Can we stop Bulevirtide? Lessons learned from hepatitis D viral kinetics modelling

Harel Dahari, PhD, FAASLD

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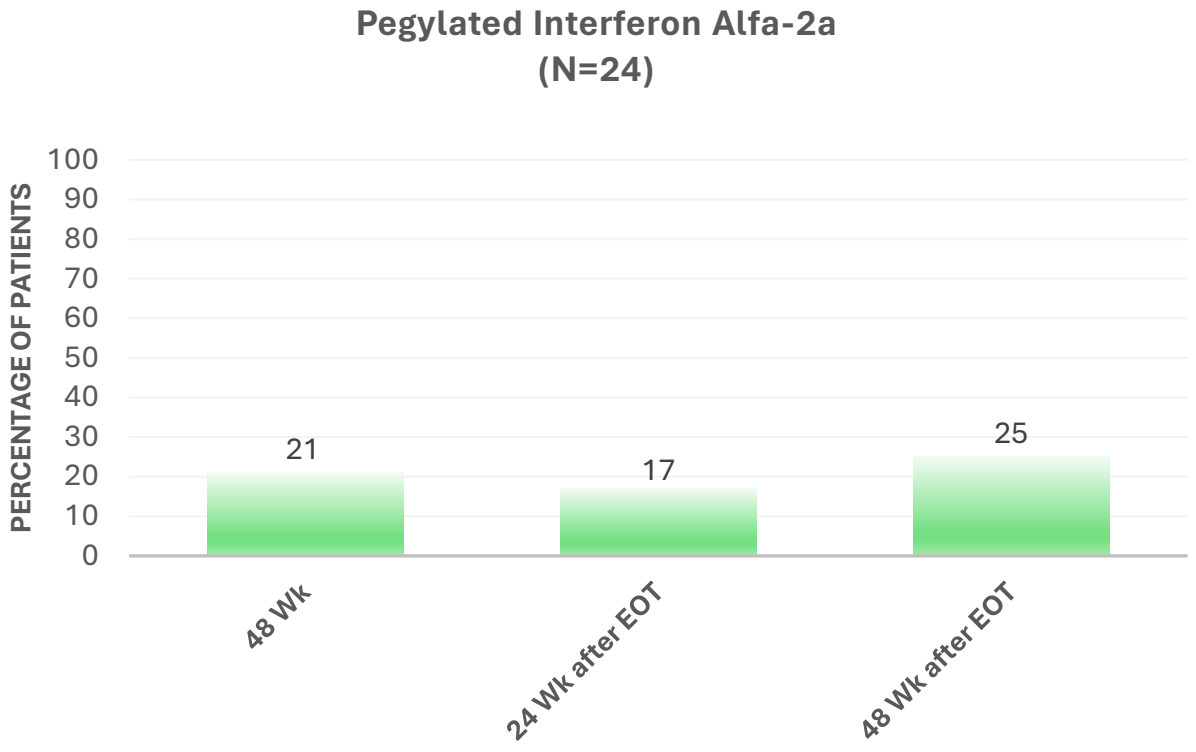
Undetectable HDV RNA during and after end of treatment with bulevirtide (BLV) and/or pegylated interferon-α (pegIFN)

Asselah et al recently reported undetectable HDV RNA during and after end of treatment (EOT) with:

(i) pegIFN alone

Off-label use of **pegIFN** therapy is **suboptimal** in achieving sustained HDV RNA negativity after therapy is completed (~25%).



EOT, end of treatment

Asselah et al. N Engl J Med 2024;391:133-43

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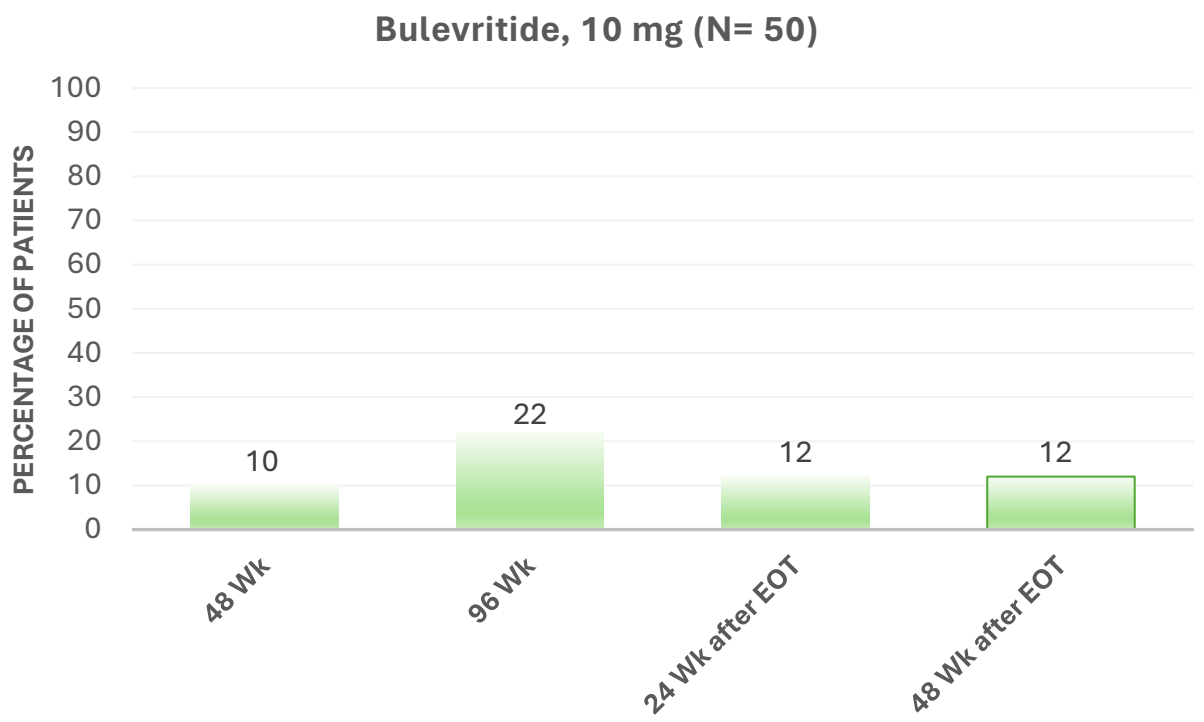
Asselah et al recently reported undetectable HDV RNA during and after end of treatment (EOT) with:

(i) pegIFN alone

(ii) BLV 10mg daily alone,

BLV monotherapy is suboptimal in achieving sustained HDV RNA negativity after therapy is completed (~12%)



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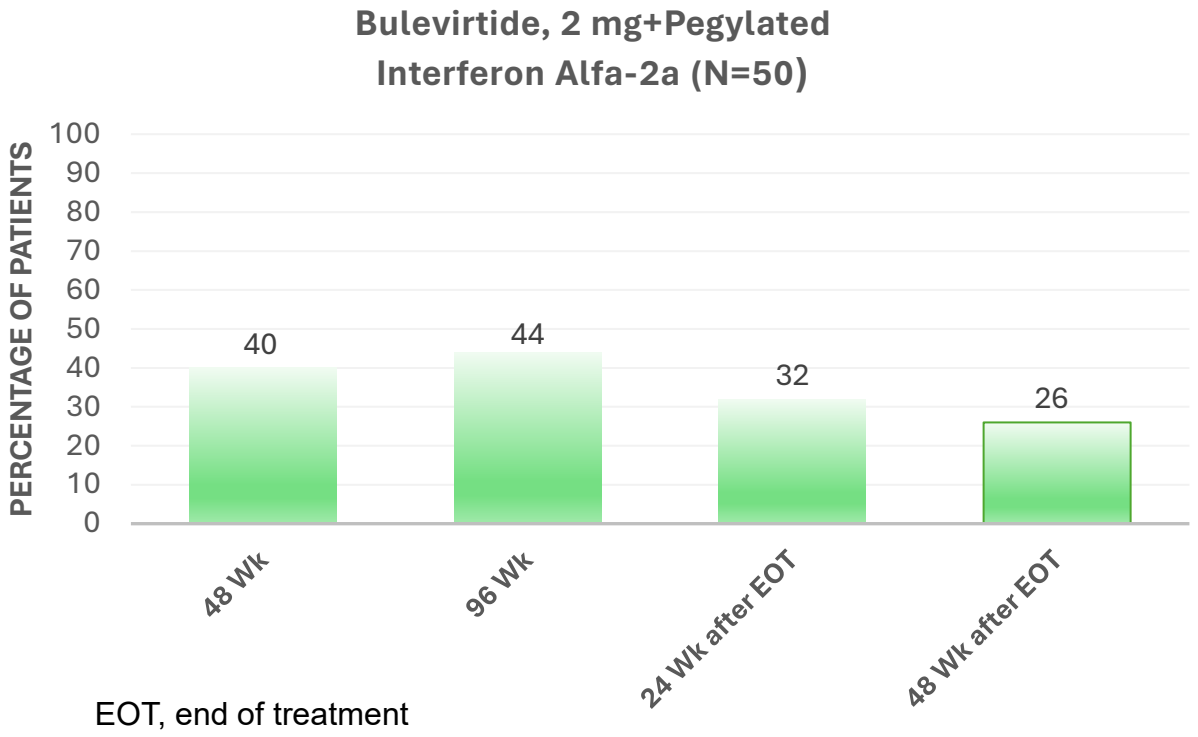
(ii) BLV 10mg daily alone,

(iii) **pegIFN + 2mg BLV daily,**



EOT, end of treatment

pegIFN + 2mg BLV daily appears to reach a higher rate of HDV negativity by EOT compared to **pegIFN alone** (44% vs 21%) but eventually achieved similar HDV negativity rates after therapy is completed (~25%).

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Asselah et al. N Engl J Med 2024;391:133-43

Undetectable HDV RNA during and after end of treatment with bulevirtide (BLV) and/or pegylated interferon-α (pegIFN)

Asselah et al recently reported undetectable HDV RNA during and after end of treatment (EOT) with:

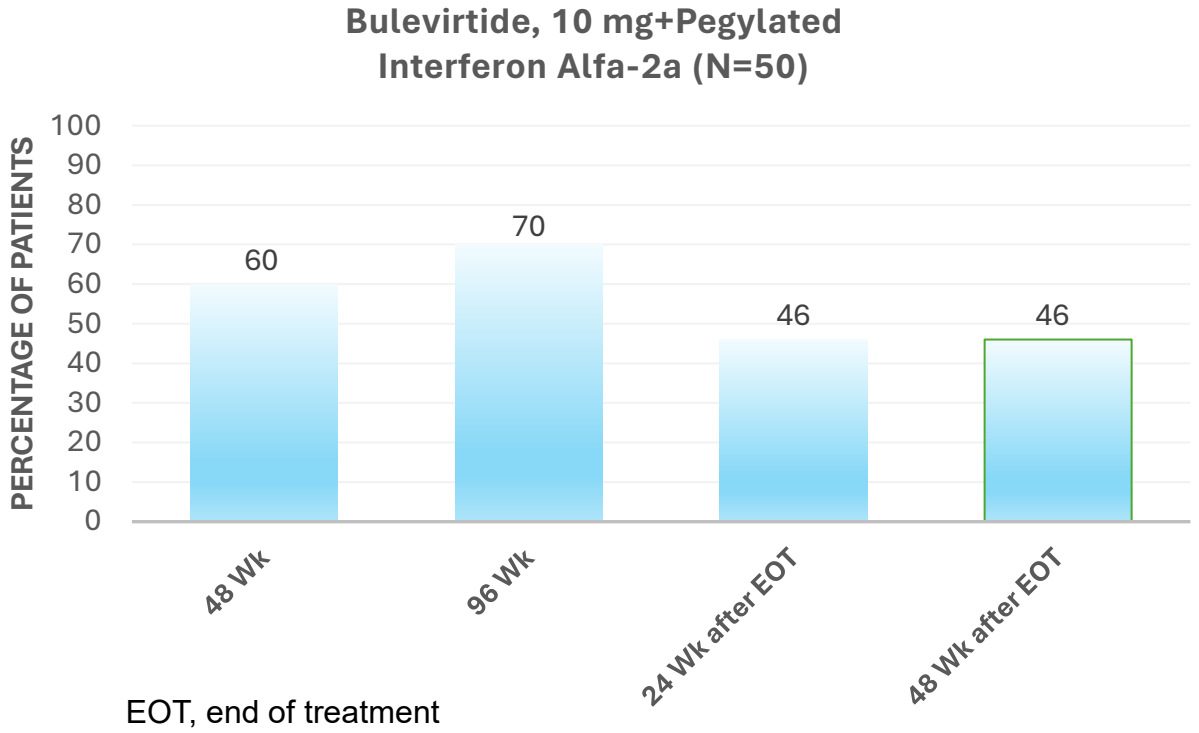
(i) pegIFN alone

(ii) BLV 10mg daily alone,

(iii) pegIFN + 2mg BLV daily,

(iv) **pegIFN + 10mg BLV daily,**

The 46% HDV negativity rate with **pegIFN + 10 mg of BLV** appears (but not statistically powered) to be higher than with **pegIFN alone** (25%).



EOT, end of treatment

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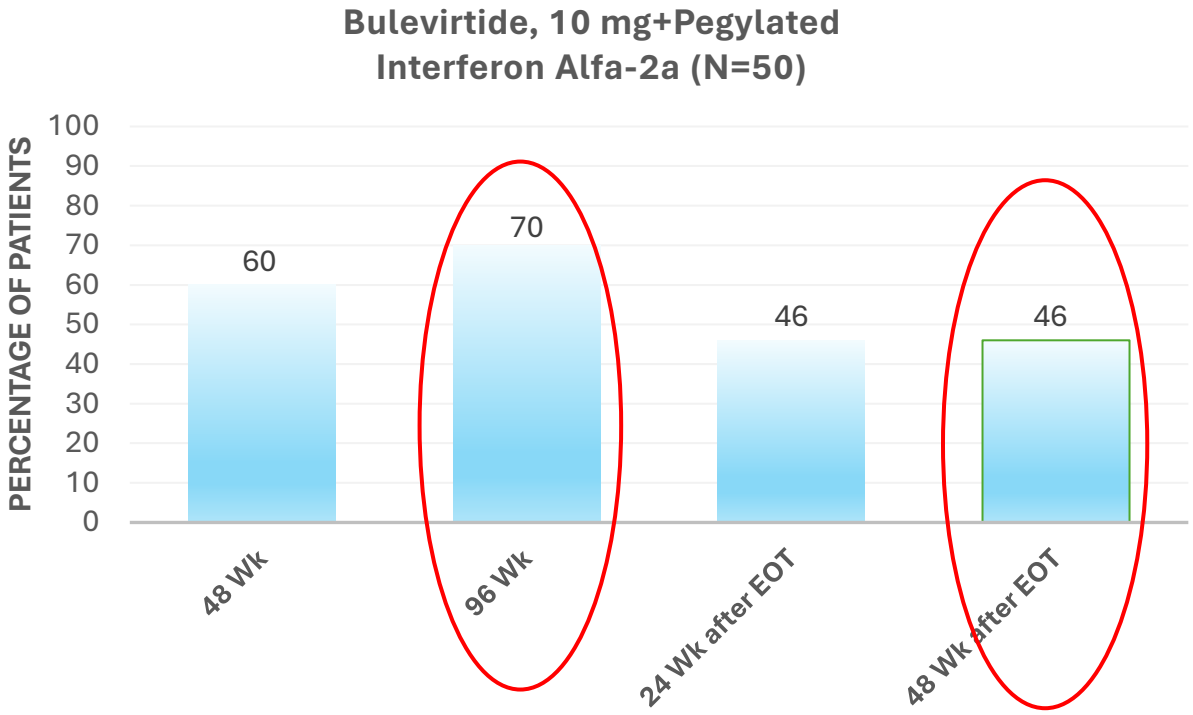
Asselah et al. N Engl J Med 2024;391:133-43

The 70% of HDV negativity at EOT and the 46% HDV negativity rate with pegIFN + 10 mg of BLV suggests a welcome advance in HDV therapy

- Historically, on-treatment hepatitis C RNA levels served as an indicator of pegIFN-based treatment outcome (Ferenci et al. Gastroenterology 2008;135:451-8).

- Since data suggests that a finite BLV-based therapy is possible but suboptimal, it is important to investigate whether on-treatment HDV kinetics can predict response.



The role of mathematical modeling of viral kinetics during antiviral treatment

- To provide insights into drug mode(s) of action (MOA)
- To estimate drug efficacy
- To understand HDV-HBsAg-host interplay during infection and treatment
- To develop and optimize response-guided therapies

What do we know about pegIFN mode of action (MOA)?

Modeling suggests that pegIFN MOA against HDV is mainly to block HDV production

Understanding Early Serum Hepatitis D Virus and Hepatitis B Surface Antigen Kinetics During Pegylated Interferon-alpha Therapy Via Mathematical Modeling

Jeremie Guedj,[1,2,3] Yaron Rotman,[4] Scott J. Cotler,[5] Christopher Koh,[4] Peter Schmid,[6] Jeff Albrecht,[6] Vanessa Haynes-Williams,[4] T. Jake Liang,[4] Jay H. Hoofnagle,[4] Theo Heller,[4] and Harel Dahari[1,5]

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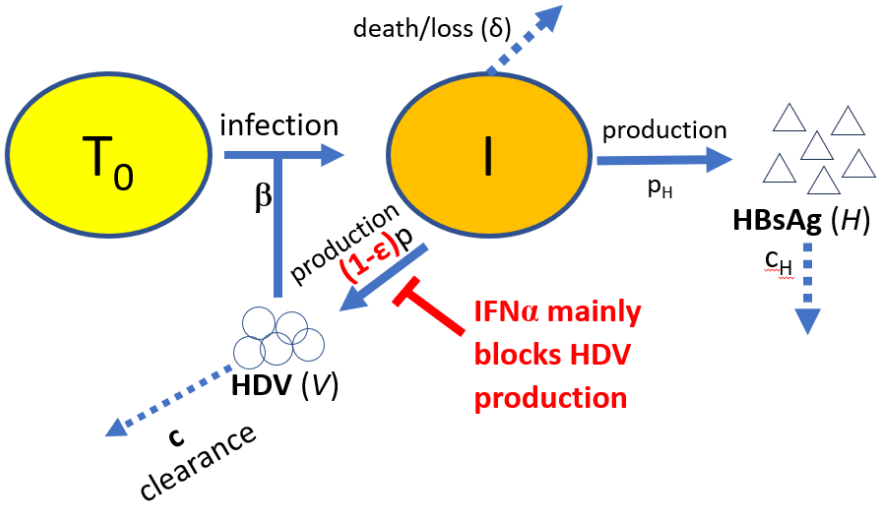
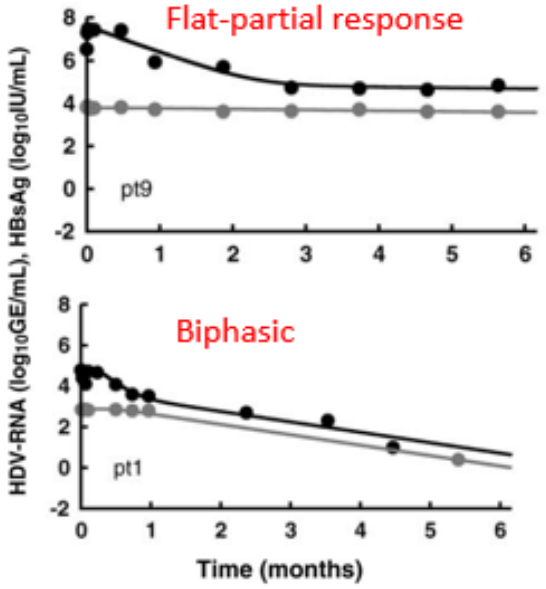
HEPATOLOGY, Vol. 60, No. 6, 2014



After a couple of days, during which HDV remained at baseline levels, two kinetic patterns were identified in responders

Black circles – HDV RNA

Gray circles - HBsAg



Solid curves – Model fits with measured data

- Target (HBsAg-infected) cells, T0, become HDV-infected cells, I, at rate β.
- Infected cells are then lost or die at rate δ.
- Infected cells also produce virions, V, at rate p.
- Virions in circulation are cleared at rate c.
- pegIFN MOA in blocking HDV production is shown using solid red line (parameter ε)

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Summary of modeling predictions during pegIFN therapy

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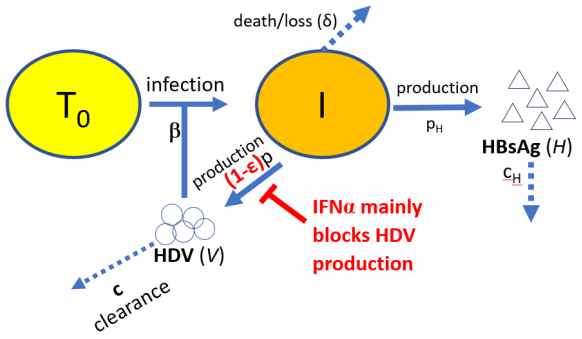
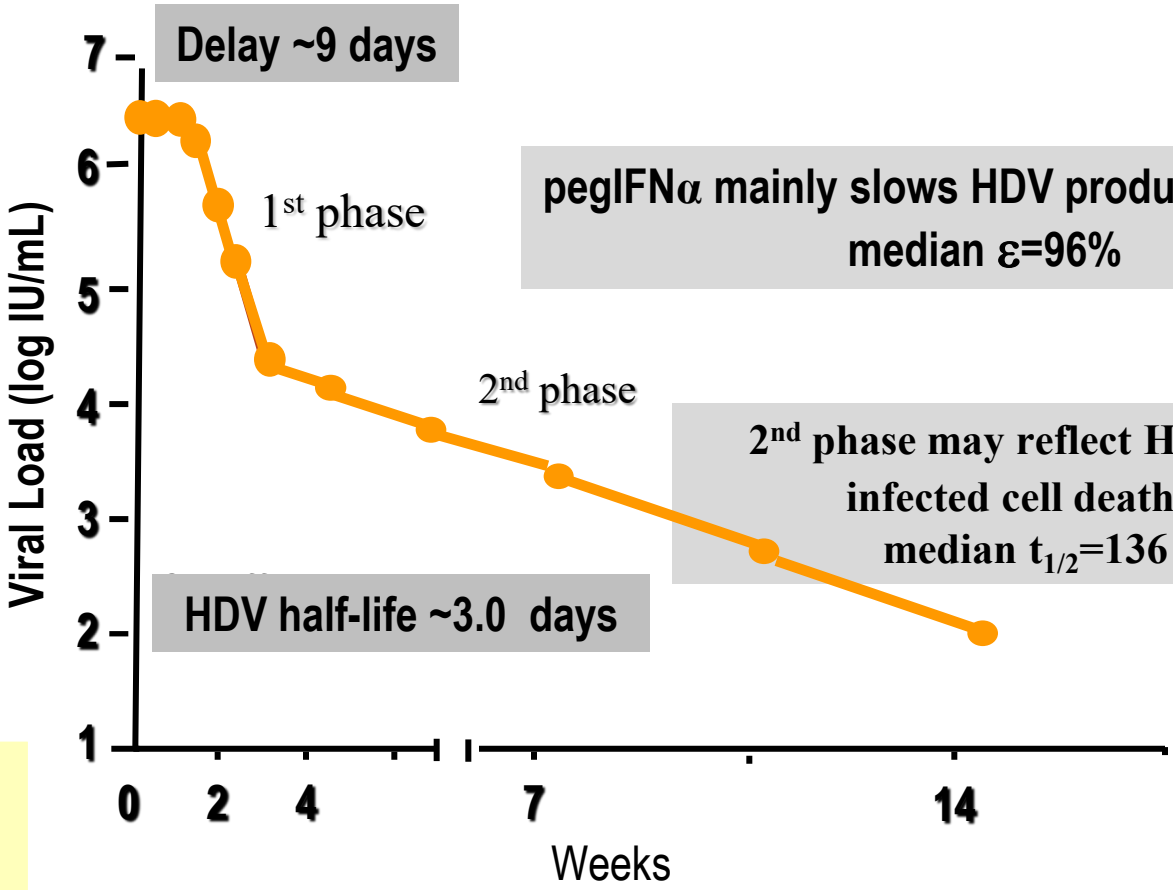
HEPATOLOGY, Vol. 60, No. 6, 2014



High HDV burden ~10^9 are produced and cleared in a patient per day



Potential clinical use

A flat second phase in HDV kinetics was associated with treatment failure, providing a potential early stopping rule during IFNα treatment

What do we know about Bulevirtide mode of action (MOA)?

Modeling predicts a monophasic viral decline under antiviral treatment that blocks virus infection

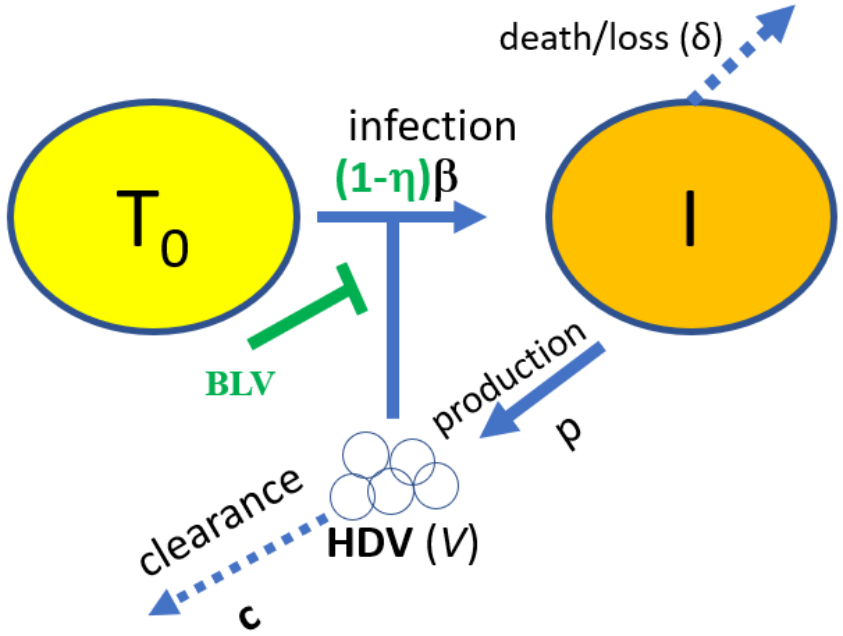
Loglio et al. measured frequent HDV kinetics in 3 patients who were treated with BLV monotherapy for up to 3 years

Journal of Hepatology
Volume 76, Issue 2, February 2022, Pages 464-469

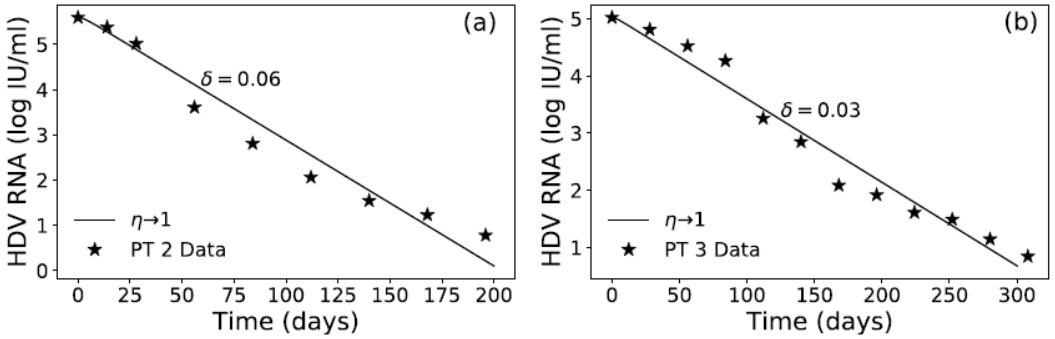
Case Report

Safety and effectiveness of up to 3 years' bulevirtide monotherapy in patients with HDV-related cirrhosis

Alessandro Loglio [1], Peter Ferenci [2], Sara Colonia Uceda Renteria [3], Christine Y.L. Tham [4], Caroline Scholtes [5], Heidemarie Holzmann [6], Florian van Bömmel [7], Marta Borghi [1], Riccardo Perbellini [1], Alessandro Rimondi [8], Elisa Farina [8], Elena Trombetta [9], Maria Manunta [10], Laura Porretti [9], Daniele Prati [10], Ferruccio Ceriotti [3], Fabien Zoulim [5], Antonio Bertoletti [4], Pietro Lampertico [1 8]



The model (solid curve) fits well with measured HDV viral decline (symbols) in 2 patients (Pt 2 and Pt 3) under monotherapy BLV



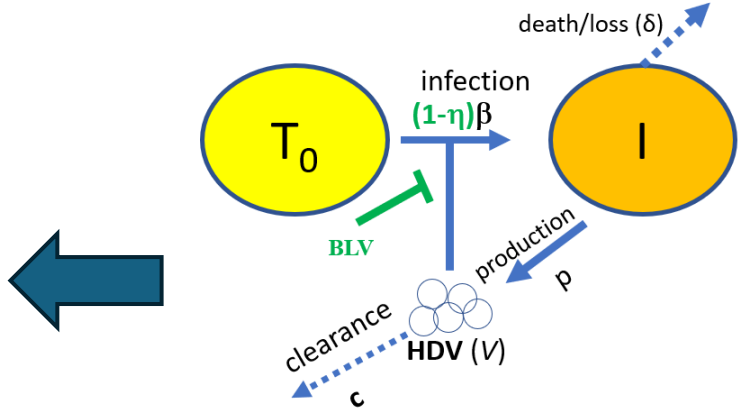
- Target (HBsAg-infected) cells, T0, become HDV-infected cells, I, at rate β.
- Infected cells are then lost or die at rate δ.
- Infected cells also produce virions, V, at rate p.
- Virions in circulation are cleared at rate c.
- BLV known MOA in blocking entry/infection is shown using solid green line (parameter η)

Shekhtman et al. J Hepatol 2022, 76(5):1229-1231

Modeling predicts a monophasic viral decline under antiviral treatment that blocks virus infection

Since it is **not** possible **to simultaneously estimate with confidence** both BLV efficacy (η) and infected cell death/loss rate (δ), **BLV efficacy in blocking infection was assumed η~100%**.

Mhlanga A et al. JHEP Reports 2024 in press.



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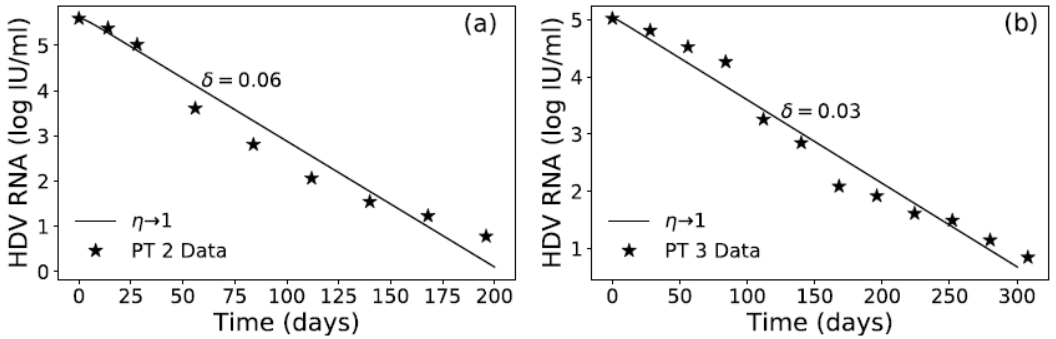

Shekhtman et al. J Hepatol 2022, 76(5):1229-1231

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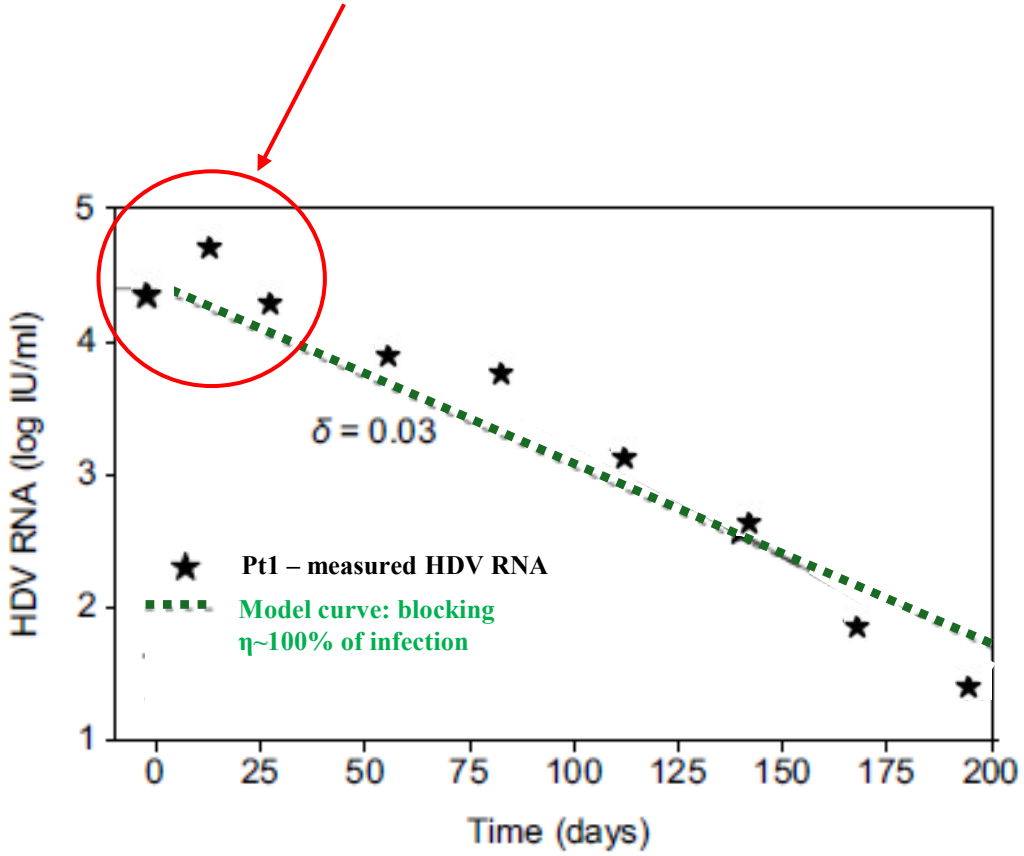
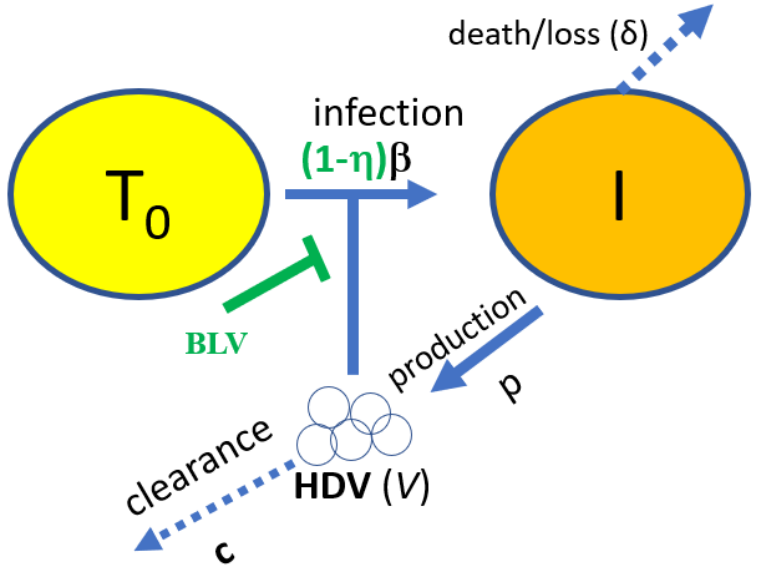
The model did not fit well one patient (Pt 1), in whom a transient viral increase was seen followed by a monophasic HDV decline





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- BLV known MOA in blocking entry/infection is shown using solid green line (parameter η)

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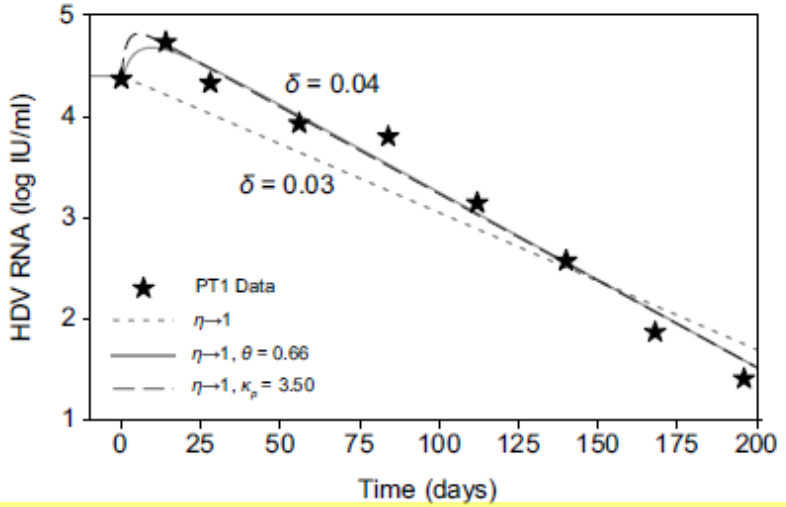
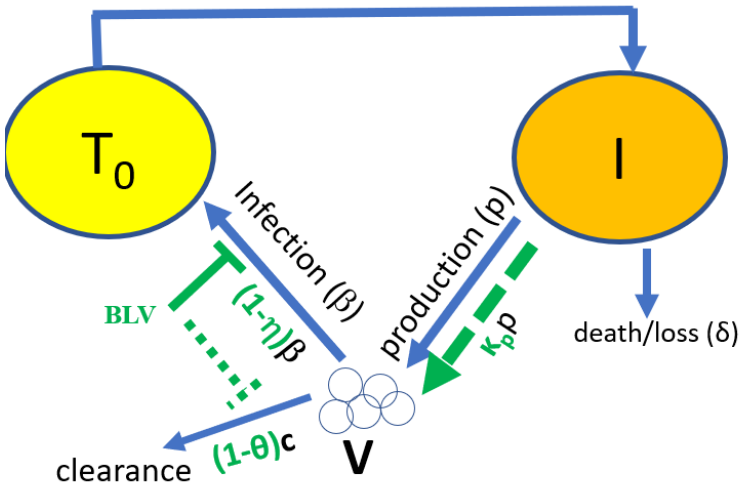
Shekhtman et al. J Hepatol 2022, 76(5):1229-1231

Theoretically, the transient viral increase can be explained if one assumes that in addition to blocking viral infection

- BLV enhances viral production (parameter κ_p) → [this is unlikely for BLV]

  or
- BLV reduces viral clearance from circulation (parameter θ)





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- Infected cells also produce virions, V, at rate p.
- Virions in circulation are cleared at rate c.
- BLV **known** MOA in blocking entry/infection is shown using **solid green** line (parameter η)
- **Theoretical** BLV MOA are shown using **dashed** green lines

❑ Reducing viral clearance by BLV may be a more plausible MOA if viral clearance from the circulation is interrupted by BLV blocking viral entry into hepatocytes.

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Shekhtman et al. J Hepatol 2022, 76(5):1229-1231

Mathematical modeling suggests that entry-inhibitor Bulevirtide may interfere with HDV clearance from circulation

The basic model predicts that in addition to BLV blocking infection η~100%, HDV clearance from blood may decrease

We recently showed for hepatitis C virus (HCV) that, in some patients, the liver not only produces virus but also clears virus from the circulation, **supporting the notion** that blocking viral entry could reduce viral clearance by the liver in patient 1.

Modeling hepatitis C virus kinetics during liver transplantation reveals the role of the liver in virus clearance

Louis Shekhtman, Miquel Navasa, Natasha Sansone, Gonzalo Crespo, Gitanjali Subramanya, Tje Lin Chung, E Fabian Cardozo-Ojeda, Sofía Pérez-del-Pulgar, Alan S Perelson, Scott J Cotler, Xavier Forns, Susan L Uprichard, Harel Dahari « see less

eLife 2021;10:e65297

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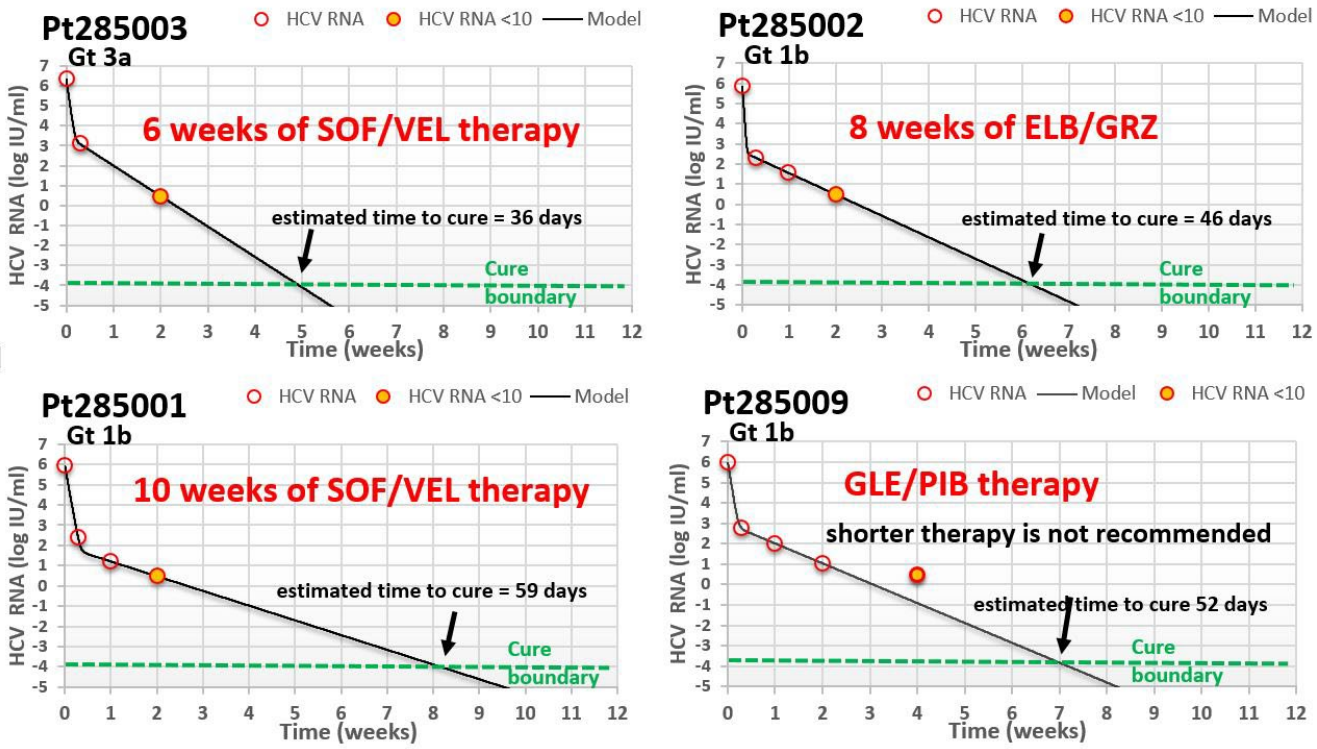
Shekhtman et al. J Hepatol 2022, 76(5):1229-1231

Bulevirtide monotherapy treatment: Undefined length of therapy

Can we use mathematical modeling to predict the duration of therapy to achieve cure?

Real-time response-guided therapy with DAA shortens treatment duration in ~40% of HCV treated patients

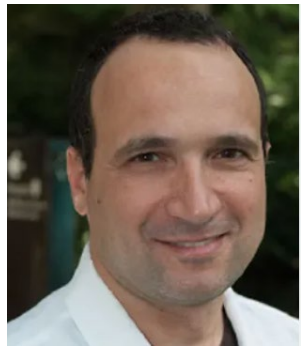


A value of $7x10^{-5}$ (IU/ml) can be used as the threshold for viral clearance (cure) as the concentration of one virion/13,500 ml = $7x10^{-5}$ IU/ml.

Response guided therapy for reducing duration of direct acting antivirals in chronic hepatitis C infected patients: a Pilot study

Ohad Etzion, Harel Dahari, David Yardeni, Assaf Issachar, Anat Nevo-Shor, Michal Cohen-Naftaly, Yaffa Ashur, Susan L. Uprichard, Orly Sneh Arbib, Daniela Munteanu, Marius Braun, Scott J. Cotler, Naim Abufreha, Ayelet Keren-Naus, Yonat Shemer-Avni, Orna Mor, Jayanah Murad, Victor Novack & Amir Shlomai

Scientific Reports **10**, Article number: 17820 (2020) | Cite this article



Amir Shlomai

Tel Aviv University.

Ohad Etzion

Director, Department of Gastroenterology and Liver Diseases

SOROKA Medical Center

The first clinical trial, in the field of viral dynamics, using on treatment (real time) modeling-based response guided therapy

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Potential clinical use of modeling-based response guided (RGT) therapy during BLV treatment

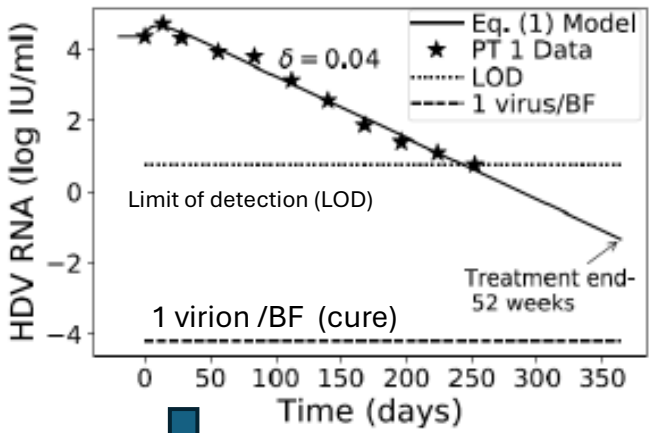
Modeling predictions of BLV (2mg/day) treatment duration to reach the cure boundary of <1 HDV copy in the total extracellular body fluid (BL).

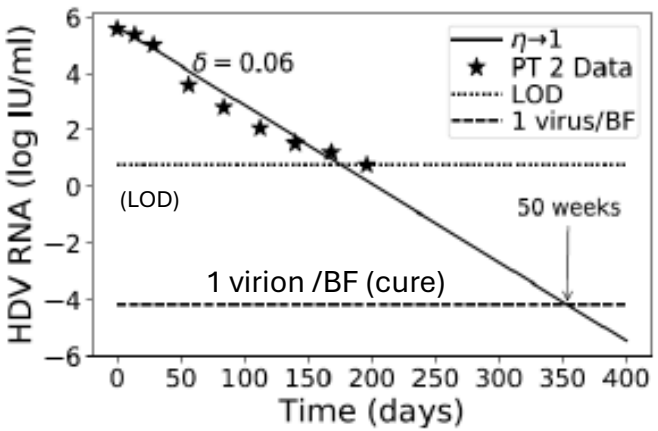
Mathematical modeling suggests that entry-inhibitor bulevirtide may interfere with hepatitis D virus clearance from circulation

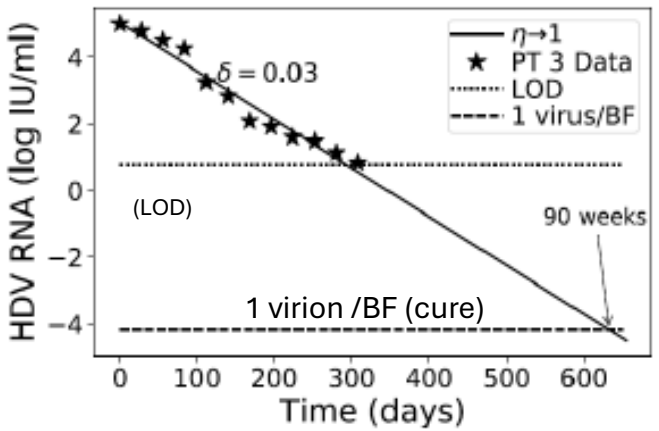
Louis Shekhtman • Scott J. Cotler • Alexander Ploss • Harel Dahari

JOURNAL OF HEPATOLOGY
The Home of Liver Research

VOLUME 76, ISSUE 5, P1229-1231, MAY 2022







modeling may explain, retrospectively, why patient 1 had viral rebound after 52 weeks of BLV

Patient 2 was recently reported (J Hepatol. 2023;78(4):876–80) to reach "cure" 72 weeks after completion of 3 years of BLV → **in agreement (retrospectively) with the modelling predictions**

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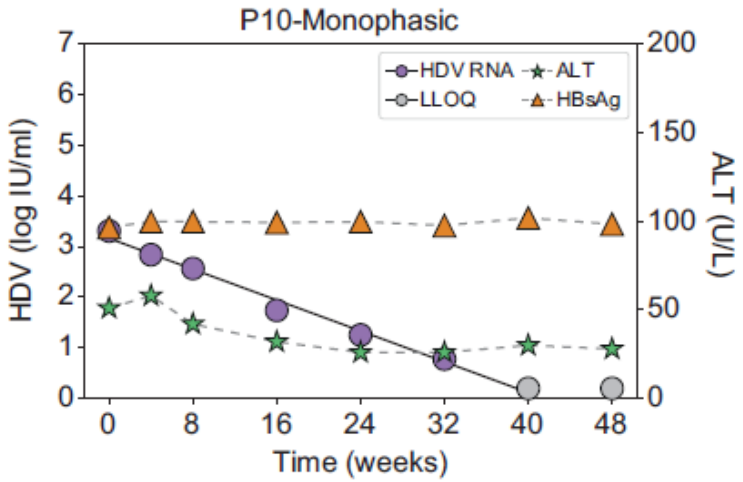
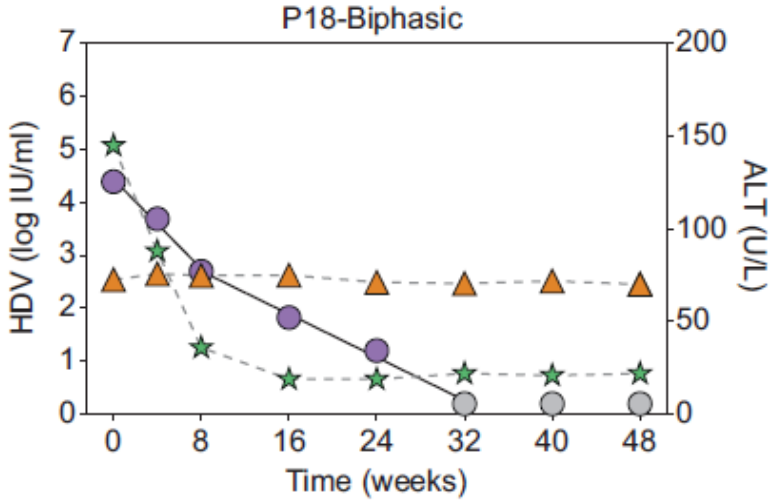
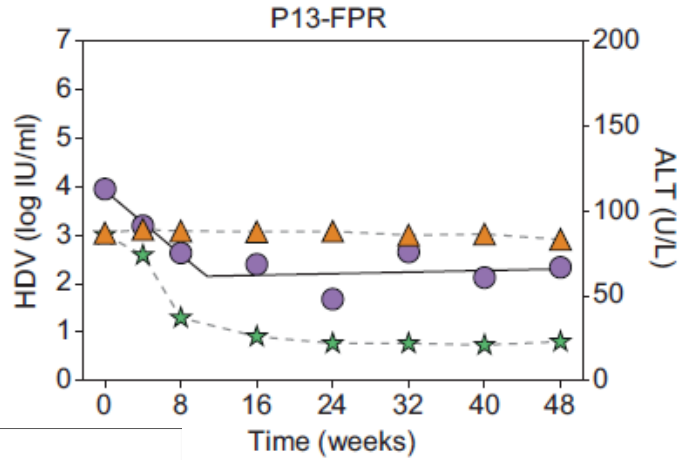
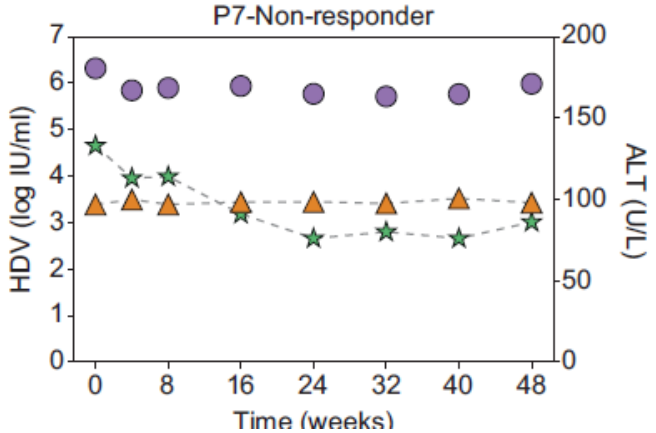
Not all patients had a monophasic HDV decline under BLV alone therapy

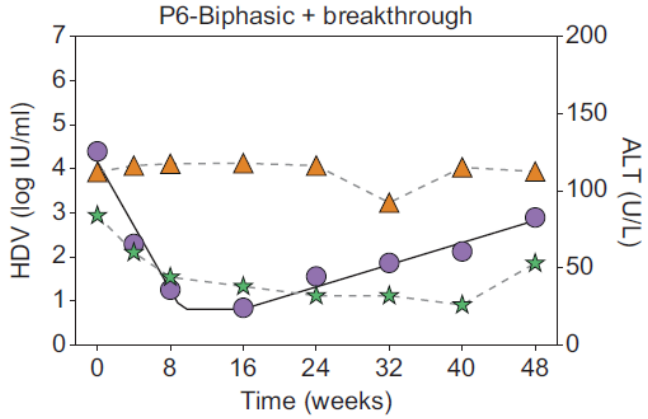




Representative kinetic patterns during 48-week treatment with BLV (2mg/day) in patients with compensated cirrhosis and clinically significant portal hypertension







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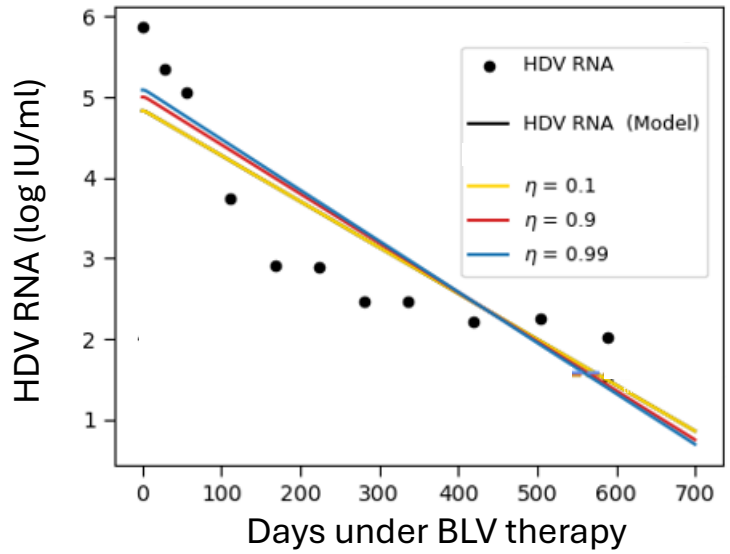
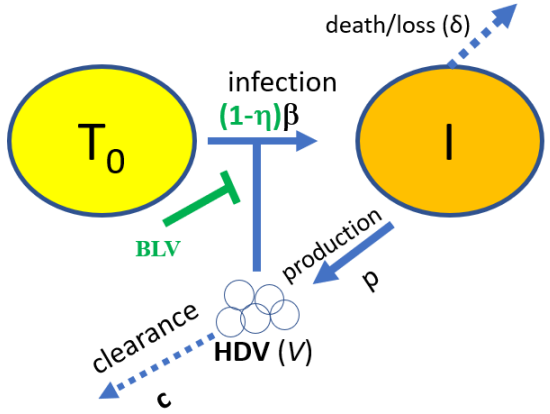
Shekhtman et al. JHEP Reports 2023 Nov 15;6(2):100966

The *basic* model cannot explain a non-monophasic viral decline under antiviral treatment that blocks virus infection

To illustrated that, we fit the *basic* model with a representative non-monophasic HDV decline case from our real-life cohort (Wasserman et al. DeltaCure 2024 meeting, poster # P30).



Assuming BLV efficacy of η=10%, 90% and 99% in blocking infection, modeling fits yielded overlapping model curves with estimates of infected cell loss rates that differed by more than an order of magnitude, ie., δ= 0.185, 0.0157, 0.0148 day^{-1}, respectively.



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- Virions in circulation are cleared at rate c.
- BLV known MOA in blocking entry/infection is shown using solid green line (parameter η)

Mhlanga A et al. JHEP Reports 2024, in press.

Nevertheless, the usefulness of the *basic* model in understanding HDV kinetics during anti-HDV treatment is reviewed in:

Shekhtman/Duehren et al. Hepatitis D Virus and HBsAg Dynamics in the era of new Antiviral Treatments. Curr Gastroenterol Rep 25, 401–412 (2023).

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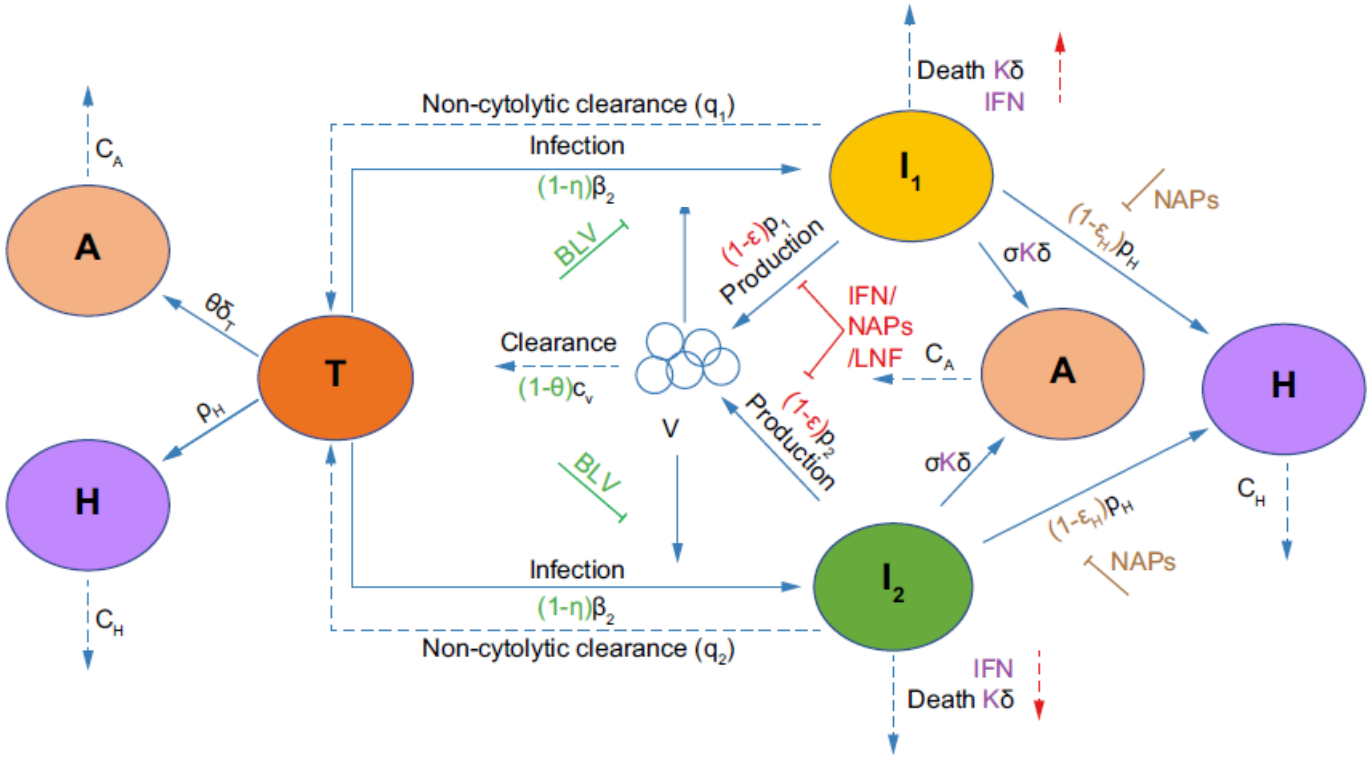
Modelling HDV kinetics under the entry inhibitor bulevirtide suggests the existence of two HDV-infected cell populations



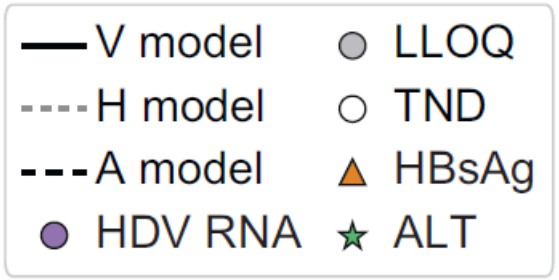
Liver:
(T), HDV-free HBsAg-infected positive HDV-naïve target cells
(I_1 and $I_{2)}$, two types of short and long lifespan HDV-infected cells, respectively

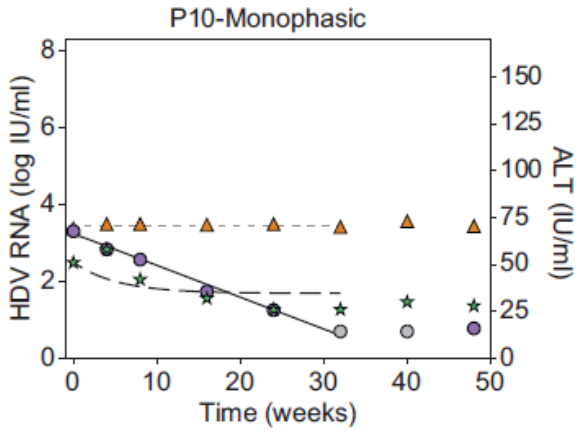
Blood:
(V), HDV
(A), ALT
(H), HBsAg

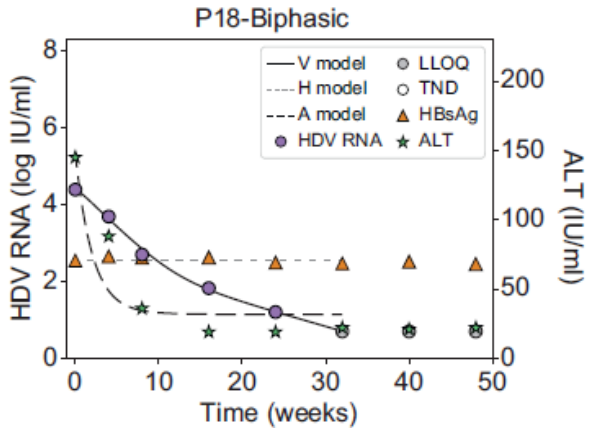
Antivirals:
BLV blocks infection with efficacy η and may reduce viral clearance with efficacy by θ.
Blocking HDV production by interferon-α, interferon-λ (IFN), lonafarnib (LNF) or nucleic acid polymer (NAP) with efficacy by ε.

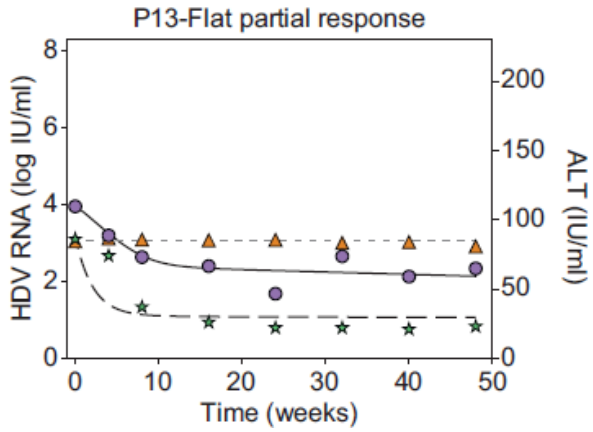
Shekhtman et al. JHEP Reports 2023 Nov 15;6(2):100966

The *two-population* model fits well HDV RNA, HBsAg and ALT kinetics during 48 weeks of Bulevirtide (2mg/day) alone treatment









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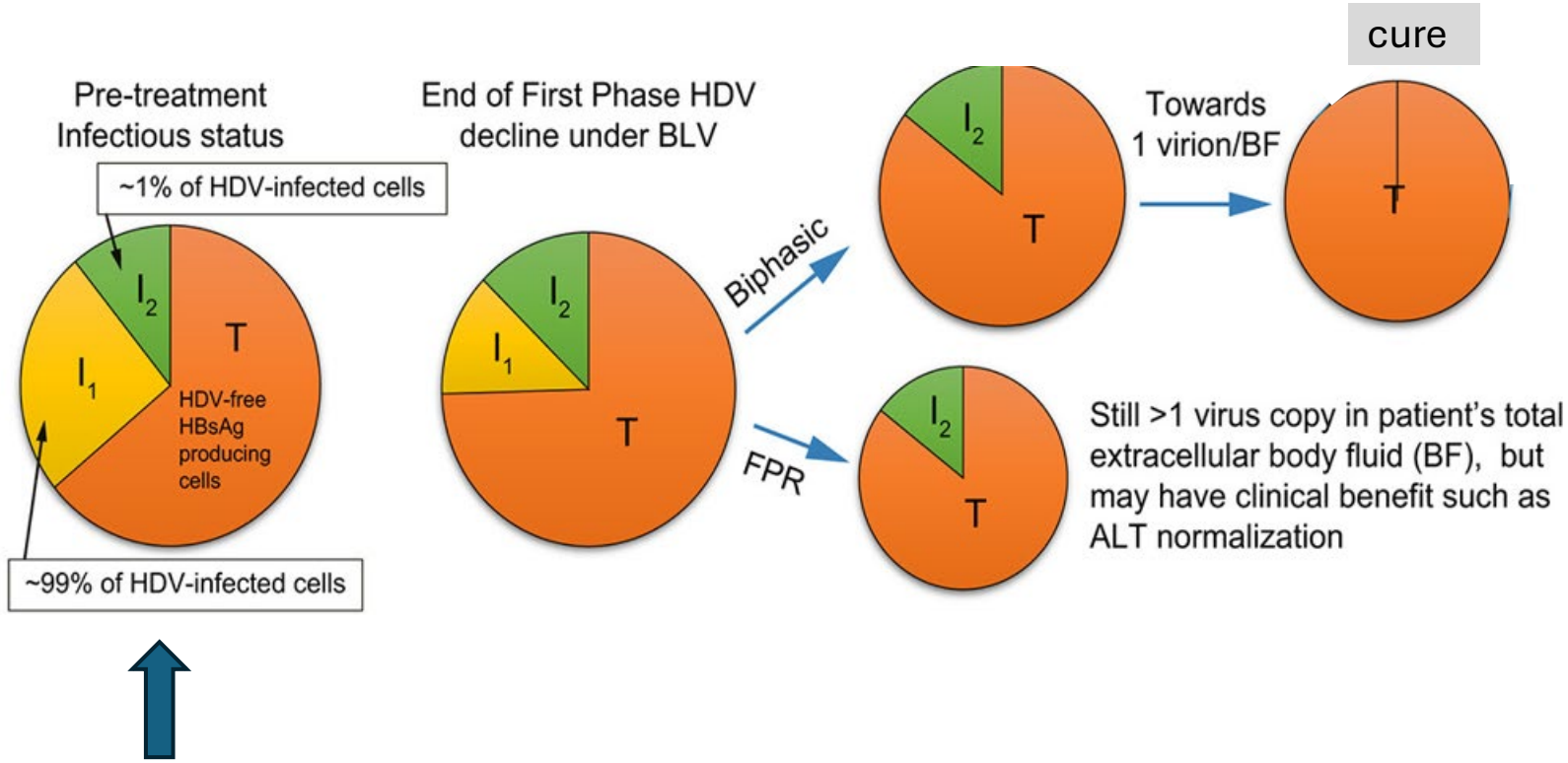
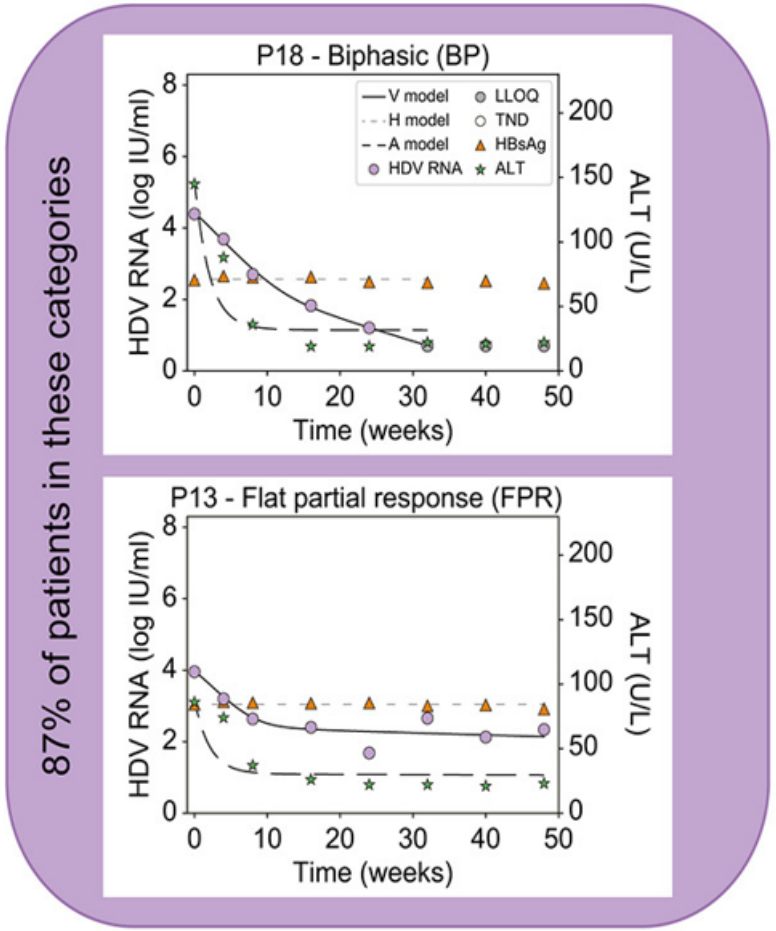
Explaining the difference between biphasic and flat partial response under 48 weeks of Bulevirtide (2mg/day) treatment



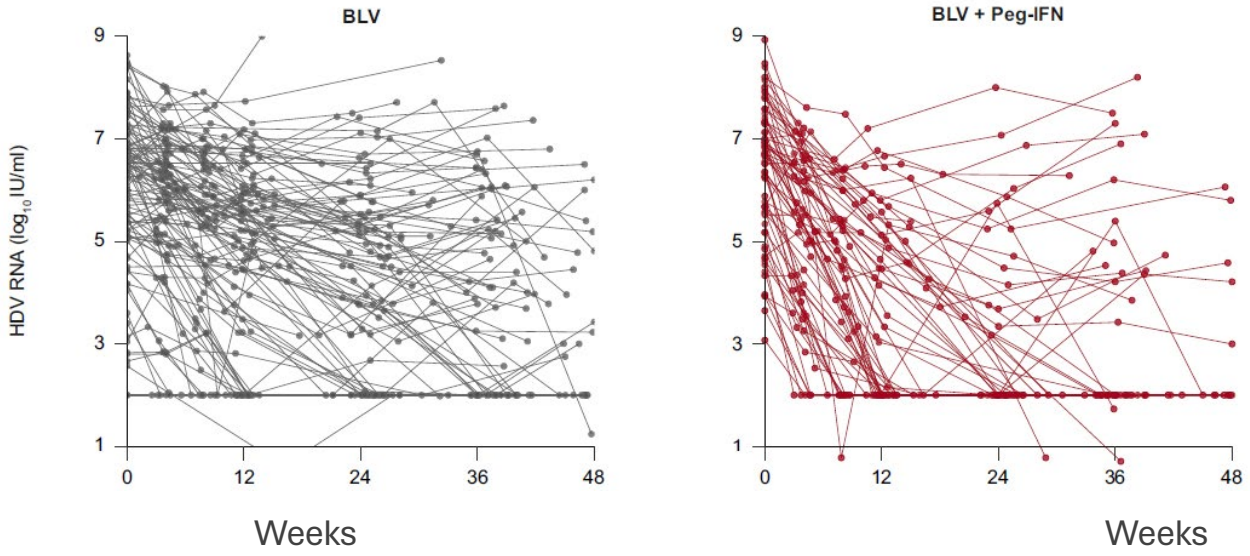
$T + I_1 + I_2$ represent <~10% of the total hepatocytes in the liver of HBeAg negative patients



Shekhtman et al. JHEP Reports 2023 Nov 15;6(2):100966

Characterization of HDV kinetics during Bulevirtide-based therapy is needed for the development of mathematical models and RGT strategies

Kinetic data from 183 treated patients (114 BLV; 69 BLV+pegIFN) who participated in two French multicenter cohort studies suggest various HDV kinetic patterns, **yet to be characterized and modeled,** during treatment .



El Messaoudi et al. JHEP Reports 2024;6:101070.

Mhlanga et al. JHEP Reports 2024 in press.

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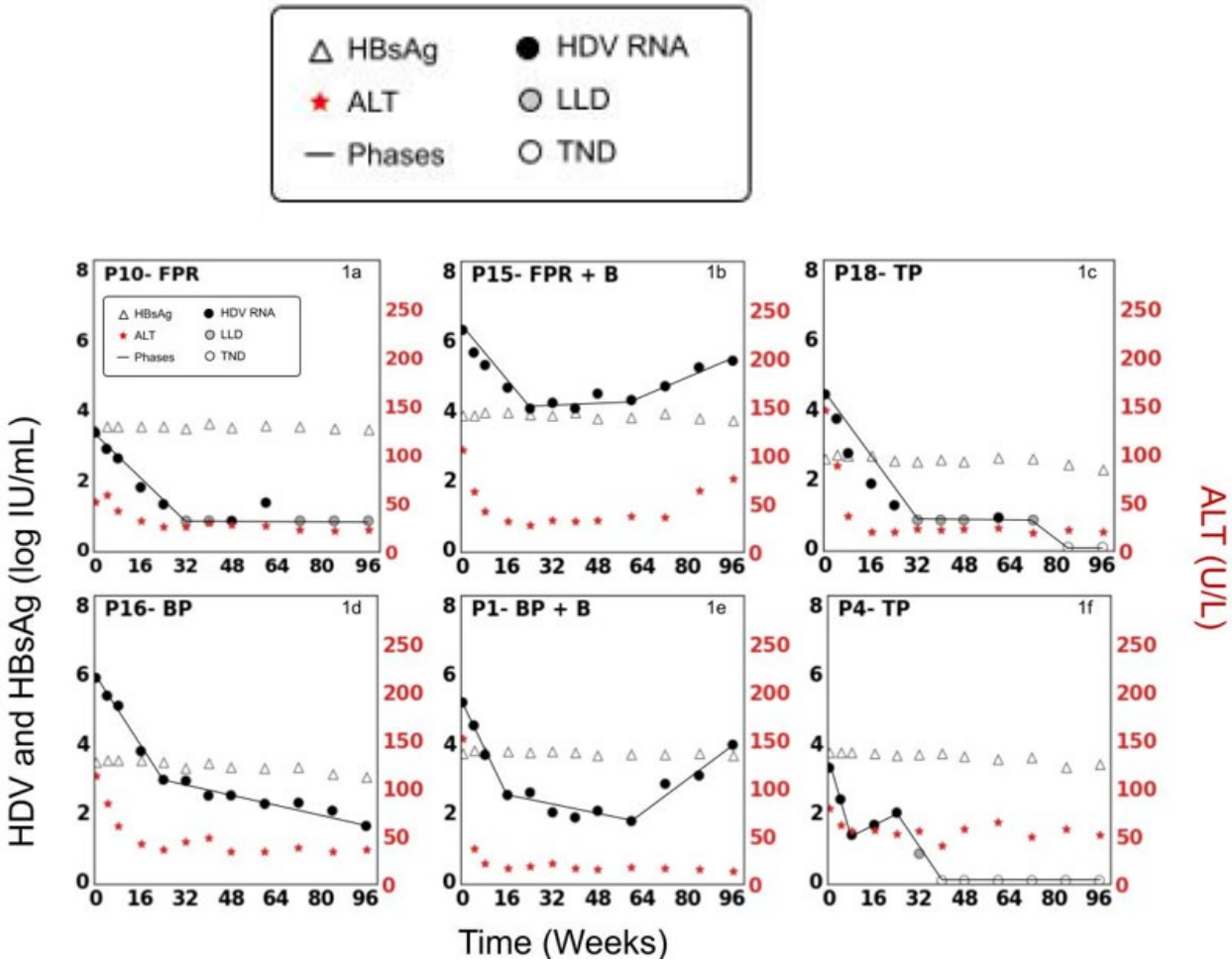
Bulevirtide (2mg/day) monotherapy in patients with compensated cirrhosis and CSPH: a 96-week interim kinetic analysis (Poster # P30)

- We aim to extend our **48-week** study (JHEP Reports 2023 Nov 15;6(2):100966) in patients (N=38) with compensated cirrhosis and clinically significant portal hypertension (CSPH) during **up to 96 weeks** of treatment.

Interim analysis finds that

- 5 (13%) patients were non-responders (<1.6 log IU/ml decline from baseline throughout treatment – not shown)
- All responders (n=33) experienced an initial rapid viral decline (0.19 ± 0.12 log/wk)
- Responders had one of these five patterns:
  - i. Flat partial response (FPR) (n=20, **Fig.1a**),
  - ii. FPR + breakthrough (FPR + B) (n=3, **Fig.1b**),
  - iii. Biphasic (BP) (n=2, **Fig.1d**)
  - iv. BP + B (n=4, **Fig.1e**)
  - v. Triphasic decline (TP) (n=4, **Fig.1c** & **f**).

- ALT normalization was achieved in 28 (76%) patients at 7.9 ± 6.5 weeks (**Fig.1**).
- HBsAg remained roughly at pre-treatment levels (**Fig.1**).



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In Conclusion

- Ongoing efforts in analyzing and modeling HDV kinetics during Bulevirtide-based therapy are likely to develop and optimize response-guided therapy (RGT) strategies for hepatitis D.

- The emerging question may be not if we can stop bulevirtide but when.

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