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ORIGINAL RESEARCH ARTICLE

Understanding the Natural History of Chronic Hepatitis D: Proposal of a Model for Cost-Effectiveness Studies

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Abstract

Background As new therapeutic options become available, better understanding the potential impact of emerging therapies on clinical outcomes of hepatits D virus (HDV) is critical.

Objective The aim of this study was to develop a natural history model for patients with hepatitis D virus.

Methods We developed a model (decision tree followed by a Markov cohort model) in adults with chronic HDV infection to assess the natural history and impact of novel treatments on disease progression versus best supportive care (BSC). The model time horizon was over a lifetime (up to 100 years of age); state transitions and health states were defined by responder status. Patients in fibrosis stages 0 through 4 received treatment; decompensated patients were not treated. Response was defined as the combined response endpoint of achievement of HDV-RNA undetectability/≥2-$\log_{10}$ decline and alanine aminotransferase normalization; response rates of 50% and 75% were explored. Health events associated with advanced liver disease were modeled as the number of events per 10,000 patients. Scenario analyses of early treatment, alternate treatment response, and no fibrosis regression for treatment responders were also explored.

Results The model was able to reflect disease progression similarly to published natural history studies for patients with HBV/HDV infection. In a hypothetical cohort of patients reflecting a population enrolled in a recent clinical trial, fewer advanced liver disease events were observed with a novel HDV treatment versus BSC. Fewer liver-related deaths were observed under 50% and 75% response (900 and 1,358 fewer deaths, respectively, per 10,000 patients). Scenario analyses showed consistently fewer advanced liver disease events with HDV treatment compared with BSC, with greater reductions observed with earlier treatment.

Conclusion This HDV disease progression model replicated findings from natural history studies. Furthermore, it found that a hypothetical HDV treatment results in better clinical outcomes for patients versus BSC, with greater benefit observed when starting treatment early. This validated natural history model for HBV/HDV infection can serve as a foundation for future clinical and economic analyses of novel HDV treatments that can support healthcare stakeholders in the management of patients with chronic HDV.

1 Introduction

Hepatitis delta virus (HDV) is the most severe form of viral hepatitis [1, 2] and is associated with more rapid disease progression to hepatic decompensation, hepatocellular carcinoma (HCC), liver transplantation, and death [3]. HDV is primarily transmitted through blood or bodily fluids, with a high prevalence among people with a history of intravenous drug use as well as those in other high-risk groups, such as commercial sex workers, hemodialysis recipients, human immunodeficiency virus-positive individuals, those with hepatitis C, and those from HDV endemic countries of origin [4]. HDV propagation in the liver requires the hepatitis B virus (HBV) surface antigen (HBsAg); thus, HDV presents as superinfection of a chronic HBV infection or as a co-infection with HDV and HBV [5]. The reported global prevalence of HDV infection in HBsAg-positive persons ranges from 5 to 13%, although this is likely underestimated due to insufficient testing of HBsAg-positive persons (particularly in those with advanced liver disease), as well as variability in the performance of serological tests and heterogenous sampling [3, 6]. Ultimately, up to

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Key Points for Decision Makers

There is a need to better understand and evaluate the impact of emerging therapies on the clinical outcomes of hepatitis D virus (HDV).

Through the development of a validated natural history model, patients receiving a hypothetical HDV treatment compared with best supportive care achieved substantial improvements in liver disease outcomes.

A validated natural history model for HBV/HDV infection can serve as a foundation for future clinical and economic analyses of novel HDV treatments that can support healthcare stakeholders in the management of patients with chronic HDV.

72 million people worldwide may be infected with HDV, although this prevalence is not confirmed [3, 4, 6].

Untreated chronic HDV infection is associated with more rapid progression of liver disease to cirrhosis [7, 8], with earlier onset of hepatic complications and a higher likelihood of liver-related outcomes, including HCC, compared with HBV mono-infection [2, 9, 10]. As a higher risk of cirrhosis has been observed with persistent HDV viremia, timely treatment of patients with uncontrolled viremia who are at risk of rapid disease progression is critical [11]. There are currently no formally approved treatments for HDV infection in the United States (US). The historical standard of care relies on the off-label use of peginterferon alpha (PEG-IFN-α), aimed at slowing or preventing disease progression [12]. However, the efficacy of PEG-IFN-α is limited, with frequent, serious adverse effects, thus not all patients are eligible to receive treatment [13–15]. Several new therapies for HDV treatment are in phase II or III development, including bulevirtide (Hepcludex®, Gilead Sciences), which has received conditional market authorization in Europe; a myristoylated N-terminal and aminated C-terminal 47-amino acid lipopeptide [16] and lonafarnib [17].

There are challenges in modeling the long-term disease progression and treatment outcomes in chronic HDV infection, due to the limited data from epidemiological sources, natural history or effective treatment options. We developed a natural history model for HDV to evaluate the potential impact of emerging therapies on clinical outcomes. Herein, we report the development of the disease-oriented aspects of the chronic HDV model in order to best inform HDV progression and subsequent clinical and economic outcomes in the context of promising therapeutics.

2 Methods

2.1 Model Design

We developed a natural history model to evaluate the potential impact of bulevirtide versus best supportive care (BSC) for adults with chronic HDV infection with compensated liver disease through the stages of disease progression. The model simulates the natural history of chronic HDV infection while evaluating the long-term impact of HDV treatment on disease progression. The model estimates the long-term consequences of managing patients with HDV over a lifetime time horizon (up to 100 years of age). Model inputs and the model structure were reviewed and validated with four international clinical and modeling experts. In line with measurements of the primary endpoint in clinicial trials [18], the model uses a 24-week cycle length with a half-cycle correction.

2.2 Model Structure

The model was developed in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) as a decision tree followed by a Markov model, with state transitions and health state definitions stratified by responder status, similar to other viral hepatitis models [19, 20].

In the decision tree portion of the model, patients in the HDV treatment arm are considered to meet responder criteria as defined by the combined response endpoint of achievement of HDV-RNA undetectability/≥2-$\log_{10}$ decline and alanine aminotransferase (ALT) normalization [21], as recommended by the US Food and Drug Administration (FDA) [22] and is in line with guideline recommendations in Europe [23]. Prior work has shown a ≥2-$\log_{10}$ decrease in HDV RNA to be associated with histological (and by extrapolation, clinical benefit [21, 24]), which is considered in the on-treatment combined response endpoint. This is based on the assumption that persistent HDV virus replication drives the necro-inflammatory and fibrosis response, and hence disease progression, and that a ≥2-$\log_{10}$ reduction in HDV RNA and normalization of ALT contribute to slowing disease progression. Reduced disease progression in the model reflects reductions in HDV-related morbidity and mortality, and reduced risk of further disease progression.

The structure of health states for treatment responders and non-responders for the Markov model is illustrated and described in S2 Appendix in the electronic supplementary material (ESM). Patients progress from F0 (no fibrosis) through F3 (fibrosis stage 3) before developing cirrhosis. Patients with cirrhosis can maintain limited symptoms with compensated cirrhosis (CC, or F4) before developing

decompensated cirrhosis (DCC). While HDV can progress to HCC from any stage of disease, progression to more advanced disease states, with increasing fibrosis and advancement to cirrhosis, increases the risk of developing HCC. While both responders and non-responders are able to progress through all fibrosis stages, responders progress at a slower rate than non-responders, and only responders can regress through fibrosis stages (i.e., F4 to F3 and F3 to F2), reflecting clinical improvement. Patients in the DCC or HCC state may undergo liver transplant (LT). Patients with post-LT survival for at least 1 year move to the post-liver transplant (PLT) state.

2.3 Patients

At the time of model entry, all patients are assumed to be HDV-RNA-positive adults with compensated liver disease. As data regarding outcomes among patients with different genotypes associated with HDV remain heterogeneous and need validation, no HBV or HDV genotype subgroup was specified. At baseline, patients are distributed across stages of disease severity, ranging from chronic hepatitis without fibrosis to cirrhosis, and then assigned to HDV treatment or BSC. Over the course of a simulation, patients can achieve spontaneous or treatment-induced virologic responses (e.g., HBsAg loss or seroconversion, or the combined response endpoint of HDV-RNA undetectability/$\geq$2-$\log_{10}$ decline and ALT normalization) or advanced liver disease (e.g., CC, DCC, HCC, or LT). In addition to liver-related excess mortality rates, age-specific background mortality rates were derived from the US Centers for Disease Control and Prevention [25] and applied to the entire population regardless of health state.

For the sake of analyzing potential treatment outcomes for hypothetical novel treamtents for HBV/HDV infection, the mean starting age of all patients was 40.2 years, with 67% male, as observed in the baseline demographics of a recent clinical trial [18]. Distribution across fibrosis stages for F0 (11.62%), F1 (11.62%), F2 (12.45%) and F3 (17.42%) was taken from the literature [26]; distribution for F4 (CC, 46.90%) was taken from the same recent clinical trial patient demographics [18].

2.4 Hepatitis D Virus (HDV) Natural History Progression Rates

Natural history health state transition rates are provided in Table 1. Published data regarding the natural history of HDV are scarce and heterogeneous owing to the relatively rare nature of HDV and geographic variability of HDV prevalence, risk factors, socioeconomics, and health system factors. Thus, to derive values for use in the natural history model, first, transition probabilities representative of natural history for HBV mono-infected patients were sourced from published literature and prior disease models. A literature review was performed to identify studies that presented hazard ratios regarding the relative rate of progression to advanced liver disease events in HBV/HDV-infected versus HBV mono-infected patients. Studies were selected for use in the model for transition probability adjustment based on the individual transitions examined (i.e., to CC, to DCC, etc.), relative study size, and geographic scope. The faster rate of progression reflective of HBV/HDV infection was derived by applying identified hazard ratios between disease progression in HBV/HDV patients versus the transition probabilities for disease progression for HBV mono-infected patients. The model also considers an annual rate of HBsAg seroclearance for patients off-treatment, as well as for those receiving HDV treatment; both are set to 1.13% in the base case [27].

2.5 Treatments

Only patients in the F0 through F4 health states are assumed to receive either an HDV treatment or BSC. Treatment stopping rules for patients receiving HDV treatment include no achievement of the combined response outcome by week 48; treatment response with HBsAg seroclearance; or disease progression, regardless of fibrosis stage. Upon progression to DCC, HCC, LT, or PLT, patients are also assumed to discontinue treatment. Patients achieving a treatment response with HDV treatment may continue treatment until HBsAg seroclearance, or discontinue treatment with sustained (6 months) HBsAg seroconversion or loss of virological and biochemical response. The discontinuation rate for HDV treatment of 5.07% was a weighted average from the current ongoing clinical trial, converted to an annual rate [18]. This annual discontinuation rate was assumed to continue for any patients remaining on treatment beyond the first year. All patients who discontinue treatment have subsequent rates of disease progression according to the natural history of HDV.

2.6 Clinical Inputs and Health State Transitions

2.6.1 Treatment Efficacy and Safety

The efficacy of HDV treatment was modeled through one of two hypothetical scenarios, where either 50% or 75% of patients receiving HDV treatment were assumed to respond as per the defined criteria. For both scenarios, patients receiving HDV treatment who are non-responders or are not complete responders stop HDV treatment after 48 weeks; responders remain on treatment until treatment discontinuation. Responder rates in each scenario are set

Table 1 Model inputs and sources

Health state transition		Input	Source/calculation
From	To		
Annual HDV natural history health state transitions			
F0–F3	F stage + 1	15.1%	Papatheodoridis et al. [32], for baseline HBV mono-infection transition probability; HR of 3.0 applied based on range presented by Da et al. [26, 33–35]
	HCC	1.4%	Chen et al. [36], for baseline HBV mono-infection transition probability; HR of 2.77 applied based on Alfaiate [11]
F4	DCC	10.7%	Dakin et al. [37], for baseline HBV mono-infection transition probability; HR of 2.2 applied based on Fattovich et al. [34]
	HCC	6.2%	Dakin et al. [37], for baseline HBV mono-infection transition probability; HR of 2.77 applied based on Alfaiate et al. [11]
	EM	7.3%	Fattovich et al. [38], for baseline HBV mono-infection transition probability; HR of 2.0 applied based on Fattovich et al. [34]
DCC	HCC	7.8%	Dakin et al. [37], for baseline HBV mono-infection transition probability; HR of 2.77 applied based on Alfaiate et al. [11]
	LT	1.6%	Dakin et al. [37]
	EM	15.6%	Fattovich et al. [38]
HCC	LT	1.6%	Dakin et al. [37]
	EM	56.0%	Dakin et al. [37]
LT	EM	21.0%	Dakin et al. [37]
PLT	EM	5.7%	Dakin et al. [37]
Annual disease progression health state transitions for patients achieving the combined response endpoint			
F0–F3	F stage + 1	6.61%	Derived from an HR of 0.42 applied to baseline natural history TP
	HCC	0.48%	Derived from an HR of 0.34 applied to baseline natural history TP
F4	DCC	2.91%	Derived from an HR of 0.26 applied to baseline natural history TP
	HCC	2.19%	Derived from an HR of 0.34 applied to baseline natural history TP
	EM	1.63%	Derived from an HR of 0.22 applied to baseline natural history TP
HDV natural history progression HRs for risk of transition from HDV RNA− to HDV RNA+, Base-Case Value (95% CI)			
F0–3	F stage + 1	0.42 (0.23–0.65)	Sourced from a recent meta-analysis on the rate of progression in HDV RNA− vs. HDV RNA+ patients (Gish et al. [28])
F0–F2	HCC	0.34 (0.21–0.53)	
F3	HCC	0.34 (0.21–0.53)	
F4	DCC	0.26 (0.11–0.63)	
	HCC	0.34 (0.21–0.53)	
	Death	0.22 (0.15–0.46)	

CI confidence interval, *DCC* decompensated cirrhosis, *EM* excess mortality (i.e., liver-related mortality), *HCC* hepatocellular carcinoma, *HBV* hepatitis B virus, *HDV* hepatitis D virus, *HR* hazard ratio, *LT* liver transplant, *PLT* post-liver transplant, *TP* transition probabilities

to 50% or 75% at both weeks 24 and 48. The efficacy of BSC is set to 0% at 24 weeks and 2% at 48 weeks, based on observations from a recent clinical trial [18].

2.6.2 Disease Progression

The nature of the relationship between the impact of combined virologic and biochemical response as a surrogate

outcome on natural history progression in HDV has not been well quantified. In order to determine a quantifiable relationship between treatment response and disease progression for use in the model, a modified Delphi panel approach was used to determine the impact of use of the combined response endpoint (detail in S1 Appendix in the ESM) [28]. The Delphi panel formed of 11 international clinical experts reached a consensus (82%, 9/11) that the combined response endpoint would have an impact on disease progression similar to the effect observed between HDV RNA− and HDV RNA+ patients based on natural history studies. The rationale for this was that achievement of the combined response endpoint via treatment would slow histological and clinical disease progression, even if patients did not achieve RNA undetectability. For the base case, given that patients would ultimately still have HBV/HDV infection, although would have controlled HDV viremia, it was assumed that it was more appropriate to employ hazard ratios representative of reduced rates of disease progression for patients who are still HDV Ab+ but RNA− rather than apply hazard ratios that would be reflective of patients who are HBV mono-infected.

To determine these hazard ratios, a systematic literature review was first undertaken to identify cohort studies that report relationships between HDV RNA− and HDV RNA+ [28]. These data were then synthesized in a meta-analysis, where hazard ratios between HDV RNA− and HDV RNA+ on specific liver disease progression events were determined. The hazard ratios used to calculate disease progression for treatment responders are provided in Table 1. Notably, patients in the identified natural history studies did not necessarily achieve HDV RNA− versus HDV RNA+ via treatment, although some patients in these studies did receive PEG-IFN-α. However, given the limited long-term treatment outcomes with HDV RNA treatments to date, this difference in HDV RNA− versus HDV RNA+ patients was considered a suitable proxy for understanding the reduction in disease progression for those patients who respond to treatment.

Table 1 presents the annual disease progression transition rates for patients achieving the combined response endpoint. In short, the annualized transition probabilities calculated for patients with uncontrolled HDV were first converted to annual rates, which were then scaled by hazard ratios determined from a recent meta-analysis [28] and then reconverted to annual transition probabilities to reflect slowed disease progression in patients responding to treatment. In the absence of data on progression between non-cirrhotic fibrosis stages (F0–F3), the hazard ratio from non-cirrhotic to cirrhotic disease (F3 to F4) was applied to all early fibrosis stage transitional probabilities. Since patients who progress to end-stage liver disease (DCC, HCC, LT or PLT) are assumed to discontinue treatment, no subsequent reduction in disease progression is accounted for in these patients.

2.6.3 Disease Regression

Statistically significant reductions in HDV viral load following treatment response have been shown to be associated with regression of liver fibrosis and cirrhosis in chronic viral hepatitis [24, 29]. Farci et al. reported 8.8% of treatment responders with F4 could transition to F3 (non-cirrhotic disease) [24], while Marcellin et al. reported regression of cirrhosis for HBV mono-infected patients who experienced viral suppression while receiving treatment; 13.3% of responders with F3 were found to have transitioned to F2 [29]. Clinical expert consultations concurred that patients who achieve the combined response endpoint experience an improvement in fibrosis/cirrhosis with subsequent disease regression.

2.7 Model Analyses and Outcomes

2.7.1 Base-Case Analysis

Health events associated with advanced liver disease (CC, DCC, HCC, LT, and liver-related deaths) were determined for HDV treatment and BSC as the number of events per 10,000 patients for both the 50% and 75% responder scenarios.

2.7.2 Scenario Analyses

To explore the potential impact of early treatment, multiple scenario analyses were performed, including exploring the impact of earlier treatment initiation by starting all patients at an earlier given fibrosis stage. A second scenario analysis also explored the impact of assuming there would be no regression through fibrosis stages for treatment responders. Furthermore, given the uncertainty of the relationship between the achievement of the combined response endpoint and HDV progression, three additional scenario analyses were explored to test this assumption. The ‘treatment-HBV’ scenario analysis used hazard ratios for the achievement of the combined endpoint from patients with HBV mono-infection and assumed that responders would have equal disease progression to treated HBV mono-infected patients (Table 2). The ‘treatment-ALT’ scenario analysis used hazard ratios based on the relationship of ALT normalization and reduction of liver disease events observed in patients with treated HBV mono-infection (Table 2).

Table 2 Annual disease progression hazard ratios for patients achieving the combined response endpoint in the 'treatment-HBV' and 'treatment-ALT' scenario analyses

Health state transition		Hazard ratio (source)	
From	To	Treatment-HBV analysis	Treatment-ALT analysis
FX	FX+1	0.33 (Da et al. [33])	0.51 (Wong et al. [39])
F0–F2	HCC	0.36 (Alfaiate et al. [11])	0.51 (Wong et al. [39])
F3	HCC	0.36 (Alfaiate et al. [11])	0.51 (Wong et al. [39])
F4	DCC	0.45 (Fattovich et al. [38])	0.51 (Wong et al. [39])
	HCC	0.36 (Alfaiate et al. [11])	0.51 (Wong et al. [39])
	Death	0.50 (Fattovich et al. [38])	0.51 (Wong et al. [39])

ALT alanine aminotransferase, *DCC* decompensated cirrhosis, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma

3 Results

3.1 Natural History Validation

To validate the model outputs, the number of advanced liver disease events for CC, DCC, and HCC, as predicted by the model, were compared with natural history studies [26, 30]. For each comparison with the natural history studies, patient characteristics such as age and initial fibrosis distribution were matched to the studies based on published data. As shown in Fig. 1a–c, this model was found to predict outcomes with a high degree of concordance with previously published natural history studies.

3.2 HDV Disease Progression

The base-case analysis showed fewer advanced liver disease events (CC, DCC, HCC, LT, and death) per 10,000 patients among those receiving hypothetical HDV treatment compared with BSC (Fig. 2a, b) for both responder rate scenarios. Patients receiving hypothetical HDV treatment had fewer new CC events (i.e., patients who progress to CC without having experienced fibrosis regression) in the base-case analysis (218 and 328 fewer cases per 10,000 on the combined response endpoint of 50% and 75% response scenarios, respectively), driven by a reduction in liver disease progression associated with the combined virologic and biochemical response. Fewer patients in the hypothetical HDV treatment arm progressed to both DCC (457 fewer per 10,000) and HCC (270 fewer per 10,000), and there were 35 fewer LTs and 915 fewer deaths per 10,000 in the hypothetical HDV treatment arm compared with the BSC arm, when a 50% responder rate was considered for those receiving hypothetical HDV treatment. Similarly for when a 75% responder rate was considered, fewer patients in the hypothetical HDV treatment arm progressed to DCC (687 fewer per 10,000) and HCC (406 fewer cases per 10,000), and there were 52 and 1375 fewer LTs and deaths, respectively, per 10,000 in the hypothetical HDV treatment arm compared with the BSC arm.

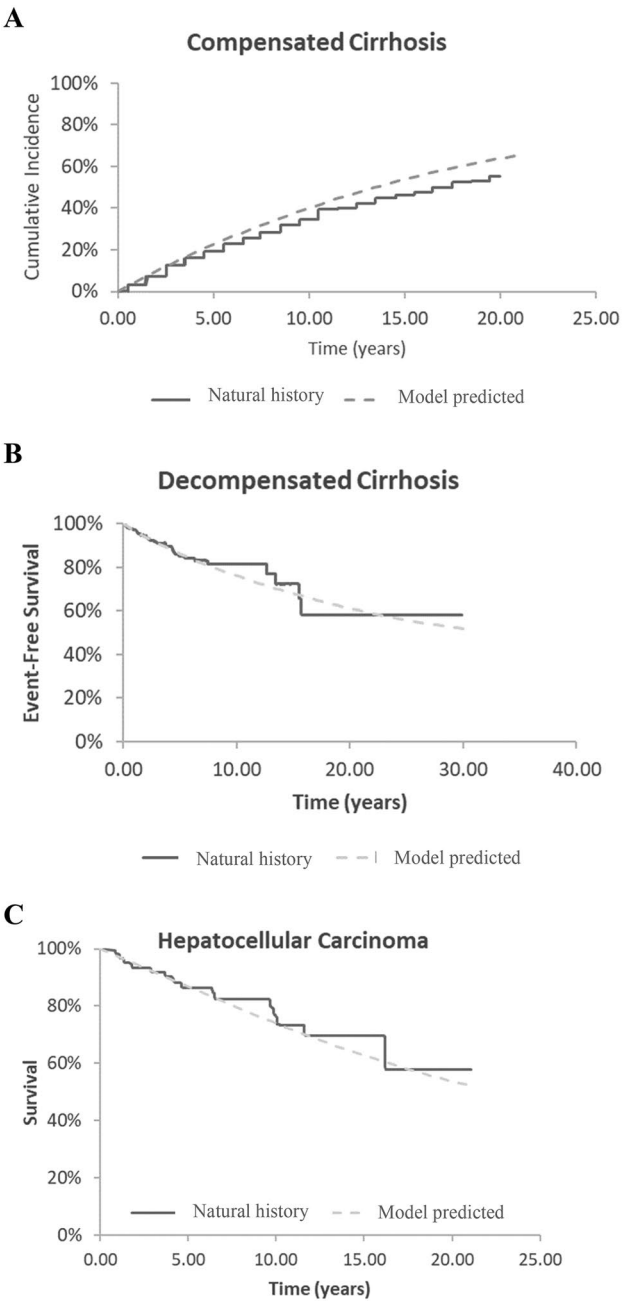

Fig. 1 Replication of natural history studies by the HDV disease model for events of **a** compensated cirrhosis, **b** decompensated cirrhosis, and **c** hepatocellular carcinoma. *HDV* hepatitis D virus

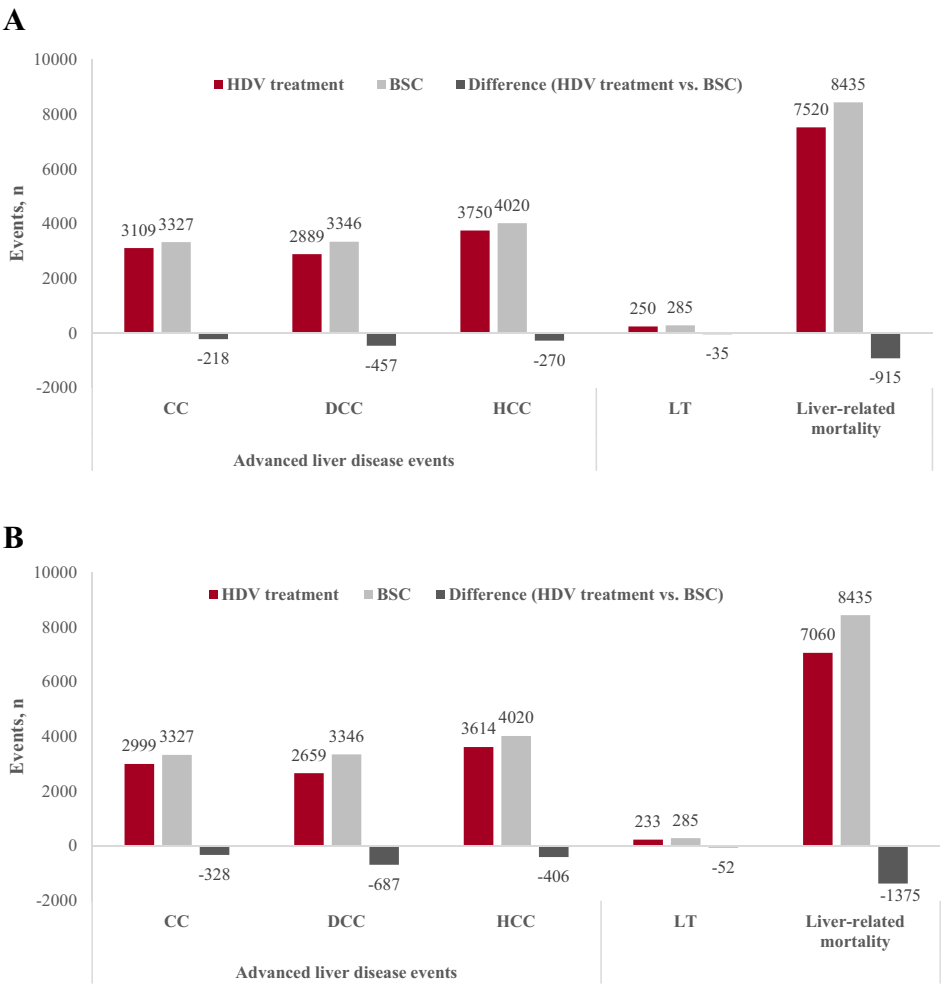

Fig. 2 Health state events for HDV treatment versus BSC (base-case analysis, per 10,000 patients): HDV treatment with combined response endpoint: **a** 50% response rate and **b** 75% response rate. *BSC* best supportive care, *CC* compensated cirrhosis, *DCC* decompensated cirrhosis, *HCC* hepatocellular carcinoma, *HDV* hepatitis D virus, *LT* liver transplant

3.3 Scenario Analyses

3.3.1 Early versus Later Treatment Initiation

Scenario analyses exploring the impact of early treatment with 100% of patients starting at a given earlier fibrosis stage showed consistently fewer events with hypothetical HDV treatment versus BSC for response rates of 50% and 75% (Table 3). For the 50% responder rate, when 100% of patients are treated at F0, F1, F2 or F3, patients receiving hypothetical HDV treatment had fewer advanced liver disease events than those receiving BSC, across all measures. When 100% of patients are treated at F4, hypothetical HDV treatment resulted in fewer liver-related events compared with BSC, with the exception of CC. Similar results were observed for the 75% responder rate.

3.3.2 Alternate Treatment Response Assumptions

The 'treatment-HBV' scenario analysis, where HBV mono-infection hazard ratios for disease progression are used for responders, showed an overall lower number of health events at both 50% and 75% response rates (Fig. 3, ESM S1 Table). As with the base-case analysis, with the exception of the CC state, hypothetical HDV treatment showed fewer events than BSC, with fewer HCC events per 10,000 patients for the 75% response rate versus the 50% response rate. The 'treatment-ALT' scenario, where hazard ratios based on ALT normalization were used, found increased health state events compared with the base-case analysis, due to faster disease progression conferred with ALT normalization only.

3.3.3 No Disease Regression for Treatment Responders

The 'no-regression' scenario analysis assumed treatment response could not induce fibrosis regression; the number

Table 3 Difference in health state events for HDV treatment versus BSC for 50% and 75% response rate in the early versus late treatment scenario analyses (per 10,000 patients)

Liver disease events (*n*)	Base case	Scenario if all patients were starting at a given fibrosis stage				
		F0	F1	F2	F3	F4
Difference for HDV tx vs. BSC	*50% response rate*					
CC	−217	−554	−522	−423	−233	0
DCC	−457	−291	−342	−420	−543	−503
HCC	−270	−518	−488	−441	−352	−80
LT	−35	−30	−32	−37	−42	−33
Liver-related mortality	−915	−921	−970	−1038	−1124	−789
Difference for HDV tx vs. BSC	*75% response rate*					
CC	−327	−833	−786	−636	−351	0
DCC	−687	−438	−515	−632	−817	−756
HCC	−406	−780	−734	−663	−529	−121
LT	−52	−44	−49	−55	−64	−50
Liver-related mortality	−1375	−1386	−1460	−1561	−1689	−1185

BSC best supportive care, *CC* compensated cirrhosis, *DCC* decompensated cirrhosis, *HCC* hepatocellular carcinoma, *HDV* hepatitis D virus, *LT* liver transplant, *tx* treatment

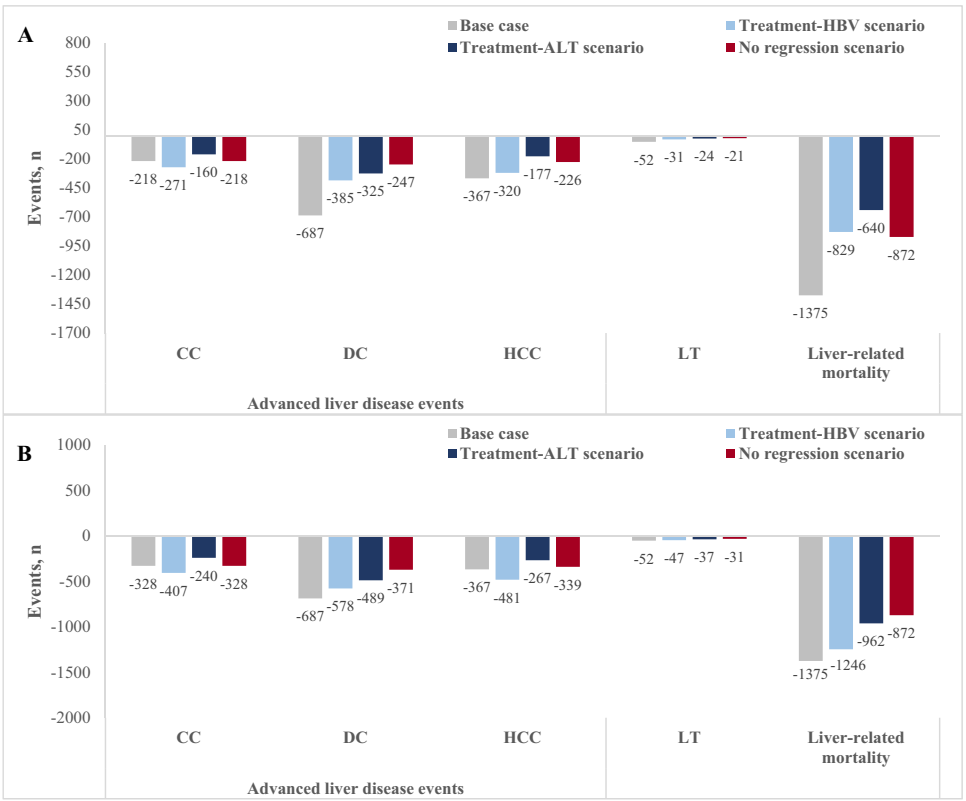

Fig. 3 Differences in health state events between HDV treatment and BSC for scenario analyses with adjusted treatment response assumptions (per 10,000 patients):[1]HDV treatment with **a** 50% response rate and **b** 75% response rate. [1]Values reflect differences in modeled events for HDV treatment versus BSC (negative values indicate fewer events in the HDV treatment arm). *ALT* alanine aminotransferase, *BSC* best supportive care, *CC* compensated cirrhosis, *DC* decompensated cirrhosis, *HBV* hepatitis B virus, HCC, hepatocellular carcinoma; *HDV* hepatitis D virus, *LT* liver transplant

of health state events (with the exception of CC) were increased from the base-case analysis as more patients remained in stages F2 through F4 (given that none regressed to earlier stages of fibrosis) [ESM S2 Table].

4 Discussion

HDV results in considerable global clinical burden. The HDV model proposed here showed that patients receiving a hypothetical novel HDV treatment compared with

BSC achieved substantial improvements in liver disease outcomes, including reductions in liver disease progression and lower liver-related mortality. The fewer advanced liver disease events (i.e., DCC, LT, and liver-related mortality) observed in the hypothetical HDV treatment arm were attributable to the efficacy of hypothetical HDV treatment (for both 50% and 75% response rates), which is associated with slower disease progression. Results were robust across scenario analyses, including alternate treatment response assumptions and not allowing the regression to earlier fibrosis stages for treatment responders; earlier versus later treatment initiation found a greater overall benefit, notably for patients with F0—across CC and HCC. Given the high concordance with natural history studies, the results observed in this study have a high degree of external validity in regard to BSC outcomes [21, 26].

To our knowledge, this is the first disease model of the natural history of HDV assessing the potential impact of novel antiviral HDV treatment. Owing to the relative paucity of studies of the natural history of HDV and historical lack of approved treatments, this model was developed using the most relevant available published information supplemented with a methodical application of clinical expertise, when necessary. Certain model assumptions and inputs followed clinical experience for patients with HBV or were derived from expert consensus. Orphan conditions often lack a substantial evidence base, and this work illustrates the need for further evidence generation efforts to improve our understanding of the real-world process and patterns of care for patients with chronic HDV infection. Such research must consider the long-term natural history of HDV and implications of novel therapies with greater impact on clinical outcomes than has been observed to date, all in the context of diverse sociodemographic, cultural, and health system factors that contribute to profound effects on disease management and patients' health and mortality. This work can support subsequent efforts to model the natural history of HDV and also the impact of novel therapies on humanistic and economic outcomes, which are central to clinical and health policy decisions for underserved populations with lifelong conditions such as HDV. Model inputs may be adapted to emerging evidence in the therapeutic landscape.

New treatments are urgently needed for HDV; however, for the impact of these treatments on natural history to be modeled, consensus on appropriate endpoints and their impact on disease progression needs to be determined. For disease progression among treatment responders, a modified Delphi panel supported using a surrogate endpoint relationship between the combined response of HDV-RNA undetectability or $\geq$2-$\log_{10}$ decline and ALT normalization [31] and measurements of disease progression in HDV RNA− versus HDV RNA+ patients. However, this approach is limited by the fact that few natural history studies examined the relationship between HDV RNA status and disease progression in patients receiving treatment for chronic HDV; thus, the relationship may not fully reflect the impact of slowed disease progression due to effective HDV treatment. This approach is also limited by the relatively short duration of follow-up of these natural history studies. In addition to defining appropriate outcomes for clinical efficacy and understanding their surrogate relationship with long-term disease outcomes in HDV patients, future research can also be directed at better understanding the impact of successful treatment on progression to advanced liver disease for those responding to novel HDV therapeutics, to further refine economic models such as the model developed herein.

This model was designed to simulate the natural history of HDV infection over a lifetime horizon, reflecting the chronic nature of the disease. Given the novel modeling approach, several assumptions were necessary. One conservative assumption is that non-complete responders will stop treatment, which may not be what is observed in clinical practice. Furthermore, we assumed that patients with only non-cirrhotic or compensated cirrhotic disease would be eligible to receive treatment. It should be noted that limited published data were available to inform transition probabilities governing the natural history of HDV and that of treatment responders. However, natural history data for patients with HBV mono-infection versus HBV/HDV infection is assumed to provide a substantive and meaningful proxy. Notably, this approach was able to replicate disease progression rates as observed across select HBV/HDV natural history studies. Furthermore, to explore the uncertainty of the impact of the combined response endpoint on disease progression rates, several scenario analyses were included based on alternative relationships informing the reduction in disease progression, such as that between HBV mono-infection versus HBV/HDV infection rates and the impact of ALT normalization from HBV mono-infection data, alongside the base-case analysis. Additional data on the rates of disease progression both in HBV/HDV patients and for those who achieve combined virologic and biochemical endpoints will be essential in further validating this disease progression framework. Furthermore, patients receiving the hypothetical HDV treatment in this analysis could continue treatment until HBsAg seroclearance or otherwise discontinuation, based on the approval by the European Medicines Agency Summary of Product Characteristic for a recently approved treatment. Applicability of this stopping rule may differ among HDV

treatments as well as decisions by other regulatory bodies. Ongoing clinical trials and additional real-world studies may provide a better understanding of treatment patterns for patients with various stages of liver disease, as well as on how patients adhere to and persist on treatment.

5 Conclusion

Determining the clinical and economic impact of HDV treatment is essential for advising healthcare stakeholders in order to optimize the management of patients with chronic HDV. This disease model was designed to support the implementation of transformative novel treatment options for patients with chronic HDV infection. While the best available data were used to inform the model, future studies can further inform the impact of novel HDV treatments.

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Declarations

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Conflicts of Interest Ankita Kaushik and Chong Kim are employees and stockholders of Gilead. Robert J. Wong has received consulting fees for Gilead Sciences, and research grants (in kind) from Gilead Sciences. George Dusheiko has received consulting fees and speaker fees from Gilead Sciences; has participated on the Data Safety Monitoring Board/Advisory Board for Janssen, Glaxo Smith Kline, Arbutus, Aligos, Vir; and has roles in the National Medical Research Council Singapore and the World Health Organization Pediatric Working Group on Viral Hepatitis. A honorary fee has been paid from Gilead to The George Institute for methodological support provided by Gian Luca di Tanna. Nathaniel J. Smith and Csilla Kinyik-Merena have no financial disclosures to declare.

Data Availability The data generated to inform the economic model are not publicly available but may be available from the corresponding author on reasonable request.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Author Contributions All authors participated in the conceptualization, methodology and validation of the model. NJS and CKM participated in the data analysis. AK and CK participated in the investigation and data curation. NJS and CKM developed the model manuscript. All authors participated in the reviewing and editing of the manuscript, and approved the final version of the manuscript submitted for publication.

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