Exploring the Relationship Between Hepatitis Delta Virus RNA–Based Surrogate Endpoints and Long–Term Clinical Outcomes in Hepatitis Delta Virus Infection: A Systematic Literature Review

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Conclusion

- This systematic literature review demonstrated that undetectable hepatitis delta virus (HDV) RNA—most often achieved as off–treatment sustained response after interferon ± nucleos(t)ide analogue therapy—was associated with reduced risk of major liver–related clinical outcomes compared with those without virologic response
- The interpretation of HDV RNA undetectability depends on treatment modality: off–treatment sustained undetectability reflects a durable disease activity signal, whereas on–treatment suppression should be contextualized by mechanism of action
- These findings reinforce the need for enhanced HDV screening in patients with hepatitis B virus to enable early diagnosis, timely care, and initiation of treatment to mitigate liver-related morbidity and mortality

Plain Language Summary

- Hepatitis delta virus infection represents the most severe form of viral hepatitis and can rapidly progress to cirrhosis, hepatocellular carcinoma, and death
- Surrogate markers are essential for evaluating treatment response in hepatitis delta virus infection, as long-term clinical trials are challenging to conduct
- This review included 17 studies to understand whether lowering or clearing HDV RNA (a marker of the virus in the blood) to undetectable limits is linked to better clinical outcomes
- Most studies defined treatment success as sustaining HDV RNA at undetectable levels for at least 6 months after treatment
- Consistently across studies, patients who achieved or sustained undetectable HDV RNA experienced better clinical outcomes compared to those with detectable HDV RNA
- Overall, the evidence suggests that treatments that reduce HDV RNA levels may play an important role in protecting people from severe liver disease

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Introduction

- Chronic hepatitis delta virus (HDV) infection is considered the most severe form of viral hepatitis, affecting nearly 10 to 20 million people globally[1]
- Evaluation of treatment response through reliable surrogate endpoints is critical for timely treatment decisions, as long-term clinical trials are challenging to conduct[2]
- However, the reliability and consistency of these markers in predicting meaningful long-term clinical outcomes remain uncertain, highlighting the need for careful evaluation of their predictive value[3]

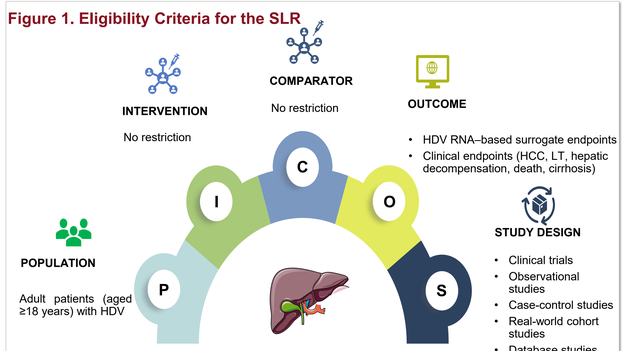
Objective

- This systematic literature review (SLR) aims to evaluate the association between HDV RNA–based surrogate endpoints and long-term clinical outcomes in adults with HDV

Methods

- This study adhered to the National Institute for Health and Care Excellence (NICE) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[4] guidelines for SLRs, following standard methodology with a transparent, reproducible, and unbiased approach
- Embase, PubMed, and Cochrane databases were searched from database inception to August 2025 to identify studies evaluating associations between HDV RNA–based surrogate endpoints and long-term clinical outcomes. The prespecified eligibility criteria are presented in **Figure 1**
- Evidence was screened using both: a manual approach (reviewer 1) and an artificial intelligence tool (reviewer 2), with a quality check by a subject matter expert as per the NICE UK[5] and Canada's Drug Agency[6] position papers

Figure 1. Eligibility Criteria for the SLR

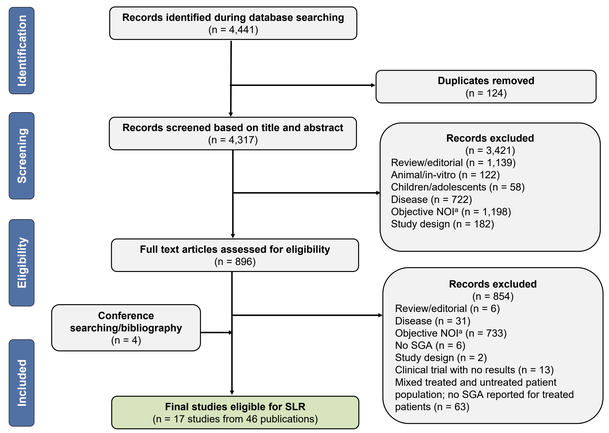


HCC, hepatocellular carcinoma; HDV, hepatitis delta virus; LT, liver transplant; SLR, systematic literature review.

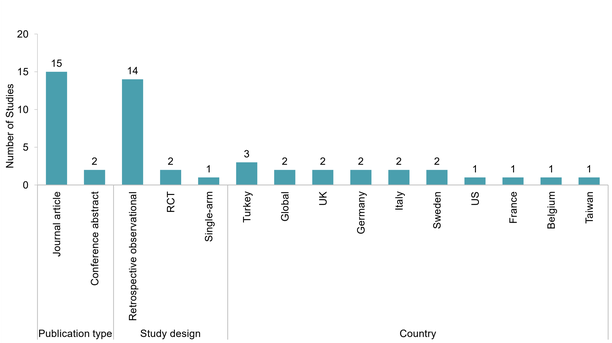
Results

- Overall, 17 studies including 2,902 patients evaluated the association between HDV RNA–based surrogate endpoints and long-term clinical outcomes. **Figure 2** depicts the PRISMA flowchart of the publications identified through the SLR
- Most were published as peer-reviewed journal articles (n = 15), while the remaining 2 were published as conference abstracts (**Figure 3**)
- In terms of study design, most studies were retrospective (n = 14), followed by randomized controlled trials (n = 2) and a single-arm study (n = 1). Geographically, most of the studies were conducted in Europe (n = 10) (**Figure 3**)
- Patients were treated with interferon ± nucleotide analogues (NAs) in the majority of studies (n = 16) and 1 study used NAs only. Further, most studies (n = 12) defined treatment response as sustained HDV RNA undetectability for at least 6 months after treatment completion (sustained virological response); however, this definition was unclear in 4 studies and not reported in 1 study
- The majority of the studies reported the association of HDV RNA undetectability with hepatic decompensation (HD) and hepatocellular carcinoma (HCC; n = 5 each) (**Table 1**)
- Overall, patients who achieved or sustained undetectable HDV RNA were consistently associated with a reduced risk of long-term clinical outcomes, with most studies reporting positive or direct associations across all clinical outcomes (hazard ratio [HR], 0.03-0.82; odds ratio [OR], 0.04-0.76)

Figure 2. PRISMA Flowchart of Publications Identified in the SLR



[a]Studies focused on genetics/epidemiology/risk factor/assays/detection/natural history. NOI, not of interest;. SGA, subgroup available; SLR, systematic literature review.



RCT, randomized controlled trial; UK, United Kingdom; US, United States

Table 1. Summary of Studies Reporting the Association of HDV RNA With Long–Term Clinical Outcomes

Study Name	Study N[a]	HD	HCC	Cirrhosis	Death	LT	Liver Events	Death or LT
Retrospective Observational Studies								
Spaan 2020	25[b]	✓HR-KM	x	x	x	x	x	x
Carey 2022	33	x	x	✓OR[c]	x	x	x	x
Wranke 2017	136	x	x	x	x	x	✓HR[d]	x
Scheller 2021	53[b]	x	x	x	x	x	✓OR/HR	x
Romeo 2009	90	✓OR[c]	✓OR[c]	x	x	x	x	x
Romeo 2014	193	x	x	✓OR[c]	x	x	x	x
Roulot 2020	1,112	✓HR	x	✓HR	x	x	x	✓HR
Furquim 2025	162	x	x	x	x	x	✓HR	x
Kamal 2020	337	x	x	x	✓[e]	x	✓HR[d]	x
Kamal 2024	310	x	x	x	x	x	✓OR[d]	x
Kılıç 2016	23[b]	x	x	✓HR-KM	x	x	x	x
Yurdaydin 2018	99[b]	✓HR-KM	✓HR-KM	x	✓HR-KM	✓HR-KM	✓OR[d]	✓HR-KM
Keskin 2023	124	x	✓OR[c]	x	x	x	x	x
Jang 2021	13	x	✓HR[d]	x	x	x	x	x
Randomized Controlled Studies								
Wranke 2020	60	x	x	x	x	x	✓HR-KM	x
Anastasiou 2024	120	✓HR-KM	✓HR-KM	x	✓HR-KM	✓HR-KM	✓HR-KM	x
Single Arm Study								
Hercun 2021	12[b]	x	x	x	✓OR[c]	x	x	x

[a]Represent the overall study population unless otherwise indicated; [b]Sample sizes are provided for combined treatment responders and non–responders only; [c]Calculated from n/N data; [d]Effect estimates reversed to present results as responders vs non-responders (1/HR or OR); [e]only *P*-values reported;. HCC, hepatocellular carcinoma; HD, hepatic decompensation; HDV, hepatitis delta virus; HR, hazard ratio; KM, Kaplan-Meier; LT, liver transplantation; OR, odds ratio

HDV RNA and HD: Four (of 5) studies reported a statistically significant association between HDV RNA and HD (*P* < .05), indicating that patients with undetectable HDV RNA had a lower risk of HD than those with detectable levels (HR: 0.10 and 0.35)[7,8] , 'not estimable' (n = 2) (**Table 2**)

- **HDV RNA and HCC:** Of the 5 studies examining the relationship between HDV RNA and the risk of HCC, 3 studies (HR: 0.39 and 0.17; OR: 0.32)[9,10,11] reported a statistically significant association (*P* < .05). The remaining 2 studies did not find a statistically significant association; however, they reported positive or direct associations. Overall, these findings suggest that suppression or absence of HDV RNA was associated with a lower likelihood of HCC (**Table 2**)
- **HDV RNA and cirrhosis:** Of the 4 studies evaluating the association between HDV RNA and cirrhosis, 3 studies reported a statistically significant association, suggesting that undetectable HDV RNA was consistently correlated with a reduced risk of cirrhosis (HR: 0.41 and 'not estimable'; OR: 0.12)[8,12,13] (**Table 2**)
- **HDV RNA and death:** Three (of 5) studies reported a statistically significant association between HDV RNA and death, suggesting that undetectable HDV RNA levels were associated with a reduced risk of death (HR: 0.22; OR: 0.04)[7,14] (**Table 2**)
- **HDV RNA and liver transplant (LT):** Only 2 studies evaluated the relationship between HDV RNA and LT. Of these, 1 study[7] (HR not estimable) reported a statistically significant association (*P* = .012), indicating that undetectable HDV RNA was linked to a reduced risk of LT. The other study did not report a statistically significant association, although it suggested a positive (direct) relationship between HDV RNA levels and the likelihood of LT (**Table 2**)
- **HDV RNA and any liver events:** Overall, 8 studies assessed the relationship between HDV RNA and any liver events (HD including ascites, encephalopathy, and variceal bleeding; LT; HCC or liver-related death). Only 3 studies (HR: 0.17 and 0.43; OR: 0.19)[9,15,7] found statistically significant associations, whereas the others observed non-significant yet positive trends, suggesting that undetectable HDV RNA levels were associated with a lower risk of liver events (**Table 2**)

Table 2. Effect Estimates Reported Across Studies Reporting the Association of HDV RNA With Long–Term Clinical Outcomes

Study Name	Effect Estimates Reported	Effect Estimates, HR/OR (95% CI) HDV RNA Undetectability vs Detectability	*P*-Value
Hepatic decompensation			
Spaan 2020	KM curve and HR (digitized from KM curve)	Not estimable	.043
Romeo 2009	OR calculated from n/N data	0.76 (0.24-2.37)	.250
Roulot 2020	HR	0.35 (NR)	.025
Yurdaydin 2018	KM curve and HR (digitized from KM curve)	0.10 (0.01-0.79)	.013
Anastasiou 2024	KM curve and HR (digitized from KM curve)	Not estimable	.009
Hepatocellular carcinoma			
Romeo 2009	OR calculated from n/N data	0.66 (0.17-2.63)	.560
Yurdaydin 2018	KM curve and HR (digitized from KM curve)	0.30 (0.08-1.04)	.052
Keskin 2023	OR calculated from n/N data	0.32 (0.08-1.08)	.040[b]
Anastasiou 2024	KM curve and HR (digitized from KM curve)	0.39 (0.15-0.99)	.041
Jang 2021	HR[a]	0.17 (0.04-0.74)	.020
Cirrhosis			
Roulot 2020	HR	0.41	.012
Carey 2022	OR calculated from n/N data	0.12 (0.02-0.71)	.019
Kılıç 2016	KM curve and HR (digitized from KM curve)	Not estimable	.017
Romeo 2014	OR calculated from n/N data	0.46 (0.13-1.59)	.220
Death			
Anastasiou 2024	KM curve and HR (digitized from KM curve)	0.45 (0.04-5.01)	.578
Yurdaydin 2018	KM curve and HR (digitized from KM curve)	0.22 (0.05-0.97)	.032
Hercun 2021	OR calculated from n/N data	0.04 (0.00-0.88)	.041
Kamal 2020	*P*-value only	NR	<.040
Liver transplantation			
Anastasiou 2024	KM curve and HR (digitized from KM curve)	0.82 (0.05-13.10)	.331
Yurdaydin 2018	KM curve and HR (digitized from KM curve)	Not estimable	.012
Any liver events			
Scheller 2021	HR, OR	HR: 0.64 (0.24-1.68) OR: 0.73 (0.22-2.39)	.360 .590
Anastasiou 2024	KM curve and HR (digitized from KM curve)	0.17 (0.03-0.78)	.006
Wranke 2017	HR[a]	0.43 (0.22-1.00)	.030
Furquim 2025	HR	0.03 (0.00-19.37)	.290
Kamal 2020	KM curve and HR (digitized from KM curve)	0.40 (0.09-1.83)[c]	.230
Wranke 2020	KM curve and HR (digitized from KM curve)	0.32 (0.08-1.20)	.050
Yurdaydin 2018	OR[a]	0.19 (0.05-0.71)	.013
Kamal 2024	OR[a]	0.72 (0.27-1.96)	.540

[a]Reversed the direction of the effect estimates to responders vs non-responders by taking the reciprocal of the hazard ratio or odds ratio (1/HR or OR); [b]Reported in the publication however the OR is calculated using n/N; [c]Cis were digitized from the KM curve. CI, confidence interval; HDV, hepatitis delta virus; HR, hazard ratio; KM, kaplan-meier curve; NR, not reported; OR, odds ratio.

Limitations

- Most included studies were retrospective and heterogeneous in design, definitions of HDV RNA response, follow-up duration, outcome reporting, and sample size; therefore, causal inferences cannot be drawn, and both comparability and statistical power to detect or confirm associations may be limited
- Several effect estimates were derived indirectly from digitized Kaplan-Meier curves or calculations based on n/N data; therefore, these results should be interpreted with caution