

# Re-estimation of Pediatric Population Pharmacokinetic Models of Dolutegravir in a Canadian Population Undergoing Therapeutic Drug Monitoring

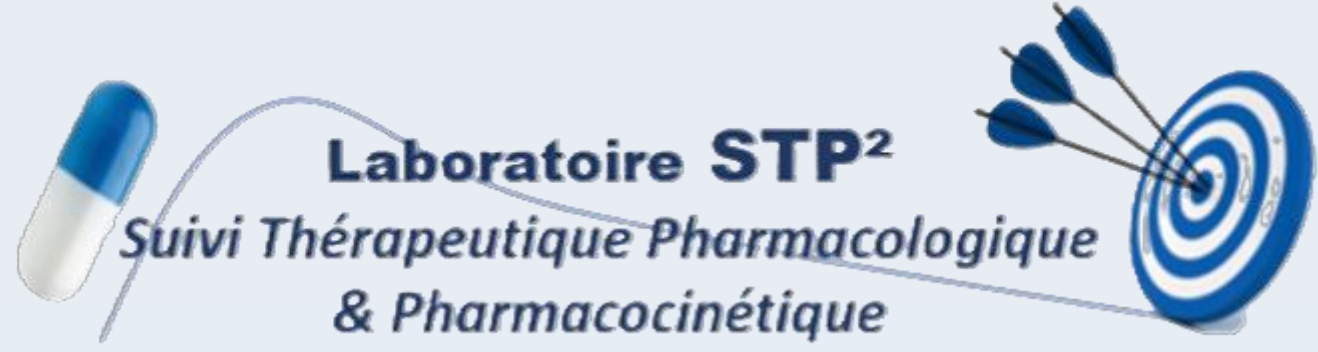
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## 1 INTRODUCTION

### Dolutegravir (DTG)

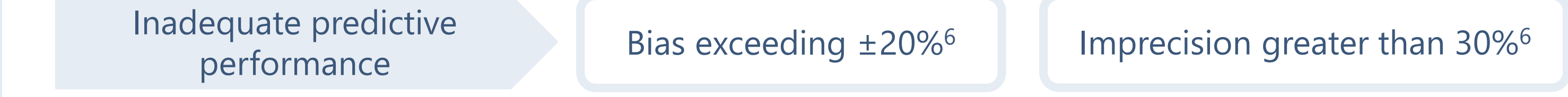
- ◆ DTG is a widely used integrase strand transfer inhibitor (INSTI) for HIV treatment.<sup>1</sup>
- ◆ Despite its well-defined pharmacokinetic profile, interindividual variability (IIV) may occur and can be influenced by patient-specific characteristics.

### In pediatrics

- ◆ In a previous study<sup>2</sup>, we reported data on DTG concentrations in Canadian pediatric patients undergoing therapeutic drug monitoring (TDM) collected retrospectively from January 1<sup>st</sup>, 2011, to March 31<sup>st</sup>, 2025.
- ◆ New strategies are needed for TDM to ensure adequate DTG exposure in pediatric patients.

### Population pharmacokinetic (PopPK) models

- ◆ PopPK models can help optimize DTG exposure, however, prior to clinical implementation, their predictive performance must first be evaluated.
- ◆ An external evaluation of published pediatric DTG PopPK models<sup>3-5</sup> (n=3) was performed.



### Objective

To perform a re-estimation with or without adjustments of these models in attempt to improve their performance in our Canadian pediatric population.

## 3 RESULTS

### Study population

Table 1: Population characteristics

| Characteristic           | Value <sup>a</sup>           | Proportion of samples:                              |
|--------------------------|------------------------------|-----------------------------------------------------|
| N subject (F/M)          | 65 (35/30)                   | ◆ With a 50 mg once daily dose → 83%                |
| N samples                | 384                          | ◆ With film-coated tablets of DTG → 92%             |
| Age (years) <sup>b</sup> | 11 (7-14; 0-17)              | ◆ With DTG taken with food → 64%                    |
| Weight (kg) <sup>b</sup> | 37.6 (23.6-50.8; 4.5-96.0)   | ◆ With an adherence of 100% → 82%                   |
| DTG concentration (mg/L) | 3.49 (1.57-4.74; 0.005-14.3) | ◆ With the presence of drug-drug interactions → 22% |
| Time post-dose (h)       | 15.1 (13.1-17.4; 1.25-38.7)  |                                                     |

<sup>a</sup> n or median (interquartile range; range); <sup>b</sup> Baseline characteristics

### Model re-estimation

Table 2: Chandasana et al.'s model re-estimation

| PK parameter          | Original model                 | Re-estimation model      |                           |
|-----------------------|--------------------------------|--------------------------|---------------------------|
|                       | Estimation (%RSE) [%Shr]       | Estimation (%RSE) [%Shr] | Bootstrap, median (CI95%) |
| CL/F (L/h)            | 1.03 (2.31)                    | 0.673 (6.0)              | 0.666 (0.597-0.753)       |
| Vd/F (L)              | 13.6 (2.42)                    | 23.8 (43.3)              | 23.0 (11.8-63.1)          |
| Ka (h <sup>-1</sup> ) | 0.854 (11.2)                   | 0.854 FIX                | -                         |
| F~food                | 1.10 (3.03)                    | 1.10 FIX                 | -                         |
| F~DT                  | 1.53 (3.26)                    | 1.53 FIX                 | -                         |
| CL~WT                 | 0.455 (4.15)                   | 0.282 (36.5)             | 0.280 (0.119-0.555)       |
| Vd~WT                 | 0.556 (3.87)                   | 1 (41)                   | 1.07 (0.151-1.83)         |
| HILL                  | 3.43 FIX                       | 3.43 FIX                 | -                         |
| TM50                  | 52.2 FIX                       | 52.2 FIX                 | -                         |
| Ka~DT                 | 2.04 (15.7)                    | 2.04 FIX                 | -                         |
| Variability           |                                |                          |                           |
| IIV CL                | 0.0863 [21.5]                  | 0.0437 (37.1) [29.2]     | 0.0380 (0.00723-0.0769)   |
| IIV Vd                | 0.0698 [22.2]                  | 0.448 (62.5) [35.8]      | 0.427 (0.164-1.30)        |
| IIV Ka                | 0.762 [33.2]                   | -                        | -                         |
| IOV CL                | 0.115 [26.6-40.7] <sup>a</sup> | -                        | -                         |
| IOV Ka                | 0.610 [39.9-73.6] <sup>a</sup> | -                        | -                         |
| Residual variability  |                                |                          |                           |
| Prop.                 | 0.0123 (18.4) [16.3]           | 0.218 (15.2) [4.4]       | 0.210 (0.151-0.279)       |
| Add.                  | 0.0900 (12.7)                  | -                        | -                         |

<sup>a</sup> Min-max of shrinkage values.

Table 3: Naidoo et al.'s model re-estimation

| PK parameter          | Original model | Re-estimation model      |                           |
|-----------------------|----------------|--------------------------|---------------------------|
|                       | Estimation     | Estimation (%RSE) [%Shr] | Bootstrap, median (CI95%) |
| CL/F (L/h)            | 0.584          | 0.346 (4.9)              | 0.346 (0.312-0.388)       |
| Vd/F (L)              | 6.98           | 5.7 (17.4)               | 5.86 (3.92-8.51)          |
| Ka (h <sup>-1</sup> ) | 1.34           | 1.34 FIX                 | -                         |
| F                     | 1 FIX          | 1 FIX                    | -                         |
| ALAG                  | 0.442          | 0.442 FIX                | -                         |
| CL~RIF                | 1.991          | 2.82 (17.1)              | 2.84 (1.85-4.25)          |
| Variability           |                |                          |                           |
| IIV CL                | 0.0529         | 0.0413 (38) [25.2]       | 0.0416 (0.0155-0.0913)    |
| IOV Ka                | 0.724201       | -                        | -                         |
| IOV F                 | 0.180625       | -                        | -                         |
| IOV ALAG              | 0.394384       | -                        | -                         |
| Residual variability  |                |                          |                           |
| Prop.                 | 0.00831744     | 0.377 (22.2)             | 0.376 (0.190-0.534)       |
| Add.                  | 0.161          | 0.841 (39.4)             | 0.796 (0.257-1.37)        |

Abbreviations: Add., additive; ALAG, absorption lag time; CI95%, confidence interval of 95%; CL, clearance; CL/F, apparent clearance; DT, dispersible tablet; F, bioavailability; HILL, Hill coefficient related to the slope of maturation; IIV, interindividual variability; IOV, inter-occasion variability; ka, absorption rate constant; Prop., proportional; RIF, rifampicin; RSE, relative standard error; Shr, shrinkage; TM50, age at which maturation reaches 50%; Vd, volume of distribution; Vd/F, apparent volume of distribution; WT, body weight.

### Model adjustment

- ◆ No additional covariates could be included in the models without impacting the re-estimation of other model parameters or without the new covariates being poorly estimated (i.e., RSE>30%).

## 2 METHODS

### Study population

- ◆ **Data:** DTG pediatric TDM data from our previous study<sup>2</sup> collected from the Québec Antiretroviral TDM Program.
- ◆ **Sample exclusion:** If the time post-dose and/or one of the PopPK models' covariate was unknown.

### Model selection

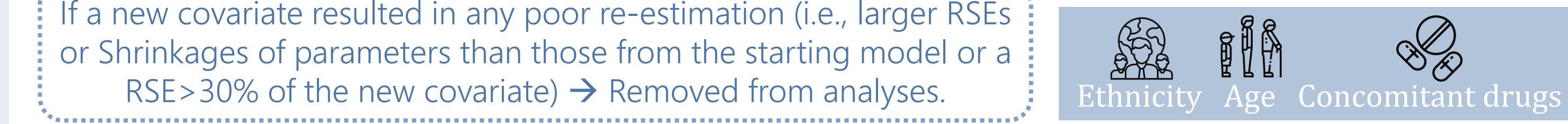
- ◆ Re-estimation of the two models with a better predictive performance in the external evaluation: Chandasana et al.<sup>3</sup> and Naidoo et al.<sup>5</sup>

### Model re-estimation



### Model adjustment

- Starting with the model's re-estimation → NONMEM7 → The inclusion of new covariates on CL/F and Vd/F was tested.
- If a new covariate resulted in any poor re-estimation (i.e., larger RSEs or Shrinkages of parameters than those from the starting model or a RSE>30% of the new covariate) → Removed from analyses.



### Model evaluation

- ◆ For the best re-estimation/adjustment of each model (i.e., Chandasana et al. and Naidoo et al.):
  - ◇ Goodness-of-fit and NPDE plots & bootstrap (n=1000)
  - ◇ Bias (MDPE) and imprecision (MDAPE)

Abbreviations: CL/F, apparent clearance; C<sub>(obs,i)</sub>, i<sup>th</sup> observed concentration; C<sub>(pred,i)</sub>, i<sup>th</sup> predicted concentration; MDAPE, median absolute prediction error; MDPE, median prediction error; N<sub>i</sub>, total number of observations for subject i; NPDE, Normalized Prediction Distribution Errors; OFV, objective function value; PE, prediction error; PE<sub>ij</sub>, prediction error of the observation j of subject i; RSE, relative standard error; RUV, residual variability; Vd/F, apparent volume of distribution.

### Model evaluation

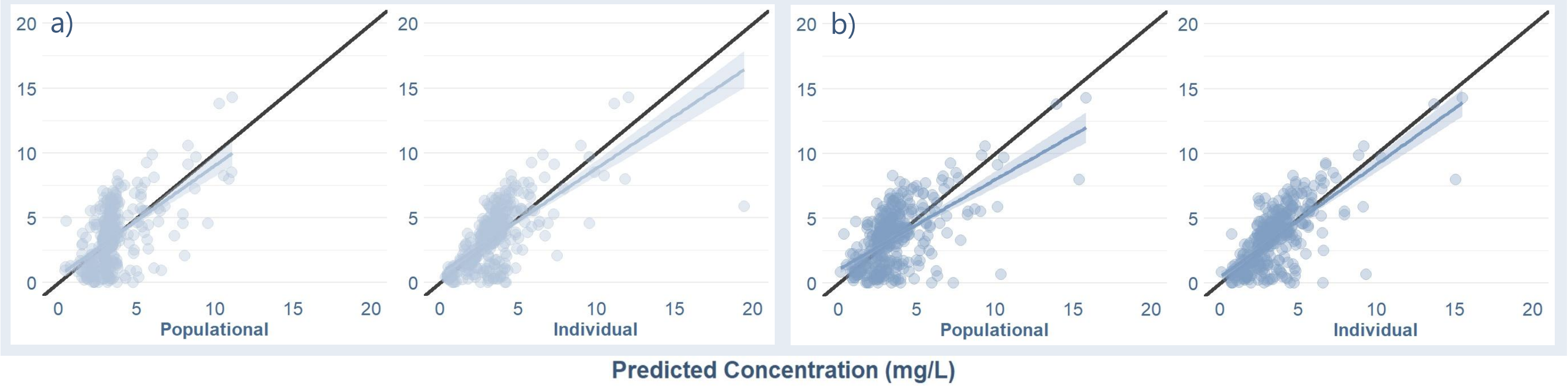
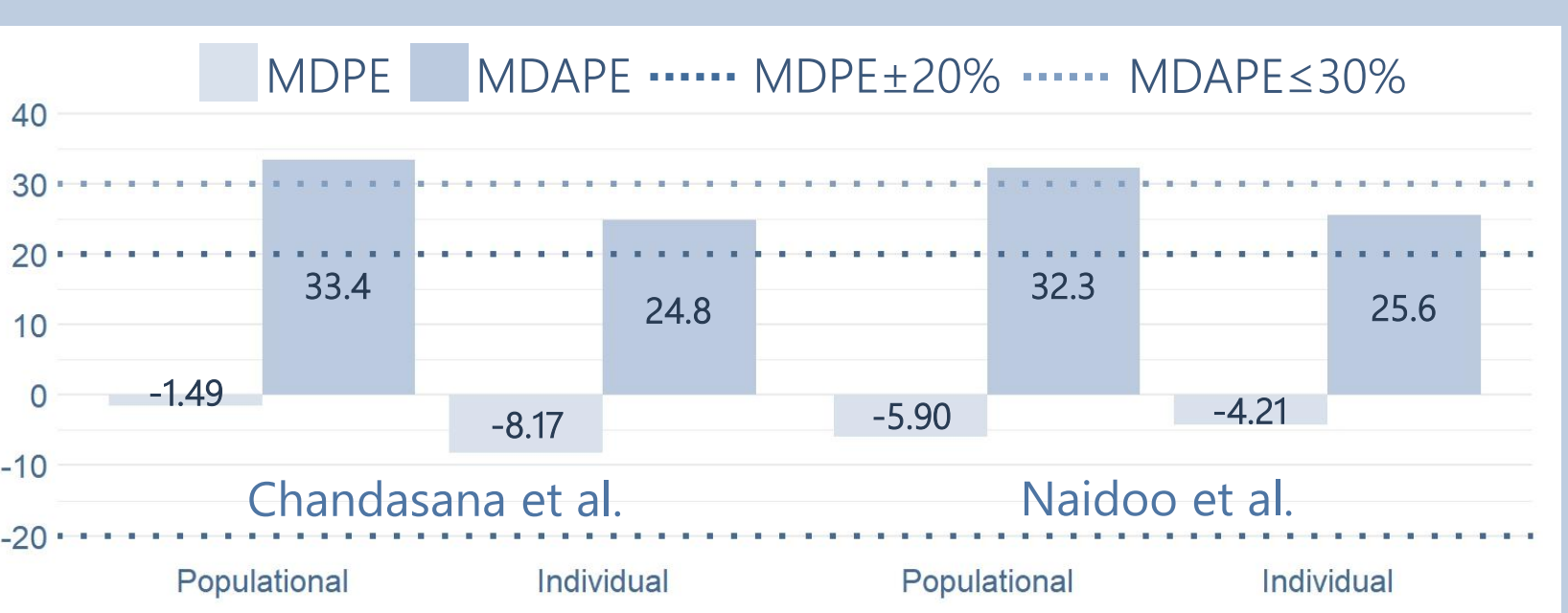


Figure 1. *Goodness-of-fit* plots. Observed concentrations vs. predicted populational and individual concentrations for a) Chandasana et al.'s and b) Naidoo et al.'s re-estimated model. Each point represents a unique sample. Black lines represent the identity line. Colored lines represent the linear regression of the scatter plots, and the shaded areas represent the 95% confidence interval.



Abbreviations: MDAPE, median absolute prediction error; MDPE, median prediction error. Figure 2. Bias (MDPE) and imprecision (MDAPE) of re-estimated models.

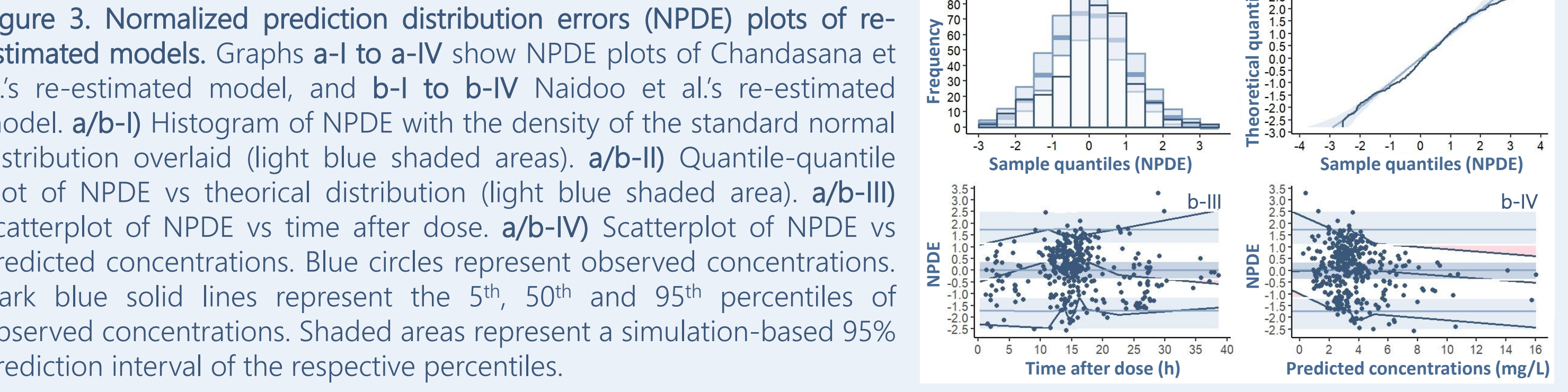


Figure 3. Normalized prediction distribution errors (NPDE) plots of re-estimated models. Graphs a-I to a-IV show NPDE plots of Chandasana et al.'s re-estimated model, and b-I to b-IV Naidoo et al.'s re-estimated model. a/b-I) Histogram of NPDE with the density of the standard normal distribution overlaid (light blue shaded areas). a/b-II) Quantile-quantile plot of NPDE vs theoretical distribution (light blue shaded area). a/b-III) Scatterplot of NPDE vs time after dose. a/b-IV) Scatterplot of NPDE vs predicted concentrations. Blue circles represent observed concentrations. Dark blue solid lines represent the 5<sup>th</sup>, 50<sup>th</sup> and 95<sup>th</sup> percentiles of observed concentrations. Shaded areas represent a simulation-based 95% prediction interval of the respective percentiles.

## 4 CONCLUSION

- ◆ Model adjustments were not possible, but re-estimation of parameters alone improved predictive performance.
- ◆ Overall, their predictive performance is now adequate, except for their *a priori* imprecision which remained slightly above the acceptability threshold (i.e., MDAPE≤30%).
- ◆ Re-estimated models may better support initial dose selection compared with the original models. Both approaches (i.e., original and re-estimated models) appear suitable for subsequent dose adjustment.

### Perspective

- ◆ Future work should focus on directly comparing dose simulations derived from the original and re-estimated models to determine their relative impact on initial dose selection and subsequent dose adjustments for concentration attainment in clinical practice.