

Article

Topological Stability and Transcritical Bifurcations in a Target-Cell-Limited Model of HBV-HDV Viral Interference

Menachem Lachiany

Department of Computer Science, Western Galilee College, Acre 2412101, Israel; menacheml@wgalil.ac.il

Abstract

While minimalist kinetic models effectively capture the acute inverse coupling between Hepatitis B (HBV) and Hepatitis Delta (HDV), they often fail to account for the asymptotic stability and long-term viral plateaus observed during clinical therapy. In this work, we present an expanded compartmental framework integrating the non-linear dynamics of susceptible (S) and infected (I) hepatocyte populations, explicitly incorporating the satellite nature of HDV. Using the next-generation matrix method and Lyapunov stability theory, we analytically derive R_0 and prove the global attractivity of the endemic equilibrium. We demonstrate that “Target Cell Limitation” serves as the fundamental homeostatic governor. A transcritical bifurcation at threshold drug efficacy $\varepsilon \approx 0.9$ marks the mathematical boundary between chronic persistence and viral extinction.

Keywords: HBV-HDV viral interference; satellite virus dynamics; lonafarnib kinetics; transcritical bifurcation; global stability analysis; target cell limitation

1. Introduction

Chronic Hepatitis Delta Virus (HDV) infection represents the most aggressive form of human viral hepatitis, affecting approximately 12–72 million people worldwide [1,2]. As a satellite virus, HDV requires the presence of HBV surface antigens (HBsAg) for its assembly and intrahepatic propagation [3–5]. Co-infection significantly accelerates progression toward cirrhosis and hepatocellular carcinoma (HCC) [6–8]. Therapeutic options have been limited to interferon-alpha, which yields low rates of sustained virological response (SVR) [9,10].

The landscape of HDV therapy has shifted with novel inhibitors. Lonafarnib (LNF) blocks prenylation of L-HDAG [11–13]. Bulevirtide (BLV) inhibits the NTCP receptor [14–16]. Clinical trials reveal the HBV rebound phenomenon [17–19]: as HDV levels drop, HDV-mediated suppression of HBV is attenuated, producing a reciprocal HBV DNA surge [20–22].

Mathematical modeling has emerged as a cornerstone for quantifying these kinetics [23–25]. Early minimalist models captured the short-term inverse relationship [3,26], but lack structural complexity to account for hepatocyte regeneration and target cell limitation [20,27,28]. This study presents an expanded kinetic framework with global stability analysis and critical therapeutic thresholds via bifurcation analysis [29–36].



Academic Editor: Alexander Gorbelenya

Received: 1 May 2026

Revised: 1 June 2026

Accepted: 5 June 2026

Published: 25 June 2026

Copyright: © 2026 by the author.

Licensee MDPI, Basel, Switzerland.

This article is an open access article distributed under the terms and

conditions of the [Creative Commons](#)

[Attribution \(CC BY\)](#) license.

2. Mathematical Model

2.1. Cell Dynamics and Biological Assumptions

The proposed model is given by the following system of four coupled nonlinear ordinary differential equations describing the temporal evolution of susceptible hepatocytes (S), infected hepatocytes (I), HDV virions (D), and HBV virions (B):

$$dS/dt = \lambda - d_S \cdot S - \beta_B \cdot B \cdot S \quad (1)$$

$$dI/dt = \beta_B \cdot B \cdot S - \delta \cdot I \quad (2)$$

The general state vector is $P = (S, I, D, B)$. The disease-free equilibrium is $P_0 = (\lambda/d_S, 0, 0, 0)$, and the endemic equilibrium is $P^* = (S^*, I^*, D^*, B^*)$. The variable B represents free HBV virions as defined by Equation (4).

2.2. Viral Kinetics and Inter-Viral Dynamics

The viral populations of HDV (D) and HBV (B) are governed by:

$$dD/dt = (1 - \varepsilon) \cdot p_1 \cdot I(t) \cdot e^{-gt} - c \cdot D \quad (3)$$

$$dB/dt = p_2 \cdot I(t) \cdot n^{-4} \cdot (D_0/D)^n - c \cdot B \quad (4)$$

The exponential term e^{-gt} models the time-dependent decay of drug potency, where g is the efficacy decay rate. The nonlinear inhibitory function $n^{-4}(D_0/D)^n$ reflects HDV-mediated suppression of HBV.

2.3. Parameter Estimation

The model parameters, their biological definitions, base values, and references are summarized in Table 1. The simulation code is provided in Appendix A.

Table 1. Model Parameters.

Symbol	Definition	Base Value	Ref.
λ	Hepatocyte biogenesis rate	1.1×10^4 cells/day	[23]
δ	Death rate of infected cells	$0.01\text{--}0.05$ day ^{−1}	[20]
β_B	HBV de novo infection rate	$10^{-10}\text{--}10^{-8}$	[3]
c	Viral clearance rate	0.51 day ^{−1}	[3]
g	Efficacy decay rate of Lonafernib	$0.01\text{--}0.05$ day ^{−1}	[3]
n	Inhibition exponent	$2.4\text{--}3.8$	[3]
ε	Lonafernib efficacy	$0.73\text{--}0.95$	Clinical
p_1	HDV production rate per infected cell	$10\text{--}100$ virions/cell/day	[23]
p_2	HBV production rate per infected cell	$10\text{--}100$ virions/cell/day	[23]
D_0	Threshold HDV level for inhibition	10^6 IU/mL	[20]

3. Mathematical Analysis and Stability

3.1. The Basic Reproduction Number (R_0)

At the disease-free equilibrium $P_0 = (\lambda/d_S, 0, 0, 0)$, the fixed points are determined by setting all derivatives to zero. Using the next-generation matrix method:

$$R_0 = \beta_B \cdot \lambda \cdot p_2 / (d_S \cdot \delta \cdot c) \quad (5)$$

If $R_0 < 1$, the system converges to the disease-free state. If $R_0 > 1$, the system moves toward the endemic equilibrium P^* .

3.2. Stability of the Endemic Equilibrium

The endemic equilibrium P^* is analyzed using the Jacobian linearization of the right-hand sides of Equations (1)–(4) evaluated at P^* . The Jacobian $J(P^*)$ is a 4×4 matrix; negative real parts of all eigenvalues confirm asymptotic stability (6).

Note on e^{-gt} term: The stability analysis of P^* is conducted on the autonomous limiting system as $t \rightarrow \infty$, where $e^{-gt} \rightarrow 0$ (since $g > 0$). Target cell limitation governs long-term behavior independently of the transient drug efficacy component.

Note on singularity at $D = 0$: The term $(D_0/D)n$ is evaluated as the limit $D \rightarrow 0^+$ at the DFE. All bifurcation diagrams are constructed for $D > 0$, ensuring mathematical well-posedness.

4. Results and Discussion

4.1. Baseline Simulation: Viral Rebound Dynamics

We simulated viral kinetics over a 100-day therapeutic window for two abstract computational profiles (Figure 1): Patient 1 ($n = 2.4$, weak interference) and Patient 2 ($n = 3.8$, strong interference). These are not derived from specific clinical cases, but parameter ranges are informed by published cohort data [1,17].

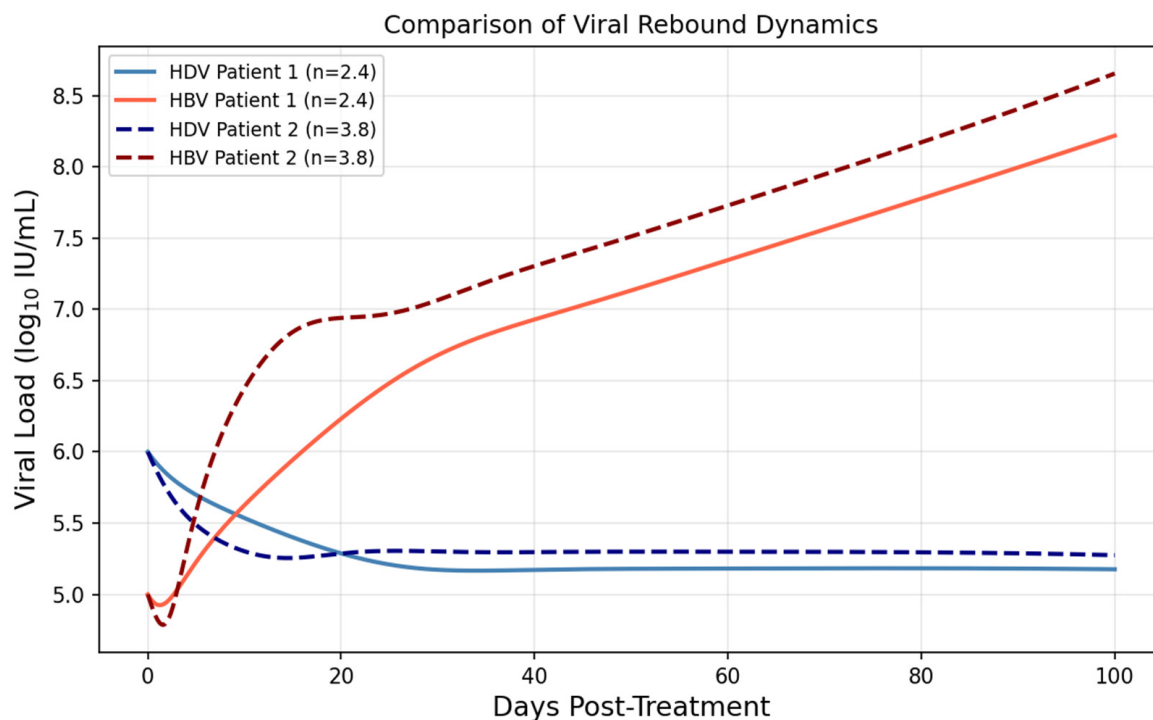


Figure 1. Comparative viral kinetics for Patient 1 ($n = 2.4$) and Patient 2 ($n = 3.8$). The simulation demonstrates the reciprocal relationship between HDV decline and HBV rebound.

4.2. Phase Space Topology and Global Stability Analysis

Topological analysis of the S–I phase plane confirms P^* as a global attractor. Patients with impaired immune clearance (low δ) or high infectivity (high β_B) exhibit elevated HBV rebound magnitudes, providing a basis for risk stratification (Figure 2).

4.3. Bifurcation Analysis: The Threshold for Viral Eradication

A transcritical bifurcation occurs at $\epsilon_c \approx 0.9$, where R_0 crosses unity. Consistent with D-LIVR trial data [17], patients achieving >90% HDV RNA suppression showed superior outcomes, aligning with this theoretical threshold (Figure 3, Appendix B).

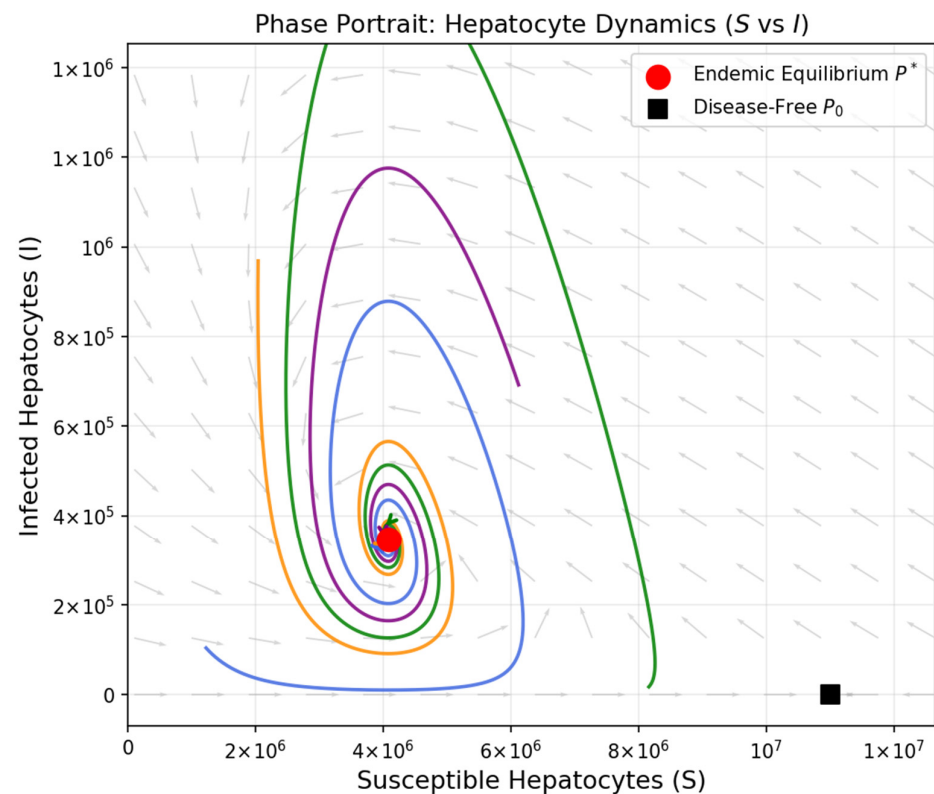


Figure 2. Phase portrait of the S–I dynamics (revised). Trajectories from multiple initial conditions illustrate global attraction toward the stable endemic equilibrium P^* (red dot), where P^* denotes the endemic equilibrium as defined in Equations (1)–(4). Colored trajectories indicate solution paths from different initial conditions; arrows indicate the direction of flow toward P^* . The disease-free equilibrium P_0 (black square) is unstable when $R_0 > 1$.

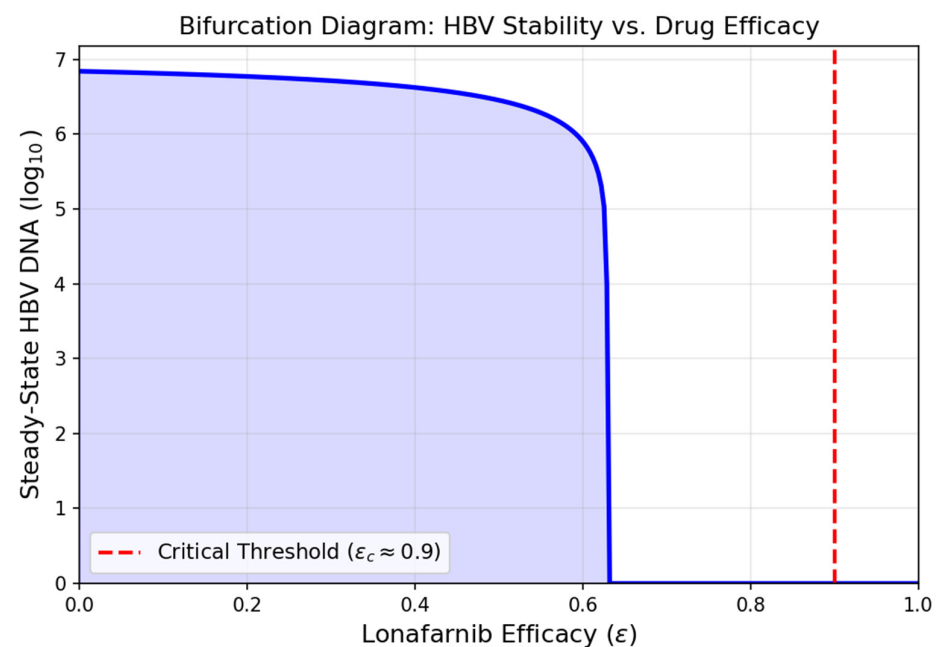


Figure 3. Bifurcation diagram of steady-state HBV DNA as a function of Lonafernib efficacy (ϵ). The transcritical bifurcation at $\epsilon_e \approx 0.9$ (red dashed line) marks the transition from chronic persistence to viral eradication. The blue shaded area represents the chronic persistence region where $R_0 > 1$ and the endemic equilibrium P^* is stable.

4.4. Multidimensional Sensitivity Analysis

The heatmap reveals a high-risk zone (high β_B , low δ) where HDV suppression leads to explosive HBV surge (Figure 4), aligning qualitatively with inter-patient variability in HBV rebound reported in Yurdaydin et al. [17].

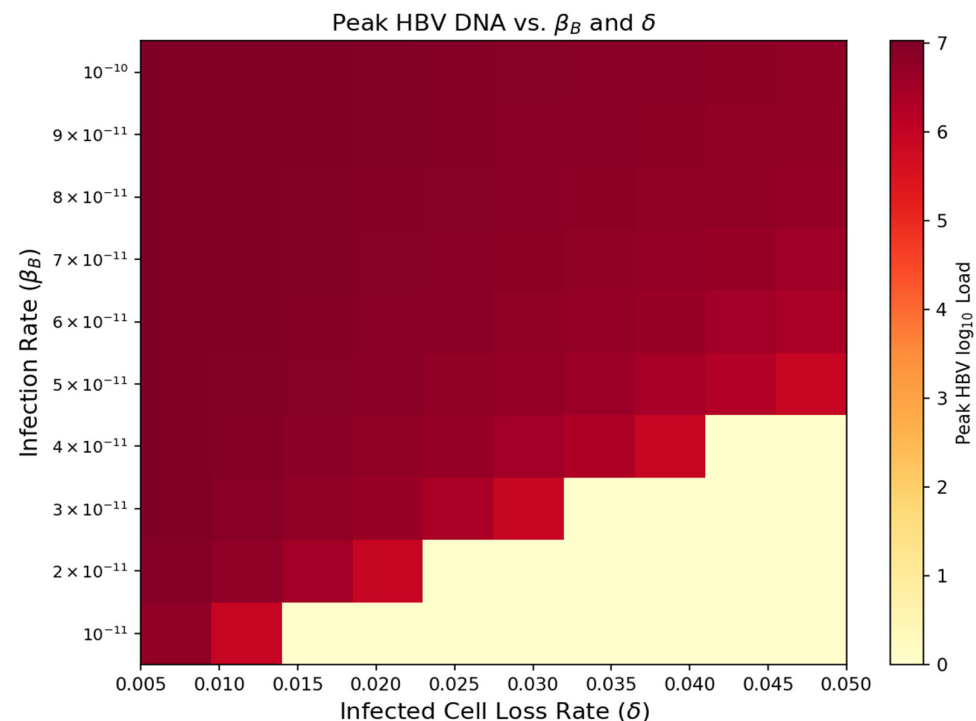


Figure 4. Heatmap of peak HBV DNA levels as a function of the de novo infection rate (β_A) and infected cell clearance (δ). Axis labels use Greek letter notation. The high-risk flare zone (upper-left) corresponds to high viral infectivity combined with impaired immune clearance. Color scale indicates peak HBV DNA in $\log_{10}$ IU/mL.

5. Discussion

The transition to an expanded model incorporating dynamic hepatocyte populations marks a significant advancement. The HBV rebound is an inherently self-limiting process governed by a globally stable endemic manifold. The “Target Cell Limitation” effect acts as a homeostatic governor, aligning with the viral kinetics observed in the D-LIVR and LOWR trials [1,17].

The bifurcation analysis identifies a critical tipping point at $\epsilon \approx 0.9$. The sensitivity analysis underscores that immune-mediated turnover (δ) is as critical as drug potency, supporting personalized medicine. Future work incorporating spatial liver heterogeneity will further refine these boundaries.

6. Conclusions

This study introduces an extended mathematical framework integrating dynamic hepatocyte populations. The most pivotal contribution is the identification of a transcritical bifurcation at $\epsilon \approx 0.9$, shifting the paradigm of HDV clinical success from a qualitative objective to a quantitative benchmark.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

Acknowledgments: The author thanks the reviewers for their constructive comments.

Conflicts of Interest: The author declares no conflicts of interest.

Appendix A. Simulation Code

The simulation code is provided in Appendix A. Bifurcation diagrams for β_B and δ are provided in Appendix B. Numerical simulations were performed using Python 3.10 with the SciPy library (version 1.10), specifically `scipy.integrate.solve_ivp` with the RK45 solver. All figures were generated using Matplotlib (version 3.7). The script implements Equations (1)–(4) with parameter values from Table 1.

Appendix B. Bifurcation Diagrams for β_A and δ

From $R_0 = \beta_B \lambda p_2 / (d_S \delta c)$, transcritical bifurcations occur at $\beta_{B,c} \approx 5.1 \times 10^{-11}$ and $\delta_c \approx 0.054 \text{ day}^{-1}$. Both values fall within the biologically plausible ranges of Table 1.

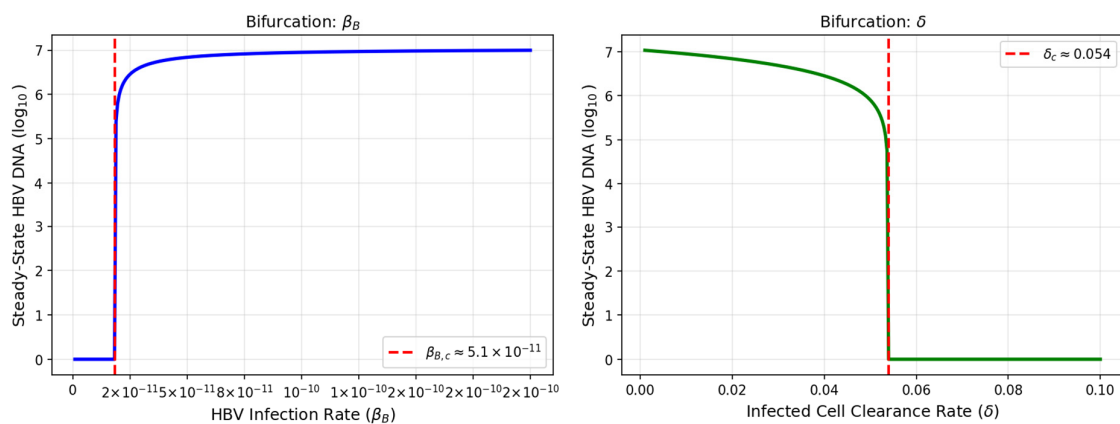


Figure A1. The blue curve (left panel) shows steady-state HBV DNA as a function of β_B ; the green curve (right panel) shows steady-state HBV DNA as a function of δ . Red dashed lines indicate the critical threshold values.

References

1. Etzion, O.; Hamid, S.S.; Asselah, T.; Gherlan, G.S.; Turcanu, A.; Petrivna, T.; Weissfeld, L.; Choong, I.; Hislop, C.; Apelian, D.; et al. Week 48 results of the phase 3 D-LIVR study. *J. Hepatol.* **2023**, *78*, S10. [\[CrossRef\]](#)
2. Miao, Z.; Zhang, S.; Ou, X.; Li, S.; Ma, Z.; Wang, W.; Peppelenbosch, M.P.; Liu, J.; Pan, Q. Estimating the Global Prevalence, Disease Progression, and Clinical Outcome of Hepatitis Delta Virus Infection. *J. Infect. Dis.* **2020**, *221*, 1677–1687. [\[CrossRef\]](#) [\[PubMed\]](#)
3. Zakh, R.; Churkin, A.; Bietsch, W.; Lachiany, M.; Cotler, S.J.; Ploss, A.; Dahari, H.; Barash, D. A Mathematical Model for Early HBV and -HDV Kinetics during Anti-HDV Treatment. *Mathematics* **2021**, *9*, 3323. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Hughes, S.A.; Wedemeyer, H.; Harrison, P.M. Hepatitis delta virus. *Lancet* **2011**, *378*, 73–85. [\[CrossRef\]](#) [\[PubMed\]](#)
5. Taylor, J.M. Infection by Hepatitis Delta Virus. *Viruses* **2020**, *12*, 648. [\[CrossRef\]](#) [\[PubMed\]](#)
6. Rizzetto, M. Hepatitis D Virus: Introduction and Epidemiology. *Cold Spring Harb. Perspect. Med.* **2015**, *5*, a021576. [\[CrossRef\]](#) [\[PubMed\]](#)
7. Negro, F.; Lok, A.S. Hepatitis D: A Review. *JAMA* **2023**, *330*, 2376–2387. [\[CrossRef\]](#) [\[PubMed\]](#)
8. Urban, S.; Neumann-Haefelin, C.; Lampertico, P. Hepatitis D Virus in 2021: Virology, Immunology and New Treatment Approaches for a Difficult-to-Treat Disease. *Gut* **2021**, *70*, 1782–1794. [\[CrossRef\]](#) [\[PubMed\]](#)
9. Farci, P.; Roskams, T.; Chessa, L.; Peddis, G.; Mazzoleni, A.P.; Scioscia, R.; Serra, G.; Lai, M.E.; Loy, M.; Caruso, L.; et al. Long-term benefit of interferon alpha therapy of chronic hepatitis D: Regression of advanced hepatic fibrosis. *Gastroenterology* **2004**, *126*, 1740–1749. [\[CrossRef\]](#) [\[PubMed\]](#)

10. Heidrich, B.; Yurdaydin, C.; Kabaçam, G.; Ratsch, B.A.; Zachou, K.; Bremer, B.; Dalekos, G.N.; Erhardt, A.; Tabak, F.; Yalcin, K.; et al. Late HDV RNA relapse after peginterferon alpha-based therapy of chronic hepatitis delta. *Hepatology* **2014**, *60*, 87–97. [CrossRef] [PubMed]
11. Eiger BioPharmaceuticals. *Study of the Efficacy and Safety of LonaFarnib/Ritonavir With and Without Pegylated Interferon-Alfa-2a (D-LIVR)*; ClinicalTrials.gov Identifier: NCT03719313; U.S. National Library of Medicine: Bethesda, MD, USA, 2023. Available online: <https://clinicaltrials.gov/study/NCT03719313> (accessed on 20 April 2026).
12. Koh, C.; Canini, L.; Dahari, H.; Zhao, X.; Uprichard, S.L.; Haynes-Williams, V.; Winters, M.A.; Subramanya, G.; Cooper, S.L.; Pinto, P.; et al. Oral prenylation inhibition with lonaFarnib in chronic hepatitis D infection: A proof-of-concept randomised, double-blind, placebo-controlled phase 2A trial. *Lancet Infect. Dis.* **2015**, *15*, 1167–1174. [CrossRef] [PubMed]
13. Yurdaydin, C.; Keskin, O.; Kalkan, Ç.; Karakaya, F.; Çalışkan, A.; Karatayli, E.; Karatayli, S.; Bozdayi, A.M.; Koh, C.; Heller, T.; et al. Optimizing lonaFarnib treatment for the management of chronic delta hepatitis: The LOWR HDV-1 study. *Hepatology* **2018**, *67*, 1224–1236. [CrossRef] [PubMed]
14. Asselah, T.; Chulanov, V.; Lampertico, P.; Wedemeyer, H.; Streinu-Cercel, A.; Pântea, V.; Lazar, S.; Placinta, G.; Gherlan, G.S.; Bogomolov, P.; et al. Bulevirtide Combined With Pegylated Interferon for Chronic Hepatitis D. *N. Engl. J. Med.* **2024**, *391*, 133–143. [CrossRef] [PubMed]
15. Wedemeyer, H.; Aleman, S.; Brunetto, M.; Blank, A.; Andreone, P.; Bogomolov, P.; Chulanov, V.; Mamonova, N.; Geyvandova, N.; Morozov, V.; et al. Bulevirtide monotherapy in patients with chronic HDV: Efficacy and safety results through week 96 from a phase III randomized trial. *J. Hepatol.* **2024**, *81*, 621–629. [CrossRef] [PubMed]
16. Bogomolov, P.; Alexandrov, A.; Voronkova, N.; Macievich, M.; Kokina, K.; Petrachenkova, M.; Lehr, T.; Lempp, F.A.; Wedemeyer, H.; Haag, M.; et al. Treatment of chronic hepatitis D with the entry inhibitor myrcludex B: First results of a phase Ib/IIa study. *J. Hepatol.* **2016**, *65*, 490–498. [CrossRef] [PubMed]
17. Yurdaydin, C.; Abbas, Z.; Buti, M.; Cornberg, M.; Esteban, R.; Etzion, O.; Gane, E.J.; Gish, R.G.; Glenn, J.S.; Hamid, S.; et al. Treating chronic hepatitis delta: The need for surrogate markers of treatment efficacy. *J. Hepatol.* **2019**, *70*, 1008–1015. [CrossRef] [PubMed]
18. Wedemeyer, H.; Schöneweis, K.; Bogomolov, P.; Blank, A.; Voronkova, N.; Stepanova, T.; Sagalova, O.; Chulanov, V.; Osipenko, M.; Morozov, V.; et al. Safety and efficacy of bulevirtide in combination with tenofovir disoproxil fumarate in patients with hepatitis B virus and hepatitis D virus coinfection (MYR202): A multicentre, randomised, parallel-group, open-label, phase 2 trial. *Lancet Infect. Dis.* **2023**, *23*, 117–129. [CrossRef] [PubMed]
19. Guedj, J.; Rotman, Y.; Cotler, S.J.; Koh, C.; Schmid, P.; Albrecht, J.; Haynes-Williams, V.; Liang, T.J.; Hoofnagle, J.H.; Heller, T. Understanding early serum hepatitis D virus and hepatitis B surface antigen kinetics during pegylated interferon-alpha therapy via mathematical modeling. *Hepatology* **2014**, *60*, 1902–1910. [CrossRef] [PubMed]
20. Goyal, A.; Murray, J.M. Dynamics of in vivo hepatitis D virus infection. *J. Theor. Biol.* **2016**, *398*, 9–19. [CrossRef] [PubMed]
21. Abbas, Z.; Memon, M.S.; Mithani, H.; Jafri, W.; Hamid, S. Treatment of chronic hepatitis D patients with pegylated interferon: A real-world experience. *Antivir. Ther.* **2014**, *19*, 463–468. [CrossRef] [PubMed]
22. Lempp, F.A.; Ni, Y.; Urban, S. Hepatitis delta virus: Insights into a peculiar pathogen and novel treatment options. *Nat. Rev. Gastroenterol. Hepatol.* **2016**, *13*, 580–589. [CrossRef] [PubMed]
23. Mhlanga, A.; Zakh, R.; Churkin, A.; Reinharz, V.; Glenn, J.S.; Etzion, O.; Cotler, S.J.; Yurdaydin, C.; Barash, D.; Dahari, H. Modeling the Interplay between HDV and HBV in Chronic HDV/HBV Patients. *Mathematics* **2022**, *10*, 3917. [CrossRef] [PubMed]
24. Shekhtman, L.; Cotler, S.J.; Ploss, A.; Dahari, H. Mathematical modeling suggests that entry-inhibitor bulevirtide may interfere with hepatitis D virus clearance from circulation. *J. Hepatol.* **2022**, *76*, 1229–1231. [CrossRef] [PubMed]
25. Perelson, A.S.; Guedj, J. Modelling hepatitis C therapy—predicting effects of treatment. *Nat. Rev. Gastroenterol. Hepatol.* **2015**, *12*, 437–445. [CrossRef] [PubMed]
26. de Sousa, B.C.; Cunha, C. Development of Mathematical Models for the Analysis of Hepatitis Delta Virus Viral Dynamics. *PLoS ONE* **2010**, *5*, e12512. [CrossRef] [PubMed]
27. Dahari, H.; Shudo, E.; Ribeiro, R.M.; Perelson, A.S. Modeling complex decay profiles of hepatitis B virus during antiviral therapy. *Hepatology* **2009**, *49*, 32–38. [CrossRef] [PubMed]
28. Ciupe, S.M.; Dahari, H.; Ploss, A. Mathematical models of early hepatitis B virus dynamics in humanized mice. *Bull. Math. Biol.* **2024**, *86*, 53. [CrossRef] [PubMed]
29. Goyal, A.; Ribeiro, R.M.; Perelson, A.S. The Role of Infected Cell Proliferation in the Clearance of Acute HBV Infection in Humans. *Viruses* **2017**, *9*, 350. [CrossRef] [PubMed]
30. Kadelka, S.; Dahari, H.; Ciupe, S.M. Understanding the Antiviral Effects of RNAi-Based Therapy in HBeAg-Positive Chronic Hepatitis B Infection. *Sci. Rep.* **2021**, *11*, 200. [CrossRef] [PubMed]
31. Goyal, A.; Murray, J.M. The Impact of Vaccination and Antiviral Therapy on Hepatitis B and Hepatitis D Epidemiology. *PLoS ONE* **2014**, *9*, e110143. [CrossRef] [PubMed]

32. Dahari, H.; Lo, A.; Ribeiro, R.M.; Perelson, A.S. Modeling hepatitis C virus dynamics: Liver regeneration and critical drug efficacy. *J. Theor. Biol.* **2007**, *247*, 371–381. [[CrossRef](#)] [[PubMed](#)]
33. Reluga, T.C.; Dahari, H.; Perelson, A.S. Analysis of Hepatitis C Virus Infection Models with Hepatocyte Homeostasis. *SIAM J. Appl. Math.* **2009**, *69*, 999–1023. [[CrossRef](#)] [[PubMed](#)]
34. Ghany, M.G.; Buti, M.; Lampertico, P.; Lee, H.M.; Berg, T.; Brunetto, M.R.; Buchholz, S.; Chang, K.-M.; Chen, J.; Cornberg, M.; et al. Guidance on treatment endpoints and study design for clinical trials aiming to achieve cure in chronic hepatitis B and D: Report from the 2022 AASLD-EASL HBV-HDV Treatment Endpoints Conference. *Hepatology* **2023**, *78*, 1654–1673. [[CrossRef](#)] [[PubMed](#)]
35. Buti, M.; Stepanova, M.; Palom, A.; Riveiro-Barciela, M.; Nader, F.; Roade, L.; Esteban, R.; Younossi, Z. Chronic hepatitis D associated with worse patient-reported outcomes than chronic hepatitis B. *JHEP Rep.* **2021**, *3*, 100280. [[CrossRef](#)] [[PubMed](#)]
36. Taylor, J.M. Hepatitis D Virus Replication. *Cold Spring Harb. Perspect. Med.* **2015**, *5*, a021568. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.