

# Characterization of the early viral kinetics in compensated cirrhotic treatment-experienced patients treated with boceprevir and telaprevir

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## CONTEXT

- Triple therapy (HCV genotype 1)
  - Bitherapy (PEG-IFN/RBV) + 1 Protease Inhibitor (PI)
    - PI: **telaprevir (TVR)** or **boceprevir (BOC)**
- Viral kinetics (VK) models has been previously published for TVR but in treatment-naïve or non-cirrhotic patients [\[1,2\]](#)
- No VK data with early frequent measurements was published with BOC
- Mathematical modeling of viral kinetic after treatment initiation has brought critical insights for the understanding of the virus pathogenesis, the drug's mechanism of action and its antiviral effectiveness [\[3\]](#)

## OBJECTIVE

- To compare early viral kinetics in compensated cirrhotic treatment-experienced patients treated with triple therapy in real-life setting

## METHODS

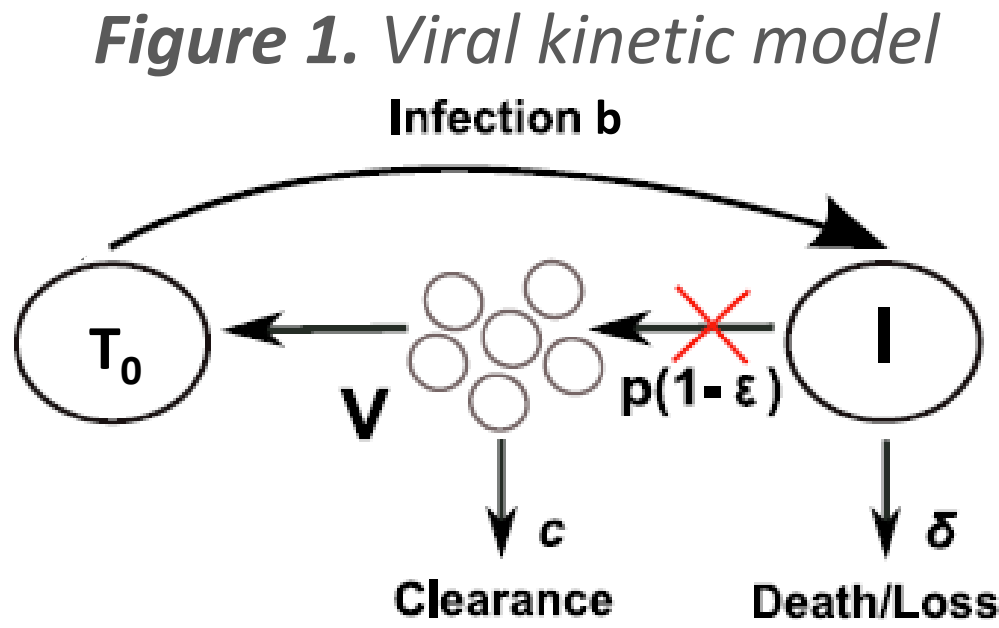
**Data = MODCUPIC - ANRS trial** (Pr Marcellin, Paris, France)

- Ancillary study of CUPIC ANRS-CO20 (Dr Hézode, Paris, France)
- Multicentric cohort of patients with HCV genotype 1 monoinfected
- Compensated cirrhosis (F4) who failed prior treatment by bitherapy
- Patients were prospectively included to receive without randomization either:
  - TVR + PEG-IFN/RBV** or
  - BOC + PEG-IFN/RBV**
- Patients in BOC group received only PEG-IFN/RBV during the first 4 weeks lead-in phase
- Frequent Viral Load (VL) measurements within 12 weeks after PI initiation

**Viral kinetic modeling:** standard Neumann *et al.* viral biphasic model [\[4\]](#)

Ordinary Differential Equations (ODE):

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



- Where:
  - I: the infected cells,
  - V: the VL,
  - T<sub>0</sub>: the target cell number (which is assumed to be constant and equal to its pretreatment value),
  - b: the rate at which target cells are infected (fixed to 10<sup>-6</sup> IU/mL/day),
  - p: the viral production rate per infected cell in absence of treatment (fixed to 10 IU/L/cell/day),
  - V<sub>0</sub>: the baseline VL,
  - c: the clearance rate of VL,
  - δ: the loss rate of infected cells,
  - ε: the drug efficacy (treatment is assumed to reduce the average rate of viral production per cell from p to p(1-ε))
- Modeling drugs combination:** we assumed that PI and PEG-IFN/RBV have a multiplicative effect with (1-ε) = (1-ε<sub>1</sub>)(1-ε<sub>2</sub>) where:
  - ε<sub>1</sub> is the effect of PEG-IFN/RBV and ε<sub>2</sub> is the effect of PI
  - ε<sub>2</sub> = 0 for BOC group during the lead-in phase

### Parameter estimation

- Viral kinetic parameters were estimated using Nonlinear mixed effect models (NLMEM) with SAEM algorithm in MONOLIX 4.1 [\[5\]](#) that take into account Below Limit of Detection (BLD) data [\[6\]](#)
- Only data until VL rebounds (if any) were fitted
- HCV RNA limit of detection (LOD) = 12 UI/mL
- Wald test was performed to detect a difference between treatment groups for each parameters (V<sub>0</sub>, c, δ and ε)
- Permutation test (n = 1000 permutations) was performed if Wald test was significant for a difference of treatment efficacy as an inflation of type I error of Wald test was expected [\[7\]](#) to obtained the distribution of the p-values under the null hypothesis of no treatment effect

## RESULTS

- Fifteen patients were included (**9 TVR**, **6 BOC**)
- Median [min-max] age: 54.6 years [43.9-58.9]; males: 13 (87%)
- HCV genotype: 1a: 8 / 1b: 4 / 1c: 2 / 1e: 1
- The biphasic model can well describe the viral kinetics in all patients (**Figure 2**) and model parameters were estimated with good precision (**Table 1**)

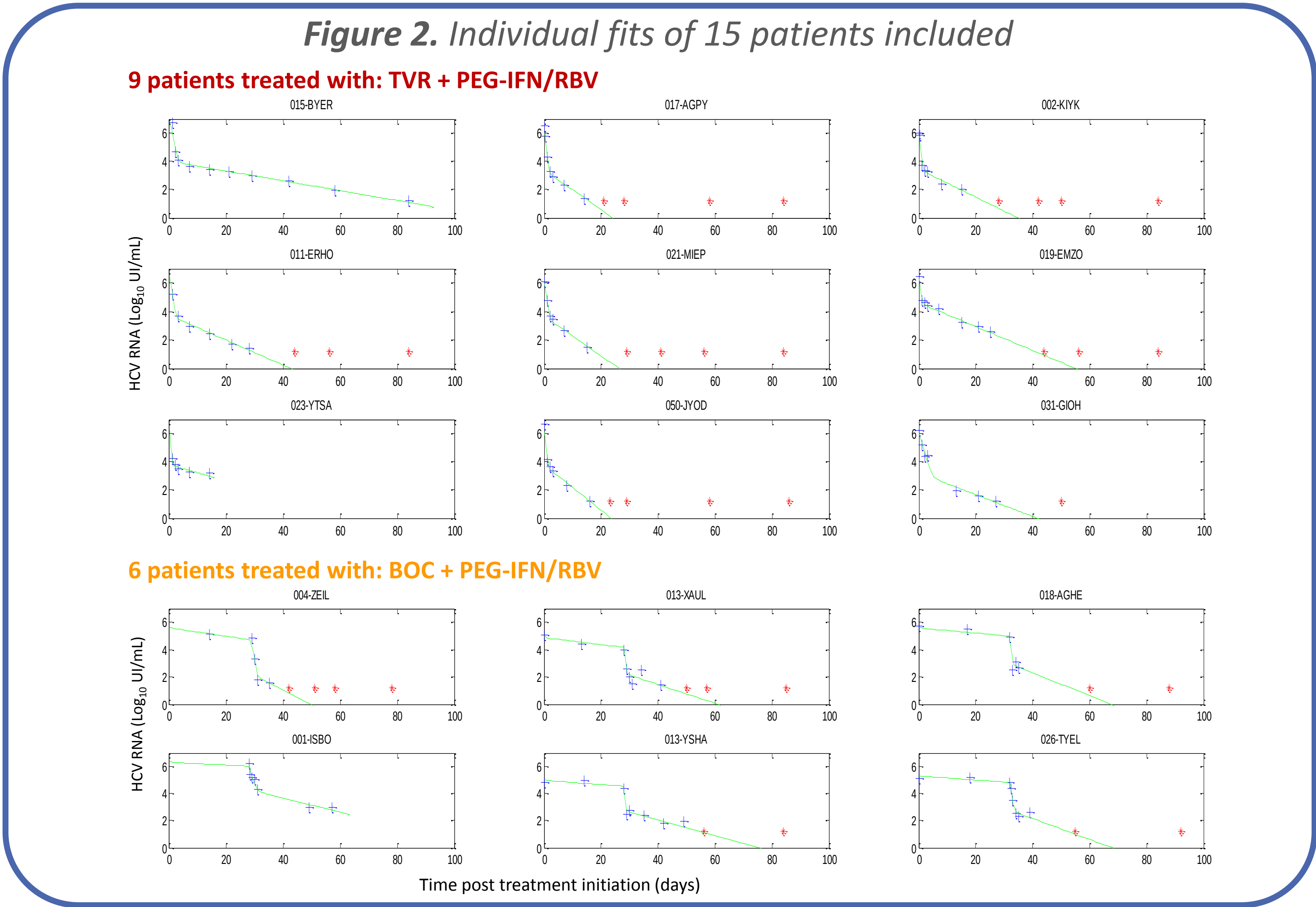


**Table 1.** Parameter estimates with relative standard errors *r.s.e.*

| Parameter (units)                                       | Estimate | r.s.e.(%) |
|---------------------------------------------------------|----------|-----------|
| V <sub>0</sub> <sup>TVR</sup> (log <sub>10</sub> IU/mL) | 6.43     | 14        |
| V <sub>0</sub> <sup>BOC</sup> (log <sub>10</sub> IU/mL) | 5.52     | 3         |
| c (day <sup>-1</sup> )                                  | 3.98     | 13        |
| δ (day <sup>-1</sup> )                                  | 0.19     | 11        |
| ε <sup>PEG-IFN</sup>                                    | 0.24     | 17        |
| ε <sup>TVR</sup>                                        | 0.998    | 0         |
| ε <sup>BOC</sup>                                        | 0.990    | 0         |
| ω <sub>V0</sub>                                         | 0.07     | 16        |
| ω <sub>c</sub>                                          | 0.48     | 19        |
| ω <sub>δ</sub>                                          | 0.44     | 15        |
| ω <sub>ε<sup>PEG-IFN</sup></sub>                        | 0.47     | 27        |
| ω <sub>ε<sup>PI</sup></sub>                             | 0.81     | 26        |
| σ                                                       | 0.25     | 9         |

- Patients in TVR group had a higher V<sub>0</sub> than in BOC group
- ε<sup>TVR</sup> and ε<sup>BOC</sup> were significantly different between treatment groups (Uncorrected p-value = 0.006; corrected p-value with permutation test = 0.04)
- c and δ were not significantly different between treatment groups

## CONCLUSIONS

- Small sample size non randomized study
- ε<sup>TVR</sup> was comparable to previously published in non-cirrhotic naive patients [\[1\]](#) and ε<sup>BOC</sup> was significantly lower than ε<sup>TVR</sup> (even adjusted on V<sub>0</sub>)
- Of note, there was a trend to allocate TVR in patients that were considered more difficult to treat (higher V<sub>0</sub> and poorer response to previous bitherapy)
- Biphasic viral decline was slower than what had been observed in non-cirrhotic naive patients during TVR monotherapy [\[1,2\]](#) and was close to typical values observed during PEG-IFN/RBV therapy [\[8\]](#)
- This feature was attributed in the model to a mean clearance of free virus, c, and a mean loss rate of infected cells, δ, three times smaller than in non-cirrhotic naive patients treated with TVR monotherapy [\[1\]](#)
- The discrepancy in viral kinetic parameters observed here could be due to impaired pharmacokinetics (PK) and lower penetration capacity of PIs in hepatocytes of cirrhotic patients
- As the viral decline was slower, cirrhotic treatment-experienced patients may need longer time to achieve viral eradication
- PK data of PI, PEG-IFN and RBV are currently analyzed and will allow to better understand the role of PK in this impaired virologic response

[\[1\]](#) Guedj, Perelson. Hepatology 2011, 53(6):1801–1808.

[\[2\]](#) Adiwijaya, Kieffer, Henshaw, Eisenhauer, Kimko, Alam, *et al.* PLoS Comput Biol 2012, 8(1):e1002339.

[\[3\]](#) Guedj, Rong, Dahari, Perelson. J Viral Hepat 2010, 17(12):825-833.

[\[4\]](#) Neumann, Lam, Dahari, Gretch, Wiley, Layden, Perelson. Science 1998, 282:103–7.

[\[5\]](#) <http://lixsoft.eu>

[\[6\]](#) Samson, Lavielle, Mentré. Comput Statist Data Anal 2006, 51:1562–1574.

[\[7\]](#) Laouénan, Guedj, Mentré. BMC Med Res Methodol 2013, 13:60.

[\[8\]](#) Chatterjee, Guedj, Perelson. Antivir Ther 2012;17:1171-1182.