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Lonafarnib for chronic hepatitis delta: Clinical mechanism of action, development, and evolving role in combination therapy

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1. Introduction

Hepatitis D virus (HDV), the smallest known human RNA virus, is a defective, satellite virus that requires hepatitis B virus (HBV)-derived surface antigen (HBsAg) proteins for virion assembly and entry (Gopalakrishna et al., 2024). HDV superinfection occurs when a person with existing HBV infection subsequently becomes infected with HDV, resulting in the most severe form of chronic viral hepatitis, accelerating progression to cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC), and death (Gopalakrishna et al., 2024). Coinfection of HBV and HDV, ie, simultaneous infection, can result in fulminant hepatic failure, although most infected individuals can clear both HBV and HDV, if infected as adults. The original discovery of delta antigen in HBsAg carriers, and subsequent characterization of the delta agent as an RNA-containing particle associated with HBsAg, established HDV as a distinct viral pathogen dependent on HBV envelope proteins (Rizzetto et al., 1977, 1980). While HDV can replicate its genome autonomously inside the hepatocyte, the virus requires HBsAg, rather than complete HBV replication, to complete virion assembly and to facilitate transmission. Experimentally, co-expression of HBsAg is sufficient to support production of infectious HDV particles, emphasizing that the key HBV contribution to HDV spread is provision of the envelope proteins (Wang et al., 2021; Winer et al., 2018). HDV uses the HBsAg proteins L, M, and S as its envelope proteins, which are required for HDV to complete its viral envelope and exit from the host cells and transmit to other hepatocytes (Bonino et al., 1986).

Compared to HBV monoinfection, chronic HDV infection with HBV increases the risk of cirrhosis by 3-fold and liver-related mortality by 2-fold (Bonino et al., 1986). Multiple studies have revealed chronic HDV infection leads to more severe liver disease than HBV monoinfection and is associated with accelerated fibrosis progression and a higher risk of developing HCC (Rizzetto, 2000; Fattovich et al., 1987).

Despite the availability of multiple direct-acting antivirals (DAAs), such as tenofovir disoproxil fumarate, tenofovir alafenamide, and entecavir, directed against HBV, none of the DAAs available have an effect on HDV (Wedemeyer and Manns, 2010; Yurdaydin et al., 2002; Lau et al., 1999; Niro et al., 2006). HBV nucleos(t)ides only reduce HBV DNA, do not affect HBsAg levels, and have no effect on HDV replication; therefore, they are ineffective against HDV infection (Lau et al., 1999; European Association for the Study of the Liver, 2012; Kabacam et al., 2012).

Global prevalence of chronic HDV is estimated at 12-20 million individuals, although this figure likely underestimates the true burden due to poor screening practices and lack of awareness (Wedemeyer and Manns, 2010; Asselah and Rizzetto, 2023). Historically, therapeutic options have been limited. Lonafarnib (LNF) is currently the only oral agent with potential for finite treatment that is in Phase III clinical development for participants with chronic HDV infection and has been studied both with and without pegylated-interferon-alfa (PEG-IFN-alfa) and pegylated-interferon-lambda (PEG-IFN-lambda) (Gopalakrishna et al., 2024; Etzion et al., 2023a; Treatment of chronic delta hepatitis). Nucleic acid polymers (NAPs) also remain in clinical development for

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chronic HDV infection. Currently, there is only one treatment approved by the European Medicines Agency (EMA) for the treatment of HDV: bulevirtide (Hepcludex), a daily subcutaneous injection for long-term administration. There is no treatment approved by the Food and Drug Administration (FDA) as of May 2026 and bulevirtide is pending FDA approval this year; therefore, there is no approved HDV treatment available in the United States. PEG-IFN-alfa (180 μg weekly for 48 weeks), while not officially approved for HDV, is consistently recommended by treatment guidelines as a therapeutic option for participants with chronic HDV and compensated liver disease (European Association for the Study of the Liver, 2023; Terrault et al., 2018; Sarin et al., 2016). There remains a major unmet medical need for new therapies that target distinct steps in the HDV replication cycle. Expanding the available therapeutic options, particularly with an oral treatment with a finite duration compatible with other treatments available or in development, would enhance clinicians' ability to effectively manage the complexities of HDV infection and optimize treatment outcomes.

Farnesylation of the large hepatitis delta antigen (L-HDAg) by the host farnesyl transferase (FT) enzyme is required for the association of L-HDAg with HBsAg to form an infectious HDV virion (Otto and Casey, 1996; Glenn et al., 1992). Among emerging therapeutic strategies, farnesyl transferase inhibitors (FTIs), particularly LNF, have gained momentum due to their host-targeted mechanism that interferes with the post-translational modification essential for HDV virion assembly. LNF exerts anti-HDV activity by blocking the assembly and release of HDV virions. HDV relies on FT for farnesylation of L-HDAg, making this step an attractive host-targeted antiviral target (Bordier et al., 2002; Yurdaydin et al., 2022).

This review explores the mechanistic rationale; cumulative clinical trial evidence including virologic and histologic endpoints; safety considerations and treatment burden; durability and clinical endpoint limitations; cost-effectiveness considerations; long-term clinical benefit with respect to hard clinical endpoints; and future directions for LNF in the treatment of HDV.

2. Mechanism of action

HDV encodes 2 forms of HDV antigen: the small antigen (S-HDAg), which promotes viral replication, and the large antigen (L-HDAg), which is required for virion assembly and secretion. L-HDAg requires prenylation, specifically farnesylation, by host FT, enabling its interaction with HBsAg (Khalfi et al., 2023). This interaction is critical for envelopment and secretion of HDV particles.

LNF is an oral, small-molecule inhibitor of FT. By blocking the farnesylation of L-HDAg, it disrupts HDV particle assembly and inhibits viral secretion, leading to the suppression of viremia and reduction in liver inflammation. Furthermore, in vitro studies suggest that LNF modulates the ratio of edited to unedited viral genomes, a factor that may influence particle infectivity and immune evasion (Thiyagarajah et al., 2023; Bordier et al., 2003; Bach et al., 2023). This unique, host-targeted mechanism distinguishes LNF from traditional antiviral agents, providing a basis for its potential in finite-duration combination regimens.

In vitro studies have also shown that blockade of HDV assembly and altered intracellular HDV-RNA handling can be associated with induction of interferons and interferon-stimulated genes (IFNs/ISGs) (Lempp et al., 2019; Verrier et al., 2022). While these data are derived from in vitro studies, they may help explain several observed clinical outcomes with LNF in chronic HDV infection. In particular, Phase 2 studies of LNF-based regimens have reported a well-tolerated, transient post-treatment increase in alanine aminotransferase (ALT) that is accompanied by subsequent HDV-RNA negativity and ALT normalization, a pattern reminiscent of interferon-induced immune-mediated flares followed by durable virologic responses (Yurdaydin et al., 2018). This interferon-like post-treatment profile—transient ALT elevation coinciding with or shortly preceding sustained HDV-RNA decline—suggests that prenylation inhibition may facilitate host immune clearance mechanisms that persist beyond the period of direct antiviral exposure.

With its host-targeted mechanism and direct impact on HDV assembly, LNF may provide an important oral therapeutic tool for physicians to support finite treatment for participants with HDV, either as monotherapy or potentially in combination with other therapies that impact HDV/HBV cell entry and/or HBsAg subviral particle assembly. As the only oral agent with direct antiviral effects against HDV, it could enhance accessibility and convenience for patients, potentially improving treatment adherence and supporting more scalable global implementation. LNF has the potential to form the backbone of successful combination antiviral therapy and has already been evaluated with and without PEG-IFN-alfa and PEG-IFN-lambda to understand the potential for optimizing treatment response for chronic HDV.

3. Clinical evidence

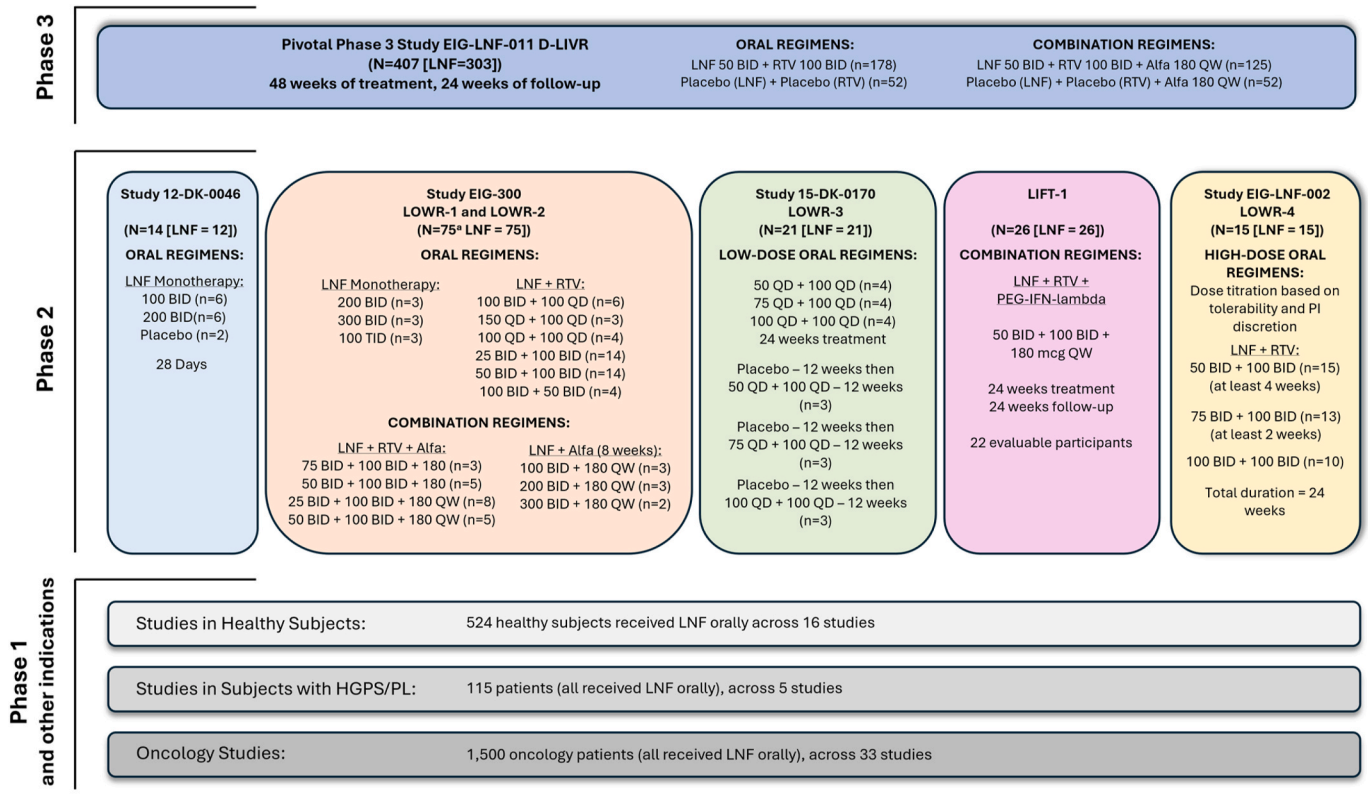
LNF has been extensively tested in Phase 1, Phase 2, and Phase 3 studies in over 2400 human participants. LNF has been administered in participants with HDV for up to 48 weeks, in participants with Hutchinson-Gilford Progeria Syndrome (HGPS) for >15 years, and in participants with cancer for >1 year, providing significant human safety for clinical use. Fig. 1 provides a comprehensive overview of the clinical development of LNF, including the LIFT-1 study.

3.1. Phase 2 trials - proof-of-concept and LOWR program

Early proof-of-concept evaluation established that oral prenylation inhibition could reduce HDV RNA, while also identifying gastrointestinal (GI) tolerability as a key dose-limiting issue, particularly at higher LNF exposures. Some participants experienced HDV-RNA rebound on treatment, and transient ALT elevations after therapy discontinuation accompanied by sustained reductions in HDV-RNA and ALT normalization, observations that helped shape later interest in response durability and post-treatment monitoring.

The EIG-300 study (LOWR-1 and LOWR-2, NCT02430181) evaluated escalating doses of LNF, both as monotherapy and in combination with ritonavir (RTV), which acts as a pharmacokinetic booster by inhibiting CYP3A4 metabolism of LNF, resulting in less LNF exposure to the GI tract but higher LNF exposure post-absorption (Yurdaydin et al., 2022; Bordier et al., 2003). The LOWR-1 study investigated various LNF dosing regimens, either as monotherapy or combined with RTV or PEG-IFN-alfa, in participants with chronic HDV (Yurdaydin et al., 2022). The study found that higher doses of LNF monotherapy initially led to greater reductions in HDV RNA but were associated with increased GI side effects. Combining LNF with low-dose RTV significantly improved antiviral efficacy and tolerability by increasing serum concentrations of LNF with less exposure to the GI tract. Additionally, combining LNF with PEG-IFN-alfa resulted in substantial and rapid HDV RNA reductions. Notably, some participants who received 12 weeks of LNF therapy experienced transient post-treatment ALT elevations followed by HDV RNA becoming undetectable, suggesting that LNF-induced post-treatment immune or inflammatory events may in some cases lead to long-term viral suppression. This is also associated with regression in fibrosis, although pretreatment predictors of which patients will experience these remarkable outcomes remain uncertain (Yurdaydin et al., 2022).

The LOWR-2 study was a Phase 2 dose-finding trial evaluating optimal dosing regimens of LNF boosted by RTV, with or without PEG-IFN-alfa, in participants with chronic HDV (Yurdaydin et al., 2022), and this was bookended by the LOWR-3 and LOWR-4 studies that explored ultra-low and ultra-high doses of LNF, respectively. GI side effects were more prevalent with higher doses of LNF, whereas low-dose regimens were better tolerated. Notably, the LOWR-2 study demonstrated that the all-oral LNF (50 mg twice daily) boosted by low-dose RTV resulted in



[a]In Study EIG-300, 8 patients were retreated during the study. Seventy-five patients represents the total number of treatment courses from the 66 unique patients enrolled in both parts of EIG-300.
Note: N= number treated with LNF. LNF and RTV units are mg; drugs were administered orally. Alfa represents PEF- INF-alfa-2a; units are mcg and drug was administered via subcutaneous injection.

Fig. 1. Comprehensive overview of the human experience with LNF alone or in combination with RTV, PEG-IFN-alfa or PEG-IFN-lambda. The D-LIVR Phase 3 represents the largest placebo-controlled trial in HDV. In LOWR 1 + 2, 66 unique participants enrolled in both parts of the study received 75 treatment courses. LIFT-1 is included as a separate Phase 2 combination study. Color coding indicates study category. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)
Abbreviations: BID, twice daily; HDV, hepatitis D virus; HGPS, Hutchinson-Gilford Progeria Syndrome; LNF, lonafarnib; PL, progeroid laminopathies; QD, once daily; QW, once weekly; Alfa, pegylated-interferon-alfa-2a; PI, principal investigator; RTV, ritonavir.

robust antiviral efficacy, with 46% (6 of 13) of participants achieving a ≥2 log10 reduction of HDV RNA or HDV RNA below the lower limit of quantification at the end of treatment (24 weeks). Adding PEG-IFN-alfa to LNF 25-mg or 50-mg/RTV regimens further enhanced efficacy, achieving this endpoint in up to 89% (8 of 9) of participants. Notably, a subset of participants experienced transient post-treatment increases in ALT, leading to sustained HDV-RNA negativity and ALT normalization. These findings support further evaluation of low-dose RTV-boosted LNF, particularly in combination with PEG-IFN-alfa, as promising therapies for HDV.

3.2. Phase 2 trial - LIFT-1 study

As most novel therapies currently in clinical development for HDV have distinct mechanisms of action, there are multiple potential combinations of novel anti-HDV therapies. The first of such combinations leveraged the successes of the Phase 2 LOWR-2 study, which demonstrated compelling antiviral synergy between LNF and PEG-IFN-alfa, and the Phase 2 LIMT-1 study (NCT02765802), which demonstrated PEG-IFN-lambda's anti-HDV efficacy without the unwanted side effects of PEG-IFN-alfa (Etzion et al., 2023a). In the Phase 2 LIFT-1 study (NCT03600714) (Treatment of chronic delta hepatitis), conducted at the National Institutes of Health (NIH), PEG-IFN-lambda 180 mcg once weekly was combined with LNF 50 mg twice daily plus RTV 100 mg twice daily to treat 26 participants for 24 weeks with 24-week follow-up.

Efficacy results included:

- 17/22 (77%) participants achieved the primary endpoint of >2 log10 decline in HDV RNA at end of treatment (EOT)
- 11/22 (50%) participants had HDV RNA below the limit of quantitation or undetectable at EOT
- 5/22 (23%) participants had a durable virologic response (DVR)
- 6/20 (30%) participants achieved the secondary endpoint of >2-point improvement in histologic activity index at 24 weeks after therapy

Adverse events were mostly mild to moderate and included GI -related side effects. The Phase 2 LIFT-2 study to be conducted at the NIH will explore a similar LNF and PEG-IFN-lambda combination extended to 48 weeks of treatment.

3.3. Phase 3 trial - D-LIVR

The D-LIVR study (NCT03719313) is the largest and most comprehensive randomized placebo-controlled Phase 3 trial in HDV patients (Etzion et al., 2023b). This study enrolled 407 participants with chronic HDV infection across 22 countries and 118 sites.

The study included 4 arms randomized to receive 1 of the following regimens:

- Oral LNF 50 mg/RTV 100 mg twice daily (n = 178)
- LNF 50 mg/RTV 100 mg twice daily combined with PEG-IFN-alfa-2a 180 μg once weekly (n = 125)
- PEG-IFN-alfa 180 μg once weekly monotherapy (n = 52)

- Placebo (n = 52)

Each arm had a 48-week treatment duration followed by 24 weeks of post-treatment follow-up. The study was designed to evaluate LNF/RTV, with or without PEG-IFN-alfa, as a potential finite treatment for chronic HDV infection.

After 48 weeks of treatment (EOT), the primary composite efficacy endpoint, defined as a reduction of ≥2 log10 in HDV RNA and ALT normalization relative to baseline, was achieved with statistical significance in both the LNF/RTV and LNF/RTV + PEG-IFN-alfa treatment arms compared to placebo. Among the 407 randomized participants, a composite virologic and biochemical response was observed in 10.1% of participants treated with LNF/RTV (P = 0.0044) and 19.2% of those treated with LNF/RTV + PEG-IFN-alfa (P < 0.0001), compared to 1.9% in the placebo group. Notably, 20.8% of participants in the LNF/RTV + PEG-IFN-alfa arm and 8.4% in the LNF 50 mg/RTV arm had HDV RNA below the limit of quantitation at week 48. Histological improvements were also observed, most notably with the majority of patients in the LNF/RTV + PEG-IFN-alfa arm demonstrating statistically significant benefits compared to placebo (35 of 66 patients with evaluable paired biopsies, P = 0.0139). Moreover, 15.6% of all oral LNF/RTV-treated patients and 29.3% of LNF/RTV + PEG-IFN-alfa-treated patients who completed treatment and 24 weeks of post-treatment follow-up achieved the composite endpoint 6 months after stopping treatment (Glenn, 2025). This is particularly meaningful in light of recent data indicating that patients who achieved such a composite endpoint 6 months after any LNF-based therapy in ≥10 years of follow-up experienced no major liver-related events, including decompensation, liver transplantation, HCC, and death (Glenn, 2025).

The D-LIVR kinetic analyses also reported HDV-RNA rebound patterns after prolonged treatment, many of which were associated with transient post-treatment ALT elevations, RNA suppression and ALT normalization (Hershkovich et al., 2024).

These data confirm that LNF, as a stand-alone oral treatment or used in combination with PEG-IFN-alfa, produces statistically and clinically meaningful improvements in virologic, biochemical, and histologic outcomes (Asselah et al., 2024a).

4. Clinical endpoints and durability of response

Most available LNF data are based on short-term virologic and biochemical endpoints, including HDV-RNA decline, HDV RNA below the lower limit of quantification, ALT normalization, composite virologic/biochemical response, and histologic activity improvement. These endpoints are clinically meaningful and are appropriate for antiviral development, but they remain surrogates for definitive outcomes in long-term follow-up studies in chronic HDV, including fibrosis progression or regression, hepatic decompensation, HCC, liver transplantation, and liver-related mortality (Glenn, 2025).

Histologic improvement in D-LIVR is an important bridge between short-term biomarker response and longer-term clinical benefit, but additional mid-term and long-term analyses are needed. Ideally, such studies should include standardized fibrosis assessment, paired noninvasive fibrosis markers, decompensation events, HCC surveillance outcomes, transplant-free survival, and patient-reported outcomes. These clinical endpoints will be particularly important when comparing finite LNF-based regimens with longer-term indefinite injectable or combination approaches (Lampertico et al., 2025).

Durability after discontinuation remains one of the main caveats of HDV therapy. Early studies demonstrated that HDV RNA can rebound after stopping LNF, or sometimes the post-treatment course is notable for a transient increase in ALT accompanied by sustained reductions in HDV RNA followed by ALT normalization. In such patients who had pretreatment liver biopsies, repeat biopsy as early as 6 months following these ALT normalizations showed regression of fibrosis (Glenn, 2025). In the LIFT-1 study, 23% of evaluable participants had a DVR 24 weeks after EOT, indicating that significant off-treatment responses can occur. Most recently, long-term follow-up analysis of the LNF Phase 2 study and part of the D-LIVR Phase 3 studies indicated that patients who achieved a composite endpoint (≥2 log10 decline in HDV-RNA + ALT normalization) 6 months after stopping any LNF-based therapy experienced no major liver-related events (no liver decompensation, no liver transplantation, no HCC, and no death) in ≥10 years of follow-up. Moreover, all LNF-treated patients, whether or not they achieved such a post-treatment composite endpoint, had greater event-free survival than historical cohorts with comparable baseline cirrhosis that were either untreated or mostly treated with PEG-IFN-alfa (Glenn, 2025). LNF is thus the only new anti-HDV therapy that has demonstrated long-term clinical benefit with respect to hard clinical endpoints following finite therapy.

4.1. LNF impact on HDV life cycle

LNF is an oral FTI that directly targets a unique step in the HDV replication cycle, specifically, the farnesylation of L-HDAg, which is essential for HDV virion assembly and release. Its distinct mechanism of action and direct impact on the virus life cycle makes it highly complementary to other drugs in development for HDV, which target different stages of the viral life cycle or host-virus interaction.

4.2. How LNF complements other HDV drugs

While some HDV patients can achieve long-term clinical benefit following a finite course of LNF-based therapy, LNF's oral dosing and its unique assembly-targeting mechanism of action suggest LNF could also play an important role in combination regimens. The clinical experience to date supports LNF/RTV, with or without PEG-IFN-alfa or PEG-IFN-lambda, as studied regimens, whereas combinations of LNF with bulevirtide, nucleic acid polymers (NAPs), or Fc-engineered monoclonal antibodies remain mechanistically plausible but require dedicated clinical trials.

As illustrated in Fig. 2 four distinct and non-overlapping mechanisms are currently under development for the treatment of chronic HDV infection. Bulevirtide, a once-daily subcutaneous injection approved by the EMA, blocks HDV entry into hepatocytes. LNF inhibits farnesylation of L-HDAg, thereby disrupting HDV particle assembly. Nucleic acid polymers aim to inhibit the assembly and secretion of HBsAg subviral particles. PEG-IFN-alfa and PEG-IFN-lambda exhibit immunomodulatory activity, providing broad antiviral effects against HDV. In addition, several monoclonal antibody strategies are in development, including VIR-3434 that aims to neutralize the HBsAg required for HDV assembly, and antibodies designed to disrupt the interaction of HBsAg and the extracellular domain of the NTCP receptor.

The D-LIVR study demonstrated the potential additive effect of LNF in combination with PEG-IFN-alfa-2a. Similarly, the MYR204 study showed a benefit of combining bulevirtide and PEG-IFN-alfa-2a (Asselah et al., 2024b). Together, these findings reinforce the need to develop therapies targeting different mechanisms of action and highlight the importance of exploring combination strategies to optimize treatment outcomes for chronic HDV infection.

4.2.1. Combination with pegylated interferons

LNF combined with PEG-IFN-alfa or PEG-IFN-lambda leads to greater reductions in HDV RNA than either agent alone, suggesting a combination benefit between direct assembly inhibition and additive immunomodulatory effects that trigger innate antiviral mechanisms.

In Phase 2 studies, the combination of LNF, RTV, and PEG-IFN-alfa achieved up to an 89% virological response at 24 weeks, compared to 46% for LNF plus RTV alone (Etzion et al., 2023a). The Phase 2 LIFT-1 study analyzed a combination of PEG-IFN-lambda, RTV, and LNF and reported a 77% virological response at the end of 24 weeks of therapy, 50% had HDV RNA below the limit of quantitation or undetectable, and

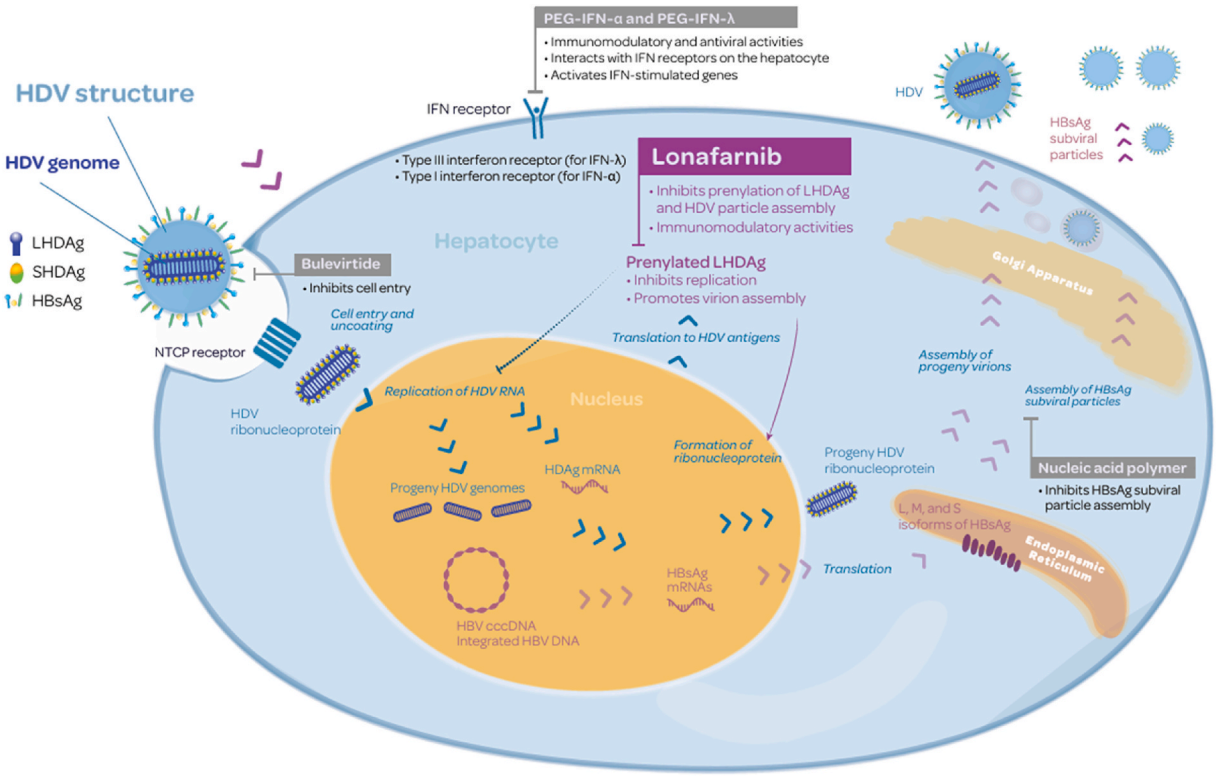


Fig. 2. HDV Life Cycle and Antiviral Targets. Circulating HDV virions comprise an envelope that consists of large (L), middle (M), and small (S) HBsAg and a ribonucleoprotein with genomic HDV RNA complexed with 2 isoforms of hepatitis D antigen (S-HDAg and L-HDAg). HDV enters hepatocytes through binding to NTCP. After entry, HDV ribonucleoprotein is transported into the hepatocyte nucleus where the HDV RNA is replicated using host enzymes. HDV mRNA is translated to S-HDAg and L-HDAg in the cytoplasm, which bind to HDV RNA to form a ribonucleoprotein. S-HDAg activates replication, whereas L-HDAg contains a farnesylation signal; farnesylation in the cytoplasm promotes virion assembly. The ribonucleoprotein is coated with HBV surface proteins and the HDV virions are secreted. Bulevirtide is shown acting at the NTCP receptor. NAPs are shown as agents aimed at inhibiting HBsAg subviral particle assembly/secretion. LNF is an inhibitor of farnesyltransferase, which is involved in the farnesylation of L-HDAg, an essential step in HDV particle assembly. In vitro IFN/ISG induction observed after FTI treatment is presented as a downstream cell-culture observation, not as an established direct in vivo immunomodulatory mechanism of LNF.
Abbreviations: cccDNA, covalently closed circular DNA; FTI, farnesyl transferase inhibitors; HBV, hepatitis B virus; HBsAg, hepatitis B virus surface antigens; HDAg, hepatitis D antigen; HDV, hepatitis D virus; IFN, interferon; ISG, interferon-stimulated gene; L-HDAg, large hepatitis D antigen; LNF, lonafarnib; mAb, monoclonal antibody; mRNA, messenger RNA; NAPs, nucleic acid polymers; NTCP, sodium taurocholate co-transporting polypeptide; PEG-IFN-alfa, pegylated-interferon-alfa; PEG-IFN-lambda, pegylated interferon lambda; S-HDAg, small hepatitis D antigen.

23% had DVR at 24 weeks after the EOT (Elazar and Glenn, 2022).

4.2.2. *Combination with bulevirtide*

Bulevirtide blocks viral entry by inhibiting the sodium taurocholate co-transporting polypeptide (NTCP) receptor, while LNF prevents virion assembly. Using both could theoretically block both the entry of new virus and the production of new infectious particles, although clinical trials are needed to confirm. LNF plus bulevirtide has not yet been established as an evidence-based clinical regimen, and clinical trials are needed to determine safety, sequencing, duration, antiviral depth, and durability. Use of these new agents either in combination or sequentially could help maximize viral suppression, improve durable effects, and reduce resistance risk, but this remains investigational.

4.2.3. *Combination with nucleic acid polymers (NAPs) and Fc-engineered monoclonal antibodies (mAb)*

NAPs inhibit the release of HBsAg particles, and mAbs are designed to bind and neutralize HBsAg-containing HDV virions. HBsAg is required for HDV virion assembly, while LNF blocks the prenylation step needed for assembly. Combining these could further disrupt the HDV life cycle at multiple points.

NAPs and LNF impact HDV at different stages of the viral life cycle. Enhanced efficacy of this combination remains a hypothesis that requires clinical studies to establish appropriate dosing, safety, patient selection, and durability.

LNF appears to be complementary to other drugs in development for HDV due to its distinct mechanism of action and its oral product profile. Combination regimens are likely to become an important part of future HDV therapy.

5. Treatment optimization, patient burden, and combinations

LNF is currently the only oral treatment in advanced clinical development for patients with chronic HDV infection. Its oral administration provides high accessibility and convenience for patients, with the potential to enhance adherence and optimize therapeutic outcomes. LNF-based regimens may involve twice-daily dosing, pharmacokinetic boosting with low-dose RTV, monitoring for drug-drug interactions, management of GI l adverse events, and, when prescribed in combination with PEG-IFN-alfa, weekly injections and interferon-associated systemic adverse effects if PEG-IFN-alfa is used instead of the better tolerated PEG-IFN-lambda. Co-administration of low-dose RTV to boost exposure through inhibition of CYP3A metabolism is a common strategy (eg, Paxlovid).

In clinical practice, treatment duration and continuation strategies will depend on regulatory status, local availability, contraindications, tolerability, and emerging durability data. Patients achieving ≥2 log10 HDV RNA reduction and/or ALT normalization by or before week 24 may be candidates to continue LNF treatment for 1 year, but response-guided strategies remain dependent on ongoing analyses. Although

the first approved LNF-based regimen is expected to be 48 weeks duration, as in the pivotal Phase 3 D-LIVR study, earlier Phase 2 studies have demonstrated that shorter regimens may be efficacious.

Patients with compensated liver disease who tolerate and have access to PEG-IFN-alfa may receive combination therapy with LNF and PEG-IFN-alfa for 1 year. If PEG-IFN-alfa is unavailable, intolerable, or contraindicated, LNF monotherapy may be administered. Combination therapy has demonstrated approximately double the efficacy of monotherapy, strongly supporting the benefit of combining agents with complementary mechanisms of action to improve patient outcomes. This is particularly beneficial in difficult-to-treat populations such as patients with HDV.

All participants treated with LNF experienced initial HDV RNA reductions. Participants who experience on-treatment viral load rebound might be producing reduced-infectivity or non-infectious virus, but this remains a hypothesis. If this hypothesis is confirmed, a higher percentage of participants with viral load rebound might experience post-treatment flares followed by sustained off-treatment responses. This hypothesis remains under investigation and will require confirmation through additional analyses.

Intermittent LNF treatment regimens, such as alternating 6-12 months on treatment with 6 months off treatment, should be explored in future clinical studies to optimize responses and assess whether immune-mediated viral suppression can be leveraged safely, as has been observed in all cases to date of LNF-induced post-treatment transient ALT elevation with suppression of HDV RNA and subsequent long-term ALT normalization. Cost-effectiveness analyses of HDV therapies will be essential, particularly as larger datasets accrue on long-term clinical outcomes. Given its oral administration, room-temperature stability, demonstrated histologic improvement, and early evidence suggesting durable clinical benefit, LNF appears to have a favorable profile from both a clinical and health-economic perspective.

6. Safety, tolerability, and practical management of side effects

LNF has been widely studied in over 2400 participants. Because LNF is given orally, the most common adverse events associated with LNF have been GI in nature, including nausea, diarrhea, abdominal discomfort, vomiting, constipation, decreased appetite, and weight loss. GI adverse events were dose-related in early studies and were particularly notable in very high-dose monotherapy arms. However, the proposed clinical regimen is LNF 50 mg/RTV 50 mg taken twice daily. This low-dose LNF regimen administered with RTV to boost exposure is optimized to maximize antiviral activity while minimizing GI side effects. GI side effects were manageable in most cases, but they can be clinically meaningful during treatment onset and dose escalation. In the D-LIVR trial, 33% of participants experienced a dose reduction, with most (53%) of these participants subsequently had their dose increased, indicating improved tolerability following the initial treatment period. Importantly, there was no difference in dropout rates between the LNF/RTV with or without PEG-IFN-alfa-2a groups compared to placebo (Yurdaydin et al., 2018).

6.1. Anticipating and managing side effects

GI adverse reactions to LNF treatment are often transient and typically diminish over time as the participant acclimates to the medication, and they can often be mitigated with proactive use of appropriate agents.

In particular, to better anticipate and mitigate these side effects:

- Prophylactic or symptomatic treatment may be initiated to manage common side effects:
  1. Antiemetics for nausea and vomiting
  2. Antidiarrheal agents for diarrhea
  3. Laxatives or dietary fiber for constipation
- Dietary modifications, such as taking the medication with food or avoiding irritating foods, may also help reduce GI discomfort.
- Weight, hydration status, electrolytes when clinically indicated, and patient-reported symptom burden should be monitored, particularly during early therapy.
- Medication reconciliation is important because RTV boosting can affect CYP3A4-mediated drug metabolism and may complicate use in patients with polypharmacy. Since there is no need to emergently initiate LNF therapy for HDV, one can readily address any issues ahead of time (as opposed to Paxlovid for acute COVID infection).

Close monitoring during the early phases of treatment allows for timely intervention and improved patient adherence. Viral hepatology specialists are experienced with management of a range of antiviral adverse reactions, and management of transient GI adverse reactions is becoming common with the widespread use of GLP-1 agonist medicines with a similar tolerability profile.

6.2. Ultra-long-acting formulations

Ultra-long-acting (XLA) antiviral formulations have been proposed for chronic viral hepatitis based on advances in medicinal chemistry and drug delivery that can extend antiviral exposure for months or longer (Soriano et al., 2022). In principle, an XLA formulation of an HDV assembly inhibitor could reduce daily pill burden, support adherence, and maintain steady drug exposure. However, no XLA formulation of LNF has been clinically established. Therefore, XLA concepts are promising but currently speculative for LNF.

6.3. Genotypic activity

HDV is classified into 8 major genotypes with variable geographic distribution and clinical aggressiveness. Genotype 1 is most prevalent globally and often associated with severe disease, while genotype 3 (common in the Amazon basin) is considered most virulent (Le Gal et al., 2017). A 2021 preclinical study examined the impact of HDV and HBV genotype pairings on viral assembly and infectivity (Wang et al., 2021). LNF activity was evaluated against HDV genotypes 1, 2, 3, 5, 6, 7, and 8 and in the context of HBV genotype B envelope proteins. HDV genotype 4 was not included in the LNF potency table because of insufficient viral titer or assay constraints. IC50 values ranged from 0.2 to 7.1 nM and IC90 values ranged from 4.2 to 30.9 nM across the tested genotypes, indicating some potential genotype-dependent variability in potency under the assay conditions, although clinical exposures of LNF are in the micromolar range, making any meaningful differences in response to clinical LNF treatment unlikely between HDV genotypes.

6.4. Durability and follow-up

Week 72 follow-up data from D-LIVR, ie, 24 weeks after treatment, revealed that up to 30% of patients with LNF/RTV + PEG-IFN-alfa achieved a composite endpoint ($\geq$2 log10 decline in HDV-RNA + ALT normalization) 6 months after stopping treatment. Moreover, a recent long-term follow-up study showed that patients who achieve such a composite endpoint 6 months after any LNF-based regimen remain free of major liver-related events for $\geq$10 years of follow-up, demonstrating long-term clinical benefit (Glenn, 2025).

7. Conclusion

LNF is expected to be an important tool in the physician's therapeutic arsenal for managing the complex disease of chronic HDV. Its utility as both a monotherapy and a backbone for combination therapy with agents targeting distinct steps in the HDV life cycle highlights its role in the evolving treatment landscape. LNF is currently the only potential oral and finite treatment option for patients with chronic HDV infection

with or without PEG-IFN-alfa. Patients can first be given the opportunity for achieving long-term clinical benefit following a finite course of oral LNF-based therapy. Those who do not respond to monotherapy, can either be retreated with LNF-based therapy as a combination of LNF with other available anti-HDV agents.

FT inhibition, led by LNF, represents a paradigm shift in the management of chronic HDV. Its host-targeted mechanism disrupts viral assembly, leading to meaningful reductions in viremia and improvements in liver inflammation and histology. The D-LIVR trial confirms its efficacy, particularly in combination with PEG-IFN-alfa. Continued efforts to optimize duration, predict responders, manage GI burden, evaluate cost-effectiveness, and enhance durability are ongoing. Importantly, however, the D-LIVR study showed that nearly 30% of patients can achieve a composite endpoint ($\geq$2 log10 decline in HDV RNA + ALT normalization) 6 months after stopping treatment and long-term follow-up studies indicate that achieving a composite response leads to improved long-term clinical outcomes $\geq$10 years of follow-up. For those patients who do not achieve such a composite endpoint, they can be retreated with a LNF-based regimen, or a combination of LNF with other available agents having orthogonal mechanisms of action. Rather than being the end of the road, LNF is a gateway to rational combination strategies aimed at finite, effective viral suppression and potentially a functional cure. While other agents such as bulevirtide and monoclonal antibodies experience HDV relapse upon treatment cessation, combining these agents with LNF may increase the finite treatment responses associated with LNF. Next steps for LNF include developing a final pathway for regulatory approval as a monotherapy and combination therapy, and initiating both confirmatory studies to evaluate long-term clinical benefit in broad populations and exploratory trials of advantageous combination therapy with current and emerging orthogonal treatments.

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Declaration of competing interest

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Data availability

Data will be made available on request.

References

Asselah, T., Chulanov, V., Lampertico, P., et al., 2024b. Bulevirtide combined with pegylated interferon for chronic hepatitis D. N. Engl. J. Med. 391 (2), 133–143. https://doi.org/10.1056/NEJMoa2314134.

Asselah, T., Etzion, O., Gish, R., et al., 2024a. What have we learned from the lonafarnib and pegIFN lambda trials?. In: Presented At: Delta Cure 3rd International Meeting; Milan, Italy.

Asselah, T., Rizzetto, M., 2023. Hepatitis D virus infection. N. Engl. J. Med. 389, 58–70. https://doi.org/10.1056/NEJMra2212151.

Bach, C., Lucifora, J., Delphin, M., et al., 2023. A stable hepatitis D virus-producing cell line for host target and drug discovery. Antivir. Res. 209, 105477. https://doi.org/10.1016/j.antiviral.2022.105477.

Bonino, F., Rosina, F., Rizzetto, M., et al., 1986. Chronic hepatitis in HBsAg carriers with serum HBV-DNA and anti-Hbe. Gastroenterology 90 (5), 1268–1273. https://doi.org/10.1016/0016-5085(86)90395-1.

Bordier, B.B., Marion, P.L., Ohashi, K., et al., 2002. A prenylation inhibitor prevents production of infectious hepatitis Delta virus particles. J. Virol. 76 (20), 10465–10472. https://doi.org/10.1128/jvi.76.20.10465-10472.2002.

Bordier, B.B., Ohkanda, J., Liu, P., et al., 2003. In vivo antiviral efficacy of prenylation inhibitors against hepatitis Delta virus. J. Clin. Investig. 112 (3), 407–414. https://doi.org/10.1172/JCI17704.

Elazar, M., Glenn, J.S., 2022. Combination of novel therapies for HDV. Viruses 14 (2), 268. https://doi.org/10.3390/v14020268.

Etzion, O., Hamid, S., Asselah, T., et al., 2023b. Week 48 results of the phase 3 D-LIVR study, a randomized double-blind, placebo-controlled trial evaluating the safety and efficacy of lonafarnib-boosted with ritonavir with or without peginterferon alfa in patients with chronic hepatitis Delta. In: Presented At: European Association for the Study of the Liver Congress; Vienna, Austria.

Etzion, O., Hamid, S., Lurie, Y., et al., 2023a. Treatment of chronic hepatitis D with peginterferon lambda-the phase 2 LIMT-1 clinical trial. Hepatology 77 (6), 2093–2103. https://doi.org/10.1097/HEP.0000000000000309.

European Association for the Study of the Liver, 2012. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J. Hepatol. 57 (1), 167–185. https://doi.org/10.1016/j.jhep.2012.02.010. Erratum in: J Hepatol. 2013;58(1): 201.

European Association for the Study of the Liver, 2023. EASL clinical practice guidelines on hepatitis Delta virus. J. Hepatol. 79 (2), 433–460. https://doi.org/10.1016/j.jhep.2023.05.001.

Fattovich, G., Boscaro, S., Noventa, F., et al., 1987. Influence of hepatitis Delta virus infection on progression to cirrhosis in chronic hepatitis type B. J. Infect. Dis. 155 (5), 931–935. https://doi.org/10.1093/infdis/155.5.931.

Glenn, J., 2025. Lonafarnib as finite treatment for chronic hepatitis D: long-Term follow-up data. In: Abstract #2270. Poster Presented At: American Association for the Study of Liver Diseases (AASLD) - the Liver Meeting; San Diego, CA.

Glenn, J.S., Watson, J.A., Havel, C.M., White, J.M., 1992. Identification of a prenylation site in Delta virus large antigen. Science 256 (5061), 1331–1333. https://doi.org/10.1126/science.159857.

Gopalakrishna, H., Mironova, M., Dahari, H., Koh, C., Heller, T., 2024. Advances and challenges in managing hepatitis D virus: evolving strategies. Curr. Hepat. Rep. 23, 32–44. https://doi.org/10.1007/s11901-024-00643-w.

Hershkovich, L., Dahari, H., Cotler, S.J., et al., 2024. Characterization of HDV RNA kinetic patterns during treatment: the D-LIVR phase 3 study. Late-breaking abstract #5023. Hepatology 79, E55–E56.

Kabacam, G., Onder, F.O., Yakut, M., et al., 2012. Entecavir treatment of chronic hepatitis D. Clin. Infect. Dis. 55 (5), 645–650. https://doi.org/10.1093/cid/cis459.

Khalfi, P., Kennedy, P.T., Majzoub, K., Asselah, T., 2023. Hepatitis D virus: improving virological knowledge to develop new treatments. Antivir. Res. 209, 105461. https://doi.org/10.1016/j.antiviral.2022.105461.

Lampertico, P., Anolli, M.P., Roulot, D., Wedemeyer, H., 2025. Antiviral therapy for chronic hepatitis Delta: new insights from clinical trials and real-life studies. Gut 74 (5), 853–862. https://doi.org/10.1136/gutjnl-2024-332597.

Lau, D.T., Doo, E., Park, Y., et al., 1999. Lamivudine for chronic Delta hepatitis. Hepatology 30 (2), 546–549. https://doi.org/10.1002/hep.510300217.

Le Gal, F., Brichler, S., Drugan, T., et al., 2017. Genetic diversity and worldwide distribution of the deltavirus genus: a study of 2,152 clinical strains. Hepatology 66, 1826–1841. https://doi.org/10.1002/hep.29574.

Lempp, F.A., Schlund, F., Rieble, L., et al., 2019. Recapitulation of HDV infection in a fully permissive hepatoma cell line allows efficient drug evaluation. Nat. Commun. 10, 2265. https://doi.org/10.1038/s41467-019-10211-2.

Niro, G.A., Ciancio, A., Gaeta, G.B., et al., 2006. Pegylated interferon alpha-2b as monotherapy or in combination with ribavirin in chronic hepatitis Delta. Hepatology 44 (3), 713–720. https://doi.org/10.1002/hep.21296.

Otto, J.C., Casey, P.J., 1996. The hepatitis Delta virus large antigen is farnesylated both in vitro and in animal cells. J. Biol. Chem. 271 (9), 4569–4572. https://doi.org/10.1074/jbc.271.9.4569.

Rizzetto, M., 2000. Hepatitis D: virology, clinical and epidemiological aspects. Acta Gastroenterol. Belg. 63 (2), 221–224.

Rizzetto, M., Canese, M.G., Arico, S., et al., 1977. Immunofluorescence detection of new antigen-antibody system (delta/anti-delta) associated to hepatitis B virus in liver and in serum of HBsAg carriers. Gut 18 (12), 997–1003. https://doi.org/10.1136/gut.18.12.997.

Rizzetto, M., Hoyer, B., Canese, M.G., Shih, J.W., Purcell, R.H., Gerin, J.L., 1980. Delta agent: association of Delta antigen with hepatitis B surface antigen and RNA in serum of delta-infected chimpanzees. Proc. Natl. Acad. Sci. USA 77 (10), 6124–6128. https://doi.org/10.1073/pnas.77.10.6124.

Sarin, S.K., Kumar, M., Lau, G.K., et al., 2016. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol. Int. 10, 1–98. https://doi.org/10.1007/s12072-015-9675-4.

Soriano, V., Alvarez, C., Edagwa, B., et al., 2022. Ultra-long-acting (XLA) antivirals for chronic viral hepatitis. Int. J. Infect. Dis. 114, 45–50. https://doi.org/10.1016/j.ijid.2021.10.052.

Terrault, N.A., Lok, A.S.F., McMahon, B.J., et al., 2018. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 67 (4), 1560–1599. https://doi.org/10.1002/hep.29800.

Thiyagarajah, K., Basic, M., Hildt, E., 2023. Cellular factors involved in the hepatitis D virus life cycle. Viruses 15, 1687. https://doi.org/10.3390/v15081687.

Treatment of chronic Delta hepatitis with lonafarnib, ritonavir and lambda interferon. clinicalTrials.gov identifier: NCT03600714. https://www.clinicaltrials.gov/study/NCT03600714. (Accessed 19 July 2025).

Verrier, E.R., Salvetti, A., Pons, C., Michelet, M., Rivoire, M., Baumert, T.F., et al., 2022. Loss of hepatitis D virus infectivity upon farnesyl transferase inhibitor treatment associates with increasing RNA editing rates revealed by a new RT-ddPCR method. Antivir. Res. 198, 105250. https://doi.org/10.1016/j.antiviral.2022.105250.

Wang, W., Lempp, F.A., Schlund, F., Walter, L., Decker, C.C., Zhang, Z., et al., 2021. Assembly and infection efficacy of hepatitis B virus surface protein exchanges in 8 hepatitis D virus genotype isolates. J. Hepatol. 75 (2), 311–323. https://doi.org/10.1016/j.jhep.2021.03.025.

Wedemeyer, H., Manns, M.P., 2010. Epidemiology, pathogenesis and management of hepatitis D: update and challenges ahead. Nat. Rev. Gastroenterol. Hepatol. 7 (1), 31–40. https://doi.org/10.1038/nrgastro.2009.205.

Winer, B.Y., Shirvani-Dastgerdi, E., Bram, Y., Sellau, J., Low, B.E., Johnson, H., et al., 2018. Preclinical assessment of antiviral combination therapy in a genetically humanized mouse model for hepatitis Delta virus infection. Sci. Transl. Med. 10 (447). https://doi.org/10.1126/scitranslmed.aap9328 eaap.9328.

Yurdaydin, C., Bozkaya, H., Gurel, S., et al., 2002. Famciclovir treatment of chronic Delta hepatitis. J. Hepatol. 37 (2), 266–271. https://doi.org/10.1016/s0168-8278(02)00162-9.

Yurdaydin, C., Keskin, O., Kalkan, C., et al., 2018. Optimizing lonafarnib treatment for the management of chronic Delta hepatitis: the LOWR HDV-1 study. Hepatology 67 (4), 1224–1236. https://doi.org/10.1002/hep.29658.

Yurdaydin, C., Keskin, O., Yurdcu, E., et al., 2022. A phase 2 dose-finding study of lonafarnib and ritonavir with or without interferon alpha for chronic Delta hepatitis. Hepatology 75 (6), 1551–1565. https://doi.org/10.1002/hep.32259.