

Modeling hepatitis C viral kinetics to compare antiviral potencies of two protease inhibitors: a simulation study under real conditions of use

Cédric Laouénan (1,2), Jérémie Guedj (1,3), France Mentré (1,2)

(1) Université Paris Diderot, Sorbonne Paris Cité, INSERM, UMR 738, Paris, France; (2) AP-HP, Hôpital Bichat, Service de Biostatistique, Paris, France; (3) Los Alamos National Laboratory, New Mexico, USA.

Context

- Chronic Hepatitis C Virus (HCV) infection**
 - One of the most common causes of chronic liver disease
 - Standard of care:** bitherapy = weekly injections of pegylated interferon + daily oral ribavirin
 - New tritherapy:** bitherapy + oral *tid* Protease Inhibitor (PI): telaprevir (TVR) or boceprevir (BOC) (marketing authorization since September 2011 in France for genotype 1)

MODCUPIC - ANRS trial

- Cohort of patients with HCV genotype 1 infection with compensated cirrhosis (F4) who failed prior treatment by bitherapy
- Main objective: provide for the first time a precise description of early viral kinetics under tritherapy in real conditions of use
- Inclusion of 60 patients scheduled (30 per PI)
- Frequent Viral Load (VL) measurements (table 1)

Table 1. VL measurement in MODCUPIC

	D0	D0.33	D1	D2	D3	W1	W2	W3	W4	W8	W12
VL measurement	x	x	x	x	x	x	x	x	x	x	x

Mathematical modeling of viral kinetic after treatment initiation

- Describe by Ordinary Differential Equations (ODE)
- Critical insights for the understanding of the virus pathogenesis, the drug's mechanism of action and its antiviral effectiveness [1]
- Nonlinear mixed effect models (NLMEM):** appropriate to estimate parameters of these models and their inter-patients variability

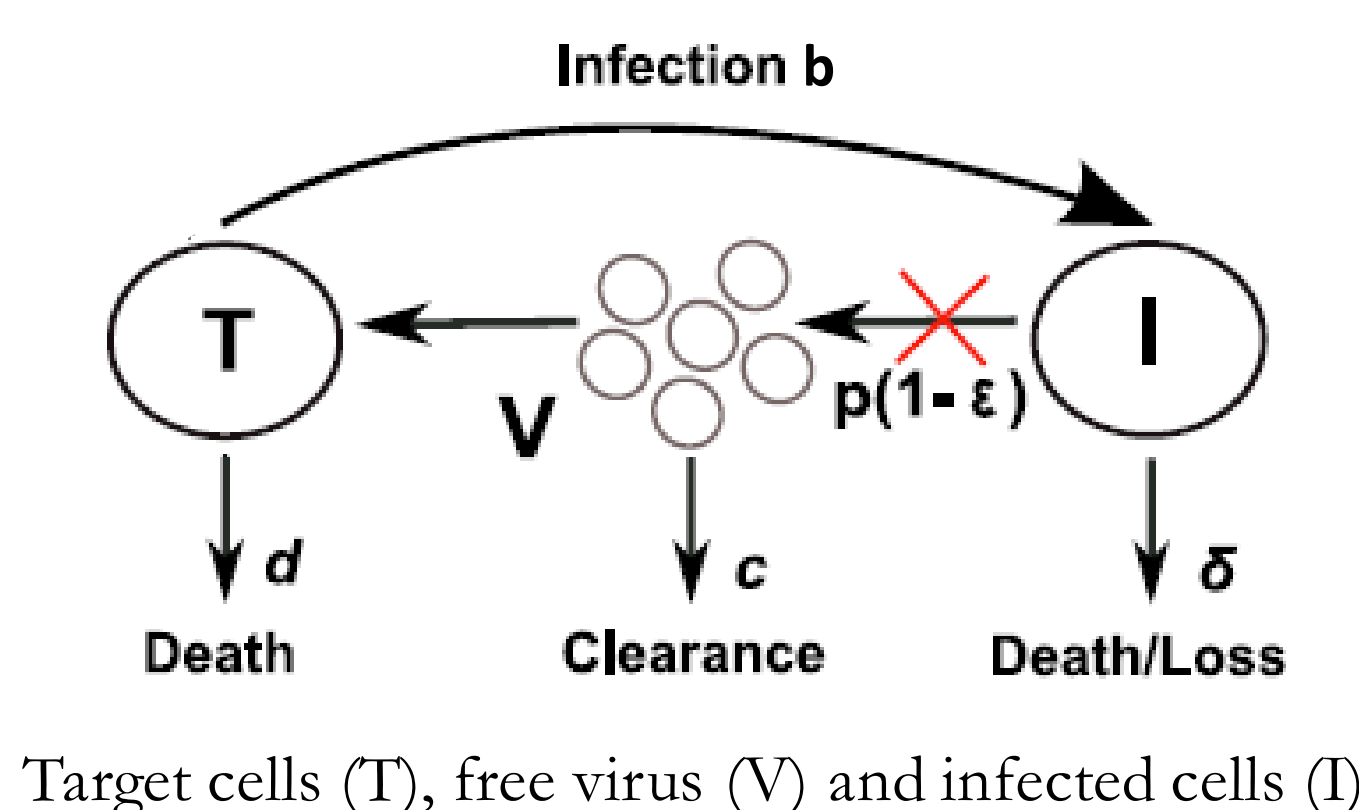
Objectives

- To evaluate by simulation:**
 - the estimation performance for the chosen MODCUPIC's design
 - the power to detect a difference of potency between TVR and BOC using an HCV dynamic model

Model and methods

Neumann et al. viral dynamic model [1]

Figure 1. Viral dynamic model and system of ODE



Hypothesis : T constant (short term model)

$$\begin{cases} \frac{dI}{dt} = bVT_0 - \delta I \\ \frac{dV}{dt} = p(1-\varepsilon)I - cV \end{cases}$$

Protocol simulation

- Values of parameters and inter-individual variations proposed by Guedj *et al.* [2]

Table 2. Values and distributions of population parameters and values of additive random effect

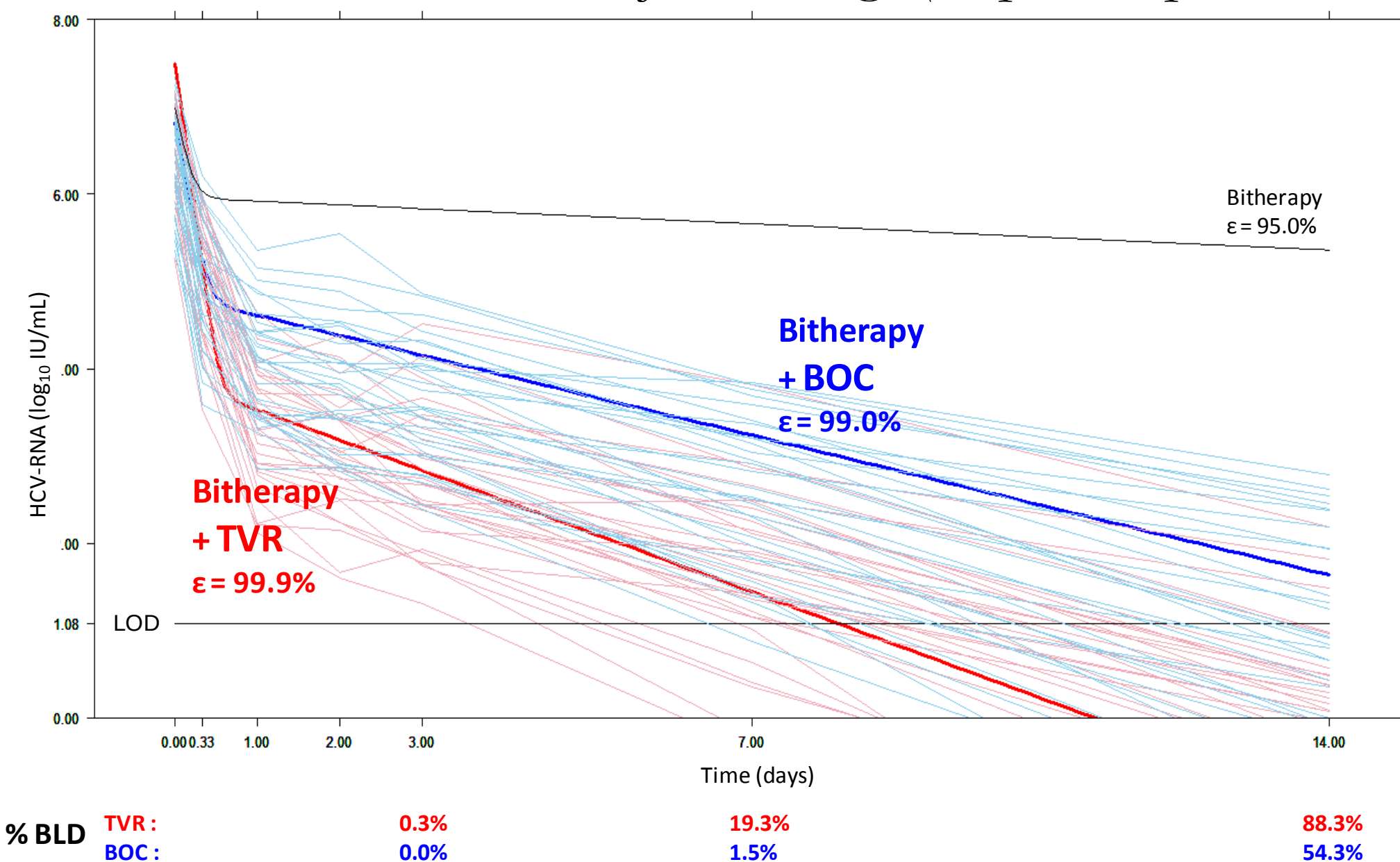
	V_0 (UI/mL)	c (j ⁻¹)	δ (j ⁻¹)	ε
Fixed effect	$2.44 \cdot 10^6$	13.4	0.58	0.999
Distribution	lognormal	lognormal	lognormal	logistic-normal
Inter-individual variation (ω)	1.09	0.248	0.245	0.61

- Parameters fixed: $p = 10$ UI/L/mL/cell/day and $b = 10^{-6}$ (UI/mL)⁻¹/day
- Analysis of $\log_{10}(\text{VL})$ with additive residual error: $\sigma = 0.19$
- ε = antiviral potencies (percentage of blockage of virion production)
 $\varepsilon^{\text{TVR}} = 99.9\%$ and $\varepsilon^{\text{BOC}} = 99.8\%, 99.5\%$ or 99.0%
- Treatment effect: $\beta = \text{logit}(\varepsilon^{\text{TVR}}) - \text{logit}(\varepsilon^{\text{BOC}})$
- Limit Of Detection (LOD) = 12 UI/mL
- Designs:
 - Reference design = 7 VL (0, 0.33, 1, 2, 3, 7, 14 days) and 30 patients per PI
 - 10, 50 or 100 patients per PI
 - 5 VL = without VL at D0.33 and D1
- 500 datasets were simulated for each scenario (R software)
- Population parameters were estimated using SAEM algorithm [3,4] in MONOLIX 4.2 [5] that take into account Below Limit of Detection (BLD) data [6]

- Test to compare the antiviral potency between PIs**
 - By modeling:** Wald test on treatment effect β
 - Without modeling:** Wilcoxon test to compare $\log_{10}(\text{VL})$ differences between D0 and D14

Type I error = % of the 500 datasets where p-value < 0.05 under H_0
Power = % of the 500 datasets where p-value < 0.05 under H_1
Empirical threshold correction in case of inflation of the type I error [7]

Figure 2. Simulated dataset with the reference design (30 patients per PI and 7 VL)



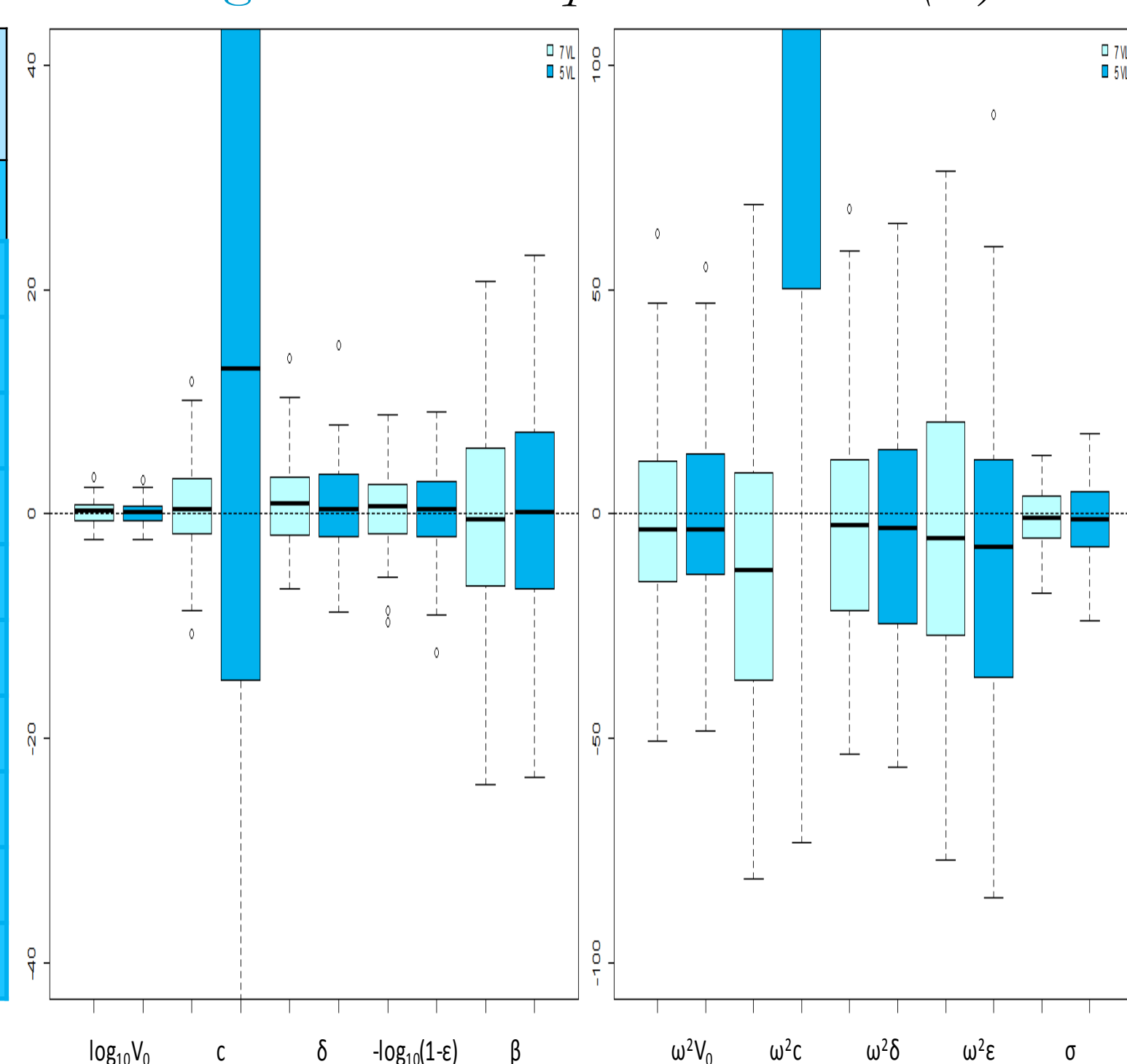
Results

Parameter estimates (with 30 patients per PI, $\varepsilon^{\text{TVR}} = 99.9\%$ and $\varepsilon^{\text{BOC}} = 99.0\%$)

Table 3. Relative bias and RMSE

Number of VL	Biases (%)		RMSE (%)	
	7 VL	5 VL	7 VL	5 VL
$\log_{10}(V_0)$ (UI/mL)	0.17	0.14	1.01	0.99
c (j ⁻¹)	0.62	34.08	4.11	78.76
δ (j ⁻¹)	0.84	0.58	3.71	3.73
$-\log_{10}(1-\varepsilon)$	0.43	0.34	3.09	3.60
β	-0.49	0.39	8.48	9.93
$\omega^2 V_0$	-0.97	-0.53	19.01	19.30
$\omega^2 c$	-10.86	236.64	32.90	358.29
$\omega^2 \delta$	-2.33	-2.38	24.46	24.91
$\omega^2 \varepsilon$	-4.51	-9.86	32.01	36.33
σ	-0.72	-1.32	6.15	7.99

Figure 3. Relative prediction errors (%)



Type I error and power to detect a difference of potency between PIs

Figure 4. Type I error of the Wald test

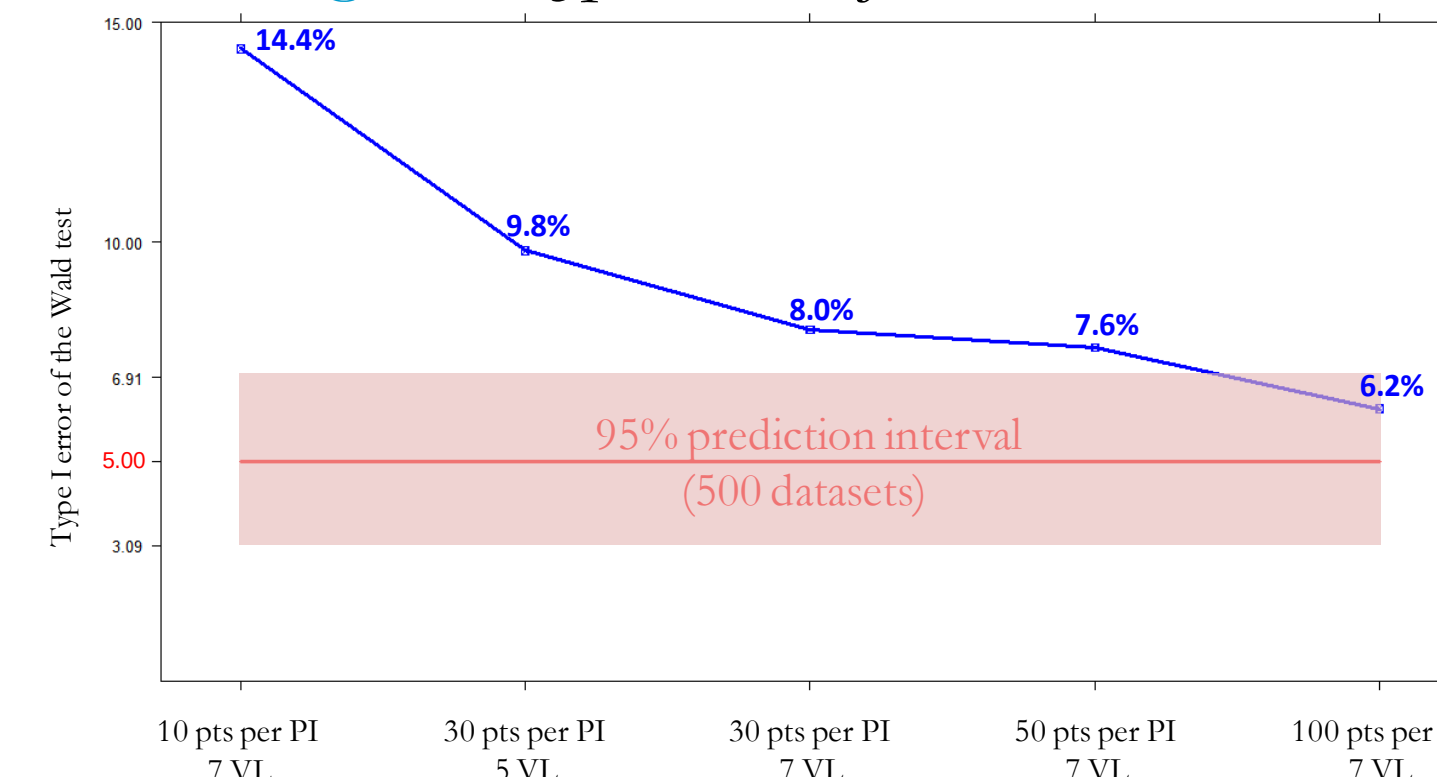


Table 4. Power estimated (%) with $\varepsilon^{\text{TVR}} = 99.9\%$ according to the design

Design	30 patients per PI 7 VL			30 patients per PI 5 VL			10 patients per PI 7 VL		
ε^{BOC}	99.8%	99.5%	99.0%	99.8%	99.5%	99.0%	99.8%	99.5%	99.0%
Wald test (uncorrected)	94.0	100	100	89.4	100	100	62.2	99.8	100
Wald test (corrected)	89.2	100	100	82.6	100	100	44.2	98.4	100
Wilcoxon test	7.4	31.0	67.0	7.4	31.0	67.0	6.6	11.2	26.8

Conclusion

- The use of viral dynamic modeling approaches along with NLMEM in our simulation study validates the design of MODCUPIC's trial
 - Accurate estimation of the parameters
 - Good power to compare the antiviral potency of TVR and BOC, even with sparse initial sampling
- Compared with standard approach (Wilcoxon test), modeling approach (Wald test) provides a more powerful tool
- The Wald test is asymptotic: threshold correction needed with small samples
- Modeling with the lead-in phase for BOC is ongoing

References

[1]Neumann AU et al. Science 1998; [2]Guedj et al. Hepatol 2011; [3]Delyon B et al. Ann Stat 1999; [4]Lavielle M et al. Biometrics 2010; [5]<http://software.monolix.org>; [6]Samson et al. Comput Statist Data Anal 2006; [7]Bertrand J et al. Biometrics 2012.