
- insufficient efficacy
- excessive toxicity

Remedies

- accurate predictions
- rational dose adjustments

Predicting PK DDI

- DDI study design: single-dose crossover[1,2]
- Non-compartmental analysis (NCA)
- AUC & C_{max} of victim drug w/wo perpetrator drug
- Geometric mean of ratios (GMR) reported



[1] EMA CHMP, *Guideline on the Investigation of Drug Interactions.*
[2] FDA, *Guidance for Industry Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations - draft*

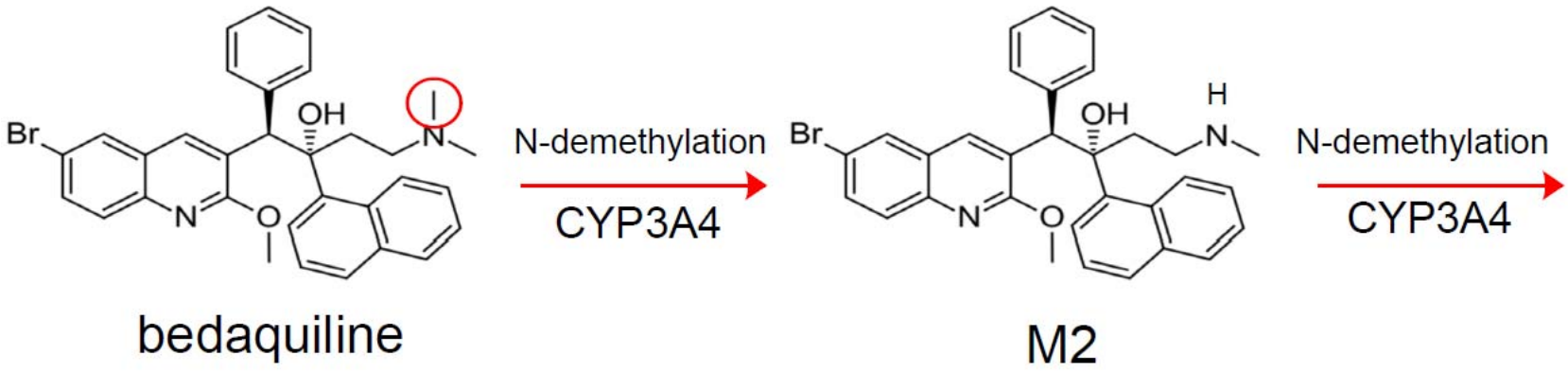
Objective

Case: Drug-drug interactions for drugs with long t½

- Summarize experiences
- Simulation study
  - Evaluating standard methodology (NCA)
  - Demonstrate benefits of a model-based approach and factors influencing its informativeness

Example: Bedaquiline (BDQ)

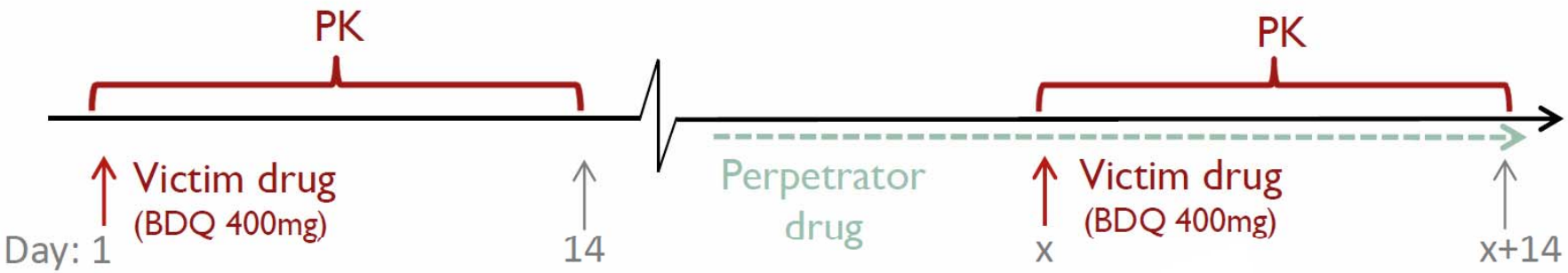
- Recently approved anti-tuberculosis drug
- Substrate of cytochrome P450 3A4
- N-demethylation to M2
- Terminal $t_{1/2}$ ~5.5 months



bedaquiline M2

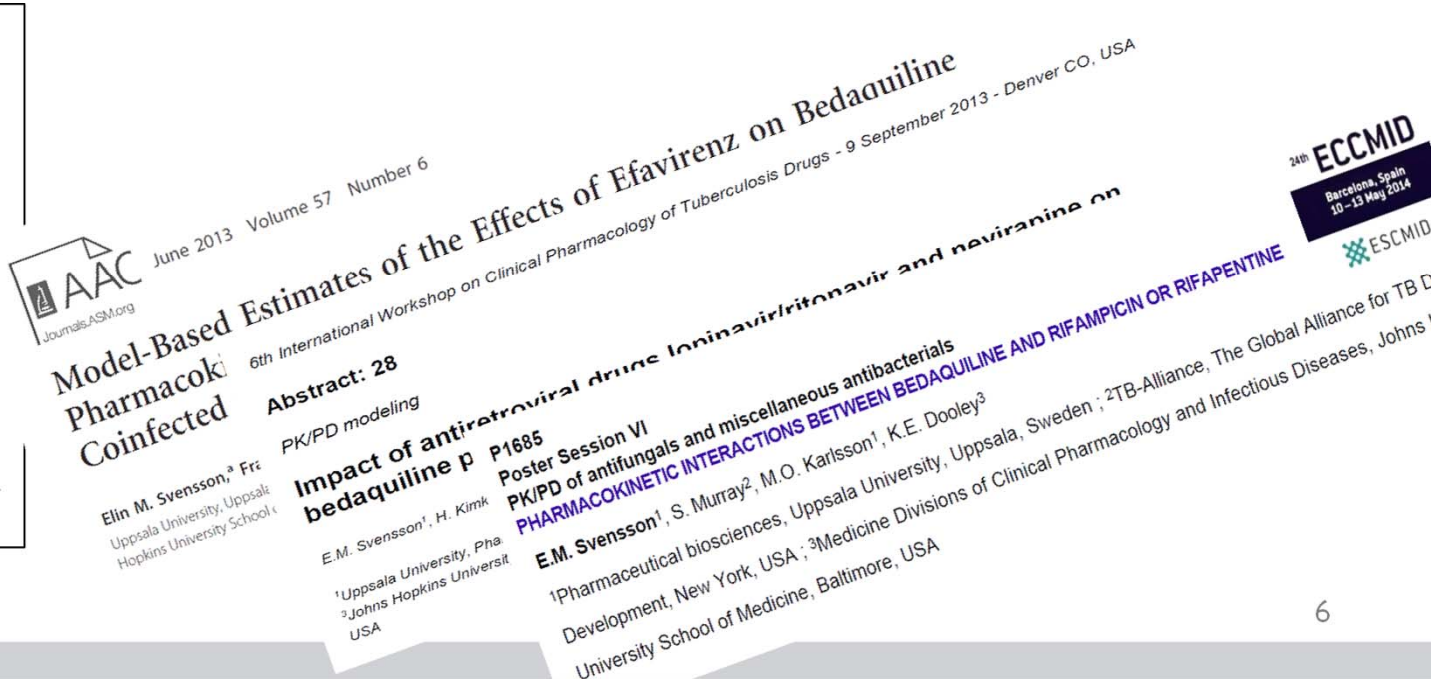
Methods

DDI study design



BDQ DDI studies

- efavirenz
- nevirapine
- rifampicin
- rifapentine
- lopinavir/ritonavir



Methods

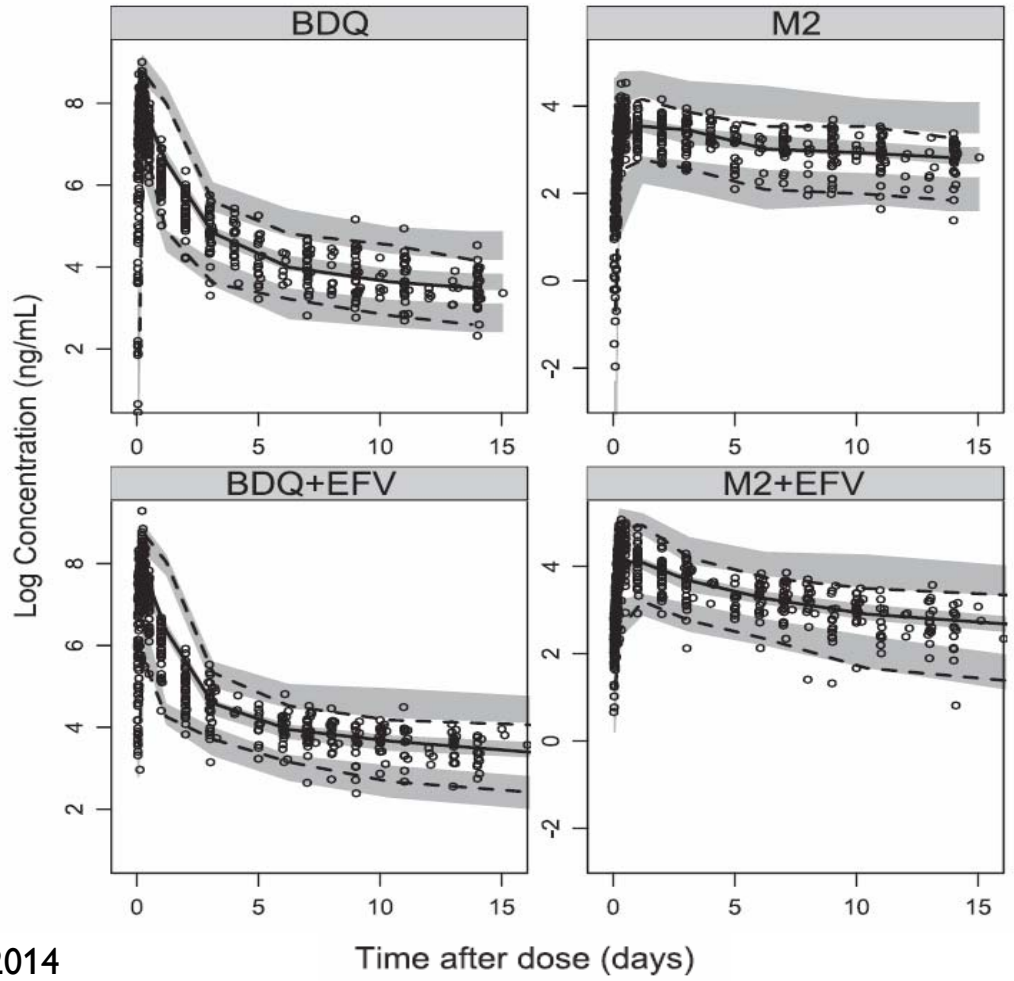
Simulation study

Clinical data

PopPK model of BDQ and M2 with efavirenz DDI
Svensson *et al.*
AAC, 57(6) 2013

↓

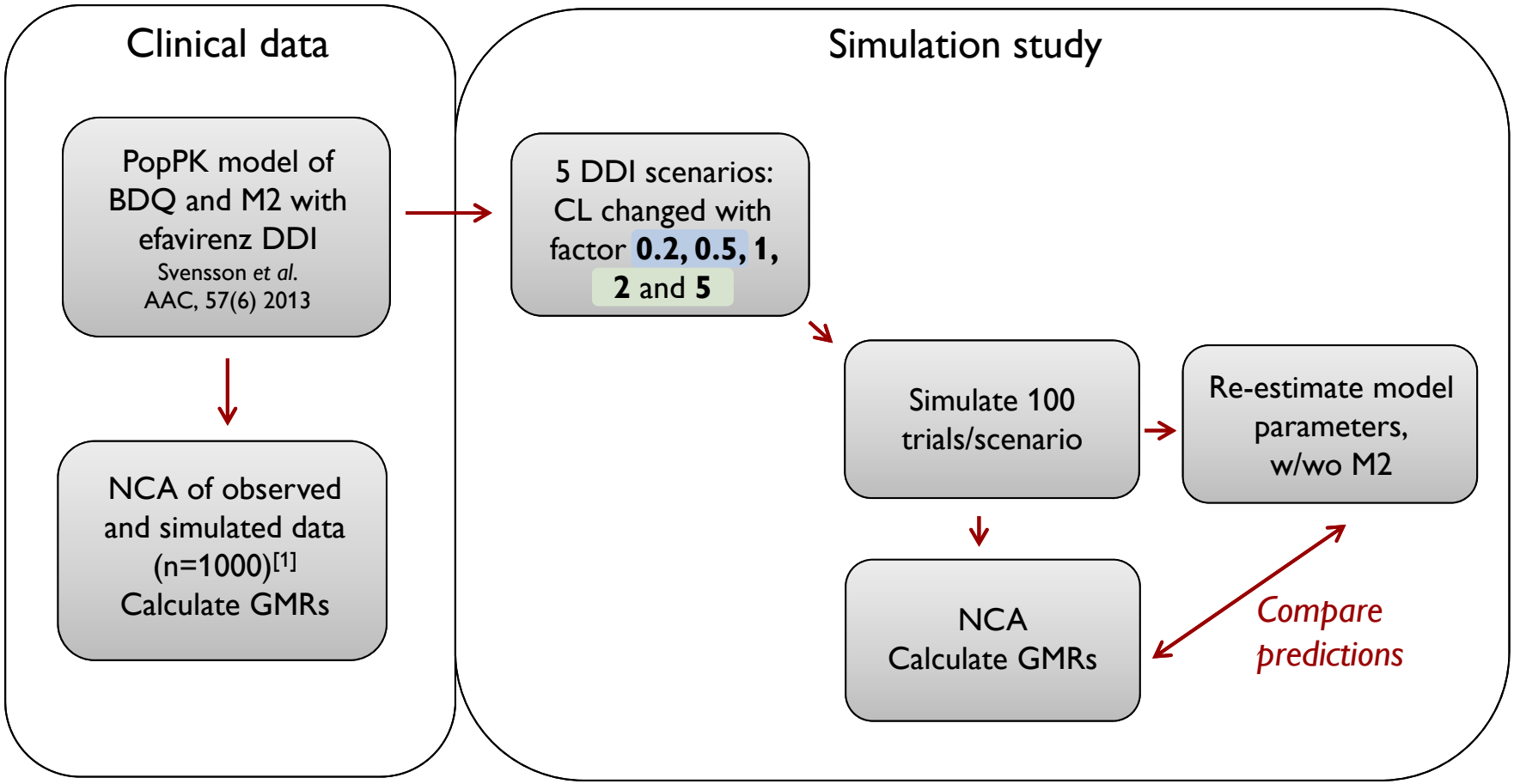
NCA of observed and simulated data (n=1000)[1]
Calculate GMRs



[1] Acharya *et al.* PAGE 23, Abstr 3103, 2014

Methods

Simulation study



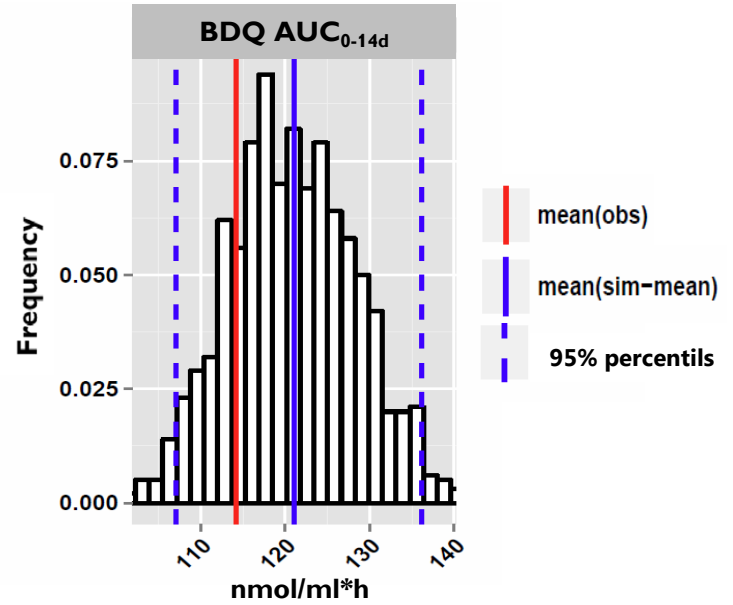
[1] Acharya *et al.* PAGE 23, Abstr 3103, 2014

Results

NCA on observed and simulated data

- Factor change in BDQ and M2 CL with EFV: **2.07**
  → $C_{ss,avg}$: **48.3%** of normal

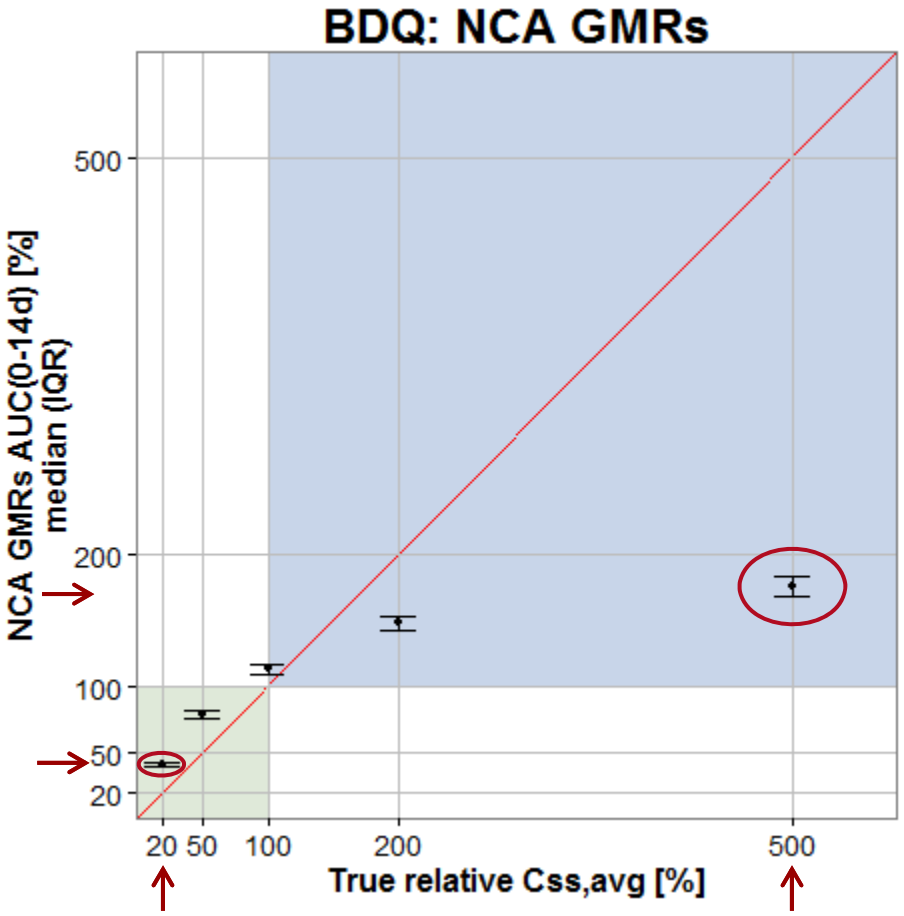
- Mean $AUC_{0\text{-}14d}$ of observed and simulated data in good agreement

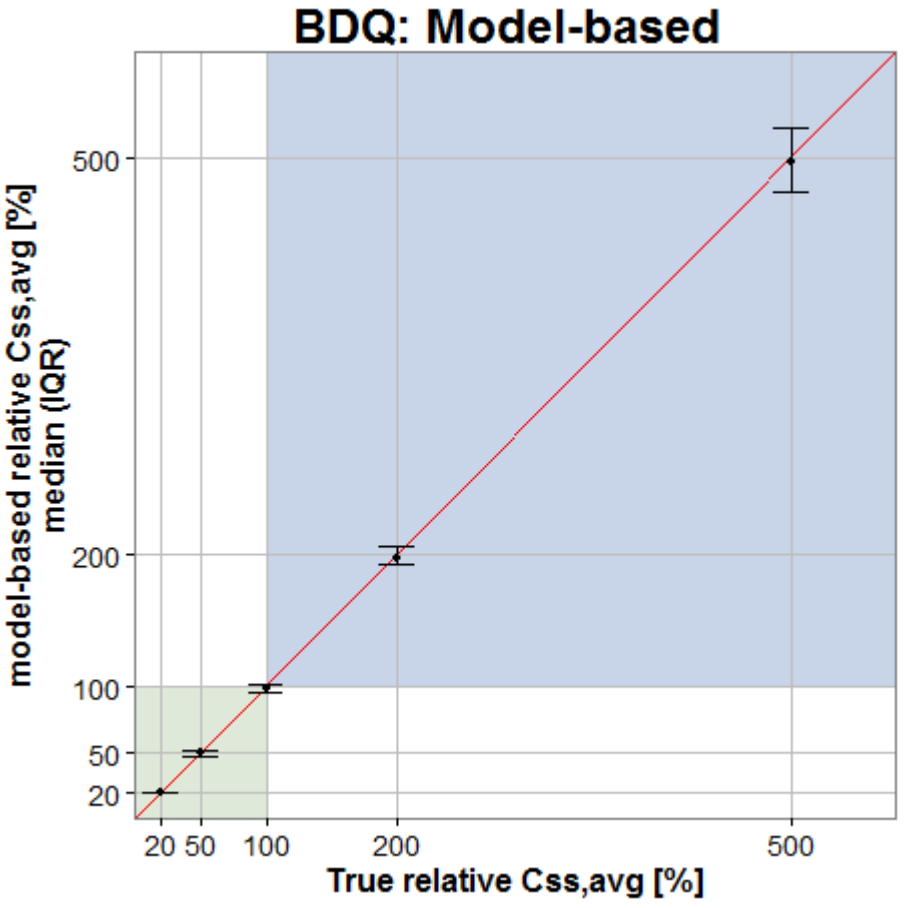


Exposure GMRs	Observed data	Simulated data median (95% CI)
BDQ	86.8%	78.5% (69.9-88.5%)
M2	128%	120% (107-134%)

Results

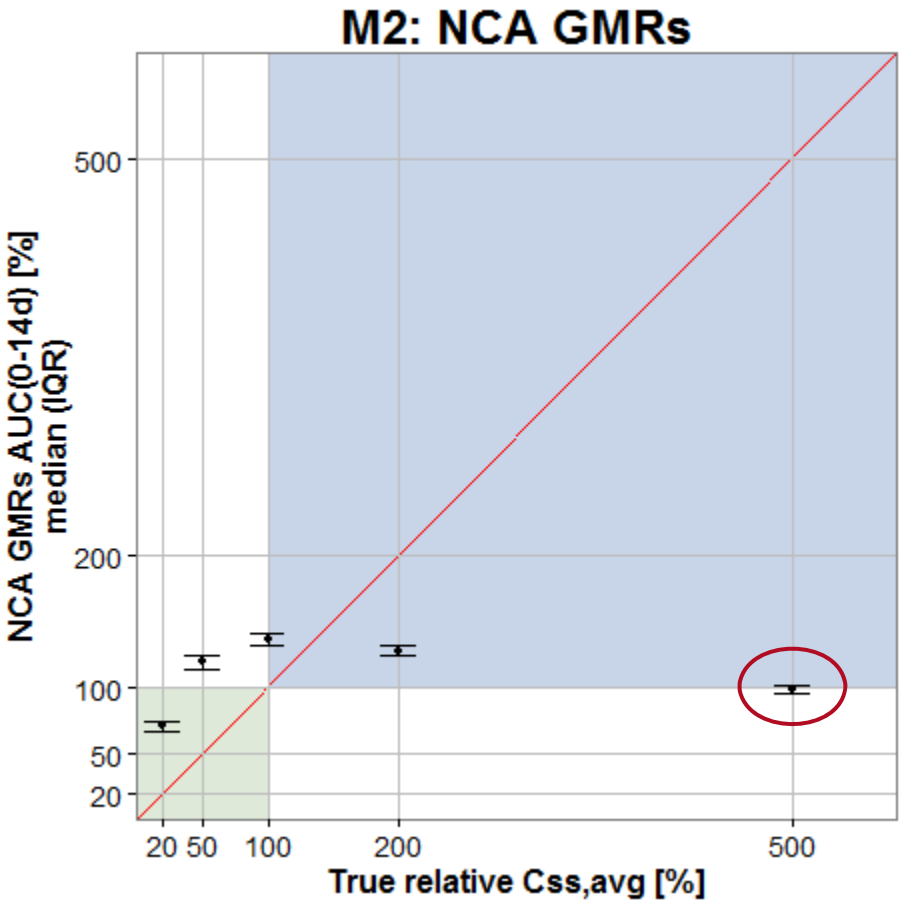
Simulation study: BDQ

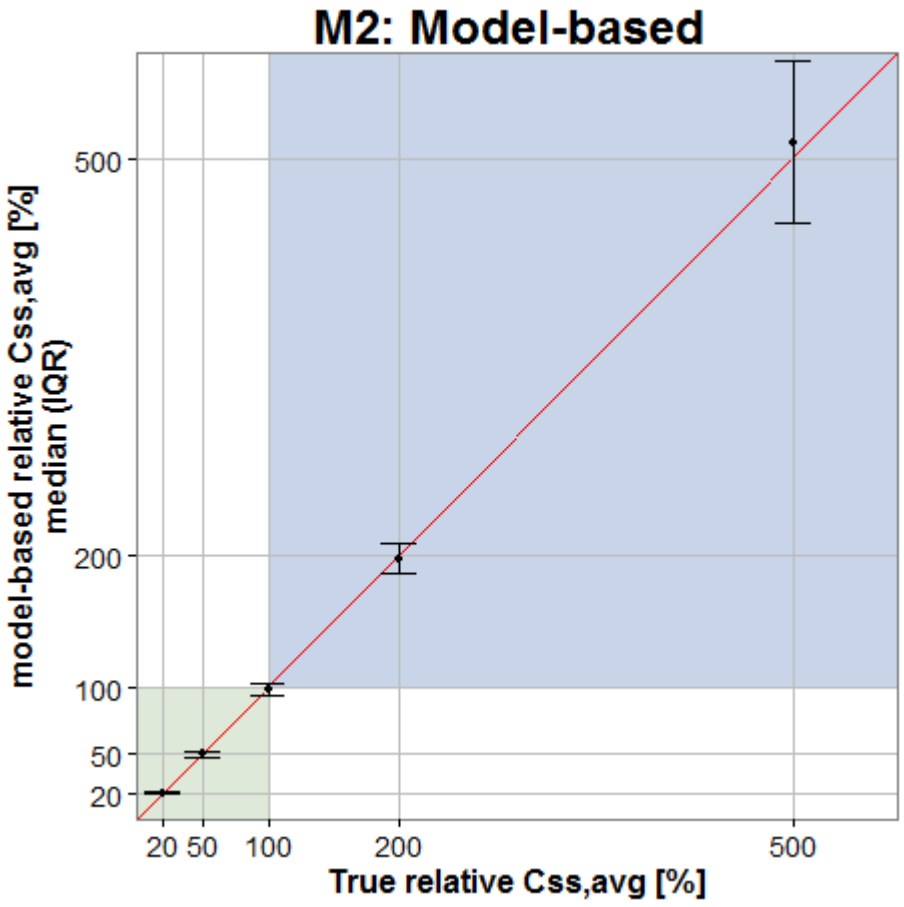




Results

Simulation study: M2





Reasons for biased predictions

- Small part of total AUC observed
- The observed part changes with the interaction

Factor change in CL	BDQ $AUC_{0\text{-}14d}/AUC_{inf}$	M2 $AUC_{0\text{-}14d}/AUC_{inf}$
0.2	15%	3%
0.5	31%	12%
1	**48%**	**29%**
2	65%	54%
5	83%	81%

Results

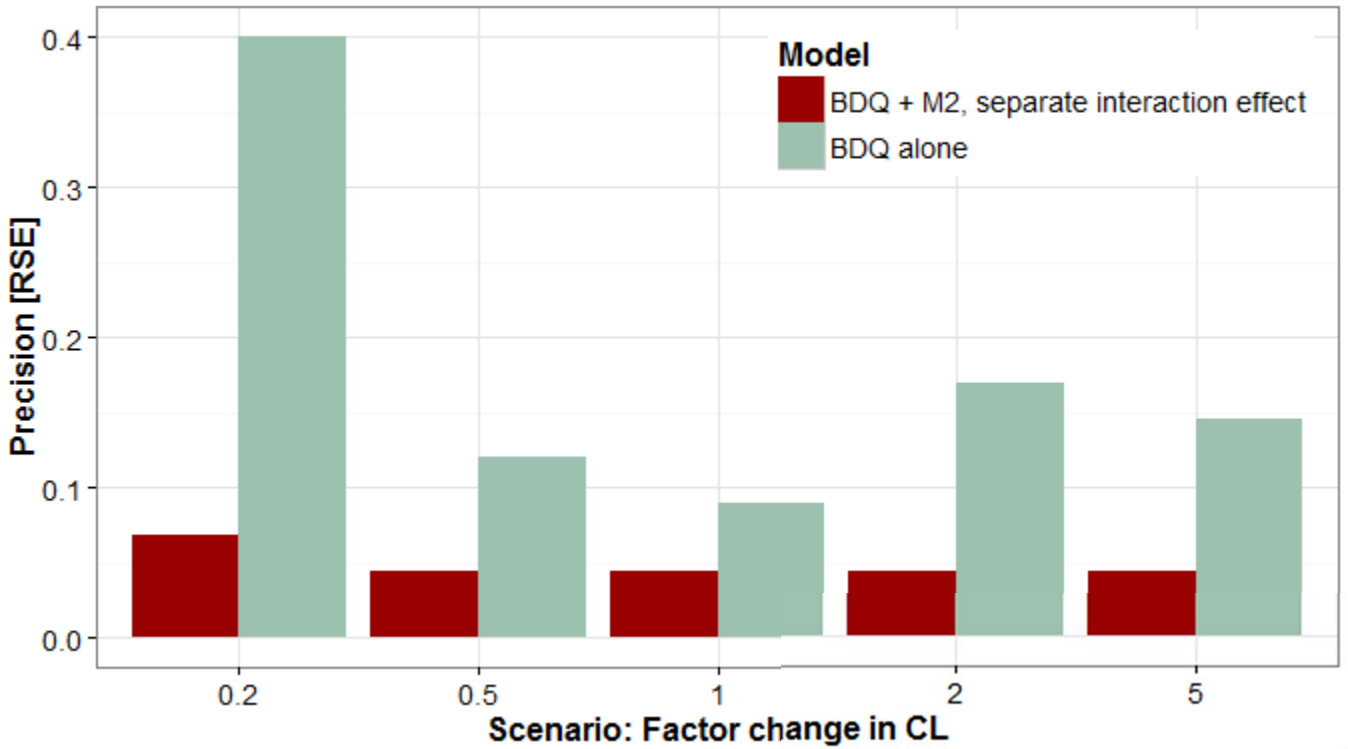
Summary BDQ DDI predictions

Perpetrator drug	NCA prediction	Model-based prediction
efavirenz	- 18%[1]	- 52%[4]
nevirapine	No change[2]	No change[5]
rifampicin	- 59%[3]	- 79%[6]
rifapentine	- 57%[3]	- 75%[6]
lopinavir/ritonavir	**+ 22%**[2]	**+ 188%**[5]

[1] Dooley *et al.* J AIDS, 59(5), 2012
[2] Janssen Pharmaceuticals. Sirturo, United States Product Insert
[3] Everitt *et al.* Nineteenth International AIDS Conference, abstract MOAB0304, Washington, USA, 2012
[4] Svensson *et al.* AAC, 57(6), 2013
[5] Svensson *et al.* IWCPTB, abstract 28, Denver, USA, 2013
[6] Svensson *et al.* ECCMID, poster 1685, Barcelona, Spain, 2014

Results

Value of metabolite data



Standard error of parameter for interaction effect on BDQ CL estimated without M2 data

- Simulation study: **2- to 6.5-fold** increased
- Clinical data: **5-fold** increased

Increasing precision!

Need of model-based analysis

- Avoid biased predictions
  - Underestimating impact of interaction
  - Risk of wrong decision regarding dosing
- Accurately account for carry-over
- More mechanistic
- Make use of metabolite data
  - Better precision → smaller studies
- Simulate dose adjustments

True regardless of half-life!

- Update regulatory guidelines about analysis of DDI studies

Acknowledgements

Funding

The research leading to these results has received funding from the Innovative Medicines Initiative Joint Undertaking (www.imi.europa.eu) under grant agreement number 115337, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution

Data for earlier work

AIDS Clinical Trials Group

Janssen Research & Development, LLC

The Global Alliance for TB Drug Development

Valuable input

Siv Jönsson, Uppsala University

Eva Gil Berglund, Swedish Medical Products Agency

Thomas Dorlo, Utrecht University

Colleagues in Uppsala Pharmacometrics Research Group