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Population pharmacokinetics of bedaquiline (TMC207) and its M2 and M3 metabolites with efavirenz demonstrate reduced exposure

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ACTG AIDS CLINICAL TRIALS GROUP

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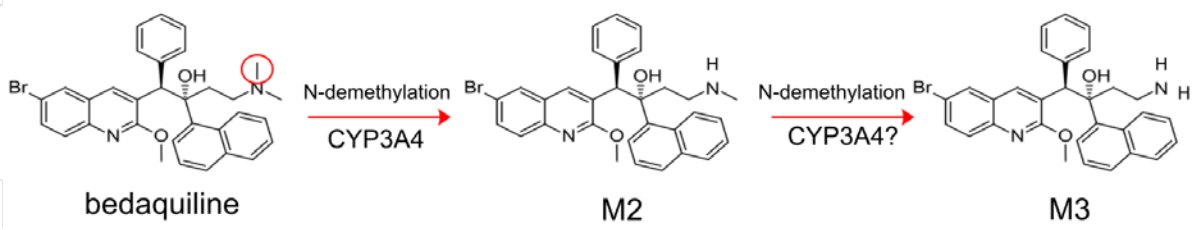
Background

- Co-infection with tuberculosis (TB) and HIV is common
- Bedaquiline is an investigational anti-TB agent
- CYP3A4 activity is induced by efavirenz and bedaquiline is a substrate of CYP3A4



bedaquiline M2 M3

- M2 and M3 are less active *in vitro* against *M. tuberculosis,* monitor for safety reasons

Objective: To develop a population model that describes the effect of efavirenz induction on the PK of bedaquiline and M2 and M3 metabolites after multiple doses.

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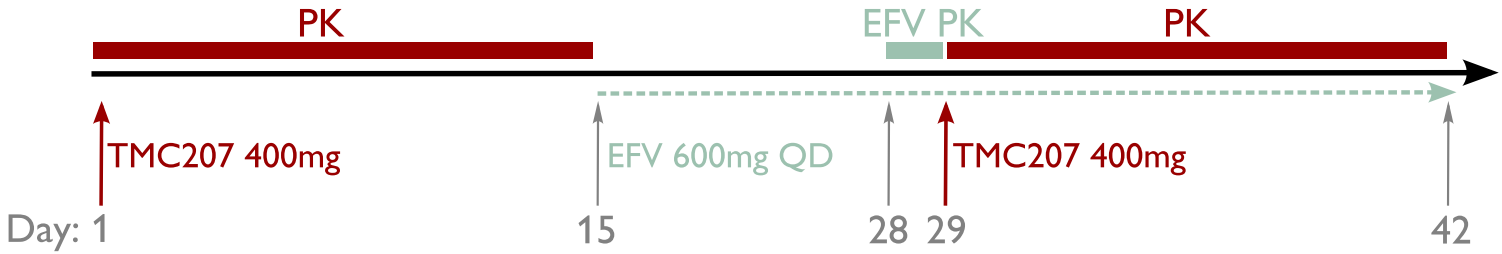
Methods: Data from ACTG Study 5267

- 2 doses of 400 mg in 33 healthy volunteers
- PK sampling over 14 days after dose
- Bedaquiline, M2 and M3 assayed
- EFV started at day 15, PK measured at day 28



Dooley *et al.* J Acquir Immune Defic Syndr, 2012;59(5)

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Methods: Limitations

- Given the long terminal half-lives, extrapolation from single dose to steady state is limited
- Potential differences in PK between healthy volunteers and patients
- Relationship between PK parameters and treatment response not well characterized, hence the clinical importance of a changes is hard to assess

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Methods: Model building

- Non-linear mixed effects models
- Software: NONMEM 7.2
  - Additional tools: PsN, Xpose4, Pirana
- Models selection based on:
  - Objective function value
  - Graphical analysis (goodness of fit plots and visual predictive checks)
- Evaluation of a range of structural assumptions

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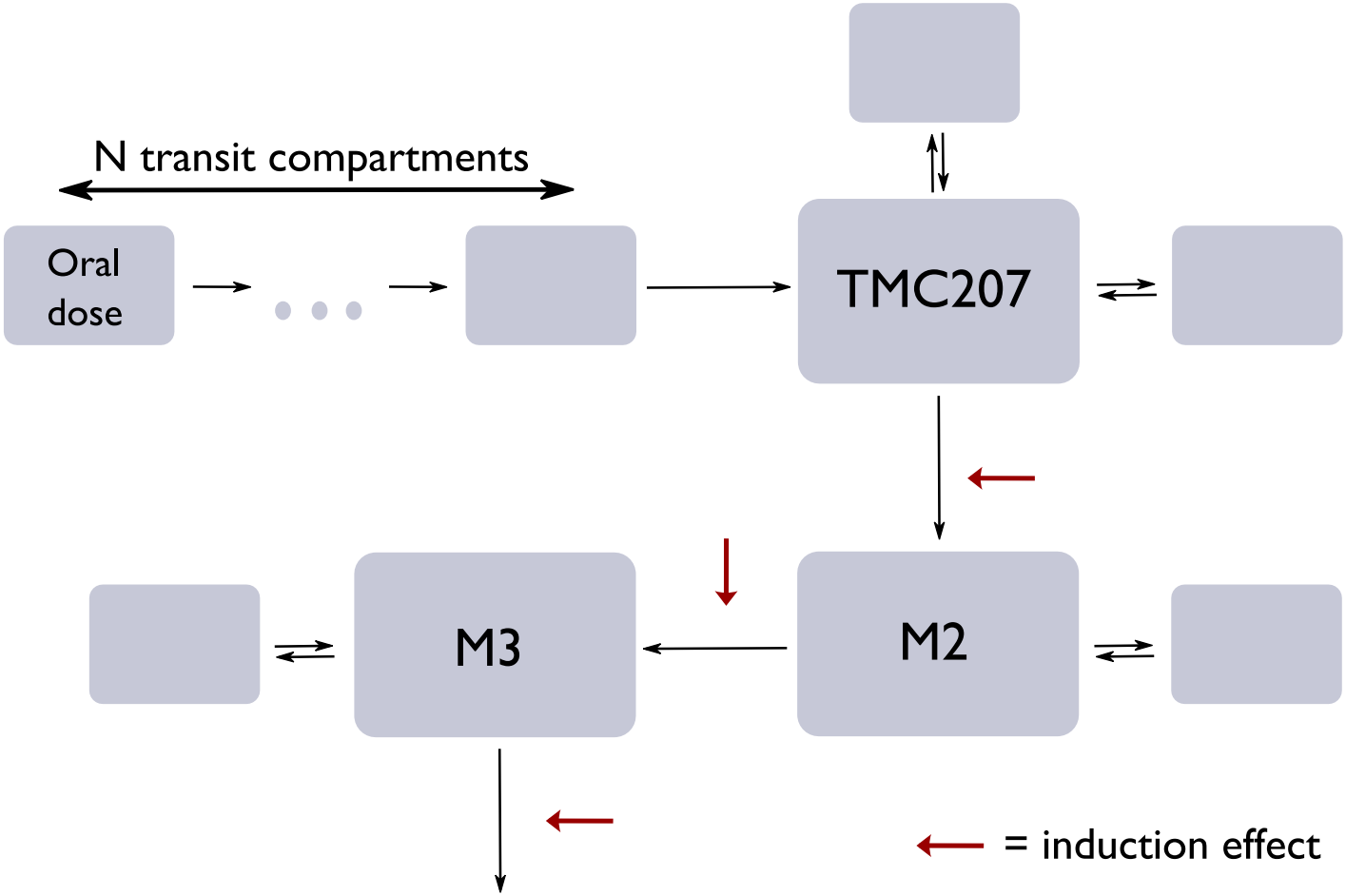
Results: Structural model



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Results: Model features

- Simultaneous analysis
- Full induction effect starting after one week of EFV treatment
- No significant difference in the magnitude of the induction effect on bedaquiline and M2
- Estimated factor change in CL with induction:
  bedaquiline and M2: **2.07** (RSE 3.6%)
  M3: **1.12** (RSE 3.6%)
- Correlations between CL and induction effects for bedaquiline, M2 and M3

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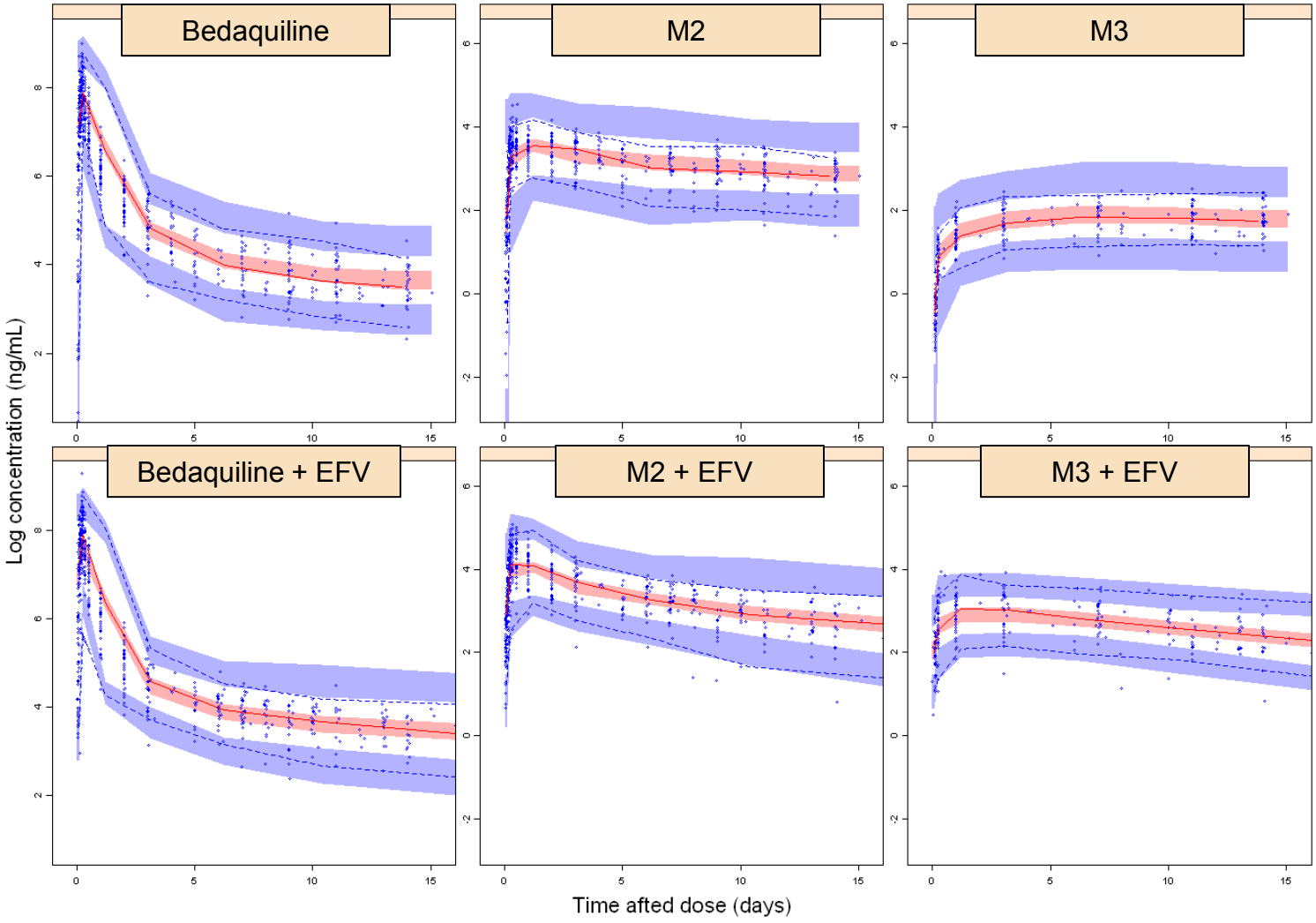
Results: Visual predictive check



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Results: Impact on exposure

$$C_{ss,av} = \frac{F \cdot Dose}{CL \cdot \tau} \Rightarrow Rel_{C_{ss,av}} = \frac{C_{ss,av(EFV)}}{C_{ss,av}} = \frac{CL}{CL_{(EFV)}}$$

	Bedaquiline	M2	M3
Rel $C_{ss,av}$ (SE)	48 (1.9)%	48 (1.9)%	88 (3.7)%
Inter individual variability [CV] in Rel $C_{ss,av}$ (SE)	21 (2.7)%	29 (7.7)%	35 (9.8)%

Calculated from simulated (n=10000) individual CL values from each of 93 sets of parameter estimates obtained in a bootstrap of the primary model.

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Results: Alternative models

Evaluate different assumptions regarding:

- the fractions of bedaquiline converted to M2 and of M2 converted to M3
- the time for onset of induction
- the induction effect on bioavailability

The results were robust:

Bedaquiline, M2 and M3 exposures on EFV induction were estimated to between 48-64%, 48-60% and 85-110% respectively of the non-induced condition under all assumptions

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Results: Possible dose adjustments

Standard regimen:

2 weeks 400 mg QD + 22 weeks 200 mg thrice weekly (TIW)

Scenario:

- Patient diagnosed with TB and HIV simultaneously
- EFV treatment initialized at start of week 3 of bedaquiline treatment

Evaluated cases:

Unchanged bedaquiline dosing

2 weeks 400 mg QD + 22 weeks 200 mg TIW

Alt. 1: Change dosing frequency

2 weeks 400 mg QD + 22 weeks **200 mg QD**

Alt. 2: Increase dose

2 weeks 400 mg QD + 22 weeks **400 mg TIW**

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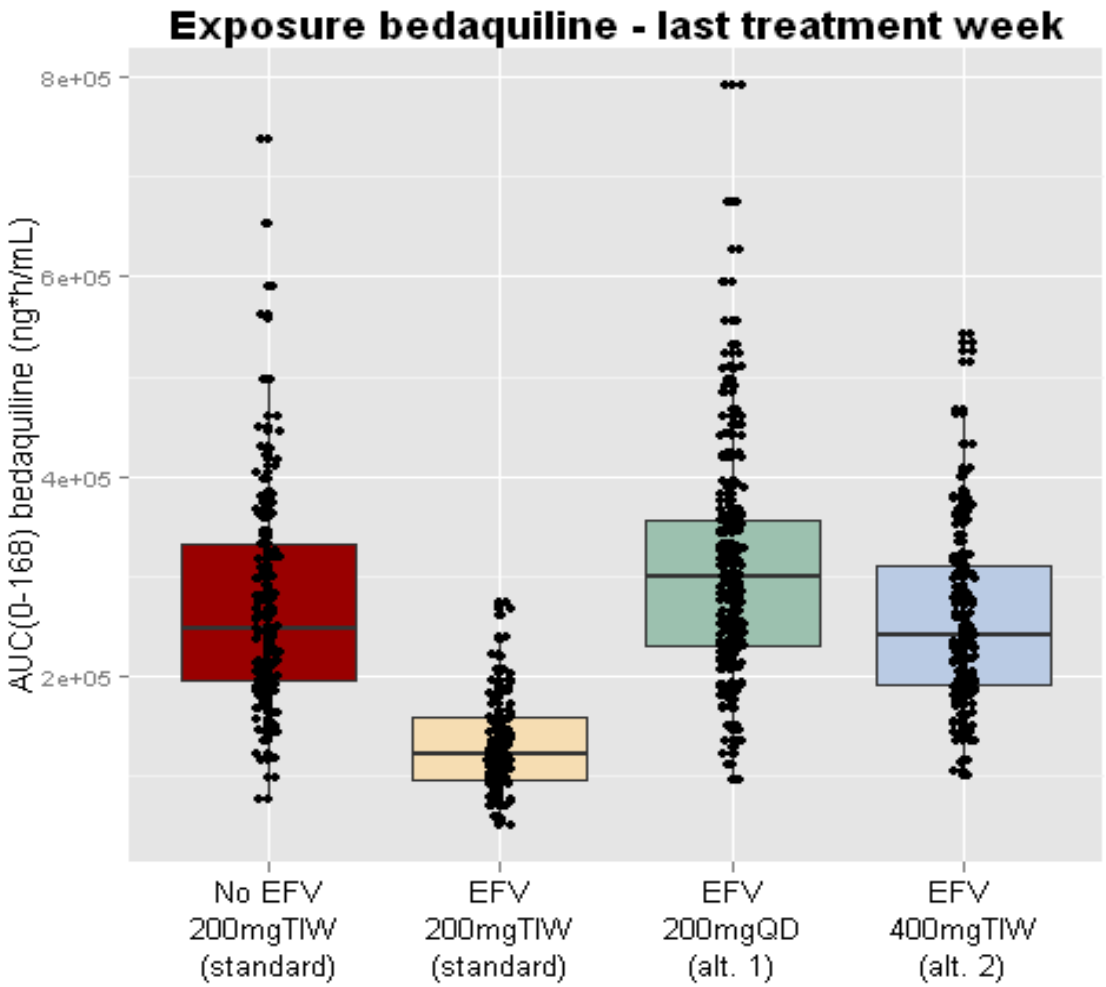
Results: Possible dose adjustments



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Conclusions

- EFV may **reduce the typical exposure to bedaquiline and M2 by up to 52%** upon chronic co-administration
- The result was robust under a range of plausible model assumptions
- Simulations of dose adjustments suggest that alternative dosing strategies could mitigate the effects of EFV induction on bedaquiline, but these must be tested prospectively

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