

PBPK Modeling to Recommend Nevirapine Dosing in HIV and HIV-TB Co-infected Patients: Leveraging Enzyme Auto-Induction, Drug Interactions, and Ethnic Variability



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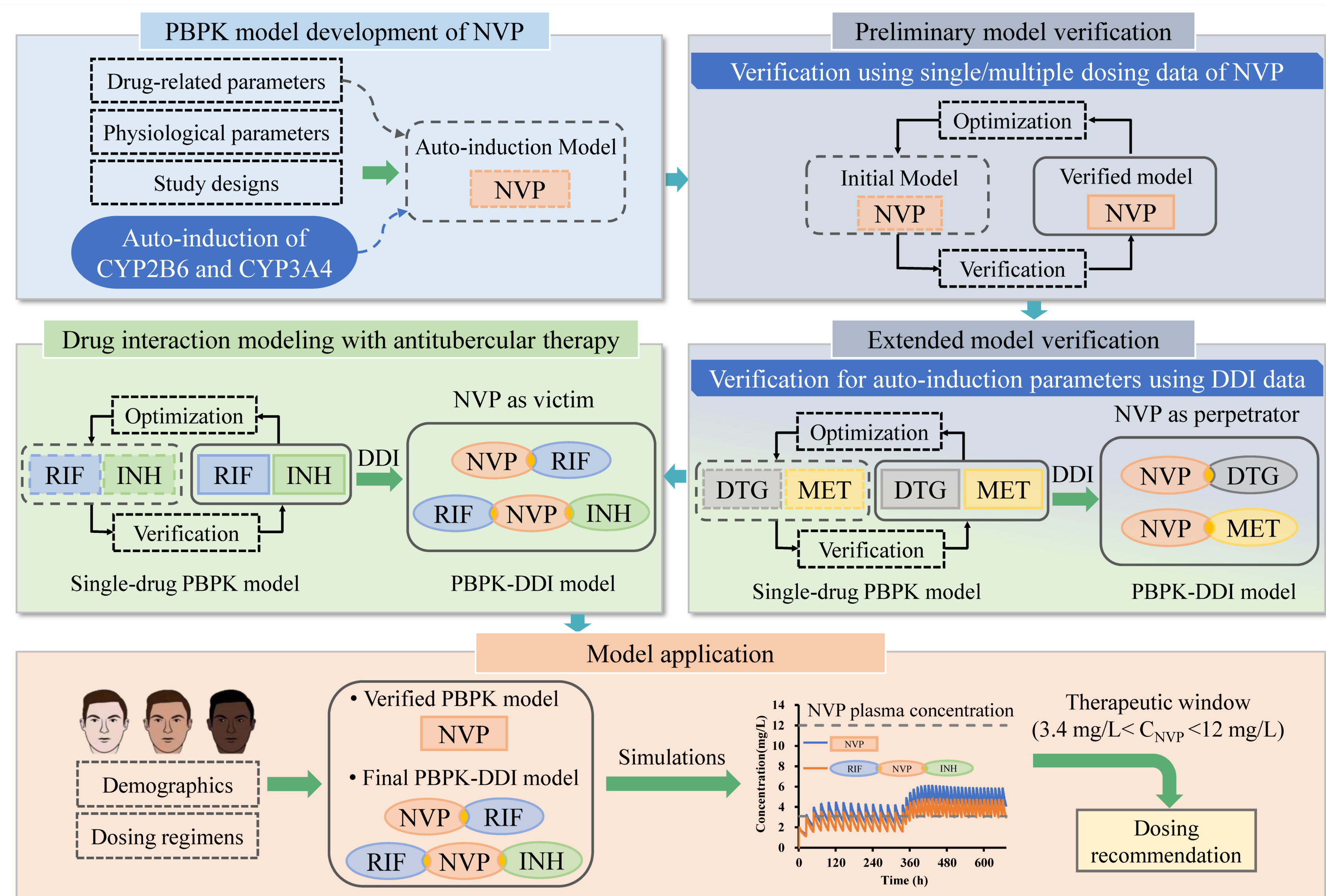
Background

- TB remains a major opportunistic infection among HIV-infected individuals, concomitant anti-HIV and anti-TB agents improve survival in **HIV-TB co-infection**¹.
- Anti-HIV agent **Nevirapine**, primarily metabolized by CYP3A4/CYP2B6, exhibits enzyme **auto-induction** and **ethnic variability** in its pharmacokinetics (PK)²⁻³.
- DDIs** between nevirapine and rifampicin (a CYP3A4/2B6 inducer) /isoniazid (a CYP3A4 inhibitor) based anti-TB therapy remains challenging.
- PBPK modeling** is a powerful tool for predicting DDIs and guiding clinical dosing.

Objective

- Employing PBPK modeling approaches to investigate:
 - Enzyme auto-induction in nevirapine PK;
 - Combined effects of anti-TB therapy on nevirapine PK;
 - Optimal nevirapine dosing regimens for HIV and HIV-TB co-infected patients across different ethnic populations.

Workflow



Results: Dose Regimens Evaluation

- Nevirapine monotherapy (Figure 4)

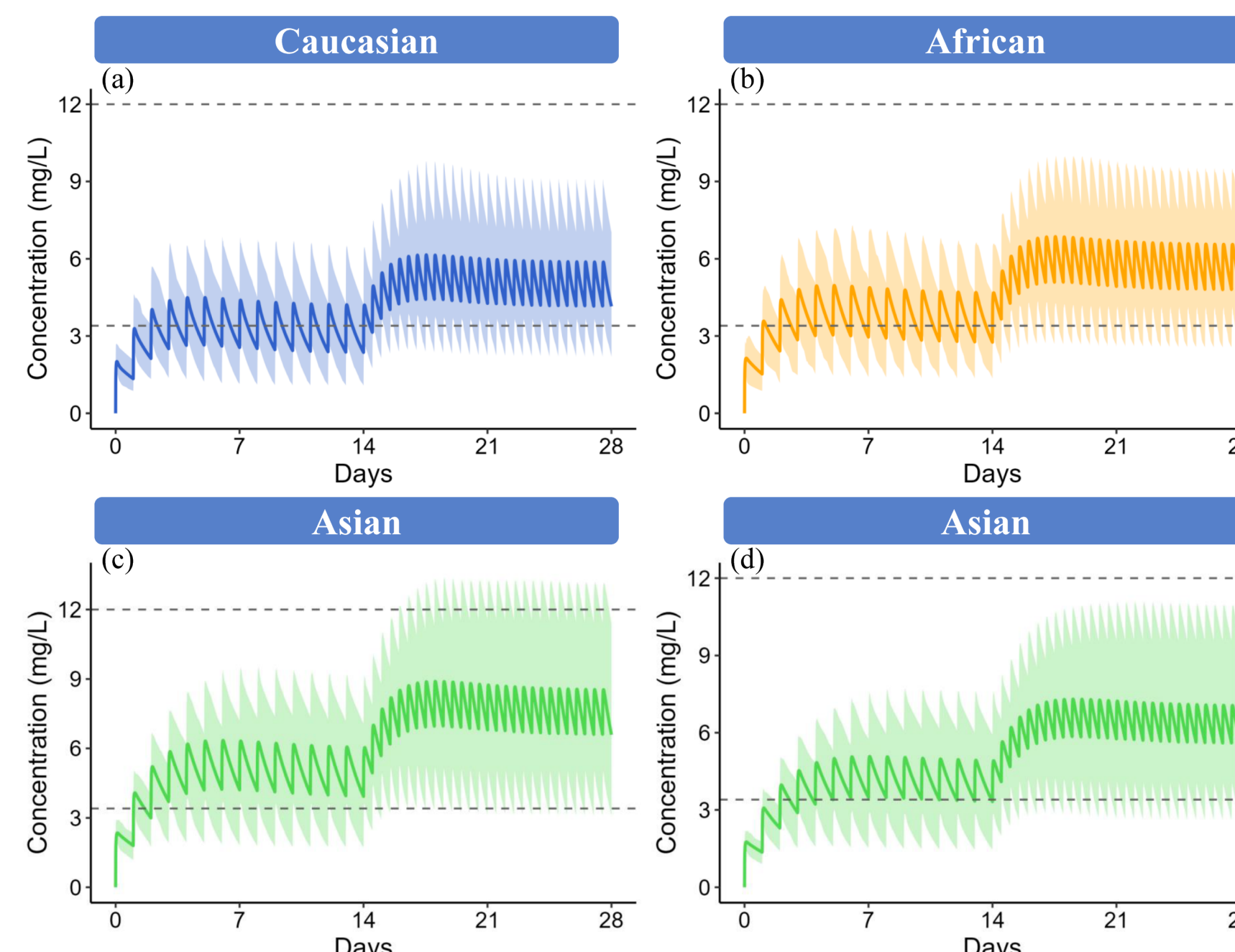


Figure 4. Simulated plasma concentration-time profiles of nevirapine at standard dose in three ethnic populations (a, b, c) and at a lower dose in Asian population (d).

- Nevirapine with concomitant rifampicin-based anti-TB therapy (Figure 5)

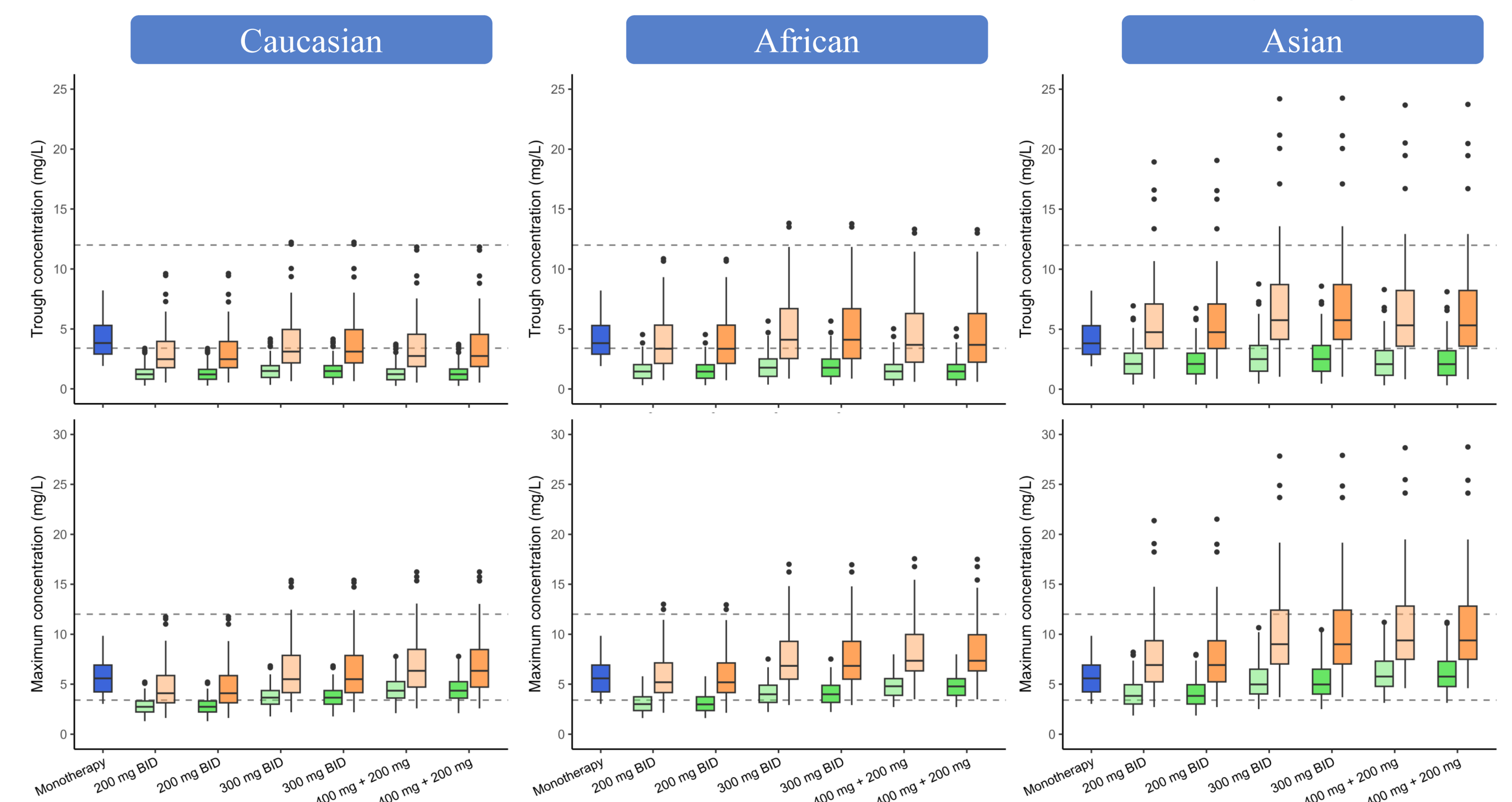


Figure 5. Predicted nevirapine steady-state C_{max} and C_{trough} under different dose regimens when concomitant with rifampicin-based anti-TB treatment, with (orange) or without (green) isoniazid.

- Nevirapine co-administration may not be recommended for Caucasian population.
- A similar reduced nevirapine dose may be appropriate for Asian patients.
- African patients may require a higher dose (lead-in: 200 mg QD, maintenance: 300 mg BID), with careful consideration of toxicity risks.

Results: PBPK Model Performance

- Nevirapine PBPK model successfully described the observed plasma concentration-time profiles (Figure 1).

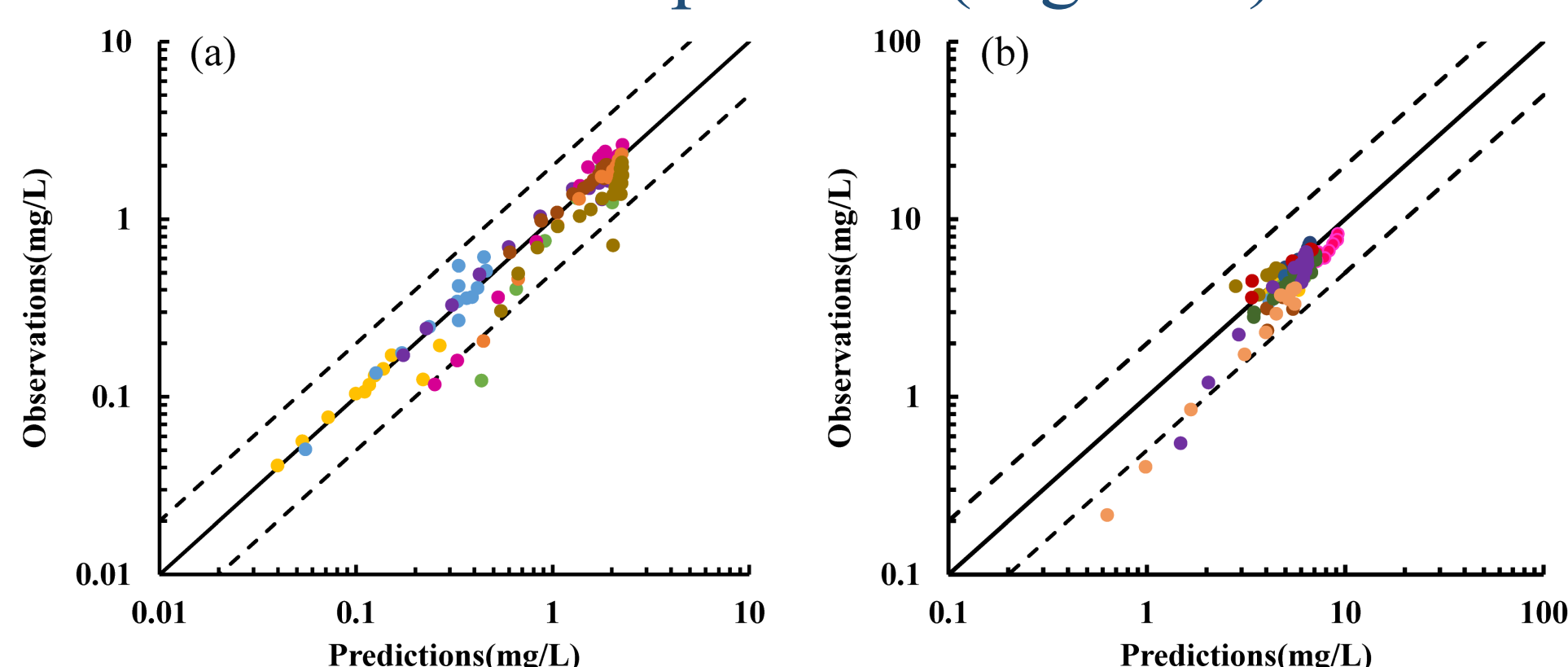


Figure 1. Observed vs predicted nevirapine conc in single- (a) and multi- (b) dose studies.

- Nevirapine PBPK model with enzyme auto-induction accurately predicted altered PK profiles of the CYP3A4 substrates (Figure 2).

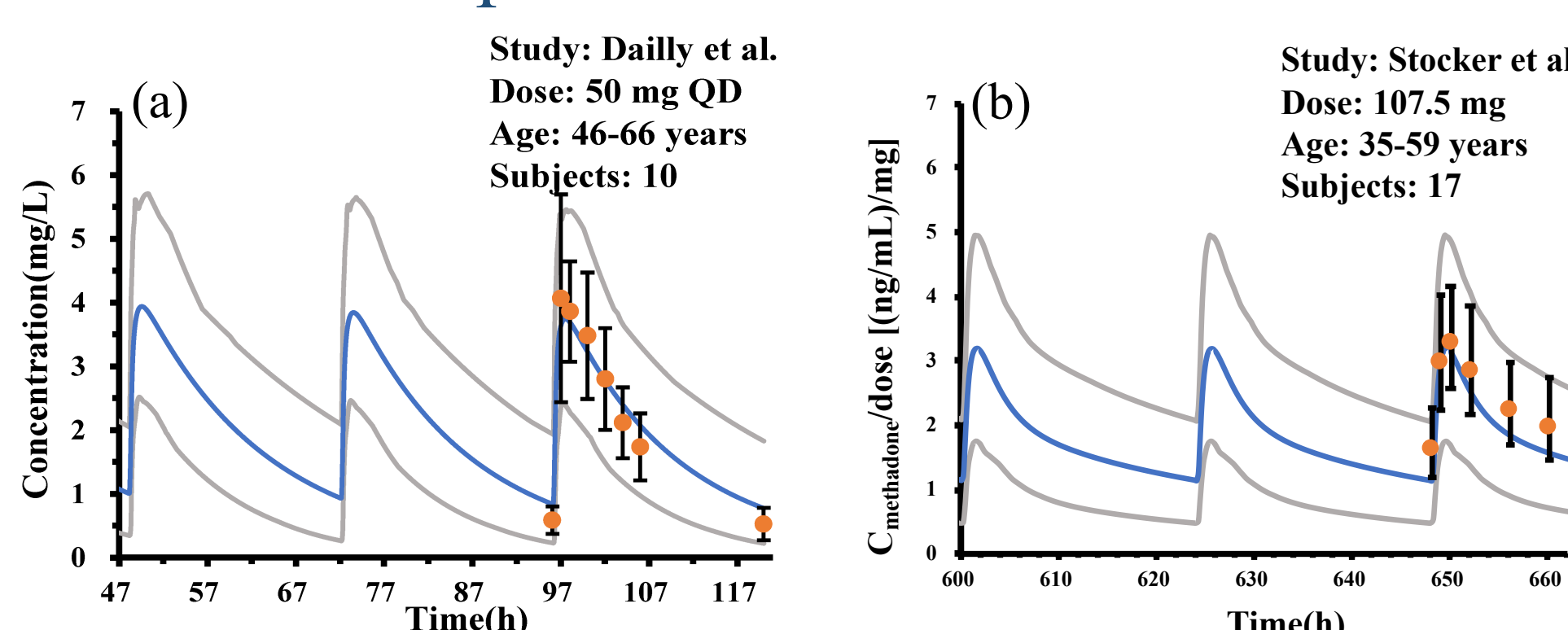


Figure 2. Observed vs predicted plasma PK profiles of dolutegravir (a) and methadone (b).

- The PBPK-DDI model of nevirapine and rifampicin-based anti-TB treatment accurately described the observed data across Caucasian, African and Asian population (Figure 3).

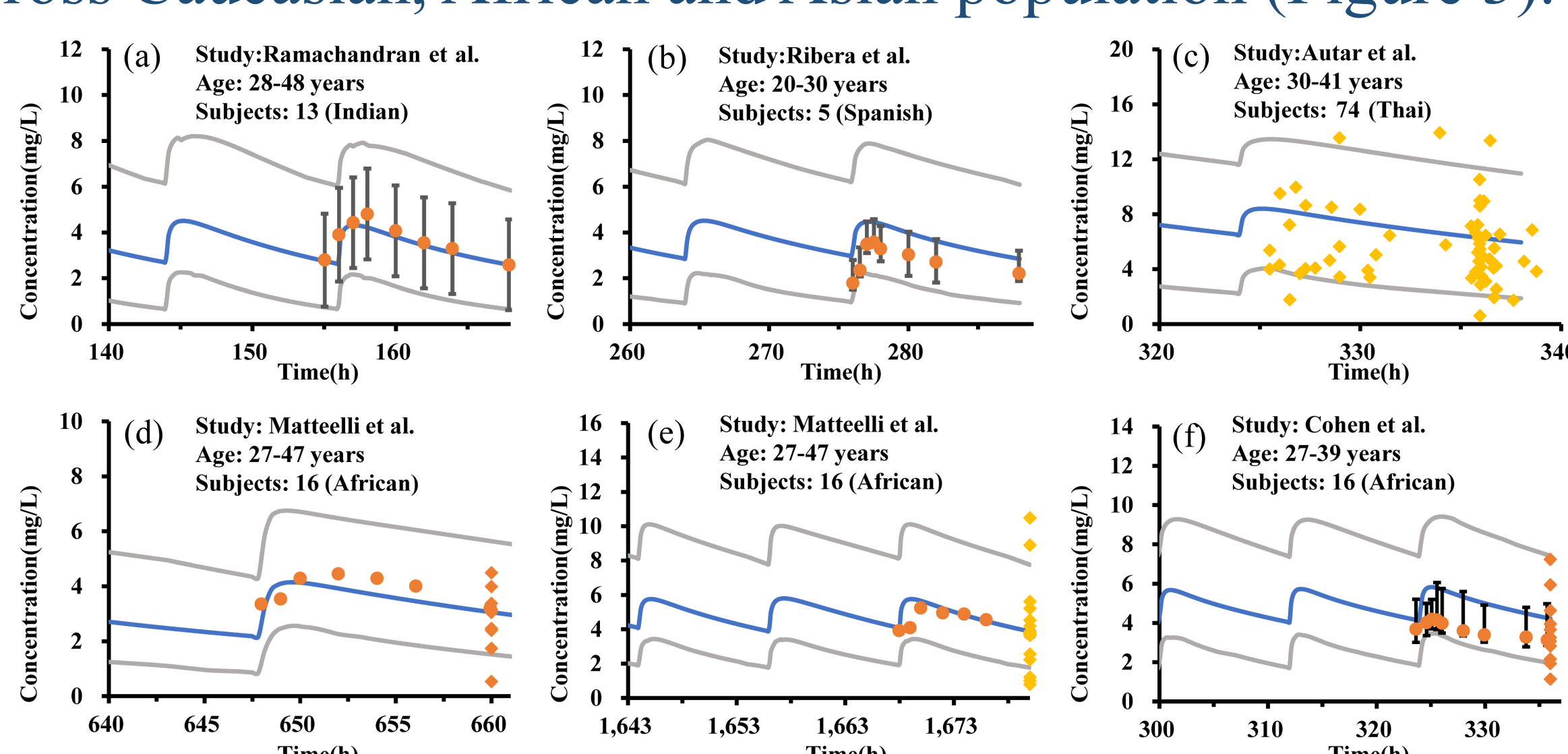


Figure 3. Observed versus predicted plasma PK data of nevirapine concomitant with rifampicin (a) or with rifampicin/isoniazid-based antituberculous treatment (b-f).

