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HCV Viral Load Kinetics during Acute Hepatitis C in HIV-Infected Patients: a Model-Based Analysis

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Background & objectives

- Timing of treatment initiation in patients with acute hepatitis C (AHC) unclear.
- Spontaneous clearance (SC) may occur but time at which it occurs unknown because infection can rarely be dated.
- Relationship between viral kinetics and SC occurrence not evaluated in the past.

- **Objectives**:
- 1st: to model HCV viral load kinetic during the acute phase of hepatitis C in HIV-infected patients in the absence of HCV treatment;
- 2nd: to use this model to determine frequency of SC occurrence over time.

Methods

***Based on available medical literature*[1-10]**: Four phases for HCV RNA kinetic during AHC have been considered: ① ramp-up, ② plateau, ③ drop, and ④ stabilization (Figure 1); the two last phases being different according to whether the patient is a spontaneous clearer (SpC) or a chronic evolver (CE).

Based on the individual HCV RNA data from 261 HIV-HCV co-infected patients in acute phase of HCV and data available in the literature: 33% of untreated patients were SpC.

For each phase, random distributions were determined and Kolmogorov-Smirnov and Shapiro-Wilk tests were used to provide reliability.

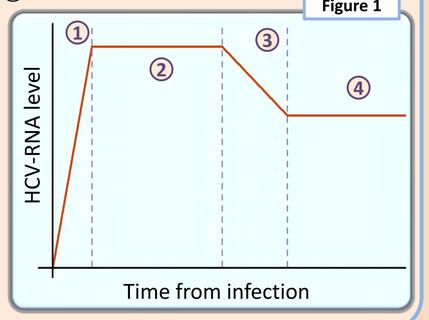
The trajectory of 50,000 virtual patients has been simulated to obtain cumulative frequency of SC over time. SC occurrence is defined as first undetectable HCV RNA.

Sensitivity analysis

In addition to base-case simulating a population in which both early (12%) and delayed seroconversions (76%) occurred (Table 1), two alternative scenarios were considered: one with only early seroconversions (88%, Scenario S1) and one with only delayed seroconversions (88%, Scenario S2), whereas 12% have no seroconversion.

Figure 1: 4 phases in HCV viral load kinetics. ① ramp-up; ② plateau; ③ drop; ④ stabilization

Figure 1



Results

- Data were fitted according to distributions and estimated parameters reported in the Table 1.
- For the drop phase, we identified five different profiles: four for CEs (CE1 to CE4) and one for SpC (Figure 2).
- In the base-case analysis the model estimated a median time from infection to SC occurrence of 187 days (IQ 130-263), i.e. around 6 months; no SC was observed before 35 days and 10% occurred after more than one year (Table 2)(Figure 3).

Figure 2

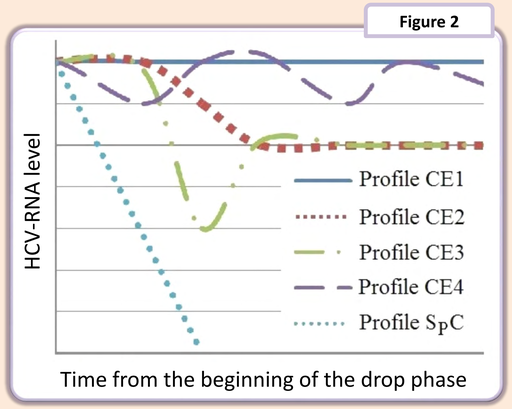


Figure 2: Different profiles identified for the drop phase. CE1-CE4 profiles stand for chronic evolvers. SpC profile concerns spontaneous clearers.

Table 1: Statistical distributions of kinetics parameters found from real data according to the phases presented in figure 1 and the different profiles for drop phase shown in figure 2.

Table 1

Phase	Parameters	Distribution
Ramp up	Doubling time of HCV RNA (in hours)	Uniform on [8-10]
	Maximal viral load in log (IU/mL)	Normal (mean=6.37, sd=0.75)
Plateau[11]	Time from first PCR+ to seroconversion in days*	
	Early seroconversion (B: 12%, S1: 88%, S2: 0%)	Uniform on [0-90]
	Delayed seroconversion (B: 76%, S1: 0%, S2: 88%)	Weibull (shape=1.71, scale=128.97)
	No seroconversion (B, S1, S2: 12%)	-
Drop		
CE2	Loss rate in log (IU/mL) /day	Uniform on [0.01-0.05]
	Final level in log (IU/mL)	Uniform on [2.75-5.5]
CE3	Loss rate in log (IU/mL) /day	Uniform on [0.015-0.055]
	Lowest level in log (IU/mL)	Uniform on [2.5-4.2]
	Rise rate in log (IU/mL) /day	Weibull (shape=0.85, scale=0.04)
	Final level in log (IU/mL)	Normal (mean=5.72, sd=1.05)
CE4	Amplitude of fluctuations in log (IU/mL)	Uniform on [0.4-1.6]
	Half-period in days	Uniform on [75-150]
SpC	Loss rate in log (IU/mL) /day	Weibull (shape=1.64, scale=0.12)

* Percentages in brackets give repartitions used during simulation for the base-case analysis (B) and the sensitivity analyses (S1 and S2). Regarding S1 and S2 scenarios, 88% represent the merging of both early and delayed seroconversions which were present in the base-case analysis.

Results of sensitivity analysis

Results in terms of time to SC occurrence are shown in Table 2 and Figure 3. No SC was observed before 35 days, similar to base-case. In scenario S1, only 5% of all SCs were achieved after more than one year, versus 10% in the base-case analysis and scenario S2.

Table 2

Scenario	Days from contamination to SC occurrence: median (IQ range)
Base-case analysis	187 (130 - 263)
S1: Early seroconversions	128 (95 - 175)
S2: Delayed seroconversions	196 (141 - 272)

Figure 3

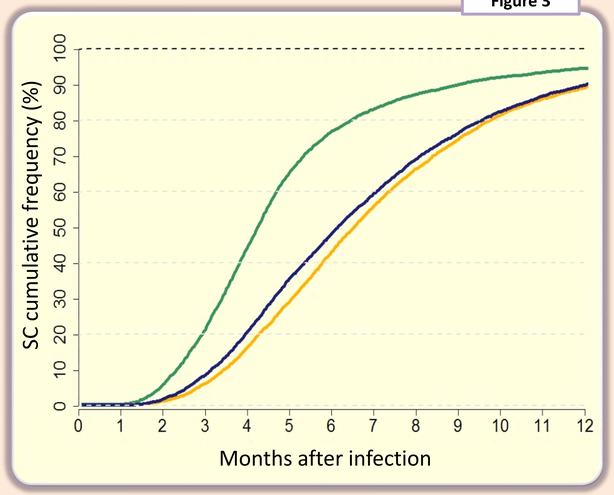


Figure 3: Cumulative repartition of time to SC occurrence from infection among spontaneous clearers. **Blue: Basis analysis**; **Green: Scenario S1**; **Orange: Scenario S2**.

Conclusion

This model informs clinicians on the time to SC occurrence. It also highlights the diversity of HCV viral loads evolution profiles after infection in HIV-infected individuals. These predictions could help optimizing the timing of treatment initiation during acute hepatitis C.

References:

1. Glynn et al., *Transfusion* 2005 ; **2.** Hajarizadeh et al., *Nat Rev* 2013; **3.** Thomson et al., *Gut* 2011; **4.** Nubling et al., *Transfusion* 2002; **5.** Dahari et al., *Gastroenterology* 2005; **6.** Ribeiro et al., *Plos Pathog* 2012; **7.** Thomas et al., *J. of Hep.* 2013; **8.** Lavillette et al., *J Virol* 2005; **9.** Leroy, *Hepato-Gastro* 2008; **10.** Sallie, *J Virol* 2005; **11.** Thomson et al., *AIDS* 2009

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