Mathematical modeling of HDV RNA kinetics suggests high peginterferon lambda efficacy in blocking viral production: Insights from the *LIMT-1* study

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- **This study provides, for the first time, a dynamic description of HDV response under IFN-λ monotherapy.**
- **IFN-λ blocks viral production with high efficacy.**
- **HDV kinetics depend on IFN-λ efficacy, the baseline fraction of noninfected hepatocytes and their proliferation rates.**
- **Additional theoretical and experimental efforts are needed to further refine our understanding of IFN-λ mode of action against HDV.**

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1 Introduction

We previously reported that peginterferon lambda (Lambda) therapy had better antiviral activity and tolerability compared to historical data for peginterferon alfa [1] and identified four main HDV RNA kinetic patterns under Lambda therapy [2].

2 Aim

To provide insights into HDV-host dynamics and Lambda efficacy using a mathematical modeling approach in participants receiving Lambda therapy

3 Methods

- Thirty-three chronic HDV infected patients participated in a randomized, open-label, Phase 2 clinical study (*LIMT-1*) of Lambda 120 µg (n=19) or 180 µg (n=14), administered once weekly by subcutaneous injections for 48 weeks, with 24 weeks of follow-up.
- All participants were on background tenofovir or entecavir.
- Kinetic data were obtained at Week 1 and every four weeks during and post-Lambda therapy. HDV RNA was measured by Robogene® 2.0 (limit of quantification of 14 IU/mL, horizontal dotted line in **Fig. 1**).
- Six patients were excluded from HDV modeling analysis; 3 due to null response and 3 because HDV levels were below LLOQ throughout treatment. The remaining 27 patients were previously categorized into 4 HDV kinetic patterns [2]: monophasic (**Fig. 1a**), biphasic (**Fig. 1b**), flat-partial response (**Fig. 1c**) and triphasic/staircase (**Fig. 1d**).
- We used a mathematical model (**Fig. 2)** of virus dynamics with or without proliferation of HDV-susceptible and HDV-infected hepatocytes to recapitulate the 4 HDV kinetic patterns and assess the impact of Lambda in blocking viral production and infection.
- We fit the models to the HDV data using a population, nonlinear mixed-effects approach. HDV clearance rate was fixed to 0.43 day^{-1} as previously estimated under lonafarnib [3]

4 Results

*We found that only a model with hepatocyte proliferation (**Fig. 2**) of HDV-susceptible and HDV-infected cells (**Fig. 1**) can recapitulate all 4 HDV kinetic patterns (**Fig. 1a-d**).*

The model predicts that:

- *Population median half-life of HDV-infected hepatocytes is 9 days (equivalent to death/loss rate of 0.08 day^{-1} [%RSE=38%]),*
- *Lambda blocks virus production with population median efficacy of 99% (%RSE=0.5%).*
- *Participants with monophasic (**Fig. 1a**) and biphasic (**Fig. 1b**) HDV kinetic patterns have a high fraction of noninfected hepatocytes at the start of treatment compared to those with triphasic/staircase and flat-partial response (**Fig. 1e**).*
- *Those with biphasic kinetics (**Fig. 1b**) had a ~3.5-fold faster hepatocyte proliferation compared to the monophasic group **(Fig. 1f)**. However, hepatocytes proliferation in those with biphasic kinetics were ~2-fold slower than those in the triphasic/staircase and flat-partial response groups.*

4 Results (cont)

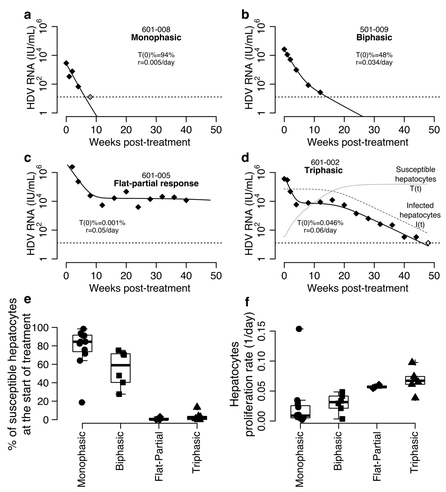

*Figure 1. HDV kinetic patterns and model fits and parameter estimates. **a-d.** Representative modeling calibration (solid curves) with patient's HDV RNA (symbols) during 48-week IFN-λ monotherapy for **a**. monophasic, **b**. biphasic, **c**. flat-partial response and **d.** triphasic kinetics - shoulder phase- The "shoulder phase" occurs (thick solid line) when the majority of hepatocytes are infected at baseline (i.e., T/I is <1) before therapy, and ends when T~I (see dotted and dashed curves, respectively).*

*$T(0)\%$ is the estimated percentage of non-infected susceptible hepatocytes at the start of Lambda monotherapy and r is the hepatocytes proliferation rate. Distributions of the estimated **e.** $T(0)\%$ and **f.** r using the best model fits.*

Horizontal dashed lines represent HDV RNA limit of limit of quantification.

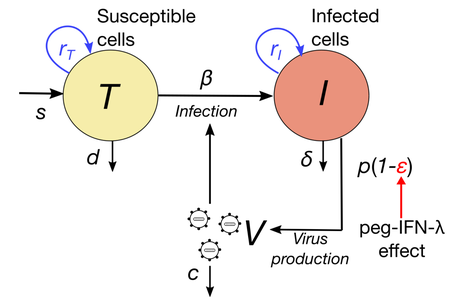

Figure 2. Schematics of the virus dynamics model. In the model T and I represent HDV-susceptible and -infected cells, respectively, and V represents the HDV virions. Susceptible cells are produced at s, die at rate d and are infected at rate β. Susceptible and infected cells proliferate with maximum rates r_T and r_I, respectively. Infected cells die at rate δ and produce new virions at rate p that are cleared at rate p. Lambda blocks virus production with efficacy ϵ.

We explored Model 1 where $r_T = r_I = 0$ (i.e., no hepatocytes proliferation) and Model 2 where $r_T = r_I > 0$, $i.e.$ assuming hepatocytes proliferation.

5 Conclusions

The model predicts that the HDV kinetic patterns depend on Lambda efficacy in blocking viral production, the fraction of noninfected hepatocytes at the beginning of treatment and their proliferation rates.

6 Acknowledgements

This work was supported by NIH grants R01AI144112 and R01AI146917.

7 References

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