

Therapeutic drug monitoring strategies for Envarsus in *de novo* renal transplant patients using population modelling and simulations

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Background & objectives

Tacrolimus is a pivotal immunosuppressant agent used in solid-organ transplantation necessitating **therapeutic drug monitoring (TDM)**, due to its narrow therapeutic window. Several formulations have been previously developed, such as Prograf®, an immediate-release capsule to be administered twice daily, and Advagraf®, an extended-release capsule to be administered once daily. **Envarsus®** has been developed recently to be administered once daily: the MeltDose® drug delivery technology enables a broader absorption throughout the gastro-intestinal tract and a sustained consistent tacrolimus concentration.

Objectives:

- to develop a **population PK model** for tacrolimus concentrations after Envarsus administration, in *de novo* renal transplant recipients,
- to explore by simulation the performance of **TDM strategies**.

Methods

Patients & Data: Data were issued from a study evaluating the PK and safety of Envarsus tablets or Advagraf capsules, administered once-daily in adult *de novo* kidney transplant recipients.

33 patients receiving Envarsus for 28 days were monitored:

- treatment initiated at 0.17 mg/kg; then adjusted on specific study days based on **tacrolimus trough level (TTL)**
 - Target range of 5 – 15 ng/mL from day 2 to 14
 - Target range of 5 – 10 ng/mL from day 15 to 22

A total of **1951 tacrolimus concentrations** were collected:

- 1612 observations over 24-hour periods on day 1, 3, 7 and 14
- 339 observations at trough on day 2, 3, 4, 5, 6, 7, 8, 14, 15, 21 and 28

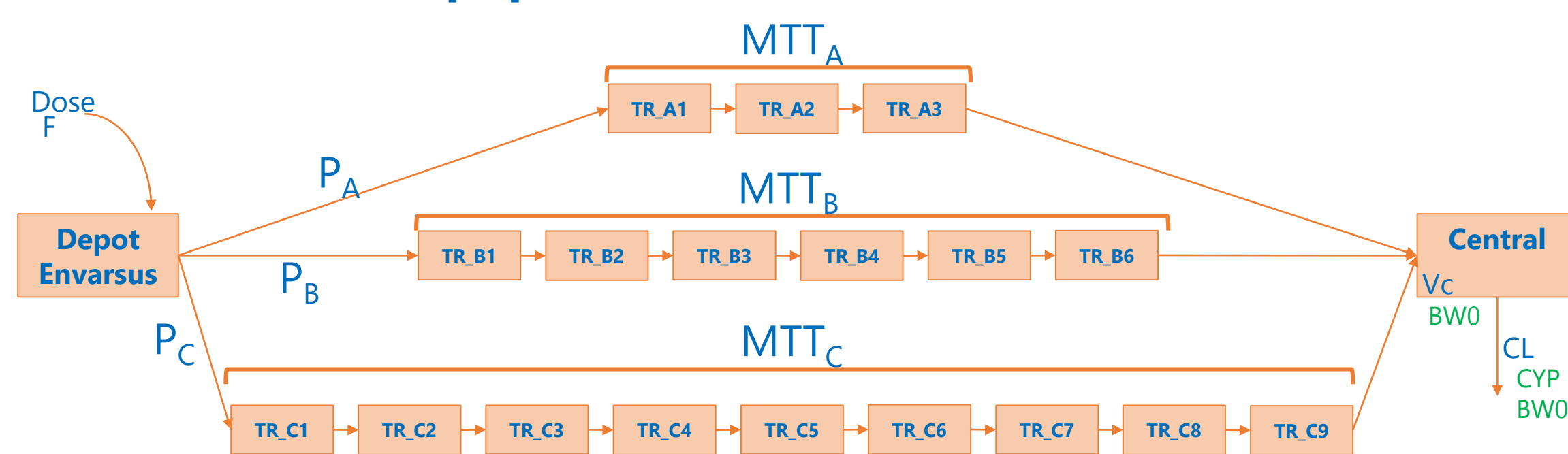
Model Characteristics:

- Population approach, accounting for inter-individual variability (IIV) on PK parameters. Inter-occasion variability (IOV) was included between each 24-hour PK profile, and a separate residual error distribution for TTL
- Static and dynamic covariates evaluated by forward selection and backward deletion procedure

Results

A **one-compartment disposition** model, with first-order elimination and multi-phasic absorption was proposed (**Figure 1**): absorption was characterised by three parallel chains composed respectively 3, 6 and 9 compartments, allowing a **3-phase absorption profile** ($P_A\%$ follows fast absorption MTT_A , $P_B\%$ medium absorption MTT_B and $P_C\%$ slow absorption MTT_C). **Inter-occasion variability** was implemented on relative bioavailability (applied on $P_A+P_B+P_C$). Residual error was additive on the log-scale, with a different magnitude for 24-hour PK profiles, and TTL observations.

Figure 1: Schema of the pop PK model for Envarsus.



CYP3A5 polymorphism (*1/*3 versus *3/*3) was found significant on clearance, and bodyweight (BW) had an effect on clearance and volume.

Parameter estimates are reported in **Table 1**, and visual predictive checks (VPC) stratified on occasion in **Figure 2**.

Table 1: Estimates of Envarsus PK model parameters

Parameter	Unit	Description	Value	RSE (%)	IIV (CV %)	RSE (%)
CL	L.h ⁻¹	Clearance from central compartment	20.0	5.85	29.4	27.1
V	L	Volume of central compartment	451	12.1	54.2	24.4
RATIO *	-	Logit of proportion of drug to be absorbed in chain A	-1.87	15.8	20.1	20.4
MTTA	h	Mean Transit Time of chain A	1.06	8.43	39.9	27.7
MTTB	h	Mean Transit Time of chain B	4.82	12	68.8	26.6
RATIO2 *	-	Difference to RATIO for absorption in chain A or B	2.94	9.05	-	-
MTTC	h	Mean Transit Time of chain C	25.9	4.63	-	-
IOV	-	Inter-occasion variability on relative bioavailability	-	-	43.2	32.2
Res. Err.	-	Additive residual error on log-scale for full profiles	0.269	5.24	-	-
Res. Err. TTL	-	Additive residual error on log-scale for trough levels	0.356	12.7	-	-
BW0_CL		Effect of basal BW on CL (allometry)	0.75 FIX	-	-	-
BW0_V		Effect of basal BW on V (allometry)	1 FIX	-	-	-
CYP_CL		Effect of CYP3A5 polymorphism on CL	1.66	7.89	-	-

$$P_A = \frac{\exp(\text{Ratio})}{1 + \exp(\text{Ratio})} = 0.134 \quad P_B = \frac{\exp(\text{Ratio} + \text{Ratio2})}{1 + \exp(\text{Ratio} + \text{Ratio2})} - P_A = 0.611 \quad P_C = 1 - (P_A + P_B) = 0.255$$

Conclusions

Tacrolimus daily dosage for adequate trough levels maintenance in early post-transplant days is crucial to avoid acute allograft rejection. The PK model provided confirms the starting dose appropriateness and could help healthcare practitioners in fine-tuning the Envarsus dose on a daily basis.

Simulations of TDM strategies:

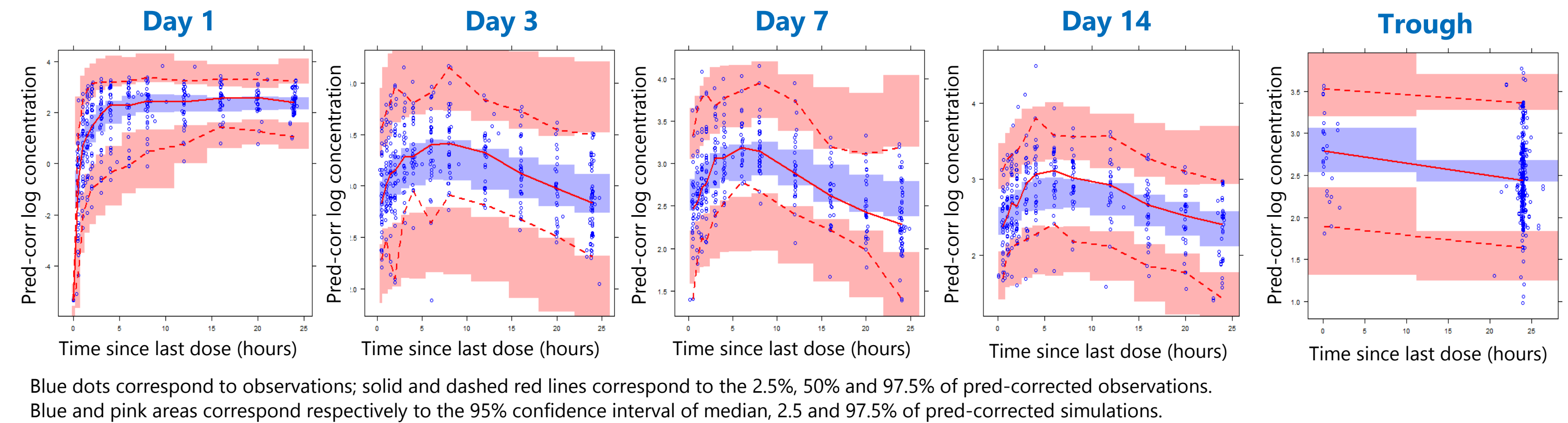
TTL profiles were simulated in populations of patients according to several scenarios for the choice of Envarsus doses:

- **for a priori treatment initiation** (on Day 1 and Day 2):
 - based on bodyweight (e.g. 0.17 mg/kg)
 - based on PK covariates (bodyweight and CYP3A5 polymorphism)
- **for a posteriori treatment adaptation** (from Day 3):
 - based on TTL observations after the before-latest dose (to account for a 24-hour delay between TTL sample and adjusted dose)
 - adjusting to the middle value in the target range; or adjusting to a higher value ($2/3$, $3/4$ or the upper limit of the target range) in order to avoid too low TTL values.

Comparisons of TDM strategies were done in terms of Envarsus dose, TTL profiles and the proportion of patients within, above (risk of nephrotoxicity) and below (risk of graft rejection) the target range.

Model development, parameter estimations and simulations were performed with NONMEM 7.3.

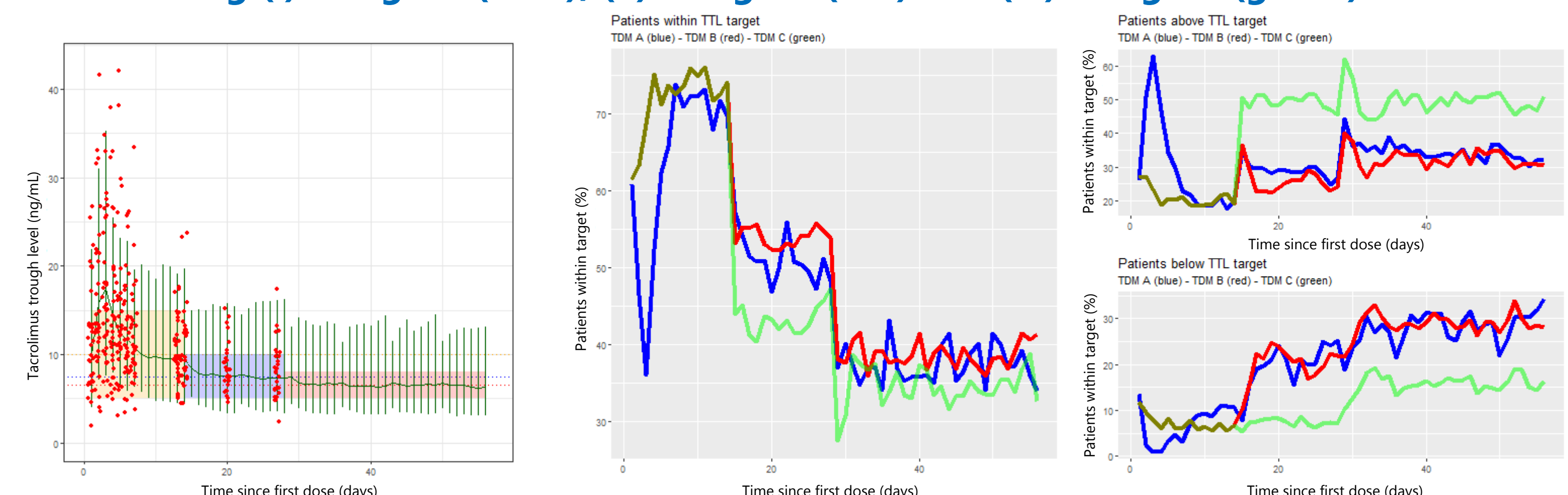
Figure 2: Pred-corrected VPC of plasma concentration as a function of time since last dose on each occasion



Simulations of the design A, similar to the protocol in the original study, were in accordance with the observed TTL profiles (**Figure 3, left**). Design B allowed a larger proportion of patients within target range (**Figure 3, middle**), but the risk to be below the target range was above 20% (**Figure 3, right**). Adjusting to a higher value decreases the risk of under-dosing but increases the risk of over-dosing. Considering tacrolimus inherent intra-individual variability, the best design will be a compromise between the risks of lack of efficacy and toxicity, to get the best chance of success of the immunosuppressive therapy.

Design A	Design B	Design C
A priori treatment initiation $Dose_{Day1} = 0.17 \cdot BW$ mg $Dose_{Day2} = 0.17 \cdot BW$ mg with BW = Bodyweight	$Dose_{Day1} = 11.26 \cdot \left(\frac{BW}{70}\right)^{1.80} \cdot 1.45^{CYP}$ mg $Dose_{Day2} = 5.25 \cdot \left(\frac{BW}{70}\right)^{1.71} \cdot 1.76^{CYP}$ mg with CYP=0 for CYP3A5 *3/*3 patients; CYP=1 for *1/*3 patients	
A posteriori treatment adaptation $Dose_{DayN} = Dose_{DayN-2} \cdot \frac{Target}{TTL_{DayN-2}}$	Target the middle value of the target range: • 10 [5 – 15] ng/mL from Day 2 to 14 • 7.5 [5 – 10] ng/mL from Day 15 to 28 • 6.5 [5 – 8] ng/mL from Day 29 to 56	Target the upper value : • 10 [5 – 15] ng/mL from Day 2 to 14 • 10 [5 – 10] ng/mL from Day 15 to 28 • 8 [5 – 8] ng/mL from Day 29 to 56

Figure 3: TTL observations and simulated profiles with design A (left) and proportion of patients within (middle), above and below (right) target range, simulating (i) design A (blue), (ii) design B (red) and (iii) design C (green)



Left panel: Red dots correspond to TTL observations (original data). Thick solid green line corresponds to the simulated median TTL, vertical green lines correspond to 90%CI. Orange, blue and red areas correspond to target range; orange, blue and red dotted lines correspond to TTL targets (middle of target range).
Middle and right panel: Blue lines correspond to the original TDM strategy (weight-based initiation and TTL-based adaptation); Red line correspond to a covariate-based initiation and TTL-based strategy, targeting the middle of target range; green lines correspond to a covariate- and TTL-based strategy, targeting the upper limit of target range.