Modeling early viral kinetics during observed HCV acute infection in post lung transplantation recipients

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INTRODUCTION

- A large proportion of potential organ donors currently test positive for hepatitis C virus (HCV) infection.
- Although treatment after transplantation appears effective, prevention of infection would be preferable.
- In vitro, exposure of HCV to ultraviolet C (UVC) light reduces viral infectivity (Galasso M, Feld JJ, Watanabe Y et al. Nat Comm 10(1): 2019)
- Transplantation from HCV-infected donors to uninfected recipients provides a unique opportunity to evaluate very early HCV kinetics during acute infection and to assess mechanisms for effects of UVC on HCV

AIM

To characterize HCV kinetics from infection to steady state in immunosuppressed recipients of lung transplantation from HCV-infected donors with and without exposure to UVC light during organ preservation to develop an agent-based model (ABM) to provide insights into viral-host dynamics.

METHODS

- We evaluated HCV infection kinetics in patients who received lung transplants from HCV-infected donors in a single center prospective study.
- Donor lungs meeting functional criteria for transplantation were sequentially assigned to one of two groups during organ preservation:
  i. normothermic ex vivo lung perfusion (EVLP) (control group, n=11)
  ii. EVLP with perfusate exposure to ultra-violet C light (UVC group, n=11).
- After 4-6 hours of EVLP lungs were transplanted into consented recipients.
- Recipients were tested daily for the first week and then weekly for the first 12 weeks for HCV RNA using Abbott RealTime PCR.
- All patients who became viremic received sofosbuvir/velpatasvir (Epclusa) for 12 weeks starting no earlier than 2 weeks after transplant.
- Only HCV kinetic data from patients who achieved viral plateau (or steady state) before the initiation of antiviral treatment were used for modeling.
- Post-operative immunosuppression and transplant care were carried on as usual.

MODELING METHODOLOGY

Agents

- **Hepatocyte**: characterized by their number and disease state in a lattice.
- **Hepatitis C virus (V) :** represented as a single global agent; characterized by amount, infectiousness and clearance rate.

Modeling assumptions and initial conditions

- In the model (**Fig. 1**), uninfected hepatocytes (T) are represented as individual agents with the introduction of free virus (V) into the blood.
- When uninfected agents are exposed to HCV, they become infected and enter an eclipse phase (I_E) in which they do not secrete virus.
- Infected hepatocytes then proceed to a productive phase (I_P) in which they release virions that go on to infect additional cells/agents.
- Initial viral and host parameters were defined based on trial design, measured kinetics and previous estimates (**Table 1**).

Figure 1. ABM model of HCV infection in patients post lung transplantation (p.t.)

Table 1. Model initial conditions and parameters

Parameters	Description	Unit	Value
T_0	Total susceptible hepatocytes		$3x10^5$
c	Virus clearance rate constant	hr^{-1}	0.78
Ω	Duration of eclipse phase	Hr	3-12*
ρ	fraction of infectious virus		0.5

* Normal distribution

Viral production cycle

- In the ABM (**Fig. 1**) we include a viral production cycle function that allows for viral production from productively infected cells (I_P) to change by amount and frequency over time.
- The number of virions produced by an infected cell at time τ is:

$$P(\tau) = \frac{P_{st}}{1+e^{-\omega(\tau-\alpha)}}$$

  - $P(\tau)$ represents the production of virus by cells at τ.
  - P(τ) is rounded up to the nearest integer. τ is the production cycle.
  - P_{st} represents the viral production at steady. P_{st} is estimated at steady state where all cells are infected (Ipst=T_0), i.e., $P_{st} = cV_{st}/I\rho st$.
  - α is the number of cycles to reach to 50% of P_{st}
  - γ is the steepness of the production curve.
- The interval between production cycles is determine by:

$$L_\tau = \partial e^{-\omega\tau},$$

L_τ, represents the length of production cycle (h). τ = production cycle. ∂ = the scaling factor indicating the initial production cycle length, ω = decay constant.

RESULTS

Viral kinetics

- 10 patients (n=5 non-UV and n=5 UV; 6M,4F) reached HCV steady state prior to DAA therapy, which was initiated at 31 days (median) post transplant (**Fig. 2**)
- HCV had 3 kinetic phases: **Phase I** -lower plateau (i.e. viral eclipse), **Phase II** -amplification and **Phase III** -steady state (**Fig. 2**)
- Individual viral amplification kinetics (Phase II) could be stratified into rapid (n=2; **Fig.2 A and C**) and slow (n=8; **Fig.2 B and D**), reaching viral plateau (median 6.15 vs 6.93 log IU/ml) at 7 vs 14 days post transplantation, respectively.
  - Interestingly, two patients transplanted from the same donor had rapid and slow Phase II viral amplification (**Fig.2 A and B**)
- Phase I in the UVC group was 2-fold longer than the non-UVC group and median steady state viral load in the non-UVC appeared (P=0.31) higher (7.44 log IU/ml, interquartile range [IQR] 1.83) than in the UVC (6.42 [IQR=0.5] log IU/ml).

Preliminary modeling results

- Overall, the model fits the measured HCV RNA data very well (**Fig. 2**).
- In all cases (and regardless of UVC), eclipse phase duration (Ω) is predicted to last between 3-12 hr.
- Patients with rapid viral increase (n=2) had 5-fold higher infection rate(Fig. 1, parameter β), compared to patients with a slow increase (n=8; **Fig. 2A and B**)
- Despite receiving lungs from the same donor, Pt3 had shorter virus production cycles than Pt4 (**Fig. 3A**)

UVC group compared to non-UVC group had:

- Longer Phase 1 prior to beginning of the amplification phase (Fig 3B)
- Higher number of production cycles to reach to 50% of P_{st}, i.e., parameter α (P=0.008) (**Fig. 3B**).
- Higher initial viral load (4 [IQR=2] log IU/ml) vs 1.54 [IQR=0.41] log IU/ml).

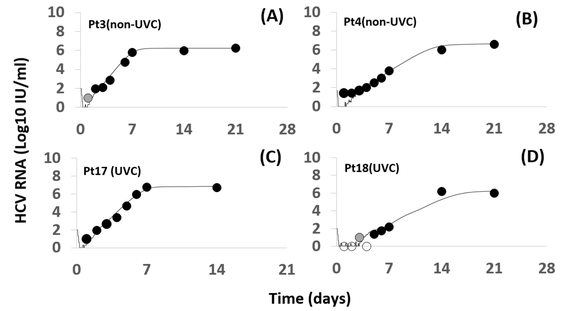

Figure 2. Representative viral kinetics (circles) and ABM *educated* fits (solid lines) post lung transplantation. Black circles, measured HCV RNA [> 15 IU/ml]; Grey circles, detected HCV RNA but not quantifiable [<=15 IU/ml]; Empty circles, HCV RNA not detected.

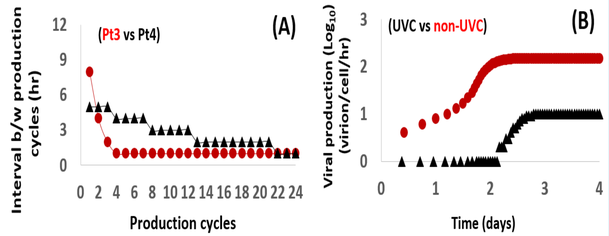

Figure 3. Predicted viral production cycles and magnitude. (A) representative viral production intervals between rapid (Pt3) and slow (Pt4) HCV amplification cases; **B)** median viral production magnitude of UVC vs non-UVC groups

CONCLUSIONS

- Treatment of donor lungs from HCV donors using UVC during EVLP is safe.
- HCV exhibits a simple infection pattern (i.e. viral eclipse, exponential amplification, culminating in viral steady state) that provides a framework to understand viral-host dynamics in acute HCV infection.
- The rapid vs slow viral kinetic amplification, especially in two lung recipients from the same donor (**Fig. 2A** vs **B**), suggests this may be related to variable host factors (e.g. innate immune signaling, degree of immunosuppression, or genetic polymorphisms in host factors involved in HCV infection).
- Although prevention of transmission was not achieved by UVC by the EVLP strategy in most patients, a longer Phase I was observed suggesting that UVC may affect viral production (**Fig. 3B**) .
- Considering the relatively small amount of HCV expected to be introduced into the recipient from the perfused lung, the surprising high initial transmitted virus load predicted by the model (4 log IU/ml) also needs further investigation.
- Further verification and validation of the model are necessary to ensure the robustness of the emerging patterns and their dynamic nature.

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