

External evaluation of a population pharmacokinetic model of Cabotegravir in HIV-1-infected patients treated with long-acting Cabotegravir and Rilpivirine

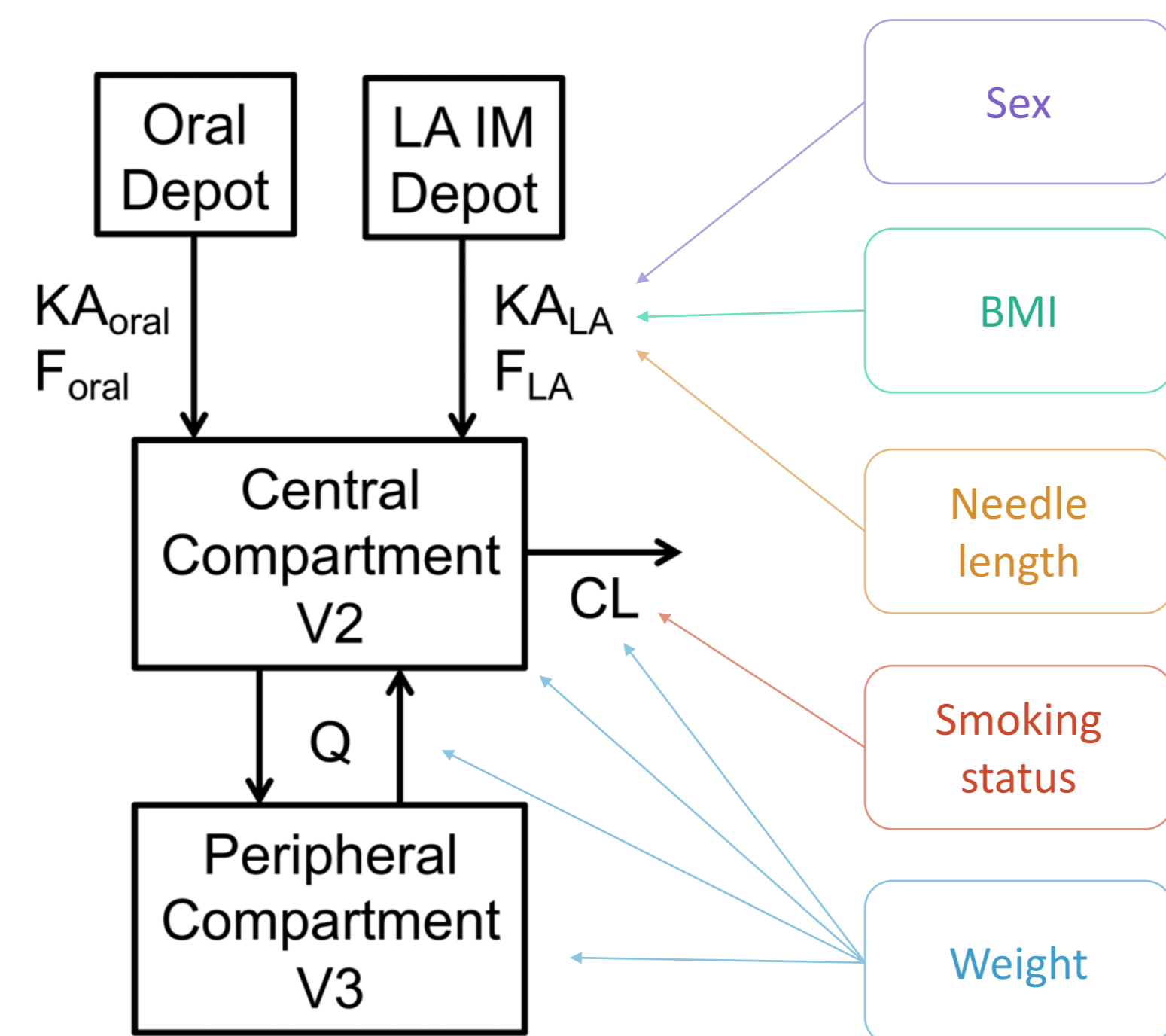
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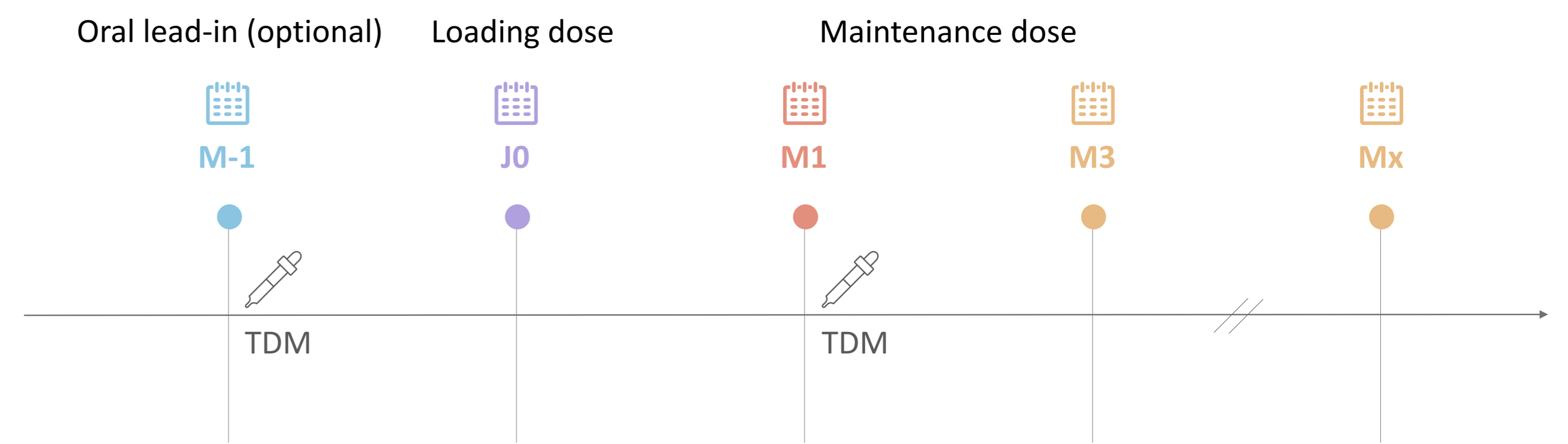
Background

- The long-acting (LA) intramuscular (IM) combination of cabotegravir (CAB) and rilpivirine (RPV) is the first approved regimen for the maintenance treatment of HIV-1 infection.
- Important inter-individual variability (IIV) in trough plasma concentrations (C_{min}) of CAB and RPV has been observed in phase III studies. (1)
- 69% of patients with virological failures (VF) had C_{min} below the median. (1)
- ⇒ Therapeutic drug monitoring (TDM) is recommended during follow-up
- Concentration-effect relationship is not clearly characterized, resulting in a lack of validated target concentrations.
- A POP-PK model was developed by HAN et al. using phase I, II and III studies. (2)

Han et al model



LA CAB-RPV Recommended dosing regimen



Objectives

To evaluate the performance of the POP-PK model of HAN et al. and to use it in an interactive Bayesian tool for TDM.

Methods

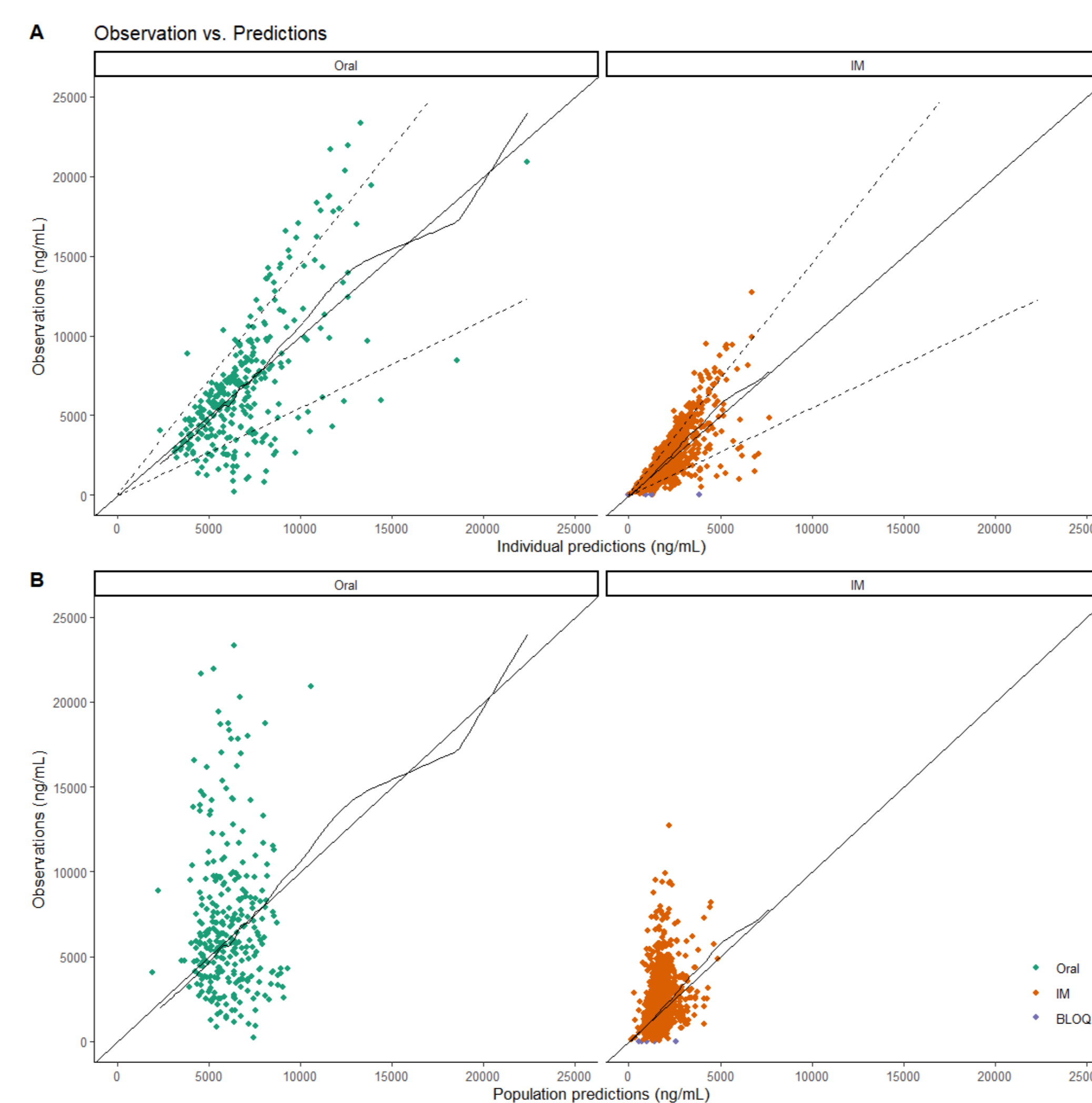
- Data from the multicenter (n=12) and observational ANRS-MIE 0255 CARLAPOP study were used to evaluate the model. Patients treated with LA CAB-RPV, for whom plasma CAB concentrations were determined as part of routine TDM between January 2022 to December 2022 were included.
- Predictive performance was evaluated by :
 - Goodness-of-fit plots : population predictions (PRED) and individual predictions (IPRED) versus the observed CAB concentrations plots, conditional weighted residuals (CWRES) versus time and PRED
 - Prediction-based diagnostic : mean and median prediction error (MPE, MDPE) , median absolute prediction error (MDAPE) and relative root mean squared error (rRMSE)
 - Simulation-based diagnostic : visual predictive checks (VPC)

Study population N=735

Baseline characteristics	Mean (SD), Median [Range] or n (%)
Female	155 (21%)
Age (years)	46 [20 - 79]
Time since infection (years)	11 [1 - 38]
Bodyweight (kg)	74 [43 - 130]
Missing	18
BMI (kg/m ²)	24.5 [16.2 - 44.8]
<25	400 (54%)
25 - 30	231 (31%)
>30	78 (11%)
Missing	26 (3.5%)
ASAT (IU/L)	24 [11 - 105]
ALAT (IU/L)	23 [0 - 227]
Missing	98
HIV subtype	
A	10 (1.4%)
B	265 (36%)
Other	171 (23%)
Missing	289 (39%)
Plasma HIV RNA (copies/mL)	20 [9 - 317,000]
< 50	693 (94%)
>=50 x <200	15 (2.0%)
>200	7 (1.0%)
Missing	20 (2.7%)
CD4 count (cells/mm ³)	762 [144 - 2,067]
>=500	371 (50%)
350-500	56 (7.6%)
<350	24 (3.3%)
Missing	284 (39%)
Oral lead-in	422 (57%)
Smoking status	
Current smoker	226 (31%)
Missing	90 (12%)
Needle length (mm)	
50	81 (11%)
30	629 (86%)
Missing	25 (3.4%)

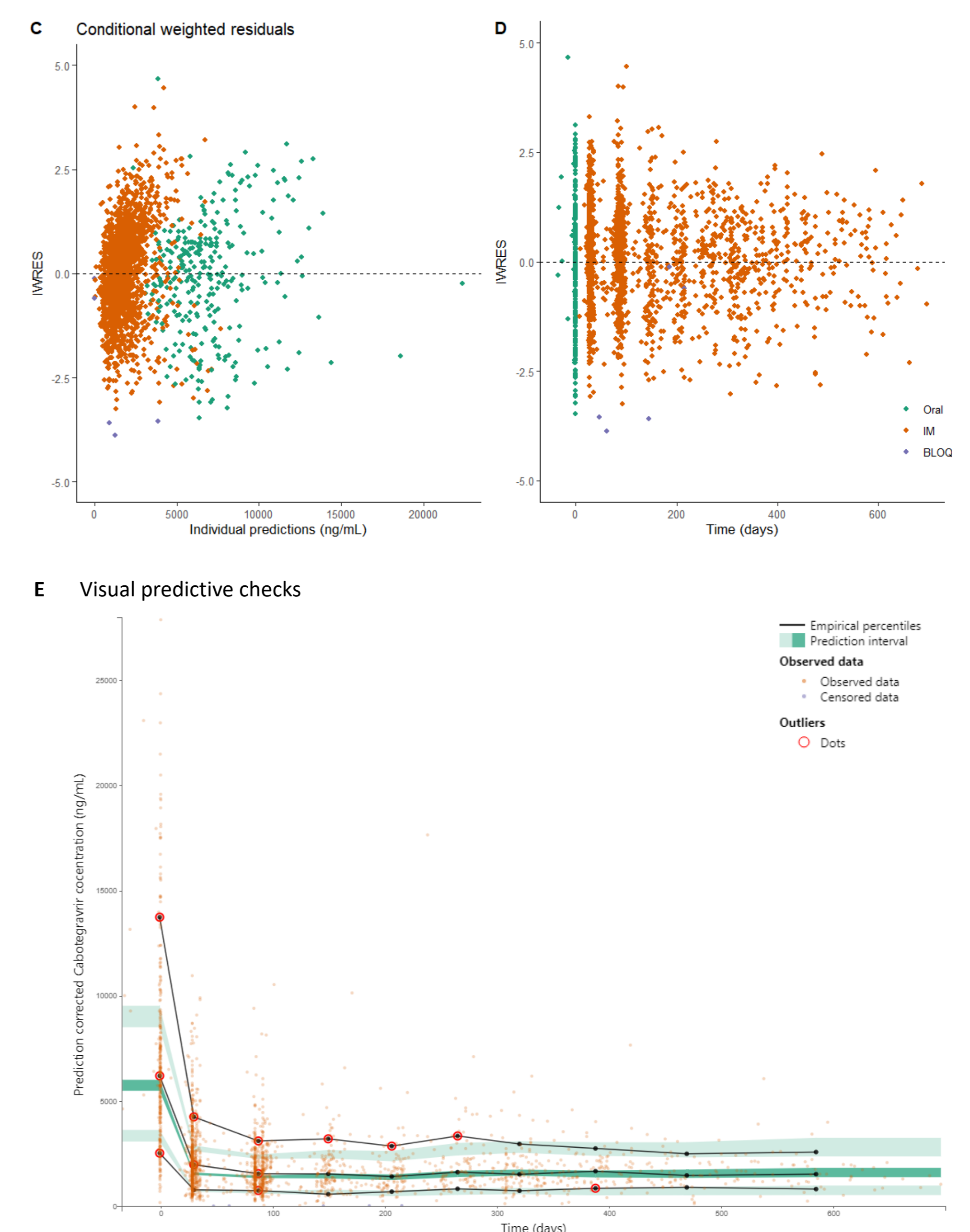
BMI, body mass index ; ALAT, alanine aminotransferase ; ASAT, aspartate aminotransferase ; IU, international unit ; HIV, human immunodeficiency virus

Results



Model performances						
	Route	MPE	MDPE	MDAPE	RMSE (ng/mL)	rRMSE
IPRED	Oral	41%	0,94%	22%	3178	196%
	IM	44%	-4,58%	18%	815	961%
PRED	Oral	37%	-5,42%	35%	4583	220%
	IM	63%	-1,13%	36%	1329	764%

- The prediction-based metrics of the POP-PK model show significant bias and poor precision. Additionally, the goodness-of-fit plots are not satisfactory.
- Bias and precision were significantly different between centers of our study.
- Upper threshold for outliers was calculated, for each route of administration, as : 3rd quartile + 1.5 × Interquartile range. Outliers' depletion didn't significantly improve predictive performances.



Discussion and perspectives

- The model does not fully capture the variability in our data, which may be due to population differences. Unlike real-life patients, those in clinical trials are selected according to strict criteria.
- The predictive performance of the model differs between centers, highlighting the difficulty to perform external validation in a multicenter study. The reasons for these differences remain to be explored.
- The performance of the HAN et al. model could be improved by adjusting the effect of covariates.
- A recently published POP-PK model of CAB developed using real-life data needs to be evaluated. (3)

Conclusion

The aim of this study was to evaluate the applicability of this model to clinical TDM practice. The accuracy and precision of the predictions were inadequate to use the model in clinical practice. An updated model could be used to characterize the PK variability and concentration-effect relationship of CAB, and to validate recommended therapeutic regimens and concentration thresholds.

References

- Cutrell AG, Schapiro JM, Perno CF, et al., *AIDS*, 2021
- Han, Kelong et al., *British journal of clinical pharmacology*, 2022
- Thouelle P, Saldanha SA, Schaller F, et al., *Clin Pharmacol Ther.*, 2024